# Sudden Cardiac Death: Methods of Risk Prediction

6

John Alvin Gayee Kpaeyeh Jr., Dean M. Abtahi, and Michael R. Gold

**Abstract**

Sudden cardiac death (SCD) is the leading cause of cardiovascular mortality, accounting for more than 50% or greater than 300,000 deaths in the United States annually. As such, this is a major health care problem. Identifying high risk patients that may benefit from preventative strategies has been studied for decades. The implantable cardiac defibrillator (ICDs) has had a major impact on the treatment of SCD. However, this therapy has been largely used in patients with left ventricular dysfunction. A changing epidemiology of SCD with fewer patients having marked reductions in left ventricular ejection fraction (LVEF) has renewed the focus on identifying other high risk populations. This chapter summarizes the current understanding of the diverse clinical, genetic, electrocardiographic and imaging techniques available to detect patients most at risk. Despite many identified risk factors, no single predictor has been shown to have sufficient predictive value to be used to guide preventative therapy and reduce mortality. More recent effort has been directed towards combining markers to increase the sensitivity of identifying high risk cohorts.

**Keywords**

Sudden cardiac death (SCD) • Risk stratification • Implantable cardioverter defibrillator (ICD) • Ventricular tachycardia (VT) • Genome-wide association studies (GWAS) • Left ventricular ejection fraction (LVEF) • QRS duration • QT interval • Heart rate turbulence • T-wave alternans • Cardiac magnetic resonance imaging (cMRI) • Scar assessment • Sympathetic denervation • Positron emission tomography (PET) • Radioiodinated metaiodobenzylguanidine (mIBG) • Signal Averaged ECG (SAECG) • Electrophysiologic study (EPS) • Holter monitoring

## Introduction

Sudden cardiac death (SCD) is most commonly defined as death from unexpected circulatory arrest occurring within an hour of the onset of symptoms or during sleep [1]. In the majority of cases, SCD is triggered by an arrhythmic event, most frequently ventricular tachycardia, ventricular fibrillation and asystole, although recently, pulseless electrical activity has been noted more frequently.

The leading cause of death in the United States, according to the Centers for Disease Control and Prevention, is cardiovascular disease (611,000 deaths annually) [2]. Other

**Disclosures:** Dr. Gold has received research grants and served as a consultant to Boston Scientific, St Jude and Medtronic.

J.A.G. Kpaeyeh Jr., M.D. • D.M. Abtahi, M.D.
M.R. Gold, M.D., Ph.D. (✉)
Division of Cardiology, Medical University of South Carolina, Charleston, SC 29425, USA
e-mail: kpaeyeh@musc.edu; abtahi@musc.edu; goldmr@musc.edu



P. Kowey et al. (eds.), *Cardiac Arrhythmias, Pacing and Sudden Death*, Cardiovascular Medicine,
DOI 10.1007/978-3-319-58000-5_6

common causes of death include malignancy (584,000), chronic respiratory disease (149,000), accidents (130,000), and strokes (128,000) [2]. Despite a dramatic decline in mortality from heart disease over the past 30 years, SCD remains the leading cause of cardiovascular death. It is estimated that SCD accounts for more than 300,000 deaths in the United States annually and approximately 50% are the first known cardiac event [2, 3]. Even this may be an underestimation, as the majority of patients who suffer out of hospital cardiac arrest never survive the initial event [2].

In order to reduce the burden of SCD, much effort has been directed to identify and better treat those most at risk. It is well described that underlying structural heart disease in the context of ischemia, systolic heart failure and fibrosis often trigger sustained arrhythmias that may lead to cardiovascular collapse and death. However, a broad range of at risk populations for SCD exists, including patients with family history of coronary artery disease, heart failure with reduced ejection fraction (HFrEF), ambient ventricular arrhythmia (PVC, non-sustained ventricular tachycardia (VT), sustained VT), prior cardiac arrest, advanced age, male sex, African American race, left ventricular hypertrophy, congenital heart disease, and cardiac conduction abnormalities, such as bundle branch block. Additionally, patients with underlying channelopathies, including long QT syndrome and Brugada syndrome as well as arrhythmic myopathies, for example arrhythmogenic right ventricular cardiomyopathy, Wolf Parkinson White syndrome and hypertrophic cardiomyopathy, present differently than those with traditional risk from ischemic and non-ischemic cardiomyopathies. Various electrical markers may predict SCD including T-wave alternans, late potentials on signal averaged electrocardiography, inducibility of sustained tachyarrhythmia by programmed electrical stimulation, prolonged QRS and QT intervals, and/or abnormal heart rate variability or turbulence and abnormal baroreflex sensitivity. Additionally, there are further co-morbidities that contribute to and complicate risk stratification including smoking, hypertension, hyperlipidemia, obesity, diabetes mellitus, renal failure, drug abuse, and congenital heart disease. Finally, life style and social factors play a predictive role including activity levels, socioeconomic status, as well as stress (emotional or physical) [1, 4]. Given the complexity and diversity of these factors, it is not surprising that risk stratification of SCD remains a major challenge.

A series of large, multicenter randomized trials demonstrated the benefit of the implantable cardioverter defibrillators (ICD) for preventing sudden death in selected populations [5–7]. This led to a rapid expansion of this therapy, which has likely contributed to a significant decline in incidence of ventricular fibrillation [2, 8, 9] and deaths [8] during out of hospital cardiac arrest. Due to this success and the changing epidemiology of SCD, there has been a renewed focus on risk stratification in this population [3, 10]. However, despite advances in our understanding, SCD remains a significant problem primarily because of a lack of a comprehensive and validated approach to detecting patients at risk. The major risk factors evaluated are presented in Table 6.1 and will be summarized in this chapter.

**Table 6.1** Summary of risk stratification tools for sudden cardiac death

| | |
|---|---|
| History | Post-MI |
| | Parental history of premature SCD (age < 65) |
| | VT/VF |
| | Age |
| | Male sex |
| | African American race |
| | Traditional coronary risk factors |
| Anatomic abnormalities | Low LVEF |
| | Myocardial scar |
| Autonomic abnormalities | Heart rate turbulence: Ambulatory ECG |
| | Sympathetic denervation: MIBG, PET |
| *ECG abnormalities* | |
| Resting ECG | Prolonged QRS duration |
| | Prolonged QT interval |
| | Brugada syndrome: ST-segment elevation and T-wave inversion in V1 and V2 |
| | Arrhythmogenic right ventricular dysplasia: Epsilon waves, prolonged duration of S-wave and T-wave inversion in V1 and V2 |
| | Wolf-Parkinson-White: delta waves, narrow PR and prolonged QRS duration |
| | Late Potentials on signal averaged ECG |
| Ambulatory ECG | Ventricular ectopy |
| | NSVT |
| | Heart rate turbulence |
| Exercise ECG | NSVT |
| | T-wave alternans |
| EP study | Inducibility of sustained VT |

*MI* myocardial infarction, *LVEF* left ventricular ejection fraction, *SCD* sudden cardiac death, *MIBG* meta-iodobenzylguanidine, *PET* positron emission tomography, *ECG* electrocardiogram, *NSVT* non-sustained ventricular tachycardia

## Genetics and Genomics

Multiple population based studies exist suggesting a strong genetic contribution to individual SCD risk, independent of traditional cardiovascular risk factors. The landmark Paris Prospective Study showed increased risk of SCD in middle aged men with parental sudden death (RR 1.80 (95% CI, 1.11–2.88) [11]. Similarly, the Seattle case-controlled study, demonstrated increased risk of SCD (odds ratio (OR) = 2.69, 95% CI = 1.35–5.36) among patients with a parental history of early onset sudden death (age < 65) [12]. Additionally,

family history of sudden death has been shown to be an independent risk factor (OR 2.72, 95% CI 1.84–4.03) for primary ventricular fibrillation in acute myocardial infarction [13]. Despite the multiple studies demonstrating a strong association between family history and SCD, there has yet to be a specific genetic variant or clinical marker identified that has proven effective in predicting individual risk. Furthermore, due to the variability in the mechanism of SCD, there is likely a broad spectrum of heritability of SCD in different populations.

In individuals under 40 years of age, SCD occurs in a Mendelian pattern with cardiomyopathies and electrical disorders being the most prevalent [14]. In individuals above 40 years old, which account for the majority of events, SCD is most commonly caused by ventricular fibrillation in the setting of acute or prior myocardial infarction. To attain a better understanding, genome-wide association studies (GWAS) are now being performed to isolate genetic variants modulating SCD risk, with specific interest in genes that play a role in structural abnormalities, as well as heart rate and ECG indices of slowed conduction and abnormal repolarization [14–18].

GWAS use dense maps of hundreds of thousands of single nucleotide polymorphism (SNP) arrays to identify genotype patterns associated with a particular phenotype [14], in this case SCD. An increasing number of genetic variants are starting to be uncovered with strong associations [19, 20] for SCD, and this approach holds future promise as costs decrease and gene-scanning technologies improve. However, these observations are limited in clinical applicability at this time due to small sample size.

## Left Ventricular Ejection Fraction

Left ventricular systolic function, estimated by ejection fraction (LVEF), is the most common studied marker of SCD risk, and it is clearly a powerful predictor of cardiac mortality [21–23]. LVEF is easy to measure, reproducible and predictive in both ischemic and non-ischemic cardiomyopathies. In clinical practice, LVEF has become the primary criterion used for ICD placement. The MADIT II trial demonstrated a significant reduction in SCD and all-cause mortality after ICD placement among patients with previous myocardial infarction and LVEF ≤30% [24]. The SCD-HeFT trial demonstrated decreased all-cause and sudden death mortality after ICD placement in patients with both ischemic and non-ischemic cardiomyopathy, NYHA class II or III functional status and LVEF ≤35% [7]. However, not all studies show a benefit of ICDs among patients with reduced LVEF. The CABG-Patch trial showed no benefit of ICD therapy in patients with EF < 35% undergoing surgical coronary revascularization [25], possibly due to the antiarrhythmic effect or the improved systolic function following revascularization. Similarly, the DINAMIT and IRIS studies showed no benefit of early implantation of ICDs following myocardial infarction despite a reduced ejection fraction [26, 27]. Again, this may be due to improvement in LVEF post MI or competing non-arrhythmic causes of mortality [26]. Hence, the timing of LVEF assessment and of intervention and changes in underlying myocardial status are also important variables to consider. Finally, as noted above, most patients that survive cardiac arrest in more contemporary studies only have mildly depressed or near normal systolic function [5, 28] and the predictive role of LVEF is therefore limited in these populations without significant underlying cardiomyopathy.

## Resting Electrocardiogram (QRS and QT Intervals)

The resting electrocardiogram is a non-invasive, inexpensive diagnostic tool that is available in most clinical settings and can provide useful prognostic information. QRS duration represents interventricular conduction time and when prolonged may promote ventricular arrhythmias by altering electrical and mechanical function through abnormal dispersion of depolarization and repolarization and resultant cardiac dyssynchrony. QRS prolongation may also be a marker of more advanced LV dilation and dysfunction. QRS prolongation (≥120 ms) has been shown to predict both overall mortality and SCD in patients with ischemic and non-ischemic cardiomyopathy, independent of LVEF [29]. In a subgroup analysis of the MUSTT trial, QRS duration and the presence of left bundle branch block were found to be independent predictors of overall mortality and SCD in patients with ischemic cardiomyopathy [30]. Despite the above findings, there are a number of conflicting ICD trials that were unable to demonstrate an effect of QRS duration on mortality independent of LVEF [31, 32], limiting its overall predictive value.

The QT interval represents ventricular repolarization, which is routinely corrected for heart rate or RR interval and measured as QTc. A QTc duration greater than 420–440 ms (longer upper limit of normal in females than in males) is associated with a two to threefold increase in cardiac mortality [33–35] among patients with and without coronary artery disease. Applied to the general population, a prolonged QT interval and/or increased QT interval dispersion (the maximal inter-lead QT variance in 12 lead electrocardiogram) predicts increased cardiac and total mortality [36]. However, in patients with advance heart failure, QT interval and interval dispersion were unable to predict mortality independent of LVEF [37], also limiting its clinical applicability in patients with significant underlying cardiomyopathy. Of note, these studies did not include subjects with genetic

**Table 6.2** Composite risk scores for SCD in Primary Prevention Cohorts

| Prediction model | MADT-II | PAREPET | PACE |
|---|---|---|---|
| | NYHA Class > II | Percentage of denervated myocardium (>37%) | Cr ≥2.0 |
| | | | Point(s) – 2 |
| | Age > 70 years | LVEDV Index >99 mL/m$^2$ | LVEF ≤ 20% |
| | | | Point – 1 |
| | Blood Urea Nitrogen >26 | Creatinine >1.49 mg/dL | Age > = 70 |
| | | | Point – 1 |
| | QRS duration >0.12 s | Lack of angiotensin inhibition | Peripheral artery disease |
| | | | Point – 1 |
| | Atrial fibrillation | | |
| Low risk | Zero risk factors | Zero risk factors | |
| Intermediate risk | Two risk factors | One risk factor | Less than 3 points |
| High risk | Three or more risk factors | Two risk factors | 3 or more points |

[94–96]

channelopathies including Long QT syndrome in whom a QTc > 500 ms (or the rarer Short QT syndrome with QTC < 350 ms) is associated with increased risk of SCD independent of structural heart disease [38, 39].

Finally, there are a number of ECG abnormalities recognized that carry an increased incidence of SCD in specific situations including Brugada syndrome, Arrhythmogenic Right Ventricular Dysplasia and Wolf Parkinson White Syndrome (Table 6.2).

## Ambulatory Electrocardiogram (Holter Recording of Ventricular Ectopy and Heart Rate Turbulence)

Historically, long term ambulatory electrocardiography by Holter monitoring was used to predict SCD in survivors of myocardial infarction. Patients with complex ventricular ectopy defined as more than 10 premature ventricular beats per hour or non-sustained ventricular tachycardia (NSVT) were shown to have increased mortality [40, 41]. However, in one more recent multivariate analysis performed in the thrombolytic/reperfusion era, complex ventricular ectopy was not shown to be an independent predictor of mortality and the presence of post infarct NSVT no longer predicted mortality or arrhythmic events [42]. Studies evaluating complex ventricular ectopy, specifically NSVT among patients with non-ischemic cardiomyopathy have also had conflicting results [43–45].

Heart rate turbulence is a non-invasive marker of electrical instability that can be assessed on Holter monitor and has been shown to identify patients at high risk for all-cause mortality and sudden death, specifically in post-infarction and congestive heart failure patients [46–49]. Heart rate turbulence is believed to reflect baroreflex sensitivity and is a surrogate marker of cardiac autonomic tone. Under normal conditions, a ventricular premature beat (VPB) results in a transient drop in blood pressure triggering baroreceptor activated inhibition of vagal tone and subsequent increase in heart rate. Increased myocardial contractility following a VPB then results in a transient increase in blood pressure with a decrease in sinus node activity. To analyze, the RR intervals following VPBs are assessed for an initial short acceleration followed by a deceleration of heart rate. Absent or diminished biphasic pattern reflects an abnormal response and increased risk of cardiac arrhythmic death [49].

## Exercise Electrocardiogram (NSVT and T-wave Alternans)

Exercise stress testing is a commonly performed, non-invasive test used to detect myocardial ischemia and to evaluate exercise capacity and cardiovascular function. Exercise induced NSVT is associated with increased cardiovascular mortality within the next decades [50]. However, exercise induced NSVT rarely occurs in structurally normal hearts (other than in RVOT ventricular ectopy syndromes) and in otherwise healthy individuals is not associated with an increase in cardiovascular or total mortality [51, 52]. NSVT does not predict long term mortality in patients with myocardial infarction treated with coronary artery reperfusion and beta-blockers or dilated cardiomyopathy, independent of LVEF. However, NSVT does have prognostic significance in patients with hypertrophic cardiomyopathy and certain genetic channelopathies [50].

Microvolt T-wave alternans (TWA) is a beat to beat alternation in the morphology and amplitude of the ST-segment or T-wave that has been associated with increased propensity for sustained ventricular arrhythmias [53]. Only rarely is the variability higher than the microvolt range and actually visible to the eye on routine electrocardiographic strips. The effect of TWA is further augmented by increased heart rate, ventricular premature beats, ischemia from coronary artery

occlusion or reperfusion, adrenergic stimulation and mental stress [53]. The underlying mechanism is believed to involve enhanced sympathetic nerve activity and abnormal calcium handling that disturbs cardiac repolarization in vulnerable myocardium leading to discordant alternans of repolarization of myocytes. Risk stratification is based on peak TWA measured during symptom limiting bicycle or treadmill exercise testing at a target heart rate range of 105–110 beats/min (and during post-exercise recovery) or during 24 h ambulatory ECG recording. Early studies showed that TWA was a powerful electrocardiographic tool in predicting risk of cardiovascular mortality and SCD in patients with myocardial infarction, as well as in cohorts with ischemic and non-ischemic cardiomyopathy. The predictive value of TWA in patients not utilizing beta-adrenergic blockade agents is significantly less than those on beta-adrenergic therapy [53, 54]. This phenomenon is likely the result of the beta-adrenergic blocker's effect on the sympathetic nervous system [53], and indicates that beta blockers should not be withheld before the procedure.

Despite considerable enthusiasm over TWA, subsequent large prospective trials failed to validate the role of TWA for risk stratification in patients with reduced LVEF. The TWA SCD HeFT [55] study showed no predictive value to predict mortality or arrhythmic events among patients in the SCD HeFT trial. In addition, the Master study showed that TWA did not predict appropriate ICD therapy in a large cohort of subjects implanted for standard primary prevention indications [56]. These studies have tempered the enthusiasm for this technique in patients with significant underlying cardiomyopathy. More recently, a different analytic approach was developed to assess T-wave alternans in the absence of exercise. This is a somewhat different measure despite the common name. Ongoing studies are assessing its role in stratifying risk of life threatening arrhythmias and SCD among patients with LVEF >35%, specifically to be used in conjunction with other markers of electrical instability such as signal-averaged ECG, heart rate turbulence or heart rate recovery (see CARISMA and AVID studies under Electrophysiology Study). In this capacity, TWA in the presence of one other factor increased hazard ratios up to 212% and positive predictive value by 78% [53]. In this subgroup of patients, its clinical utility remains undetermined.

## Signal Averaged Electrocardiography

Signal averaged electrocardiography (SAECG) is a method of recording and averaging electrocardiographic data with the goal being to detect late potentials [57]. This test was initially found to be a promising marker of sudden cardiac death in patients with ischemic cardiomyopathy and later non-ischemic cardiomyopathy [57–60]. In a study of 182 patients post acute myocardial infarction from 1992 with 14 month follow up, and primary outcome of sustained ventricular arrhythmia or SCD, SAECG was found to be a significant predictor of SCD with a 2.7 fold increase in risk [61]. El-Sherif et all found similar results when they compared SAECG to clinical acumen, ejection fraction, and ventricular arrhythmia and showed that SAECG provided that best predictive criterion [62]. Despite these findings, some studies that have tried to use SAECG was to predict utility of prophylactic ICD implantation in patients with coronary artery disease and depressed ejection fraction at time of elective coronary bypass surgery have shown no survival benefit of ICD implantation if patients with abnormal SAECG [63].

With regard to non-ischemic cardiomyopathy, Mancini et al., in 1993 were able to show that patients with an abnormal SAECG had a significant increase in their risk for sustained ventricular arrhythmias as compared to patients with normal SAECG or bundle branch block (BBB) [57]. Goedel-Meinen et al. in 2001 demonstrated that SAECG was a useful independent prognostic factor for SCD, mortality, and cardiac events [64]. Subsequent studies have shown conflicting and less promising results. A more recent study performed comparing mIBG to SAECG, heart rate variability, and QT dispersion showed that mIGB and not SAECG, heart rate variability or QT dispersion was a predictor of SCD in patients with mild to moderate ejection fraction [65]. It should also be noted that in a study by Brembilla-Perrot et al. showed, that in 128 patients with dilated non-ischemic cardiomyopathy, that in the presence of BBB the predictive value and specificity of SAECG is significantly diminished and that the SAECG itself did could not predict the risk of sudden cardiac death and mortality [66].

A head to head comparison between TWA and SAECG for predicting arrhythmia risk assessment showed that TWA a was more sensitive predictor of ventricular tacharrhythmia and death. It did validate the ability of SAECG to predict risk of spontaneous ventricular arrhythmias though not as well as TWA [67]. Therefore, while an abnormal SAECG may be a marker of risk for SCD, its value, especially as compared to newer modalities, is limited especially when it comes to predicting need for ICD. However, it may be useful in combination but not in isolation.

## Electrophysiology Study

Electrophysiology study (EPS) is an invasive procedure designed to diagnose disorders of the cardiac conduction by placing catheters in the right atrium, right ventricle and across the triscupid valve. With this tool and the prospect of delineating high risk patients for sudden cardiac death and malignant ventricular arrhythmias, both the MADIT and the

Multicenter Unsustained Tachycardia Trial (MUSTT) were designed and implemented [68].

In MUSTT, patients with coronary artery disease, left ventricular ejection fraction less than or equal to 40% and asymptomatic non-sustained ventricular tachycardia were enrolled at 85 study sites [68]. Patients who met inclusion criteria and had sustained VT induced by EPS were randomized to cardiac medications only or a strategy of arrhythmia suppression first with antiarrhythmic drugs to suppress the inducibility of VT and if unsuccessful then an ICD. A survival benefit only among patients treated with ICDs and not antiarrhythmic drugs [68]. There was an absolute reduction in risk of cardiac arrest or death from arrhythmia by 7% after 5 years of follow up [68].

The Multicenter Automatic Defibrillator Implantation Trial (MADIT), which enrolled as a similar population with a lower ejection fraction, equal to or less than 35%. In MADIT, patients with inducible VT were randomized to an ICD or to "conventional care" [69]. These trials were followed up by the Multicenter Automatic Defibrillator Implantation Trial (MADIT) II which implanted ICDs in patients with ischemic cardiomyopathy in the absence of EP study for risk stratification [70]. This study included patients with a left ventricular ejection fraction ≤30%. A substudy of MADIT II performed programmed ventricular stimulation through the implanted ICD. This showed that inducible ventricular tachycardia (VT) did correlate with instances of VT but there was an inverse relationship with ventricular fibrillation requiring defibrillation [70]. Interestingly they showed that patients with non-inducible VT had a substantial burden of VT and a higher ventricular fibrillation burden than inducible patients, which casts major doubts on the utility and predictive value of EPS [70].

The above findings are supported by the Antiarrhythmics Versus Implantable Defibrillators (AVID) trial and the Electrophysiologic Study Versus Electrocardiographic Monitoring (EVSEM) trial [70, 71]. The AVID trial included patients with both ischemic and non-ischemic cardiomyopathies [71]. Investigators found that EPS had a limited predictive value for death though it did predict recurrent VT or ventricular fibrillation in patients with inducible VT with rates less than or equal to 200 beats per minute and tended to predict recurrent VT or ventricular fibrillation in patients with coronary artery disease [71]. However, again, EPS tended to miss patients who were at risk for VT or ventricular fibrillation by classifying them as non-inducible [71].

The CARISMA trial was designed to evaluate the predictive value of both invasive and non-invasive strategies of risk assessment for potentially lethal arrhythmias [72]. The study enrolled 5869 patients who had recent myocardial infarctions in ten European countries [72]. The inclusion criteria included left ventricular ejection fraction less than or equal to 40% measured 3–5 days after acute myocardial infarction not undergoing coronary artery bypass surgery [72]. The primary endpoint, unlike earlier studies, was not mortality but rather fatal or near fatal arrhythmias that could have been treated after consensus agreement by a five member committee reviewing the case [72]. Secondary endpoint was all-cause mortality in this study [72]. Monitoring was performed primarily with implantable loop recorders [72]. Risk factors evaluated included LVEF by echocardiography, heart rate variability by Holter Monitoring, TWA, SAECG, EPS, and QT analysis with 12 lead electrocardiogram at index and 6 weeks post acute myocardial infarction [72]. Investigators found that heart rate variability and turbulence at 6 weeks rather than index was the most significant predictor of potential lethal arrhythmia [72]. EPS was a predictor of the primary endpoint but less so than heart rate variability [72]. Interestingly, LVEF and TWA were not found to be a statistically significant predictor of treatable arrhythmia [72]. Another recent study, the ABCD trial, which was designed to evaluate the utility of TWA, EPS or combination, in selecting patients with ischemic cardiomyopathy with an ejection fraction less than or equal to 40% who may benefit from ICD therapy [73]. This study suggested that TWA and EPS were comparable at 1 year and additive in combination in their relative predictive values and might be a tool to help determine patients who would benefit least from ICD therapy in a time dependent way [73]. The utility of EPS may be in these select populations but even so, is limited and not specific enough to be used in a more broad patient population.

## Imaging: Assessing Scar Burden

Contrast enhanced cardiac magnetic resonance (cCMR) is an imaging modality that utilizes the power and spatial resolution of MRI images to understand and evaluate cardiac anatomy more accurately [74, 75]. Kim et al. were one of the first groups to demonstrate the potential power of cCMR in that it can distinguish between reversible and irreversible ischemic injury independent of wall motion or infarct age [74]. There are two temporal MRI images that can be used to understand cardiac anatomy and scar burden [74, 75]. The early contrast enhancement phase images are acquired within seconds and reflect perfusion while delayed/late contrast enhancement phase images are captured after several minutes and reflect a myriad of pathophysiological information, including, most importantly, myocardial scar [74, 76].

In 2007, Roes et al. published data that suggested cCMR delineated myocardial scar may be a superior predictor of mortality than LVEF and LV volume in patients with healed myocardial infarction [77]. Despite a number of studies showing a clear association between risk of malignant arrhythmia and myocardial scar, a quantitative continuous relationship has not yet been demonstrated [78]. This suggests

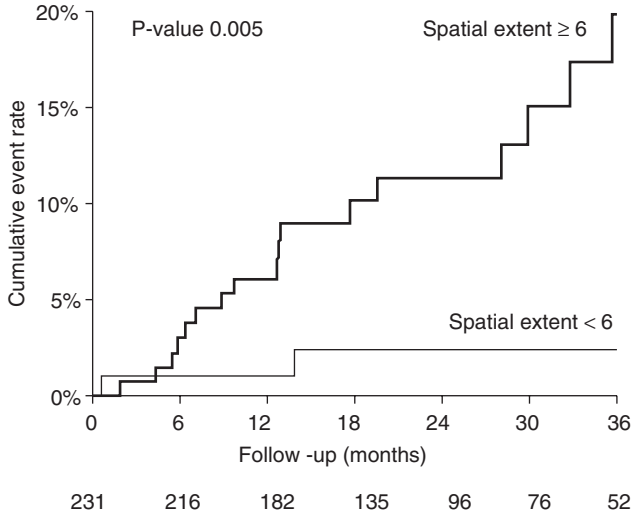


**Fig. 6.1** Impact of scar on mortality. Kaplan-Meier curve analysis showing difference in mortality when patients are stratified according to a large extent (>6) vs. a small extent (<6) of scar tissue on contrast enhanced MRI (Reproduced with permission from Roes et al. [77])

that, while scar is an important substrate for VT in patients with ischemic cardiomyopathy, it alone does not correlate with risk for malignant arrhythmia [78] (Fig. 6.1).

In 2009, Kadish et al. designed The Defibrillators To Reduce Risk By Magnetic Resonance Imaging Evaluation study (DETERMINE) as a prospective, multi-center, randomized, clinical trial to investigate the effects of ICD implantation in patients with coronary artery disease (CAD) and mild to moderate LV dysfunction [2, 79]. Their goal was to test the hypothesis that patients with LV infarct mass greater than or equal to 10% of myocardium, by cCMR, on both medical therapy and a functional ICD had a mortality benefit over medical therapy alone [2, 79]. Unfortunately, because of poor enrollment this study was discontinued [2].

## Imaging: Assessing Sympathetic Denervation (MIBG)

The autonomic nervous system consists of the sympathetic and parasympathetic components. Under normal circumstances, there is a balance with shifts from one system to the other depending on physiologic requirements. Chronic imbalances may occur in the setting of decreasing LVEF, heart failure and increasing left ventricular end diastolic pressure that may further worsen ventricular dysfunction [2, 80, 81].

In 1993, Mitrani et al. first showed in a small cohort of 18 patients with sympathetic denervation an increase in risk of ventricular tachycardia, even in the absence of coronary artery disease [82]. Ischemic heart disease is a major risk factor for the development of sympathetic denervation, even if only for short durations (minutes) [83]. As part of the remodeling process, denervation leads to increased sympathetic tone resulting in decreased pre-synaptic norepinephrine uptake and post-synaptic beta-adrenoceptors mass in a tachyphylaxis like response resulting in global left ventricular remodeling [84]. The over-stimulation by the sympathetic nervous system results in both supraventricular and ventricular arrhythmias by increasing automatic, triggering automaticity, and reentrance [85, 86].

Computed tomography using radioiodinated metaiodobenzylguanidine (mIBG) is now recognized as a powerful tool to identify inhomogeneity of the sympathetic nervous system within the cardiac myocardium, a potentially important substrate for sudden cardiac death [86–88]. mIBG was initially developed as a marker for adrenal medulla and related adrenergic tumors [87]. It is an analog of norepinephrine that is able to concentrate in sympathetic neurons within the heart [89]. The concentration of mIBG within cardiac neurons directly correlate with the neuronal integrity and function [89]. In 1979, mIBG was first synthesized and tested in both animals and humans [87]. In the human myocardium, mIBG, is preferentially transported by the cardiac neuronal norepinephrine transporter into cardiac sympathetic neurons [87]. mIBG is not metabolized and therefore can be imaged using planar or single photon emission computed tomography after uptake as it is not metabolized as norepinephrine [84]. In a study of 116 patients who underwent mIBG imaging prior to implantation of ICD, Boogers and colleagues showed that this marker was an independent predictor of ventricular arrhythmias that would require ICD therapy [84].

The late heart to mediastinum ratio (HMR) on mIBG has also been found to be an independent predictor of mortality [84]. Early images are typically obtained within an hour of infusion while late images are acquired after 3 h [84]. Late HMR is calculated dividing the regions of interest of the heart mean counts (H) by the regions of interest of the mediastinum mean counts (M) [84]. In the prospective AdreView Myocardial Imaging for Risk Evaluation of Heart Failure (ADMIRE-HF) study of 961 patients with NYHA functional class II/III CHF with an LVEF less than 35%, 237 subjects experienced functional class progression, life threatening arrhythmic events or cardiac death [90]. These investigators compared patients with a late HMR less than 1.6 to those with values greater than or equal to 1.6 [90]. They observed that patients with HMR less than 1.6 were at significant risk for all endpoints including progression of heart failure, arrhythmic events, cardiac death and all-cause mortality (Fig. 6.2), [90]. Multivariable analysis found that HMR, LVEF, BNP, and NYHA class were independent contributors to risk model [90].

Finally, the wash out rate (WR), which assesses the retention of norepinephrine by neurons, has been shown to be a

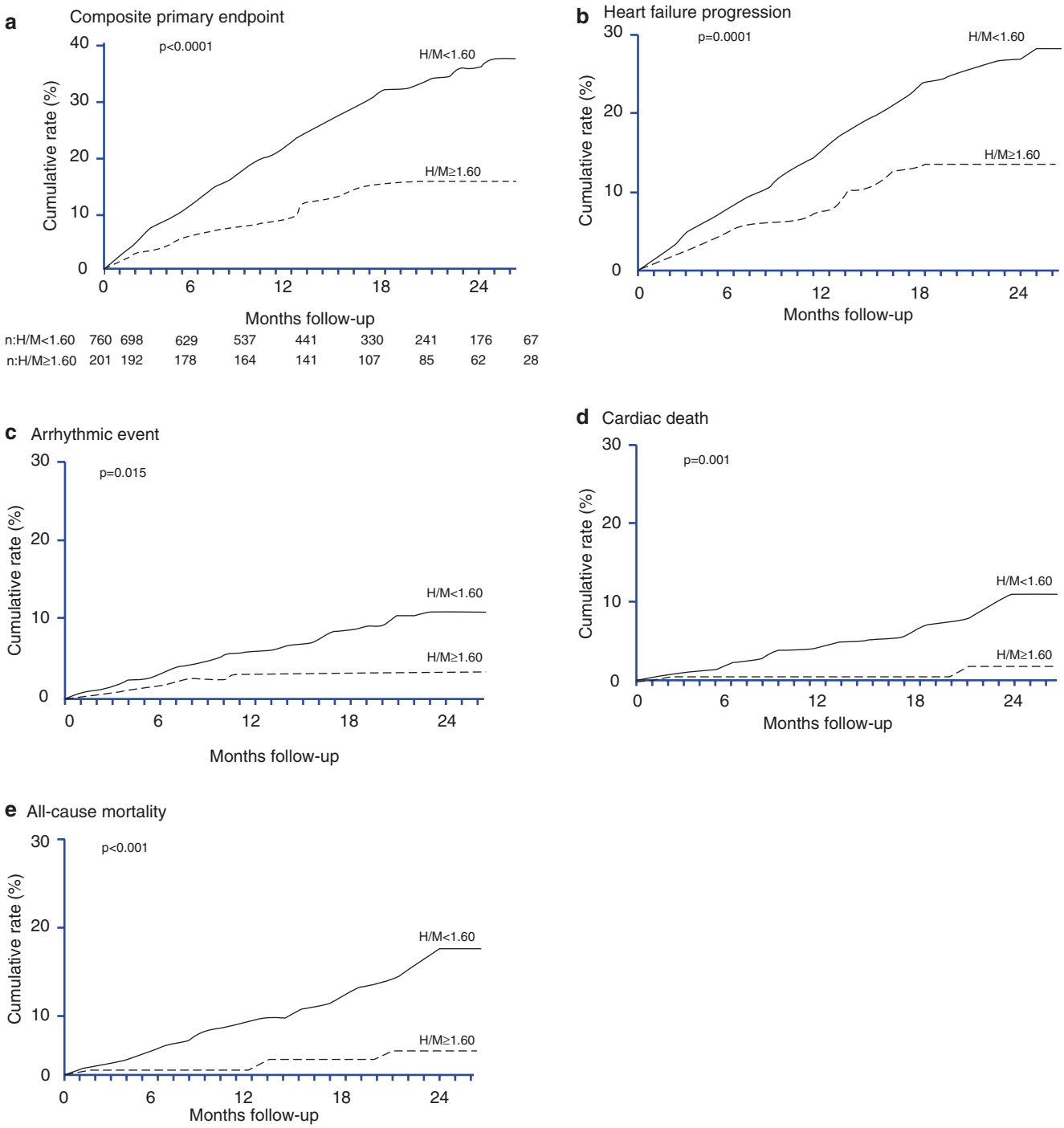


**Fig. 6.2** Sympathetic denervation and cardiac outcomes. Cumulative event curves comparing subjects with H/M <1.6 vs. >1.6. (**a**) Composite primary end point; (**b**) heart failure progression; (**c**) arrhythmic event; (**d**) cardiac death; (**e**) all cause mortality. H/M = heart/mediastinum ratio on Computed tomography using radioiodinated metaiobenzylguanidine (mIBG) (Reproduced with permission from Jacobson et al. [90])

potent predictor of sudden cardiac death [84]. Washout is calculated by subtracting the difference between the early H and M by the difference between the late H and M all divided by the difference between early H and M [84]. Tamaki et al. enrolled 106 patients with congestive heart failure, as defined by Framingham criteria, with an LVEF less than 40% [65]. Patients needed to be stable on angiotensin-converting enzyme inhibitor (ACEI), diuretics, and digoxin for at least 3 months [65]. Their exclusion criteria included significant renal failure, insulin dependent diabetes, autonomic neuropathy and beta blockers use [65]. Multivariate analysis showed that abnormal WR (>27%) and depressed LVEF were both

independent predictors of sudden cardiac death. Among patients with LVEF >35%, there was a significantly higher rate of sudden cardiac death in those with abnormal WR [65]. Their results were validated by meta-analysis of 18 studies with a total of 1755 patients by Verberne et al. [91]. WR has also been shown to be a significant independent predictor of MACE in patients with STEMI [92]. The applicability of this approach may be limited as beta blocker use is ubiquitous and a Class I indication among patients with ischemic myocardial infarction.

## Imaging: Assessing Sympathetic Denervation (Positron Emission Tomography)

Positron emission tomography (PET) is another imaging modality used in the evaluation of myocardial sympathetic innervation [2]. PET scanners work by detecting the radiation released by isotope emitting positrons after their annihilation within tissues [93]. PET is typically paired with computed tomography or magnetic resonance imaging [93]. In addition to evaluating myocardial sympathetic innervation, PET can also assess myocardial perfusion, metabolism (stunned or hibernating myocardium), and systolic function [93].

[11C]-meta-Hydroxyephedrine (HED) is a radioligand developed for PET to evaluate the sympathetic nervous system. It is a catecholamine analog labeled with 11C with a half-life of approximately 20 min that was developed based on metaraminol [90]. Like mIBG, HED is not metabolized by catechol-O-methyl transferase (COMT) or monoamine oxidase (MAO) [90]. Therefore it can remain in the sympathetic neurons long enough to be imaged. Based on uptake and retention of HED, Luisi et al. were able to show that hibernating myocardium in farm-bred pigs has significant regional reduction in norepinephrine reuptake [88].

The PAREPET trial was a prospective observational trial designed to study the hypothesis that inhomogeneity in human myocardial sympathetic innervation and/or hibernating myocardium could predict risk for arrhythmic death independent of left ventricular function [94]. This study enrolled 204 patients with inclusion criteria of ischemic heart disease and heart failure with LVEF >35% on optimal medical therapy who were not candidates for coronary revascularization and not eligible for primary prevention ICD [94]. Exclusion criteria included patients with prior cardiac arrest or ICD discharge, recent infarction (less than 30 days), or revascularization (PCI within 3 months or bypass grafting within last year) [94]. They also evaluated perfusion, using 13 N–ammonia, and viability using 18F-2deoxyglucose [94].

The primary endpoint of this trial was sudden cardiac arrest, which was defined as arrhythmic death or ICD discharge for ventricular fibrillation or ventricular tachycardia greater than 240 beats per minute over a 4 year follow up period [94]. Infarct volume and LVEF were not predictors of sudden cardiac arrest [94]. However, patients who later suffered from sudden cardiac arrest had a greater sympathetic denervation burden as seen in viable denervated myocardium (33 ± 10% vs. 26 ± % of LV; p = 0.001). Using multivariate analysis they developed a four component prediction system that focused on independent variables that predicted arrhythmic risk [94]. These variables included percentage of denervated myocardium (>37.6%), left ventricular end-diastolic volume index (>99 mL/m$^2$), creatinine (>1.49 mg/dL), and no angiotensin inhibition therapy (Fig. 6.3). More than 40% of the study population had none of the independent risk factors and an annual rate of sudden cardiac arrest of less than 1%, which is lower than the rate of arrhythmic death in patients with known coronary artery disease and LVEF between 35 and 50% [94]. About 36% of the cohort had only one predictive risk factor and an annual risk of sudden cardiac arrest of approximately 4% [94]. The remainder of the population, approximately 20%, had two or more independent risk factors and an annual rate of sudden cardiac arrest of ~12% [94]. Interestingly, infarct size, left ventricular ejection fraction, BNP and other variables did not improve their predictive model.

Despite these encouraging results, the multivariate analysis was post hoc so it needs to be replicated to strengthen this observation. Other limitations include the use of HED, which has a short half-life requiring close proximity to cyclotron, and exclusions of patients with recent myocardial infarction, non-ischemic cardiomyopathy and patients with more preserved left ventricular systolic function. Of note, 18-Flourine labeled norepinephrine analogs may improve clinic utility of PET because of improved half-life as compared to HED.

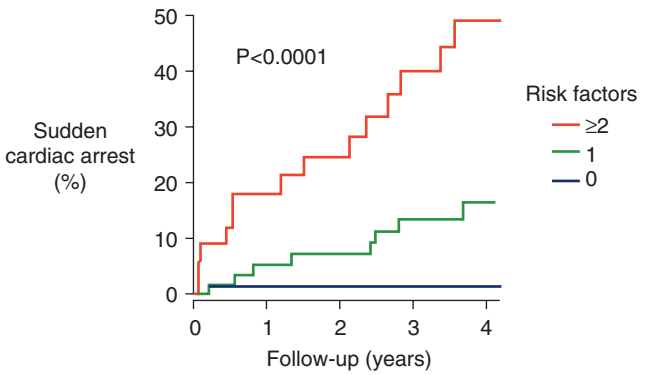


**Fig. 6.3** PET Scan and other Clinical Factors to Predict SCD. Kaplan-Meier curves illustrating significant differences in the incidence of sudden cardiac arrest (SCA) in relation to the number of risk factors present ($p < 0.0001$). Subjects with no risk factors had an annual rate of SCA < 1%; 1 risk factor had an annual rate of ~4% and 2 or more risk factors had an annual risk of ~12% (Reproduced with permission from Fallavollita et al. [94])

**Table 6.3** Patient subgroup evaluations for primary prevention ICD placement

| Patient population | History | Imaging | Other tests |
|---|---|---|---|
| CAD | >40 days post MI | LVEF ≤30% | |
| | | LVEF 35–40% | EPS |
| CHF | 3 months post onset of symptoms | LVEF ≤35% | |
| | Medical therapy optimized | | |
| | NYHA II, III and ambulatory IV | | |
| LQTS | QTc > 500 ms | | Genetic testing optional |
| | Syncope on beta blocker | | |
| HCM | Syncope | IVS ≥ 30 mm | Stress test for hemodynamic response |
| | FH SCD | | Holter monitor |
| Brugada Syndrome | Syncope | | ECG |
| | FH SCD | | EPS optional |
| Sarcoidosis | Syncope | MRI or PET | EPS |
| | Pacemaker indication | | |

## Summary

SCD remains a major health care problem, particularly in western cultures. Early studies identified LVEF, ischemic heart disease, heart failure and ambient arrhythmias as predictors of events. This led to large multicenter trials establishing the role of the ICD for primary prevention of SCD. However, a changing epidemiology of SCD has confirmed an unmet need for risk stratification. In addition, there is interest in improved risk stratification of ICD eligible patients. In this regard, newer imaging, advanced electrocardiographic and genetic techniques raise hope that specific markers or a combinations of tests will allow identification of high risk subjects who can benefit from specific antiarrhythmic therapy, including those with uncommon arrhythmia substrates. A summary of risk stratification approaches for different groups at risk for SCD is summarized in Table 6.3. However, despite these newer techniques and promising markers of SCD, most studies remain observational with frequent posthoc analysis. Accordingly, contemporary risk stratification and guidelines for therapy have changed little over the past decade to address the unmet need of prevention of SCD.

Beyond clinical interest, the cost and practicality of risk stratification strategies and ICD implantation is significant. The cost of genetic testing, ejection fraction evaluation, resting electrocardiograms, exercise electrocardiogram, ambulatory electrocardiogram, SAECG, EPS, imaging of myocardial scar, and innervation studies is significant. It is unlikely that funding aimed at limiting testing and device therapy could be funded any other way than by public means, which is on the decline. However understanding both the cost and benefit of evaluation of SCD should of major importance to governments, institutions, providers and patients as medical costs continue to rise. Thus far there has been no cost benefit and cost effectiveness studies looking at SCD that could help guide a reasonable and appropriate approach to SCD risk stratification wide scale. Studies of this nature would need to compare cost of strategy to cost of devices and patient benefit indices. While this would be a daunting task, it would also be an extremely worthwhile and immensely beneficial enterprise.

## References

1. European Heart Rhythm Association, Heart Rhythm Society, Zipes DP, Camm AJ, Borggrefe M, Buxton AE, et al. ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death). J Am Coll Cardiol. 2006;48(5):e247–346.
2. Goldberger JJ, Basu A, Boineau R, Buxton AE, Cain ME, Canty JM Jr, et al. Risk stratification for sudden cardiac death: a plan for the future. Circulation. 2014;129(4):516–26.
3. Johnson CC, Spitz MR. Childhood nervous system tumours: an assessment of risk associated with paternal occupations involving use, repair or manufacture of electrical and electronic equipment. Int J Epidemiol. 1989;18(4):756–62.
4. Huikuri HV, Castellanos A, Myerburg RJ. Sudden death due to cardiac arrhythmias. N Engl J Med. 2001;345(20):1473–82.
5. The Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. N Engl J Med. 1997;337(22):1576–83.
6. Greenberg H, Case RB, Moss AJ, Brown MW, Carroll ER, Andrews ML, et al. Analysis of mortality events in the Multicenter Automatic Defibrillator Implantation Trial (MADIT-II). J Am Coll Cardiol. 2004;43(8):1459–65.
7. Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med. 2005;352(3):225–37.

8. Hulleman M, Berdowski J, de Groot JR, van Dessel PF, Borleffs CJ, Blom MT, et al. Implantable cardioverter-defibrillators have reduced the incidence of resuscitation for out-of-hospital cardiac arrest caused by lethal arrhythmias. Circulation. 2012;126(7):815–21.
9. Bunch TJ, White RD, Friedman PA, Kottke TE, LA W, Packer DL. Trends in treated ventricular fibrillation out-of-hospital cardiac arrest: a 17-year population-based study. Heart Rhythm. 2004;1(3):255–9.
10. Stecker EC, Reinier K, Marijon E, Narayanan K, Teodorescu C, Uy-Evanado A, et al. Public health burden of sudden cardiac death in the United States. Circ Arrhythm Electrophysiol. 2014;7(2):212–7.
11. Jouven X, Desnos M, Guerot C, Ducimetiere P. Predicting sudden death in the population: the Paris Prospective Study I. Circulation. 1999;99(15):1978–83.
12. Friedlander Y, Siscovick DS, Arbogast P, Psaty BM, Weinmann S, Lemaitre RN, et al. Sudden death and myocardial infarction in first degree relatives as predictors of primary cardiac arrest. Atherosclerosis. 2002;162(1):211–6.
13. Dekker LR, Bezzina CR, Henriques JP, Tanck MW, Koch KT, Alings MW, et al. Familial sudden death is an important risk factor for primary ventricular fibrillation: a case-control study in acute myocardial infarction patients. Circulation. 2006;114(11):1140–5.
14. Kolder IC, Tanck MW, Bezzina CR. Common genetic variation modulating cardiac ECG parameters and susceptibility to sudden cardiac death. J Mol Cell Cardiol. 2012;52(3):620–9.
15. Arking DE, Junttila MJ, Goyette P, Huertas-Vazquez A, Eijgelsheim M, Blom MT, et al. Identification of a sudden cardiac death susceptibility locus at 2q24.2 through genome-wide association in European ancestry individuals. PLoS Genet. 2011;7(6):e1002158.
16. Hong KW, Lim JE, Kim JW, Tabara Y, Ueshima H, Miki T, et al. Identification of three novel genetic variations associated with electrocardiographic traits (QRS duration and PR interval) in East Asians. Hum Mol Genet. 2014;23(24):6659–67.
17. Arking DE, Reinier K, Post W, Jui J, Hilton G, O'Connor A, et al. Genome-wide association study identifies GPC5 as a novel genetic locus protective against sudden cardiac arrest. PLoS One. 2010;5(3):e9879.
18. Aouizerat BE, Vittinghoff E, Musone SL, Pawlikowska L, Kwok PY, Olgin JE, et al. GWAS for discovery and replication of genetic loci associated with sudden cardiac arrest in patients with coronary artery disease. BMC Cardiovasc Disord. 2011;11:29.
19. Albert CM, MacRae CA, Chasman DI, VanDenburgh M, Buring JE, Manson JE, et al. Common variants in cardiac ion channel genes are associated with sudden cardiac death. Circ Arrhythm Electrophysiol. 2010;3(3):222–9.
20. Keating MT, Sanguinetti MC. Molecular and cellular mechanisms of cardiac arrhythmias. Cell. 2001;104(4):569–80.
21. Multicenter Postinfarction Research Group. Risk stratification and survival after myocardial infarction. N Engl J Med. 1983;309(6):331–6.
22. Huikuri HV, Tapanainen JM, Lindgren K, Raatikainen P, Makikallio TH, Juhani Airaksinen KE, et al. Prediction of sudden cardiac death after myocardial infarction in the beta-blocking era. J Am Coll Cardiol. 2003;42(4):652–8.
23. 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(23):2883–91.
24. Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med. 2002;346(12):877–83.
25. Suliman FA. Prophylactic use of implanted cardiac defibrillators in patients at high risk for ventricular arrhythmias after coronary-artery bypass graft surgery. N Engl J Med. 1998;338(17):1228.
26. Hohnloser SH, Kuck KH, Dorian P, Roberts RS, Hampton JR, Hatala R, et al. Prophylactic use of an implantable cardioverter-defibrillator after acute myocardial infarction. N Engl J Med. 2004;351(24):2481–8.
27. Steinbeck G, Andresen D, Seidl K, Brachmann J, Hoffmann E, Wojciechowski D, et al. Defibrillator implantation early after myocardial infarction. N Engl J Med. 2009;361(15):1427–36.
28. Connolly SJ, Gent M, Roberts RS, Dorian P, Roy D, Sheldon RS, et al. Canadian implantable defibrillator study (CIDS): a randomized trial of the implantable cardioverter defibrillator against amiodarone. Circulation. 2000;101(11):1297–302.
29. 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(6):1085–91.
30. Zimetbaum PJ, Buxton AE, Batsford W, Fisher JD, Hafley GE, Lee KL, et al. Electrocardiographic predictors of arrhythmic death and total mortality in the multicenter unsustained tachycardia trial. Circulation. 2004;110(7):766–9.
31. Singh JP, Hall WJ, McNitt S, Wang H, Daubert JP, Zareba W, et al. 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(9):1712–20.
32. Kadish A, Dyer A, Daubert JP, Quigg R, Estes NA, Anderson KP, et al. Prophylactic defibrillator implantation in patients with nonischemic dilated cardiomyopathy. N Engl J Med. 2004;350(21):2151–8.
33. Peters RW, Byington RP, Barker A, Yusuf S. Prognostic value of prolonged ventricular repolarization following myocardial infarction: the BHAT experience. The BHAT Study Group. J Clin Epidemiol. 1990;43(2):167–72.
34. Schouten EG, Dekker JM, Meppelink P, Kok FJ, Vandenbroucke JP, Pool J. QT interval prolongation predicts cardiovascular mortality in an apparently healthy population. Circulation. 1991;84(4):1516–23.
35. Karjalainen J, Reunanen A, Ristola P, Viitasalo M. QT interval as a cardiac risk factor in a middle aged population. Heart. 1997;77(6):543–8.
36. Elming H, Holm E, Jun L, Torp-Pedersen C, Kober L, Kircshoff M, 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(9):1391–400.
37. Brendorp B, Elming H, Jun L, Kober L, Malik M, Jensen GB, et al. Qt dispersion has no prognostic information for patients with advanced congestive heart failure and reduced left ventricular systolic function. Circulation. 2001;103(6):831–5.
38. Berul CI. Congenital long-QT syndromes: who's at risk for sudden cardiac death? Circulation. 2008;117(17):2178–80.
39. Patel C, Yan GX, Antzelevitch C. Short QT syndrome: from bench to bedside. Circ Arrhythm Electrophysiol. 2010;3(4):401–8.
40. 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(2):250–8.
41. Maggioni AP, Zuanetti G, Franzosi MG, Rovelli F, Santoro E, Staszewsky L, et al. Prevalence and prognostic significance of ventricular arrhythmias after acute myocardial infarction in the fibrinolytic era. GISSI-2 results. Circulation. 1993;87(2):312–22.
42. Hohnloser SH, Klingenheben T, Zabel M, Schopperl M, Mauss O. Prevalence, characteristics and prognostic value during long-term follow-up of nonsustained ventricular tachycardia after myocardial infarction in the thrombolytic era. J Am Coll Cardiol. 1999;33(7):1895–902.

43. Grimm W, Christ M, Maisch B. Long runs of non-sustained ventricular tachycardia on 24-hour ambulatory electrocardiogram predict major arrhythmic events in patients with idiopathic dilated cardiomyopathy. Pacing Clin Electrophysiol. 2005;28(Suppl 1):S207–10.
44. Zecchin M, Di Lenarda A, Gregori D, Merlo M, Pivetta A, Vitrella G, et al. Are nonsustained ventricular tachycardias predictive of major arrhythmias in patients with dilated cardiomyopathy on optimal medical treatment? Pacing Clin Electrophysiol. 2008;31(3):290–9.
45. de Sousa MR, Morillo CA, Rabelo FT, Nogueira Filho AM, Ribeiro AL. Non-sustained ventricular tachycardia as a predictor of sudden cardiac death in patients with left ventricular dysfunction: a meta-analysis. Eur J Heart Fail. 2008;10(10):1007–14.
46. Kusmirek SL, Gold MR. Sudden cardiac death: the role of risk stratification. Am Heart J. 2007;153(4 Suppl):25–33.
47. Berkowitsch A, Zareba W, Neumann T, Erdogan A, Nitt SM, Moss AJ, et al. Risk stratification using heart rate turbulence and ventricular arrhythmia in MADIT II: usefulness and limitations of a 10-minute holter recording. Ann Noninvasive Electrocardiol. 2004;9(3):270–9.
48. Schmidt G, Malik M, Barthel P, Schneider R, Ulm K, Rolnitzky L, et al. Heart-rate turbulence after ventricular premature beats as a predictor of mortality after acute myocardial infarction. Lancet. 1999;353(9162):1390–6.
49. Cygankiewicz I. Heart rate turbulence. Prog Cardiovasc Dis. 2013;56(2):160–71.
50. Katritsis DG, Zareba W, Camm AJ. Nonsustained ventricular tachycardia. J Am Coll Cardiol. 2012;60(20):1993–2004.
51. Fleg JL, Lakatta EG. Prevalence and prognosis of exercise-induced nonsustained ventricular tachycardia in apparently healthy volunteers. Am J Cardiol. 1984;54(7):762–4.
52. Marine JE, Shetty V, Chow GV, Wright JG, Gerstenblith G, Najjar SS, et al. Prevalence and prognostic significance of exercise-induced nonsustained ventricular tachycardia in asymptomatic volunteers: BLSA (Baltimore Longitudinal Study of Aging). J Am Coll Cardiol. 2013;62(7):595–600.
53. Verrier RL, Klingenheben T, Malik M, El-Sherif N, Exner DV, Hohnloser SH, et al. Microvolt T-wave alternans physiological basis, methods of measurement, and clinical utility—consensus guideline by International Society for Holter and Noninvasive Electrocardiology. J Am Coll Cardiol. 2011;58(13):1309–24.
54. Chan PS, Gold MR, Nallamothu BK. Do Beta-blockers impact microvolt T-wave alternans testing in patients at risk for ventricular arrhythmias? A meta-analysis. J Cardiovasc Electrophysiol. 2010;21(9):1009–14.
55. Gold MR, Ip JH, Costantini O, Poole JE, McNulty S, Mark DB, et al. Role of microvolt T-wave alternans in assessment of arrhythmia vulnerability among patients with heart failure and systolic dysfunction: primary results from the T-wave alternans sudden cardiac death in heart failure trial substudy. Circulation. 2008;118(20):2022–8.
56. Chow T, Kereiakes DJ, Onufer J, Woelfel A, Gursoy S, Peterson BJ, et al. Does microvolt T-wave alternans testing predict ventricular tachyarrhythmias in patients with ischemic cardiomyopathy and prophylactic defibrillators? The MASTER (Microvolt T Wave Alternans Testing for Risk Stratification of Post-Myocardial Infarction Patients) trial. J Am Coll Cardiol. 2008;52(20):1607–15.
57. Mancini DM, Wong KL, Simson MB. Prognostic value of an abnormal signal-averaged electrocardiogram in patients with nonischemic congestive cardiomyopathy. Circulation. 1993;87(4):1083–92.
58. Simson MB. Use of signals in the terminal QRS complex to identify patients with ventricular tachycardia after myocardial infarction. Circulation. 1981;64(2):235–42.
59. Kuchar DL, Thorburn CW, Sammel NL. Late potentials detected after myocardial infarction: natural history and prognostic significance. Circulation. 1986;74(6):1280–9.
60. Gomes JA, Winters SL, Stewart D, Horowitz S, Milner M, Barreca P. A new noninvasive index to predict sustained ventricular tachycardia and sudden death in the first year after myocardial infarction: based on signal-averaged electrocardiogram, radionuclide ejection fraction and Holter monitoring. J Am Coll Cardiol. 1987;10(2):349–57.
61. Steinberg JS, Regan A, Sciacca RR, Bigger JT Jr, Fleiss JL. Predicting arrhythmic events after acute myocardial infarction using the signal-averaged electrocardiogram. Am J Cardiol. 1992;69(1):13–21.
62. el-Sherif N, Denes P, Katz R, Capone R, Mitchell LB, Carlson M, et al. Definition of the best prediction criteria of the time domain signal-averaged electrocardiogram for serious arrhythmic events in the postinfarction period. The Cardiac Arrhythmia Suppression Trial/Signal-Averaged Electrocardiogram (CAST/SAECG) Substudy Investigators. J Am Coll Cardiol. 1995;25(4):908–14.
63. Bigger JT Jr. Prophylactic use of implanted cardiac defibrillators in patients at high risk for ventricular arrhythmias after coronary-artery bypass graft surgery. Coronary Artery Bypass Graft (CABG) Patch Trial Investigators. N Engl J Med. 1997;337(22):1569–75.
64. Goedel-Meinen L, Hofmann M, Ryba S, Schomig A. Prognostic value of an abnormal signal-averaged electrocardiogram in patients with nonischemic dilated cardiomyopathy. Am J Cardiol. 2001;87(6):809–12. A9
65. Tamaki S, Yamada T, Okuyama Y, Morita T, Sanada S, Tsukamoto Y, et al. Cardiac iodine-123 metaiodobenzylguanidine imaging predicts sudden cardiac death independently of left ventricular ejection fraction in patients with chronic heart failure and left ventricular systolic dysfunction: results from a comparative study with signal-averaged electrocardiogram, heart rate variability, and QT dispersion. J Am Coll Cardiol. 2009;53(5):426–35.
66. 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(2):154–9.
67. Gold MR, Bloomfield DM, Anderson KP, El-Sherif NE, Wilber DJ, Groh WJ, 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(7):2247–53.
68. Buxton AE, Lee KL, Fisher JD, Josephson ME, Prystowsky EN, Hafley G. A randomized study of the prevention of sudden death in patients with coronary artery disease. Multicenter Unsustained Tachycardia Trial Investigators. N Engl J Med. 1999;341(25):1882–90.
69. Moss AJ, Hall WJ, Cannom DS, Daubert JP, Higgins SL, Klein H, et al. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. Multicenter Automatic Defibrillator Implantation Trial Investigators. N Engl J Med. 1996;335(26):1933–40.
70. Daubert JP, Zareba W, Hall WJ, Schuger C, Corsello A, Leon AR, et al. Predictive value of ventricular arrhythmia inducibility for subsequent ventricular tachycardia or ventricular fibrillation in Multicenter Automatic Defibrillator Implantation Trial (MADIT) II patients. J Am Coll Cardiol. 2006;47(1):98–107.
71. Brodsky MA, Mitchell LB, Halperin BD, Raitt MH, Hallstrom AP, AVID Investigators. Prognostic value of baseline electrophysiology studies in patients with sustained ventricular tachyarrhythmia: the Antiarrhythmics Versus Implantable Defibrillators (AVID) trial. Am Heart J. 2002;144(3):478–84.
72. Huikuri HV, Raatikainen MJ, Moerch-Joergensen R, Hartikainen J, Virtanen V, Boland J, et al. Prediction of fatal or near-fatal cardiac arrhythmia events in patients with depressed left ventricular function after an acute myocardial infarction. Eur Heart J. 2009;30(6):689–98.

73. Costantini O, Hohnloser SH, Kirk MM, Lerman BB, Baker JH 2nd, Sethuraman B, et al. The ABCD (Alternans Before Cardioverter Defibrillator) Trial: strategies using T-wave alternans to improve efficiency of sudden cardiac death prevention. J Am Coll Cardiol. 2009;53(6):471–9.
74. Kim RJ, Fieno DS, Parrish TB, Harris K, Chen EL, Simonetti O, et al. Relationship of MRI delayed contrast enhancement to irreversible injury, infarct age, and contractile function. Circulation. 1999;100(19):1992–2002.
75. Kim RJ, Wu E, Rafael A, Chen EL, Parker MA, Simonetti O, et al. The use of contrast-enhanced magnetic resonance imaging to identify reversible myocardial dysfunction. N Engl J Med. 2000;343(20):1445–53.
76. Kwong RY, Chan AK, Brown KA, Chan CW, Reynolds HG, Tsang S, et al. Impact of unrecognized myocardial scar detected by cardiac magnetic resonance imaging on event-free survival in patients presenting with signs or symptoms of coronary artery disease. Circulation. 2006;113(23):2733–43.
77. Roes SD, Kelle S, Kaandorp TA, Kokocinski T, Poldermans D, Lamb HJ, et al. Comparison of myocardial infarct size assessed with contrast-enhanced magnetic resonance imaging and left ventricular function and volumes to predict mortality in patients with healed myocardial infarction. Am J Cardiol. 2007;100(6):930–6.
78. Lee DC, Goldberger JJ. CMR for sudden cardiac death risk stratification: are we there yet? JACC Cardiovasc Imaging. 2013;6(3):345–8.
79. Kadish AH, Bello D, Finn JP, Bonow RO, Schaechter A, Subacius H, et al. Rationale and design for the Defibrillators to Reduce Risk by Magnetic Resonance Imaging Evaluation (DETERMINE) trial. J Cardiovasc Electrophysiol. 2009;20(9):982–7.
80. Floras JS, Ponikowski P. The sympathetic/parasympathetic imbalance in heart failure with reduced ejection fraction. Eur Heart J. 2015;36(30):1974–82b.
81. Kishi T. Heart failure as an autonomic nervous system dysfunction. J Cardiol. 2012;59(2):117–22.
82. Mitrani RD, Klein LS, Miles WM, Hackett FK, Burt RW, Wellman HN, et al. Regional cardiac sympathetic denervation in patients with ventricular tachycardia in the absence of coronary artery disease. J Am Coll Cardiol. 1993;22(5):1344–53.
83. Inoue H, Zipes DP. Time course of denervation of efferent sympathetic and vagal nerves after occlusion of the coronary artery in the canine heart. Circ Res. 1988;62(6):1111–20.
84. Carrio I, Cowie MR, Yamazaki J, Udelson J, Camici PG. Cardiac sympathetic imaging with mIBG in heart failure. JACC Cardiovasc Imaging. 2010;3(1):92–100.
85. Zipes DP. Sympathetic stimulation and arrhythmias. N Engl J Med. 1991;325(9):656–7.
86. Klein T, Dilsizian V, Cao Q, Chen W, Dickfeld TM. The potential role of iodine-123 metaiodobenzylguanidine imaging for identifying sustained ventricular tachycardia in patients with cardiomyopathy. Curr Cardiol Rep. 2013;15(5):359.
87. Raffel DM, Wieland DM. Development of mIBG as a cardiac innervation imaging agent. JACC Cardiovasc Imaging. 2010;3(1):111–6.
88. Luisi AJ Jr, Suzuki G, Dekemp R, Haka MS, Toorongian SA, Canty JM Jr, et al. Regional 11C-hydroxyephedrine retention in hibernating myocardium: chronic inhomogeneity of sympathetic innervation in the absence of infarction. J Nucl Med. 2005;46(8):1368–74.
89. Sisson JC, Shapiro B, Meyers L, Mallette S, Mangner TJ, Wieland DM, et al. Metaiodobenzylguanidine to map scintigraphically the adrenergic nervous system in man. J Nucl Med. 1987;28(10):1625–36.
90. Jacobson AF, Senior R, Cerqueira MD, Wong ND, Thomas GS, Lopez VA, et al. Myocardial iodine-123 meta-iodobenzylguanidine imaging and cardiac events in heart failure. Results of the prospective ADMIRE-HF (AdreView Myocardial Imaging for Risk Evaluation in Heart Failure) study. J Am Coll Cardiol. 2010;55(20):2212–21.
91. Verberne HJ, Brewster LM, Somsen GA, van Eck-Smit BL. Prognostic value of myocardial 123I-metaiodobenzylguanidine (MIBG) parameters in patients with heart failure: a systematic review. Eur Heart J. 2008;29(9):1147–59.
92. de Benedictis FM, Bush A. Rhinosinusitis and asthma: epiphenomenon or causal association? 1999. Chest. 2009;136(5 Suppl):e30.
93. Anagnostopoulos C, Georgakopoulos A, Pianou N, Nekolla SG. Assessment of myocardial perfusion and viability by positron emission tomography. Int J Cardiol. 2013;167(5):1737–49.
94. Fallavollita JA, Heavey BM, Luisi AJ Jr, Michalek SM, Baldwa S, Mashtare TL Jr, et al. Regional myocardial sympathetic denervation predicts the risk of sudden cardiac arrest in ischemic cardiomyopathy. J Am Coll Cardiol. 2014;63(2):141–9.
95. Goldenberg I, Vyas AK, Hall WJ, Moss AJ, Wang H, He H, et al. Risk stratification for primary implantation of a cardioverter-defibrillator in patients with ischemic left ventricular dysfunction. J Am Coll Cardiol. 2008;51(3):288–96.
96. Kramer DB, Friedman PA, Kallinen LM, Morrison TB, Crusan DJ, Hodge DO, et al. Development and validation of a risk score to predict early mortality in recipients of implantable cardioverter-defibrillators. Heart Rhythm. 2012;9(1):42–6.