Arrhythmic risk stratification of post–myocardial infarction patients
Franco Naccarella, MD, FACC,* Giovannina Lepera, MD,* and Angelo Rolli, MD†

Post–myocardial infarction risk stratification, especially arrhythmic risk stratification, is an issue that has still not been wholly addressed in modern clinical cardiology. In the past 10 years, arrhythmic risk stratification has been approached mainly by evaluating frequency and complexity of premature ventricular contractions, detected on Holter monitoring, often in association with determination of percent ejection fraction. This methodology has been proven to be limited and fallacious according to the Cardiac Arrhythmia Suppression Trial I and II (CAST I,II) results, in which suppression of premature ventricular contractions or premature ventricular beats throughout by antiarrhythmic drugs resulted in an increase in both cardiac and arrhythmic mortality. Only amiodarone as an antiarrhythmic drug, as proven in the recent European Myocardial Infarct Amiodarone Trial (EMIAT) and Canadian Amiodarone Myocardial Infarction Trial (CAMIAT), was effective in reducing arrhythmic mortality without affecting cardiac mortality, in patients selected mainly because of a reduced ejection fraction, with and without premature ventricular contractions. Conversely, it is well known that β-blockers are effective in preventing sudden death in post–acute myocardial infarction (AMI) patients, thus reducing cardiac and arrhythmic mortality. Conversely, in other institutions, risk stratification in post-AMI patients has been performed by electrophysiologic study obtained, without any previous noninvasive arrhythmic risk stratification, in all post-AMI patients. In recent years, many other noninvasive electrocardiology parameters, such as late potentials (signal-averaged electrocardiography), heart rate variability, baroreflex sensitivity, and, more recently, T-wave alternance, have been shown to be useful, but they are associated with a low specificity in the noninvasive identification of patients at high risk for arrhythmic mortality. Conversely, in the Multicenter Automatic Defibrillation Implantation Trial (MADIT), electrophysiology confirmed that inducibility of ventricular tachycardia shows high specificity and a high predictive value for arrhythmic events. Nevertheless, the MADIT study population is not comparable to a cohort of consecutive patients who have recently had a myocardial infarction. In this setting, the highest risk of arrhythmic events can be observed in patients with depressed percent ejection fraction (< 35%) and in the first 6 months after AMI. Today, the most convincing approach seems to be the one combining both noninvasive risk stratification parameters (eg, premature ventricular beats > 10/h or reduced heart rate variability < 70 ms or a positive signal-averaged electrocardiogram) followed by a further arrhythmic risk stratification, obtained through electrophysiologic study. Several published and ongoing trials that utilize various arrhythmic risk stratification techniques as part of their protocol are reviewed.

Abbreviations

AMI acute myocardial infarction
ARS arrhythmic risk stratification
BEST ICD Best Strategy Plus ICD Study
EPS percent ejection fraction
EPS electrophysiologic study
ICD implantable cardioverter defibrillator
GISSI Gruppo Italiano per lo Studio della Sopravvivenza nell’infarto-1 Study
HRV heart rate variability
MADIT Multicenter Automatic Defibrillation Implantation Trial
NIRS noninvasive risk stratification
NSVT nonsustained ventricular tachycardia
PVB premature ventricular beat

In fact, recent clinical studies have demonstrated that antiarhythmic drugs, such as amiodarone, did not change total cardiac mortality, although they did decrease arrhythmic and sudden death mortality. Conversely, in the Cardiac Arrhythmia Suppression Trial, class IC and IA antiarhythmic drugs showed an increase in both cardiac and arrhythmic mortality (CAST I,II).

In the Multicenter Automatic Defibrillation Implantation Trial (MADIT) II and Antiarrhythmics Versus Implantable Defibrillators Trial studies, implantable cardioverter defibrillator (ICD) therapy was the most effective treatment for both primary and secondary prevention of sudden death, in comparison with conventional antiarhythmic drugs. Today the most important problem is to identify patients best suited for the treatment that will be more effective in the primary prevention of sudden death. Furthermore, physicians should be able to identify patients, both at very high risk of future arrhythmic events or sudden death who are, at the same time, at low risk of nonarrhythmic mortality.
Ventricular function
Left ventricular function, measured as percent ejection fraction (EF%) is still, even in the postfibrinolytic therapy era, the most useful indicator in predicting cardiac mortality, which it predicts better than arrhythmic mortality (Table 1) [1–22].

Ventricular arrhythmias
Frequent premature ventricular beats (PVB) still represent an independent prognostic factor for cardiac and arrhythmic mortality [1–22]. Premature ventricular beats are more frequently documented in patients with reduced EF% (31.8% of patients with EF < 35%). A two- to threefold increase in the mortality rate is observed in this subgroup of patients 6 months after AMI (data from the Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto-1 Study [GISSI] study) (Tables 1 and 2) [1,3•,5–22].

Nonsustained ventricular tachycardia (NSVT) is observed in 11% to 15% of post-AMI patients. The presence of NSVT is associated with a 21% mortality (34% mortality in patients with reduced EF%) in comparison with 8% mortality among patients without NSVT. The risk, independent of EF%, was more evident in the first 6 months after an AMI, but persisted over a 3-year follow-up period. In the GISSI study, NSVT was documented in 7% of patients (12.3% in those with reduced EF%). It did not affect total mortality, but only arrhythmic mortality, which was verified to be as low as 1%, in the first 6 months. Thus, the frequency and complexity of ventricular arrhythmias should still be assessed in the immediate posthospital phase of MI, only in patients with a reduced EF% (< 35%). These parameters identify patients at high risk of sudden death, who should be further stratified by electrophysiologic study (EPS), as proposed in the Best Strategy Plus ICD (BEST ICD) Study, to identify those at higher risk of sudden death (Tables 1 and 2).

With this purpose, EPS has previously been used, as a single and basic method, for ARS of post-AMI patients. Conversely, some other groups have used the so-called noninvasive approach. This approach focuses mainly on defining the frequency and complexity of ventricular arrhythmias by electrocardiographic recording techniques (Tables 1, 2, 3, and 4). Today, a more comprehensive approach includes EPS after the risk stratification has been completed by using EF% and ambient ventricular arrhythmia identification or other NIRS parameters. Using this approach, two studies (MADIT II and BEST AICD) have been recently proposed (Figs. 1 and 2).

The MADIT II study will verify whether the implantation of an ICD, in moderately high risk patients, will result in a significant reduction in overall mortality, when compared with no ICD treatment. Furthermore, a secondary objective will be to determine whether ventricular tachyarrhythmias and ventricular fibrillation, induced during implantation, are associated with more appropriate ICD discharge, during the follow-up, than is seen in noninducible ICD patients. This will also prove the utility of EPS in risk stratification of these patients.

The trial is also supposed to prove, as a secondary objective, whether Holter monitoring, signal-averaged electrocardiography, heart rate variability (HRV), QT dispersion, or T-wave alternance, obtained after randomization, can identify patients with higher mortality in the conventional treatment arm. Moreover, information will be collected to determine whether NIRS-identified high-risk patients have more appropriate ICD discharges [13–18,23–27,28•,29•].

Even the BEST ICD study will try to prove the utility of a combined sequential noninvasive ARS followed by EPS (Fig. 1). The main differences between MADIT II and BEST ICD, in this respect, are as follows. In the BEST ICD study, noninvasive ARS will be limited to PVB frequency on Holter monitoring or reduced HRV (< 70 ms) or positive signal-averaged electrocardiogram, whereas, in the MADIT II study, all the noninvasive electrocardiography methods for ARS will be assessed. In the BEST ICD study, EPS will be obtained after a 2:3 randomization of patients who have been previously selected by NIRS, whereas in the MADIT II study, only patients randomly assigned to receive ICD will be tested by EPS. Successively, all patients, randomly allocated between ICD and no-ICD, will be tested by NIRS.

Conversely, another study using the ICD, in both post-AMI patients with coronary artery disease or patients with dilated nonischemic cardiomyopathy with heart failure and EF% less than 35%, will not use any noninvasive ARS at all (Fig. 3). In other words, clinicians think that the NIRS methods could be more valuable in ARS of post-AMI patients without congestive heart failure, in comparison with patients with congestive heart failure,
due mainly to dilated nonischemic cardiomyopathy or minor or chronic coronary artery disease. At least, the clinical value of the NIRS methods, in association with or followed by EPS, should be more easily assessed in post-AMI patients, about whom we do have more information on the usefulness of NIRS alone or primary EPS for ARS.

**Signal-averaged electrocardiography**
Late potentials have been documented in 25% to 50% of patients 1 to 4 weeks after AMI. They are predictive of spontaneous or inducible ventricular arrhythmias or sudden death (even with a low specificity in this respect), even though they have been more frequently documented in patients with reduced EF% and their prognostic significance is independent of the EF% itself [8,19,26,28•].

A very high number of false-positive results have been observed with this method. Thus, late potentials show great limitations when used alone in this clinical setting. There is substantial agreement among cardiologists to use late potentials together with other parameters or NIRS methods or in association with EPS [26,28•].

**Neurovegetative tone measurements**
Increasingly widespread attention has been paid to the use of neurovegetative tone measurements, specifically HRV and baroreflex sensitivity in the NIRS of post-AMI patients [9,10•,19–22].

In the Multicenter Postinfarction Study (MPS), a strong correlation has been found between reduced HRV and total post-AMI mortality. The observed mortality was independent of other prognostic factors, and a fivefold increase in mortality has been observed in patients exhibiting an HRV of less than 50 ms. The change in HRV can be observed soon after an AMI and can be almost completely reversed 6 to 12 weeks after the episode, with some exceptions due to age and sex. The prognostic value of reduced HRV is more evident in the subgroup of patients with an EF% of less than 30% [10•].

Concurrent with this normalization, a reduction in mortality has been observed in the Cardiac Arrhythmia Pilot Study (CAPS). The new predictive value is preserved even if the evaluation is performed after 1 year and also after fibrinolytic therapy. Even HRV measurements, performed in the frequency domain, do not improve the positive predictive value of those indices, which have the same limitations as other NIRS parameters or methods.

Numerous technical limitations and variability of these parameters according to sex, age, and drug interferences, EF%, AMI location, and concomitant diseases have been observed. Furthermore, HRV evaluation cannot be performed in patients with atrial fibrillation or frequent arrhythmias as premature atrial or ventricular beats.

**Baroreflex sensitivity**
A linear relation has been proved between an increase in blood pressure and changes in the RR interval. This

<table>
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<tr>
<th>Study</th>
<th>Observations</th>
<th>Observations</th>
<th>VT VF, %</th>
<th>Ventricle events, %</th>
<th>EPS negative, %</th>
<th>Arrhythmic events, %</th>
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All patients: 1314 Mean value: 30.5 69.4 69.4 5

VF, ventricular fibrillation; VT, ventricular tachycardia; EPS, electrophysiologic study.
A recent Autonomic Tone and Reflexes After Myocardial Infarction Study (1284 post-AMI patients, with a mean follow-up of 21 months and a total of 49 cardiac deaths) showed that reduced baroreflex sensitivity represents a prognostic parameter independent of EF% and the presence of ventricular arrhythmias with a prognostic value in addition to that of a reduced HRV. Commentary on this study confirms that a reduced baroreflex sensitivity associated with a reduced EF% (<35%) in patients less than 65 years of age increases the relative risk of arrhythmic events to the point where no other ARS procedures would be necessary. The clinical and prognostic value of combining HRV and baroreflex sensitivity is further supported by the findings of the MADIT trial, which showed that patients with NSVT and a reduced LV-EF are at increased risk for cardiac death, with a relative risk of 2.5 compared to patients without NSVT and a normal LV-EF.

Table 4. Results of programmed electrical stimulation in post-acute myocardial infarction patients with nonsustained ventricular tachycardia

<table>
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<th>VT, %</th>
<th>VF, %</th>
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The relative risk of arrhythmic events in patients with NSVT and a reduced LV-EF is 2.5 compared to patients without NSVT and a normal LV-EF. The clinical and prognostic value of combining HRV and baroreflex sensitivity is further supported by the findings of the MADIT trial, which showed that patients with NSVT and a reduced LV-EF are at increased risk for cardiac death, with a relative risk of 2.5 compared to patients without NSVT and a normal LV-EF.
sensitivity in ARS of post-AMI patients will be strongly enhanced by the demonstration that both indices are more predictive of the occurrence or nonoccurrence of arrhythmic events, as supported by previous clinical and experimental studies.

Electrophysiologic study

Previous studies have demonstrated that the induction of sustained ventricular tachyarrhythmias during EPS performed after a recent AMI represents the strongest predictive factor for the occurrence of future arrhythmic events. The differences in the positive predictive value of EPS, observed in the medical literature, are mainly due to differences in the patient population, in the stimulation protocols, and particularly in the time intervals between EPS and AMI [12,23–27,28•,29•].

Furthermore, EPS is an invasive procedure that can only be performed in specially equipped hospitals and by fully trained personnel, can be associated with complications and risks, and is costly. Therefore, EPS should not be proposed as the main procedure for post-AMI ARS.

Table 3 gives the results of studies using EPS in a nonselected post-AMI patient population. In Table 4, similar results of EPS, obtained in patients with NSVT, are shown. Today, it is well accepted that the most appropriate use of EPS should be in patients already selected for having positive results on NIRS.

In previous studies, Pedretti et al. [22,26] showed that patients having one of certain parameters—EF% less than 40%, late potentials, frequent PVB (Lown class 4A and B)—represent 20% to 25% of all post-AMI patients. In our experience this frequency is about 10% to 15% [10•].

Furthermore, these patients showed a 30% incidence of ventricular arrhythmias in a 15-month follow-up period. In these patients, the inducibility of ventricular tachyarrhythmias during EPS has been shown to be the most effective independent variable predictive of arrhythmic events (specificity of 97% and positive predictive value of 65% of EPS vs 88% and 30%, respectively, of NIRS methods).

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

• Of special interest

•• Of outstanding interest


Shows the importance of reduced HRV and baroreflex sensitivity in post-AMI ARS. The association of reduced HRV and EP% less than 30% is even more powerful.

Arrhythmias


This article represents a prospective ongoing protocol that will assess the usefulness of ICD in medium-high-risk post-AMI patients (different subgroups) selected on the basis of an increased risk of sudden death (the BEST ICD study).


This article refers to two studies assessing the usefulness of ICD in post-AMI patients with reduced EF% (MADIT II) and in patients with congestive heart failure, New York Heart Association II and III (SCD-HeFT).