Controversies in cardiovascular medicine

Risk stratification after myocardial infarction: is left ventricular ejection fraction enough to prevent sudden cardiac death?

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Patients who have experienced a myocardial infarction (MI) are at increased risk of sudden cardiac death (SCD). With the advent of implantable cardioverter-defibrillators (ICDs), accurate risk stratification has become very relevant. Numerous investigations have proven that a reduced left ventricular ejection fraction (LVEF) significantly increases the SCD risk. Furthermore, ICD implantation in patients with reduced LVEF confers significant survival benefit. As a result, LVEF is the cornerstone of current decision making for prophylactic ICD implantation after MI. However, LVEF as standalone risk stratifier has major limitations: (i) the majority of SCD cases occur in patients with preserved or moderately reduced LVEF, (ii) only relatively few patients with reduced LVEF will benefit from an ICD (most will never experience a threatening arrhythmic event, others have a high risk for non-sudden death), (iii) a reduced LVEF is a risk factor for both sudden and non-sudden death. Several other non-invasive and invasive risk stratifiers, such as ventricular ectopy, QRS duration, signal-averaged electrocardiogram, microvolt T-wave alternans, markers of autonomic tone as well as programmed ventricular stimulation, have been evaluated. However, none of these techniques has unequivocally demonstrated the efficacy when applied alone or in combination with LVEF. Apart from their limited sensitivity, most of them are risk factors for both sudden and non-sudden death. Considering the multiple mechanisms involved in SCD, it seems unlikely that a single test will prove adequate for all patients. A combination of clinical characteristics with selected stratification tools may significantly improve risk stratification in the future.

Keywords
Sudden cardiac death • Ejection fraction • Risk stratification • Myocardial infarction

Introduction

The estimated yearly incidence of sudden cardiac death (SCD) in European countries is ~1 per 1000 inhabitants.1 The majority of cases are associated with coronary artery disease (CAD),2 mostly as a result of ventricular tachyarrhythmias after previous myocardial infarction (MI) (Figure 1). With the advent of implantable cardioverter-defibrillators (ICDs), accurate patient stratification regarding the future risk for arrhythmic events has become very relevant in clinical practice. Currently, ICD implantation for primary SCD prevention in patients who have not yet experienced a severe arrhythmic event but who are considered to have a high respective risk is mainly based on left ventricular ejection fraction (LVEF). Briefly, for primary post-MI prevention, current guidelines recommend ICD therapy in patients with LVEF ≤ 30–40% and New York Heart Association (NYHA) functional class II or III and in patients with LVEF ≤ 30–35% and functional class I.3 The reason for these recommendations is the evidence that in these patient groups, ICD therapy confers a significant survival benefit. In this review, we discuss the role of LVEF as risk stratifier for SCD in post-MI patients, its limitations, as well as the utility of other risk stratifiers.

Left ventricular ejection fraction as predictor of increased risk

The mortality risk associated with a reduced LVEF after MI has long been recognized. Thus, an LVEF < 40% was an independent mortality predictor in the Multicenter Postinfarction Research Group
in the 1980s. In the 1990s, in the Canadian Assessment of Myocardial Infarction (CAMI) study, the odds ratio for 1-year mortality after MI was 9.48 for patients with LVEF ≤ 30% compared with patients with LVEF > 50%, 2.94 for patients with LVEF 30–40%, whereas the risk was not significantly increased in patients with LVEF 40–50%. Thus, there appears to be a rough LVEF threshold level at ~40% for an increased post-MI risk.

More recent studies confirm this association. In the Autonomic Tone and Reflexes After Myocardial Infarction (ATRAMI) study, which enrolled 1284 patients with recent MI, patients with LVEF of 35–50% had a relative risk of 2.5 for cardiac mortality compared with patients with LVEF > 50%, whereas in patients with LVEF < 35%, the relative risk was 7.3.

Left ventricular ejection fraction is a strong predictor of arrhythmic death. Direct evidence for this is provided by the randomized trials of ICD implantation for primary prevention in patients with low LVEF. For instance, the Multicenter Automatic Defibrillator Implantation Trial II (MADIT-II) randomized 1232 patients with prior MI and LVEF ≤30% to ICD or conventional medical therapy. During an average follow-up of 20 months, the mortality rate was significantly lower in the defibrillator group (14.2% vs. 19.8%) (Figure 2). Similar findings were provided by the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT), which randomized 2521 patients with NYHA class II or III heart failure and LVEF ≤35% to placebo, amiodarone, or a single-lead ICD in addition to conventional therapy. The cause of heart failure was ischaemic in 52%. Implantable cardioverter-defibrillator therapy was associated with a decreased risk of death of 23% without interaction with the heart failure cause. Since the ICD affects only arrhythmic death, this mortality reduction is attributed to a reduction in SCD.

Notably, the primary prevention ICD trials were designed to evaluate the usefulness of ICD in high-risk groups, defined mainly by reduced LVEF, and not to evaluate different variables including LVEF as risk stratifiers. Thus, they show that a reduced LVEF is associated with an increased SCD risk and that ICD therapy improves survival, but do not establish LVEF as the optimal risk stratification variable.

The increased SCD risk of patients with reduced LVEF is confirmed by numerous other studies. Thus, in a multivariable analysis of the Multicenter Unsustained Tachycardia Trial (MUSTT), reduced LVEF was associated with increased risk for arrhythmic death or cardiac arrest.

Recent studies replicated these findings: in the ISAR-Risk, which studied 2343 acute MI survivors, an LVEF ≤ 30% predicted all-cause mortality, cardiac mortality, and SCD at 5 years. Sensitivity and specificity for SCD prediction were 22.1 and 95.4%, respectively. However, the positive predictive accuracy was only 12.0%. The Risk Estimation Following Infarction, Noninvasive Evaluation (REFINE) cohort study evaluated the utility of a combined assessment of different risk stratifiers in 322 patients early after MI with LVEF < 50% for prediction of cardiac death or resuscitated cardiac arrest. A reduced LVEF (≤30%) was a significant predictor for cardiac death or resuscitated cardiac arrest (hazard ratio 3.3, P = 0.005). However, the area under the receiver-operating characteristic (ROC) curve was moderate (0.62) indicating the limitations of LVEF.

**Figure 1** Electrocardiographic correlate of sudden cardiac death documented in a patient in the Electrophysiology Laboratory: sudden spontaneous onset of a polymorphic ventricular tachycardia degenerating into ventricular fibrillation. The bottom line (AOP) depicts the simultaneous invasive recording of arterial blood pressure with a scale of 0–100 mmHg.

**Limitations of left ventricular ejection fraction as sole risk stratifier**

Thus, patients with reduced LVEF represent a high-risk group for SCD. However, the use of LVEF as standalone risk stratifier has major limitations.

First, due to the fact that the majority of MI survivors maintain a preserved or only moderately reduced LVEF, the greatest number of SCD events occurs finally in exactly these patients despite the lower relative risk of that group compared with the high-risk but small group of patients with severely depressed LVEF. This has been confirmed in registries of patients who experienced SCD in the Maastricht Circulatory Arrest Registry, 51% of victims of sudden circulatory arrest with echocardiography during the study period had an LVEF > 40%. Similar observations were made in MI survivors. In 2130 MI patients, 67% of the SCD cases occurred in patients with LVEF > 35% despite the lower SCD incidence in that group (1.8 vs. 7.5% in patients with LVEF ≤ 35%).

Thus, using LVEF as sole risk stratifier, we miss the majority of SCD cases.

Second, even within the high-risk group of patients with severely reduced LVEF, only a portion will benefit from the ICD, since some still have a low individual risk. For instance, the SCD rate in the conventional group of the MADIT-II trial was 10.0%. Although this rate was higher than in the ICD group (3.8%), it is obvious that the majority would still not benefit from the ICD because they would never experience a cardiac arrest. Similarly, in the Micravolt T Wave Alternans Testing for Risk Stratification of Post-Myocardial Infarction Patients Trial (MASTER), which was conducted in 575 post-MI patients with LVEF ≤ 30%, only 12.1% experienced ventricular tachyarrhythmic events over a follow-up of 2.1 years. Likewise, in the recent Cardiac Arrhythmias and Risk Stratification after Acute Myocardial Infarction (CARISMA) study in 312 post-MI patients with reduced LVEF (≤40%), who were followed with an implantable ECG loop-recorder, VF or symptomatic sustained ventricular tachycardia (VT) was documented in only 8.0% during a follow-up of 2 years. Thus, the rate of life-threatening arrhythmic events in post-MI patients is generally lower than previously assumed.
low, partly as a result of modern therapies such as reperfusion and optimal medical treatment for prevention of ventricular remodeling, heart failure, and recurrent ischaemia.

Thus, patients with depressed LVEF carry as a group a high SCD risk, but this does not apply to all. Conversely, a considerable number will not benefit from the ICD either due to a high ‘competing’ risk of non-sudden death not preventable by the ICD. One could say that these patients are too sick to benefit from an ICD.

Third, LVEF has a limited ‘specificity’ for the underlying risk meaning that a reduced post-MI LVEF is a risk factor not only for sudden but also for non-sudden death.¹³,¹⁷ Due to these limitations, the predictive accuracy of LVEF for life-threatening arrhythmic events is limited. This was well demonstrated in a meta-analysis of 20 studies with a total of 7294 patients where the sensitivity and specificity of LVEF for major arrhythmic events post-MI were 59 and 78%, respectively.¹⁸

Other non-invasive risk stratifiers

Other clinical variables

Other clinical variables, such as atrial fibrillation or poor renal function, are associated with adverse outcome in ICD patients.¹⁹ Based on such observations, there are attempts at a more accurate prediction of the usefulness of ICD implantation considering the patient’s clinical profile. The MADIT-II investigators have presented a risk score model comprising five clinical factors: NYHA class >II, age >70 years, blood urea nitrogen >26 mg/dL, QRS duration >0.12 s, and atrial fibrillation.²⁰ Patients with blood urea nitrogen ≥50 mg/dL and/or serum creatinine ≥2.5 mg/dL were considered to be very high risk. Analysing the outcomes of the conventional therapy arm, the investigators found a U-shaped pattern for ICD efficacy: ICD was associated with a significant 49% reduction in the death risk among patients with ≥1 risk factors, whereas patients without risk factors and very high-risk patients had no benefit.

Ventricular ectopy

Ventricular ectopy has been early recognized as adverse outcome predictor after MI. Thus, the Multicenter Postinfarction Research Group reported that >10 ventricular premature beats (VPBs) per hour were an independent mortality predictor after infarction.⁴ In the fibrinolytic era, the GISSI-2 trial reported data from 8676 post-MI patients:¹¹ frequent VPBs (>10 per h) were a significant independent predictor of total (relative risk 1.62) and sudden mortality (relative risk 2.24). Six-month mortality rates were 2.01% in patients without ventricular arrhythmias, 2.7% in patients with 1–10 VPBs/h, 5.5% in those with >10 VPBs/h, and 4.8% in those with complex ventricular arrhythmias. Interestingly, the presence of non-sustained VT was not associated with worse prognosis in the adjusted analysis. In another study of 575 MI survivors, >10 VPBs/h predicted non-arrhythmic death, whereas VT runs predicted arrhythmic death in the multivariate analysis.¹⁷

Similar observations were made in patients with preserved LVEF: in 1041 post-MI patients with LVEF ≥ 40%, non-sustained VT on Holter monitoring was associated with serious arrhythmic events during follow-up in the multivariate analysis (positive predictive value 7%, negative predictive value 98.8%).²²
However, other studies yielded contradictory results: in 2130 MI patients, >10 VPBs/h predicted non-sudden but not SCD in the multivariable analysis, whereas non-sustained VT was a predictor of both sudden- and non-sudden cardiac death.13 Also, in the CARISMA study, non-sustained VT in the Holter recording did not predict VF or symptomatic sustained VT during follow-up.16

**QRS duration**

Previous reports have suggested an increased mortality in patients with prolonged QRS duration on the 12-lead ECG.23 Results from the MUSTT study confirmed this association: the presence of left bundle branch block or intraventricular conduction delay was significantly associated with total mortality (hazard ratio 1.75) and arrhythmic death or cardiac arrest (hazard ratio 1.46).9

However, further investigations failed to reproduce these findings. In ICD patients with CAD who were enrolled in the PainFREE Rx II trial, QRS duration did not predict benefit from the ICD.24 Also, in the CARISMA study, the QRS duration on the 12-lead ECG did not predict VF or symptomatic sustained VT during follow-up (adjusted hazard ratio 1.01).16

**Signal-averaged electrocardiogram**

Myocardial infarction may result in prolonged and fragmented myocardial activation leading to low-amplitude signals characterized as ‘late potentials’ that are detected at the end of the QRS complex. Signal averaging of the ECG allows noise reduction and amplification in order to detect these potentials. Since delayed and prolonged activation facilitates re-entry, abnormal signal-averaged electrocardiogram (SAECG) has been hypothesized to indicate an increased arrhythmic risk.

Several studies have indicated a usefulness of this technique for risk stratification. In 301 MI survivors, SAECG was predictive of arrhythmic events in the multivariate analysis25 and in another study with 2461 post-MI patients, the filtered QRS duration in the SAECG also predicted arrhythmic events.26 Similarly, in the MUSTT trial, a filtered QRS duration >114 ms independently predicted the primary endpoint of arrhythmic death or cardiac arrest as well as cardiac death, independent of clinical variables, ICD implantation, and antiarrhythmic drug therapy.27 The combination of LVEF <30% and abnormal SAECG identified a particularly high-risk subset and the predictive utility was also demonstrated for patients with LVEF ≥30%.

Also, in the CARISMA study, a filtered QRS duration in the SAECG ≥120 ms predicted VF or symptomatic sustained VT during follow-up (adjusted hazard ratio 2.9, P = 0.041).16 The positive and negative predictive values of a QRS width >120 ms in the SAECG were 20 and 95%, respectively.

However, other studies yielded different results. In the REFINE study, a signal-averaged QRS duration >114 ms was not a significant event predictor.11 In a study with 313 patients undergoing electrophysiology study (not necessarily post-MI), SAECG did not independently predict spontaneous ventricular arrhythmias or death in the multivariate analysis.28 Also, in 1041 post-MI patients with preserved LVEF (≥40%), late potentials were significantly associated with serious arrhythmic events during follow-up in the univariate but not in the multivariate analysis.22

**Microvolt T-wave alternans**

T-wave alternans describes the beat-to-beat alternation of the T-wave amplitude. This rate-dependent phenomenon occurs as a result of abnormal intracellular calcium handling. The required graded increase in the heart rate is mainly achieved by exercise: the occurrence of T-wave alternans at lower rates has been hypothesized to demonstrate an arrhythmic risk.

Indeed, several studies have shown that an abnormal microvolt T-wave alternans (MTWA) test is associated with increased risk for death or arrhythmias. In 768 patients with ischaemic cardiomyopathy, LVEF ≤35%, and no prior sustained ventricular arrhythmia, a non-negative MTWA test was associated with significantly increased risk for arrhythmic mortality (hazard ratio 2.29) but not for non-arrhythmic mortality.29 Microvolt T-wave alternans was also evaluated in the ABCD trial, a multicentre prospective study that enrolled patients with ischaemic cardiomyopathy with LVEF ≤40% and non-sustained VT and compared MTWA with electrophysiological study for prediction of appropriate ICD discharge or sudden death.30 One-year positive (9%) and negative (95%) predictive values of MTWA were comparable with the electrophysiological study. Also, in the prospective REFINE study, in 322 patients early after MI with LVEF <50%, an abnormal MTWA result was a significant event predictor (hazard ratio 2.75, P = 0.034) but with a moderate area under the ROC curve of 0.62.31

There are also data in patients with preserved LVEF: in 1041 post-MI patients with LVEF ≥40%, a positive MTWA test was the most significant predictor of serious arrhythmic events during follow-up with very high negative but poor positive predictive value (99.6 and 9%, respectively).22

However, a series of recent studies failed to reproduce these promising results: in a prospective sub-study of the SCD-HeFT trial, MTWA testing did not predict arrhythmic events or mortality.31 Importantly, MTWA was not significantly predictive among patients with either ischaemic or non-ischaemic heart failure cause. In the MASTER trial, a non-negative MTWA test was not associated with ventricular tachyarrhythmic events over an average follow-up of 2.1 years.15 Interestingly, total mortality was significantly increased in patients with non-negative MTWA result (hazard ratio 2.04, P = 0.02). Similarly, in the CARISMA study, an abnormal MTWA test result did not predict VF or symptomatic sustained VT during follow-up.16

Thus, the utility of MTWA remains unclear. The method has some additional limitations. Microvolt T-wave alternans cannot be measured in patients with atrial fibrillation or frequent VPBs and in patients unable to achieve a heart rate of 105–110 min. In the latter population, heart rate can be elevated by atrial pacing, but this would require an invasive procedure. Additionally, the percentage of patients with positive or indeterminate results is high: the positive result rates in the MASTER and ABCD trials and in the SCD-HeFT sub-study were 51, 46, and 37%, respectively.15,30,31 These high rates of abnormal results combined with the low event rates contribute to the low positive predictive value of the test limiting its value as risk stratifier. The rate of abnormal
results could differ in patients with preserved LVEF: in 1041 post-MI patients with LVEF ≥ 40%, positive results were observed in only 17%.

Markers of autonomic tone

An altered autonomic balance with reduced vagal activity and relative sympathetic dominance is considered a risk factor for threatening arrhythmias post-MI. The autonomic tone can be evaluated with assessment of several markers, mainly baroreflex sensitivity (BRS) and heart rate variability (HRV). Baroreflex sensitivity is assessed as the adaptation of the RR interval to a blood pressure change, most commonly achieved with intravenous phenylephrine administration. Heart rate variability is assessed in Holter recordings; the simplest marker is the standard deviation of all normal beats (SDNN) over a time period. Other markers are heart rate turbulence (HRT), which assesses the short-term oscillation of the cardiac cycle length after spontaneous PVBs, and the deceleration capacity of the heart rate.

Several studies have indicated a usefulness of these markers for risk stratification. In 416 MI survivors, an impaired HRV was a significant independent predictor of arrhythmic events. This was confirmed in the ATRAMI study. Low values of either HRV, defined as SDNN < 70 ms, or BRS < 3.0 ms per mm Hg, carried a significant multivariate risk of cardiac mortality (3.2 and 2.8, respectively).

Similar results were provided by the CARISMA study: a depressed HRV with SDNN < 70 ms was a significant predictor of VF or symptomatic sustained VT (adjusted hazard ratio 4.6, \(P = 0.006\); positive and negative predictive values 21 and 95%, respectively). In the REFINE study, an impaired BRS defined as an average slope of ≤ 6.1 ms/mm Hg and an altered HRT were significant event predictors (hazard ratios 2.71 and 2.91, respectively), whereas an abnormal HRV (SDNN < 105 ms) was not a significant predictor (\(P = 0.066\)).

The usefulness of HRV for prediction of arrhythmic mortality was also not confirmed in the Azimilide post Infarct surVival Evaluation (ALIVE) study, which investigated the effect of azimilide in patients with a depressed LVEF of 15–35% after recent MI. Among placebo patients, low HRV independently predicted mortality after control for several risk factors, but not arrhythmic mortality. Also, in the study by Mäkikallio et al., an SDNN < 70 ms predicted neither sudden- nor non-sudden cardiac death in the multivariable analysis.

Negative results have also been reported in patients with preserved LVEF: in a prospective study of 411 patients with acute MI, HRV and BRS were not significantly predictive of cardiac death and arrhythmic events in the subgroup of patients with LVEF > 35%.

After an initial report, which demonstrated impaired deceleration capacity as a powerful predictor of total mortality after MI, especially in patients with LVEF > 30%, deceleration capacity and HRT were evaluated in 2343 acute MI survivors in the ISAR-Risk study. Patients with both abnormal HRT and deceleration capacity were considered suffering from severe autonomic failure and had significantly higher all-cause mortality, cardiac mortality, and SCD rate. These higher mortality rates were also documented in the group of patients with LVEF > 30%. Among patients with LVEF > 30%, cumulative mortality rate of patients with severe autonomic failure after 5 years of follow-up was with 39% similar to the mortality rate of patients with LVEF ≤ 30% (38%), whereas the mortality of patients with LVEF > 30% and without severe autonomic failure was only 6%.

Recently, an analysis of the CARISMA and REFINE cohorts showed that HRV and HRT increase over time after an MI. An attenuated recovery of autonomic function was associated with a 9.4-fold higher risk of ECG-documented sustained VT or VF in CARISMA and a 7.0-fold higher risk of fatal or near-fatal events in REFINE. The positive accuracy was low (11%), but the negative accuracy was very high (98–99%). On the contrary, changes in HRV and HRT were not predictive of non-arrhythmic death in either cohort.

Critical appraisal of non-invasive risk stratifiers

None of the non-invasive risk stratifiers has unequivocally demonstrated its efficacy. For most of them, initial promising findings have not been uniformly confirmed in more recent investigations questioning their utility, at least if applied as lone stratifiers or combined only with LVEF. These tests have a limited sensitivity, but also a low ‘specificity’ for sudden death meaning that abnormal results represent a risk factor for both sudden and non-sudden death restricting the ability to predict benefit from ICD implantation. Furthermore, almost all studies, which demonstrated a usefulness of these markers, reported high negative but low positive predictive values.

Consequently, there remains an imperative need for improved risk stratification. For this purpose, a combination of non-invasive and invasive tests has been proposed. Recent studies have directly examined the utility of a combined approach. In the REFINE study, the combination of impaired HRT, abnormal TWA, and LVEF < 50% had a satisfactory positive predictive accuracy of 23% and a good negative predictive accuracy of 95%. However, even this combination achieved a suboptimal area under the ROC curve of 0.72. In ISAR-Risk, a combination of LVEF with autonomic markers raised the sensitivity for prediction of SCD at 5 years from 22.1% (patients with LVEF ≤ 30%) to 46.6% (patients with LVEF ≤ 30% or LVEF > 30% and severe autonomic failure) with only a small specificity decrease from 95.4 to 90.9%, but a poor positive predictive accuracy of 12.8%.

Nevertheless, a combined approach is probably the appropriate way to improve risk stratification in patients with reduced LVEF identifying subgroups that would not benefit from ICD implantation due to a low total risk or a very high competing risk for non-sudden death as well as in patients with preserved LVEF who represent the majority of SCD victims but are not considered for prophylactic ICD implantation. Although we do not know which stratifier combination yields the best results, LVEF will most probably remain part of our stratification scheme. Another principal uncertainty derives from the dynamic character of the SCD risk, which is changing over time, influenced for instance by left ventricular remodelling, development of heart failure, ischaemic episodes, or other factors that alter the electrophysiological substrate. Furthermore, the parameters used for stratification also change with time, as demonstrated for LVEF but also for other stratifiers. We currently do not know which is the
optimal post-MI time point for application of these techniques and how often a periodic reassessment should be performed.

Progress in genetics could contribute to an improved approach. Parental sudden death is a significant risk factor for sudden death, strongly suggesting a genetic component in the pathophysiology of SCD.38 However, our knowledge regarding specific genetic characteristics that influence the SCD risk in CAD patients remains limited. Recently, a genome-wide association study identified a susceptibility locus at 21q21 for VF in the setting of acute MI.39 Previously, common genetic variants influencing autonomic function were associated with increased SCD risk.40 Other potentially interesting markers for research could include genetic variants of ion channels predisposing to SCD when exposed to ischaemia.

Invasive risk stratification: the role of programmed ventricular stimulation

In the pre-ICD era, programmed ventricular stimulation (PVS) was mainly used to assess the efficacy of antiarrhythmic drugs for suppression of inducible ventricular arrhythmias or the efficacy of anti-tachycardia surgery. Although no generally accepted PVS protocol is available, most protocols involve the application of one to three increasingly premature ventricular extrastimuli at two right ventricular sites, usually the apex and the outflow tract, with two different basic cycle lengths. The prognostic value of PVS is based on the assumption that patients with inducible ventricular arrhythmias should have a high likelihood of spontaneous arrhythmic events and—vice versa—that non-inducible patients should be at low risk. However, not all inducible arrhythmias constitute a ‘positive’ test result: the type (monomorphic vs. polymorphic VT vs. VF) and duration of the induced arrhythmia (non-sustained vs. sustained) as well as the induction mode need to be considered.

In the MADIT trial, PVS was applied for identification of post-MI patients at high risk for SCD.41 Main inclusion criteria were reduced LVEF (<35%) and inducible VT not suppressed by antiarrhythmic medication. Patients were randomly assigned to an ICD or conventional medical therapy; total mortality was significantly reduced in the ICD arm (16 vs. 39%). Thus, up to the results of the MADIT-II trial, PVS was required to assess the eligibility of ICD implantation for primary SCD prevention. However, it is important to note that in MADIT, PVS was not evaluated as a risk stratification tool.

The MUSTT trial provided valuable data on the prognostic ability of PVS.42 A total of 2202 patients with CAD, reduced LVEF (<40%), and asymptomatic unsustained VT underwent programmed stimulation. Inducible patients (n = 704) were randomized to EP-guided antiarrhythmic therapy or no antiarrhythmic therapy while non-inducible patients (n = 1397) were followed in a registry. This study established that inducible sustained ventricular tacharrhythmias were associated with significantly increased total mortality as well as SCD. However, the rates of cardiac arrest or arrhythmic death in non-inducible patients were 12 and 24% at 2 and 5 years follow-up, indicating that non-inducible patients are not really low risk. Thus, as shown in prior studies, the insufficient negative predictive value is a main limitation of PVS as a risk stratification tool.

The interaction of

Figure 3 Substrate analysis in a patient with a remote anterior myocardial infarction, a large aneurysm of the left ventricle, and ventricular tachycardia. (A) The 12-lead ECG of the tachycardia with a speed of 100 mm/s. (B) The left ventricular aneurysm as depicted with left ventriculography. In this case, the novel MediGuide™ Technology (St Jude Medical Inc., St Paul, MN, USA) for catheter navigation on pre-recorded cine loops was applied. (C) Voltage mapping of the left ventricle in the Electrophysiology Laboratory with the use of the Ensite NavX™ system (St Jude Medical Inc.). In the reconstructed three-dimensional model of the left ventricle, the grey colour depicts scar, the purple depicts healthy myocardium, and the colours in-between depict diseased myocardium based on the voltage of the local electrograms at the different points of the left ventricle.
LVEF and predictive power of PVS was assessed in a MUSTT sub-study, which demonstrated that PVS is more predictive in patients with LVEF between 30 and 40% compared with patients with LVEF < 30%.43 This may reflect the contribution of progressive heart failure to the SCD rate in patients with LVEF < 30%.

In the MADIT-II trial, PVS was not required for patient enrolment: post-MI patients with LVEF ≤ 30% were randomized to ICD implantation or conventional treatment without further risk stratification.7 The significant mortality reduction in the ICD arm led to the current recommendation of ICD implantation without prior PVS for primary post-MI SCD prevention. However, as strongly encouraged by the trial protocol, 593 patients randomized to ICD implantation underwent PVS.64 Although PVS proved moderately predictive for the occurrence of monomorphic VT, the rates for VT and VF during 2-year follow-up were not significantly different between inducible and non-inducible patients. This finding further highlights the limitations of PVS.

The recent ABCD trial compared the predictive value of MTWA and PVS in patients with ischaemic cardiomyopathy, LVEF < 40%, and unsustained VT.30 All patients underwent both tests and ICD implantation was mandatory if either test was positive. At 1-year follow-up, the positive and negative predictive values of MTWA and PVS for the primary endpoint (appropriate defibrillation or SCD) were comparable. Interestingly, the results of the two stratification methods were discordant in more than half of the patients. However, non-inducible and MTWA-negative patients had a low SCD risk, indicating that invasive and non-invasive risk stratification tools may be complementary for identification of a low-risk population that would not benefit from defibrillator therapy.

Critical appraisal of invasive risk stratification

The invasive nature of PVS certainly limits its application. However, in contrast to many non-invasive risk stratifiers, PVS can be performed in the presence of atrial fibrillation, bundle branch block, or frequent ventricular ectopy. It is probably the most effective stratification technique for identification of post-MI patients at high risk for development of monomorphic VT, but the sensitivity is inadequate to predict SCD. This is particularly true for patients with LVEF < 30%. In these patients, incomplete revascularization, progressive heart failure, and time-dependent modulations of the arrhythmic substrate, factors not adequately addressed by PVS, seem to have a significant relevance. On the other hand, the ability of the technique to reliably induce monomorphic VT offers new options for risk stratification in the era of VT ablation: non-inducibility of VT seems to be a good predictor for freedom from arrhythmia recurrence. Prospective studies with hard endpoints are necessary to evaluate such potential future indications. An example of invasive substrate analysis is depicted in Figure 3.

Future directions

Left ventricular ejection fraction is not enough! Although reduced LVEF identifies patients at high risk of death, its ability to predict the mode of death (sudden vs. non-sudden) is limited. This is particularly important for the precise identification of patients who would benefit from ICD therapy: in these patients, risk factors for arrhythmic death should be present and risk factors for non-arrhythmic death should be absent. How to improve risk stratification in this patient segment? Considering the multiple mechanisms involved in the fatal event of SCD, it seems unlikely that a single test will prove adequate for all patients. This hypothesis is supported by many studies assessing the predictive power of single invasive and non-invasive risk stratifiers.

For the future, it seems that the number and composition of risk factors for sudden and non-sudden death in individual patients should deserve more attention. As described, consideration of clinical characteristics may be valuable in this respect.30 Combining a set of clinical patient characteristics with selected invasive or non-invasive risk stratification tools may significantly improve post-MI risk stratification. However, prior to implementation into clinical practice, new risk stratification algorithms need to be evaluated in a prospective fashion with hard endpoints.

The most useful methodological tool to address the delineated problems would probably be clinical prediction rules. These combine multiple parameters from the patient’s history, clinical

**Figure 4** Visualization of scar after myocardial infarction with magnetic resonance imaging and late gadolinium enhancement. (A and B) Patient with a large transmural lateral infarct. (A) Contrast-enhanced image (late gadolinium enhancement) showing high signal intensity reflecting increased contrast accumulation in necrotic myocardium in the infero-lateral myocardium. (B) Computer-aided signal intensity analysis of the late gadolinium enhancement image with colour-coded display of relative signal intensity, normalized to remote myocardium (blue contour). Yellow indicates a signal intensity of >5 standard deviations above remote, uninjured myocardium. (C and D) Patient with a small, non-transmural antero-septal infarct. (C) Contrast-enhanced image (late gadolinium enhancement). (D) Computer-aided signal intensity analysis of the late gadolinium enhancement image.
signs, diagnostic tests, etc. to predict a certain disease or outcome with the goal to guide medical decisions. An example is the CHADS<sub>2</sub> score. The need for development and adequate validation of such tools for risk stratification is crucial. Until such data are available, we unfortunately have to continue to use LVEF as the major risk stratifier. New risk stratification techniques are under intense clinical investigation. Initial experience with magnetic field imaging for prediction of arrhythmic events seems promising, but prospective data are lacking. Another interesting approach is the application of magnetic resonance imaging with late gadolinium enhancement for identification of myocardial fibrosis (Figure 4). Initial studies, mainly performed in patients with non-ischaemic cardiomyopathy and highly reduced LVEF, showed that the arrhythmic risk is probably lower in the absence of regional myocardial fibrosis. However, further studies are warranted to assess the usefulness of the technique in ischaemic cardiomyopathy. A more global perspective on the problem of SCD further stresses that ‘ejection fraction is not enough’: the great majority of SCD victims have an LVEF.<sup>30</sup> Since most of these patients suffer from CAD and SCD is not rarely the first disease manifestation, prevention of ischaemic events may be the most effective strategy.

Thus, the need of a validated combined approach incorporating clinical variables and results of various stratification techniques is evident (Figure 5). Additionally, new techniques and progress in genetics could contribute to improved risk stratification in the future.

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### References


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