**Non-invasive sudden death risk stratification**

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**Introduction**

Sudden cardiac death accounts for approximately 400,000 deaths each year in the United States and remains a health problem of epidemic proportions. Most sudden cardiac deaths are caused by fatal ventricular arrhythmias (ventricular tachycardia [VT] and fibrillation) in patients with and without known structural heart diseases. Given the large number of patients potentially at risk for developing ventricular arrhythmias, any strategy for treating them prophylactically requires efficient and effective risk stratification. Both non-invasive and invasive testing may be used for prognostic evaluation of patients with heart diseases.

The optimal way to use them in the risk stratification for sudden cardiac death will depend in part on the goals of screening. At present risk markers perform better at identifying low-risk patients who may not need an implantable cardioverter-defibrillator (ICD), because all tests have a high negative predictive accuracy. In our opinion an electrophysiological test should not be performed and an ICD should not be implanted in post-myocardial infarction patients with moderate left ventricular dysfunction (left ventricular ejection fraction 30-40%) with a preserved autonomic balance and without non-sustained VT. In MADIT II-like patients electrophysiological testing does not seem necessary and an ICD could not be implanted only in patients with a negative T-wave alternans test.

Most of the data available refer to patients with ischemic cardiomyopathy but the preliminary data on T-wave alternans suggest its usefulness in patients with non-ischemic cardiomyopathy too, although a large definitive study has not yet been completed in this important population.

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before enrollment) and severe impairment of left ventricular ejection fraction (LVEF) (< 30%). The study population included 1323 patients from 76 centers mainly in the United States. Patients were randomized with a 3:2 ratio to ICD (742 patients) or conventional medical therapy (490 patients), endpoint of the study was all-cause mortality. The main clinical and demographic characteristics as well as medical therapy resulted not significantly different in the two groups of patients. At a mean follow-up of 20 months, mortality was 19.8% in the medically treated group and 14.2% in the ICD group. Hazard ratio for the risk of death from all-causes was 0.69 (95% confidence interval [CI] 0.51-0.93, p = 0.016) with a risk reduction of 31% in patients implanted with an ICD compared with those treated with medical therapy. Kaplan-Meier survival curves diverged at 9 months from the enrollment showing a mortality reduction of 12 and 28% at 1 and 2 years, respectively. Based on these results, the prophylactic implant of an ICD improved survival in patients with prior MI and severely impaired left ventricular function.

More recently three studies further supported the clinical relevance of ICD in different groups of patients, in all cases selected by clinical data and LVEF, without additional non-invasive/invasive risk markers.

The Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) trial included 458 patients with non-ischemic dilated cardiomyopathy, LVEF < 36%, and premature ventricular complexes or non-sustained VT; mean LVEF was 21%. A total of 229 patients were randomly assigned to receive standard medical therapy and 229 standard medical therapy plus ICD. At a mean follow-up of 29 months, there were 68 deaths: 28 in the ICD group, as compared with 40 in the standard therapy group (hazard ratio 0.65, 95% CI 0.40-1.06, p = 0.08). The mortality rate at 2 years was 14.1% in the standard therapy group and 7.9% in the ICD group. There were 17 sudden deaths from arrhythmia: 3 in the ICD group, as compared with 14 in the standard therapy group (hazard ratio 0.20, 95% CI 0.06-0.71, p = 0.006). The authors concluded that in patients with severe, non-ischemic dilated cardiomyopathy the implantation of an ICD significantly reduced the risk of sudden death from arrhythmia and was associated with a non-significant reduction in the risk of death from any cause.

The Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial tested the hypothesis that prophylactic cardiac resynchronization therapy (CRT) with or without a defibrillator-backup would reduce the risk of death and hospitalization among patients with advanced congestive heart failure (CHF) and intraventricular conduction delay. A total of 1520 patients with advanced CHF (NYHA class III or IV) of both ischemic and non-ischemic etiology, QRS interval ≥ 120 ms, PR interval > 150 ms and left ventricular end-diastolic diameter > 60 mm were randomly assigned in a 1:2:2 ratio to receive optimal pharmacological therapy alone or CRT or CRT plus ICD therapy. The primary endpoint was the time to death from or hospitalization for any cause. As compared with optimal pharmacological therapy alone, both CRT and CRT plus ICD significantly reduced the primary endpoint (hazard ratio 0.81 and 0.80; p = 0.014 and p = 0.01 respectively). CRT reduced the risk of the secondary endpoint of death from any cause by 24% (p = 0.059), CRT plus defibrillator-backup reduced the risk by 36% (p = 0.003). In conclusion, in patients with advanced CHF and prolonged QRS interval, combined electrical therapy (CRT + ICD) significantly reduced all-cause mortality.

The Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) compared the impact on all-cause mortality of three different treatments in patients affected by mild to moderate CHF (NYHA class II-IIII) of both ischemic and non-ischemic etiology with LVEF ≤ 35%: placebo, amiodarone (200-400 mg/day), ICD. The primary endpoint of the study was all-cause mortality. At 45 months of follow-up, any significant difference was observed between amiodarone and placebo groups; conversely, a clear reduction in all-cause mortality was observed in patients treated with an ICD in comparison with placebo group patients (hazard ratio 0.77, p = 0.007). These data strongly support the use of ICD in such a setting of CHF patients; moreover, further evidence about the inefficacy of amiodarone in reducing deaths from any cause is showed, as well as previously found in clinical trials after MI like the European Myocardial Infarct Amiodarone Trial (EMIAT) and the Canadian Amiodarone Myocardial Infarction Arrhythmia Trial (CAMIAT).

Get with the guidelines and recommendations

On the basis of the recent recommendations of the Task Force of the European Society of Cardiology about sudden cardiac death, an ICD has to be implanted (class I) in “MADIT-MUSTT-like” patients; an ICD may also be recommended in “MADIT II-like” patients (class IIA); in non-ischemic dilated cardiomyopathy the use of ICDs for primary prevention of sudden cardiac death is still debated and ICD implantation is considered a class IIB indication. More recently in the United States a critical reappraisal of the ICD indications for primary prophylaxis of sudden cardiac death was performed: the use of an ICD has been recommended in non-ischemic and ischemic heart diseases with LVEF < 30%.

Focus on risk stratification

Prior to the above-mentioned studies, the aim of non-invasive risk stratification was at identifying pa-
tients at high enough risk to warrant treatment as ag-
gressive as an ICD (sensitivity was sacrificed in order
to maximize positive predictive accuracy). This ap-
proach was based on the assumption that ICDs are ex-
pensive, associated with some risks, and thus should
be reserved for patients who are extremely likely to
need them. Non-invasive risk stratifying tests were
judged based on their positive predictive accuracy. The
results of the above studies are now associated with a
transition to a completely different type of thinking:
specificity has been sacrificed in an attempt to maxi-
mize sensitivity. This new approach is based on the as-
sumption that ICDs can be implanted more easily, less
expensively and with smaller risk and should not be re-
served only for the highest-risk patients. The focus of
non-invasive risk stratifying testing will be on maxi-
mizing negative predictive accuracy.

This article reviews: 1) the role of heart rate vari-
ability (HRV) and baroreflex sensitivity (BRS) testing
which have been suggested by the Task Force of the Eu-
ropean Society of Cardiology as class I tools in the risk
stratification of post-MI patients with and without
CHF; 2) the role of T-wave alternans (TWA) analysis, a
more recent and promising non-invasive risk marker,
and 3) the role of electrophysiological (EP) study,
which is included in the risk stratification algorithm of
MADIT and MUSTT trials.

Heart rate variability

The last two decades have witnessed the recognition
of a significant relationship between the autonomic
nervous system and cardiovascular mortality, including
sudden cardiac death, encouraging the development of
quantitative markers of autonomic activity. HRV repre-
sents one of the most promising such markers: the phe-
nomenon is the oscillation in the interval between con-
secutive heart beats as well as the oscillations between
consecutive instantaneous heart rates. As many com-
mercial devices now provide automated measurement
of HRV, the cardiologist has been provided with a sim-
pile tool for both research and clinical studies.

Measurement of HRV may be evaluated by a number
of methods: perhaps the simplest to perform are the time-
domain measures\textsuperscript{14}. In a continuous ECG record, each
QRS complex is detected and the so-called normal-to-
normal (NN) intervals are determined. From this series of
intervals statistical time-domain measures can be calcu-
lated and the most common of these is standard deviation
of all NN intervals (SDNN)\textsuperscript{14}. The series of NN intervals
can also be converted into a geometric pattern such as the
HRV triangular index measurement which is the integral
of the density distribution divided by the maximum of the
density distribution of all NN intervals\textsuperscript{14}.

Frequency-domain analysis of HRV provides the
power spectral density which is the information of how
power (i.e. variance) distributes as a function of fre-
quency\textsuperscript{14}. Methods for the calculation of power spec-
tral density may be generally classified as non-param-
metric and parametric, which provide comparable re-
sults\textsuperscript{14}. Three main spectral components are distin-
guished in a spectrum calculated from short-term
recordings of 2 to 5 min: very low-frequency (VLF),
low-frequency (LF), and high-frequency (HF) compo-
nents\textsuperscript{14}. The representation of LF and HF emphasizes
the controlled and the balanced behavior of the two
branches of the autonomic nervous system, with LF
representing mainly sympathetic and HF parasympa-
thetic activity respectively, while VLF assessed from
short-term recording has a still unclear meaning\textsuperscript{14}.
Spectral analysis may also be used to analyze the se-
quence of NN intervals in the entire 24-hour period.
The results include an ultra-LF component in addition to
the above-mentioned ones\textsuperscript{14}.

Also non-linear methods are available for HRV
analysis because non-linear phenomena are involved in
the genesis of HRV. At present, the non-linear methods
represent promising tools for HRV assessment but stan-
dards are lacking and the full scope of this method can-
not be assessed\textsuperscript{14}.

Clinical studies. Most of clinical studies about HRV
evaluated its prognostic role after MI in 24-hour Holter
recordings before hospital discharge. The Autonomic
Tone and Reflexes After Myocardial Infarction
(ATRAMI) study, performed in the thrombolytic era,
showed that SDNN < 70 ms was associated with a sig-
nificantly higher risk of cardiac death and non-fatal car-
diac arrest at a follow-up of 2 years in a large popula-
tion of 1284 patients with a recent MI; the relative risk
of SDNN < 70 ms was 3.2\textsuperscript{15}.

Other studies showed the prognostic impact of the
geometrical methods (i.e. triangular index) in the risk
stratification of post-MI patients\textsuperscript{16,17}. In these studies a
depressed HRV triangular index was a predictor of ar-
rhythmic events independent of LVEF, ventricular late
potentials and frequent or repetitive ventricular premi-
ture beats at Holter monitoring.

An analysis performed using the Holter recordings
from the Multicenter Post-Infarction Project (MPIP)
showed that also frequency-domain analysis of HRV
significantly correlated with the occurrence of fatal ar-
rhythmic events after MI\textsuperscript{18}. Moreover, VLF spectral
component showed the highest correlation with ar-
rhythmic death at multivariate analysis (relative risk
2.5). On the contrary spectral component at LF or HF
had weak and not significant association with mortali-
ty.

A recent study focused on a novel frequency do-
main index for post-infarction risk stratification\textsuperscript{19}.
Prevalent LF oscillation index (averages of LF peaks
detected in 5-min sequences from 24-hour Holter
recordings) was determined in the placebo population
of the EMIAT trial. In a multivariate Cox regression
test including clinical risk factors, mean RR interval,
HRV index, LF and HF HRV spectral power, and heart
rate turbulence, this index was the most powerful mor-
tality predictor, with a relative risk of 4.6 (95% CI 2.2-
9.3, \( p = 0.00003 \)). Its predictive power was also blind-
ly validated in the population of the ATRAMI trial: at
multivariate analysis including age, LVEF, BRS, mean
RR interval, SDNN, LF and HF HRV spectral power,
and heart rate turbulence, only LVEF and prevalent LF
oscillation index were significant predictors, with rela-
tive risks of 4.2 (95% CI 1.5-11.7, \( p = 0.007 \)) and 3.6
(95% CI 1.3-10.5, \( p = 0.02 \)), respectively. Thus this in-
novative analysis of frequency-domain HRV provides a
new potent and independent risk marker in post-MI pa-
tients.

Few data are available about the prognostic signifi-
cance of HRV in patients affected by CHF. In the UK-
heart study, the prognostic value of HRV was examined
in 433 outpatients with CHF, NYHA class I to III, mean
LVEF 41%20. Time-domain HRV indices and conven-
tional prognostic indicators were related to death by
multivariate analysis. The annual mortality rate for the
study population in SDNN subgroups was 5.5% for
> 100 ms, 12.7% for 50 to 100 ms, and 51.4% for
< 50 ms. Concerning frequency-domain measures of
HRV, a recent study demonstrated in a cohort of pa-
tients with moderate CHF that sudden death was inde-
pendedtly predicted by a model including LF power
during controlled breathing \( \leq 13 \text{ ms}^2 \) and left ventricu-
lar end-diastolic diameter \( \geq 77 \text{ mm} \) (relative risk 3.7
and 2.6 respectively)21.

On the basis of the available data we think that some
measures of HRV are effective, simple and low-cost
tools which are available for clinicians for the risk strat-
ification of post-MI patients. Thus a larger and system-
atic use of them should be encouraged as suggested by
the Task Force of the European Society of Cardiology.

Further studies are needed to support a systematic use
of HRV as a risk marker in CHF.

**Baroreflex sensitivity**

Arterial baroreceptors play an important role in the
physiological mechanisms governing the adjustment of
cardiovascular system to several conditions. Their
stimulation induces arterial pressure changes with
modulation of sympatho-vagal activity. Many observa-
tions showed that ischemic heart disease and CHF can
modify BRS causing inappropriate activity of the sym-
pathetic system. Although several methods have been
proposed to measure BRS, the methodology most ex-
tensively used in the clinical setting relies on intra-
venous administration of phenylephrine, a pure alpha-
agonist drug that activates arterial baroreceptors and
leads to a reflex bradycardia, which can be measured as
RR interval prolongation. BRS is quantified in ms of
RR interval prolongation for each mmHg of arterial
pressure increase.

**Clinical studies.** Several studies have demonstrated
that in comparison with normal subjects, BRS is signif-
ically depressed in post-infarction patients and in pa-
tients with heart failure (Fig. 1).

In the ATRAMI study BRS was found to be a sig-
nificant predictor of cardiac mortality15; during 21
months of follow-up, BRS < 3 ms/mmHg carried a sig-
nificant multivariate risk (2.8) of cardiac mortality.
Over age 65, the predictive power of BRS declined
much more markedly than HRV; for this reason the spe-
cific prognostic value was higher below age 65 for BRS
and above age 65 for HRV.

A subanalysis performed in the ATRAMI patients
with LVEF < 35% has a particular clinical relevance22.
This analysis showed the predictive accuracy of a com-

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**Figure 1.** Results of a phenylephrine test in a patient with post-infarction left ventricular dysfunction, implanted with a cardioverter-defibrillator and a
biventricular pacemaker. Beat-to-beat changes in systolic arterial pressure (SAP) and in RR intervals are compared with baseline values (left panel). In
this patient, heart arte did not change despite a clear-cut increase in SAP. Accordingly, the slope of the regression line expressing baroreflex sensitivity
is extremely depressed (0.73 ms/mmHg) (right panel).
combined use of non-sustained VT and autonomic markers. The absence of non-sustained VT and the presence of a BRS $\geq 3$ ms/mmHg identified a subgroup of patients (55% of the studied population) who had a cardiac mortality < 5% at 2 years; on the contrary the remaining 45% of subjects who had one or both abnormal indexes had a cardiac mortality at 2 years of 15-30%. These data are particularly interesting if we focus on the identification of low-risk patients, which is the new target of risk stratification in patients with left ventricular dysfunction. From this study we can also argue that a subgroup of approximately 25% of post-MI patients with LVEF < 35%, who have a depressed BRS < 3 ms/mmHg but no episodes of non-sustained VT, may have a poor prognosis with a cardiac mortality at 2 years of approximately 20% despite the absence of spontaneous non-sustained arrhythmias. This finding suggests that in post-MI patients with > 30% LVEF $\leq 40\%$ not only the presence of non-sustained VT (MADIT-MUSTT screening algorithm), but also autonomic indexes should be investigated, for a more complete evaluation of both arrhythmic risk and indication to EP study.

As for HRV, limited data are available about the prognostic role of BRS in CHF patients. BRS was assessed in 282 CHF patients in sinus rhythm receiving stable medical therapy with moderate to severe CHF and severely depressed LVEF. The BRS of the entire population averaged 3.9 ± 4.0 ms/mmHg and was significantly related to LVEF and hemodynamic parameters. At multivariate analysis, BRS was an independent predictor of death after adjustment for non-invasive known risk factors but not when hemodynamic indexes were also considered, except for patients with severe mitral regurgitation in whom BRS provided information of incremental prognostic value.

In conclusion the analysis of BRS has a significant prognostic value in patients after MI. In such patients the assessment of BRS is highly recommended in addition to non-sustained VT in order to identify true low-risk population about those included in ICD studies. In CHF setting no enough data to prognosticate by means of BRS are available and further studies are needed to better understand its prognostic role.

**T-wave alternans**

TWA is a beat-to-beat fluctuation in the amplitude or morphology of the T wave that alternates every other beat and has been closely associated with ventricular arrhythmias and sudden cardiac death. More recently, using sensitive signal processing techniques, the detection of microvolt level, virtually unapparent TWA was found to be a potent predictor of life-threatening ventricular arrhythmias in several subgroups of patients (Fig. 2).

Several studies demonstrated macroscopic TWA in different clinical conditions that are associated with malignant ventricular arrhythmias including long QT syndrome, acute myocardial ischemia and infarction, Prinzmetal’s angina and electrolyte derangements. TWA is caused by primary alternations in the repolarization phase of the action potential. Moreover, above a critical heart rate threshold, repolarization potentials from adjacent regions of the ventricle alternated with opposite phase, that is discordant alternans, causing spatial gradients of repolarization and determining an EP substrate for functional block, reentry and ventricular fibrillation. When electrotonic uncoupling by a structural barrier is present, there is a higher probability of discordant alternans at lower critical heart rate threshold which, inducing a maximum spatial gradient of repolarization, may cause a unidirectional block, reentry, and sustained monomorphic VT. In either case, TWA suggests the presence of EP properties of the myocardium that are associated with the genesis of ventricular arrhythmias.

**Clinical studies.** The original studies of TWA included different subgroups of very high-risk patients. The first of them was published in 1994 by Rosenbaum et al. and was performed in a group of patients who underwent EP study because of non-fatal sustained ventricular tachyarrhythmias, syncope or, in a minority of cas-
es, supraventricular arrhythmias. Results showed a strong relationship between the presence of TWA evaluated during atrial pacing and the inducibility of ventricular tachyarrrhythmias during EP testing as well as 20-month arrhythmia-free survival. Subsequent similar studies confirmed the association between TWA measured during bicycle exercise and both inducible and spontaneous ventricular arrhythmias in patients who underwent EP study and also in ICD recipients. It is also important to note that a good reproducibility of both TWA testing results and TWA heart rate threshold was demonstrated during both atrial pacing and exercise-induced sinus tachycardia.

A number of small studies in patients with CHF suggest that TWA is associated with an increased risk of ventricular arrhythmias and sudden death. Klingelheben et al. evaluated 107 CHF patients without history of sustained ventricular arrhythmias over a mean follow-up period of 15 months. Patients had a mean LVEF of 28%, coronary artery disease in 67% of cases, received angiotensin-converting enzyme inhibitors and beta-blockers in 93 and 42% of cases, respectively. In this study TWA was a strong and significant predictor of arrhythmic events. Remarkably, none of the patients with a negative TWA test had an arrhythmic event showing a very high negative predictive value. Similar results were found in a study of our group which included 46 patients with CHF, NYHA class III in 35%, mean LVEF 29%, ischemic etiology in 61%; at a mean follow-up of 1.6 years a significant relationship with cardiac death was found: 7 of 23 (30%) patients with positive TWA died during follow-up. Interestingly, also in our study none of 13 patients who had negative TWA died or had malignant ventricular arrhythmias.

The prognostic value of TWA was also confirmed in patients with dilated non-ischemic cardiomyopathy. Hohnloser et al. studied 137 patients with dilated cardiomyopathy, mean age 55 years and LVEF 29%; demonstrating results similar to those found in CHF patients of both etiologies. More recently, at the last Scientific Sessions of the American Heart Association, Costantini et al. showed preliminary results of a study that included 282 patients with LVEF ≤ 40% and dilated non-ischemic cardiomyopathy. The study tested the hypothesis that a negative TWA would identify patients at low risk of death. The primary endpoint of the study was actuarial all-cause mortality at 2 years. TWA testing was normal (negative) in 95 patients (34%), and abnormal (positive or indeterminate) in 187 patients (66%). None of the patients with a normal TWA test and 12 patients with an abnormal TWA test (8.6%) died (p ≤ 0.02), further supporting the very high negative predictive value of a negative TWA.

Results of the Marburg Cardiomyopathy Study contradicted the above-mentioned promising results. In this study arrhythmia risk stratification was performed prospectively in 343 patients with idiopathic dilated cardiomyopathy, including analysis of LVEF, signal-averaged ECG, arrhythmias on Holter ECG, QTc dispersion, HRV, BRS, and TWA. During a mean follow-up of 52 months, major arrhythmic events occurred in 46 patients (13%). On multivariate analysis, LVEF was the only significant arrhythmia risk predictor in patients with sinus rhythm, with a relative risk of 2.3 per 10% decrease of ejection fraction (95% CI 1.5-3.3, p = 0.0001), whereas beta-blocker therapy was associated with a trend toward lower arrhythmia risk (relative risk 0.6, 95% CI 0.3-1.2, p = 0.13). Thus in this study TWA as well as other non-invasive risk markers did not seem to be helpful for arrhythmia risk stratification. However some criticisms should be underlined: 1) interpretation of TWA results was not based on a “negative and non-negative” classification, in fact of 38 arrhythmic events, 31 (81%) occurred in the 191 (16%) patients with a non-negative result in comparison to 7 of 72 (10%) patients with a negative TWA (p = 0.06); 2) more importantly, as reported by the same authors, the use of beta-blockers in this study was not uniform and many patients did not have beta-blocker therapy at study entry, when risk stratification was performed, and received it during follow-up (52 vs 73%); 3) beta-blockers were withheld for 24 hours before TWA testing whenever possible because the development of TWA is critically dependent on heart rate. This may have increased the proportion of false positive results, with a possible unapparent change of TWA from positive to negative during the follow-up period; 4) the rate of events was very low in the proportion of 3% per year making the follow-up significantly longer (4.3 years) than the follow-up available in the other TWA studies (in general 2 years).

On the basis of these conflicting results further studies are needed in order to define the prognostic value of this promising marker in patients with non-ischemic cardiomyopathy. A large multicenter prospective study is currently ongoing in Italy, the ALPHA Study (T-wave alternans in patients with heart failure). Its aim is to assess the prognostic power of TWA in a large cohort of patients with non-ischemic dilated cardiomyopathy in NYHA class II-III and a LVEF ≤ 40%.

TWA has also been demonstrated to be an effective tool for identifying high-risk patients after MI. Ikeda et al. evaluated the prognostic significance of TWA between 2 and 10 weeks after an acute MI in a large cohort of 850 consecutive unselected patients. During a mean follow-up of 25 months, only TWA and LVEF ≤ 40% were significant multivariate predictors for primary events, defined as sudden cardiac death or resuscitated ventricular fibrillation (relative hazard 5.9 [p = 0.007] and 4.4 [p = 0.005], respectively). In contrast, Tapanainen et al. reported that TWA was not associated with increased mortality in a study of 379 patients after MI. This study was flawed, however, because the TWA study was performed too early after MI (8.1 ± 2.4 days) when TWA is believed to be unstable and unreliable.
Interestingly, two recent studies strongly support the potential role of TWA in the risk stratification of “MADIT II-like” patients. In 129 post-MI patients all with a LVEF < 30%, TWA testing was prospectively assessed. At 24 months of follow-up, no sudden cardiac death or cardiac arrest was seen among patients who tested TWA negative, compared with an event rate of 15.6% among the remaining patients. More recently, a study evaluated the ability of microvolt TWA to identify groups at high and low risk of dying among heart failure patients who met MADIT II criteria for ICD prophylaxis. The primary endpoint was 2-year all-cause mortality. Of 177 MADIT II like patients included in the study, 32% had a QRS duration > 120 ms, and 68% had an abnormal (positive or indeterminate) microvolt TWA test. During an average follow-up of 20 months, 20 patients died and patients with an abnormal TWA test were compared to those with a normal (negative) test. The hazard ratios for 2-year mortality was 4.8 (p = 0.020) and the actuarial mortality rate was substantially lower among patients with a normal TWA test (3.8%) with a corresponding false-negative rate of 3.5%. Interestingly, in this study TWA test resulted a better predictor than QRS complex duration, an index recommended in the United States for selection of MADIT II patients suitable for ICD therapy, in identifying both high-risk and low-risk groups.

TWA is strongly associated with an increased risk of developing ventricular arrhythmias. It is important to note, however, that many of the completed studies are numerically small, and some included extremely high-risk patients (those who had already sustained ventricular arrhythmias), factors that would tend to overestimate the magnitude of risk associated with the presence of TWA.

The clinical application of TWA remains to be defined in larger clinical studies because, to date, no randomized treatment trials are available. Larger prospective epidemiological studies and treatment trials, like the ALPHA study and two other ongoing (ABCD and MASTER) trials, will be necessary to achieve a better estimate of the magnitude of the risk associated with TWA and a better definition of its clinical utility in identifying patients at increased risk of ventricular arrhythmias.

Electrophysiological testing

EP testing is an invasive tool potentially useful for post-MI risk stratification, while it is well known that this procedure is not useful for risk stratification in non-ischemic cardiomyopathy. The endpoint of EP study is the induction of sustained monomorphic VT with a heart rate < 260-270 b/min, which represents an independent predictor of arrhythmic events during the follow-up period. However, programmed ventricular stimulation alone as a predictor of sudden cardiac death in the general MI population without spontaneous arrhythmias cannot be recommended and EP study may be used for prognostic evaluation only in patients preselected by non-invasive techniques. A two-step strategy based on the combined use of non-invasive tests and EP study was for the first time prospectively evaluated in a study from our group: 303 surviving patients of acute MI underwent non-invasive evaluation, those who had ≥ 2 variables among LVEF < 40%, ventricular late potentials and repetitive ventricular premature complexes at Holter ECG were considered eligible for EP study. Of 67 eligible patients, 47 (70%) consented to undergo programmed stimulation. A positive test was found to be the strongest independent predictor of events. With a good sensitivity (81%), a two-step strategy selected a group of post-MI patients at sufficiently high risk (event rate 65%) to be considered candidates for interventional therapy. Similar results were shown later by two further studies. Moreover, it is also important to note that a two-level strategy was evaluated by Wilber et al. in patients with ischemic cardiomyopathy with LVEF < 40% and non-sustained VT. Results of this study, which showed a rate of sudden death-cardiac arrest at 2 years of 50% in inducible-not suppressed patients, were at the basis of the risk stratification algorithm of MADIT and MUSTT trials.

However, doubts now exist about the real utility of this EP test in the risk stratification cascade. Since the target of risk stratification is now the identification of low-risk patients, the negative predictive value of EP testing is not different from that of non-invasive tests, as shown by a meta-analysis of Bailey et al. (96 vs 94-96%) which analyzed data from 44 reports about arrhythmic risk stratification after MI. Moreover, according to data from the MUSTT trial registry, with regard to the endpoint “arrhythmic death or cardiac arrest”, patients who had a negative EP testing showed a high risk of events (12 and 24% at 2 and 5 years), despite a significant statistical difference in comparison to patients with inducible sustained VT. Finally in the MADIT II trial EP testing was performed in the ICD arm. According to results presented in international meetings, the MADIT II investigators reported that positive EP testing was predictive of subsequent sustained VT but not of ventricular fibrillation, as recorded by the ICD during the follow-up period, suggesting that EP testing may not be useful in the prediction of sudden cardiac death.

Temporal aspects of improved survival with the implanted defibrillator

Concerning the survival benefit induced by the ICD therapy in post-MI patients, it is important to underline the relationship between the time from the index MI and the beginning of the therapeutic intervention.
Wilber et al.\(^5\) analyzed whether mortality risk and survival benefit depend on the elapsed time from MI in the MADIT II population. The two treatment groups (ICD vs conventional therapy) were analyzed by time from MI divided into quartiles (< 18, 18 to 59, 60 to 119, and ≥ 120 months). For ICD, covariate-adjusted hazard ratios for the risk of death were 0.97 (95% CI 0.51-1.81, \(p = 0.92\)) for recent MI (< 18 months) and 0.55 (95% CI 0.39-0.78, \(p = 0.001\)) for remote MI (≥ 18 months). The authors concluded that the survival benefit associated with ICDs seems to be not significant in patients with recent MI.

Results of DINAMIT (Defibrillator in Acute Myocardial Infarction Trial) are in agreement with this finding\(^5\). This study included patients with recent MI (6-40 days), LVEF ≤ 35% and depressed HRV who were randomized to receive ICD or conventional medical therapy. Kaplan-Meier curves showed a non-significant difference in the risk of death from any cause between the two groups of patients. This is due to a significant reduction of arrhythmic death in the ICD group which is counterbalanced by an equal increase in the risk of non-arrhythmic death.

In a recent further analysis from MADIT II the rate of non-sudden cardiac death was significantly higher in the ICD than in the conventional therapy group (\(p = 0.003\)) in the early post-MI period, while the rate of late non-sudden cardiac death was similar in the two treatment arms (\(p = 0.11\)).\(^5\) These data suggest a relevant question about the optimal timing for both risk stratification and ICD implantation after MI. Probably the first months after the ischemic event are characterized by dynamic changes in both left ventricular function and EP properties of the myocardium due to both remodeling process, residual ischemic burden, and late therapy effects and do not represent the best time for prognostic evaluation, which should be postponed later, when more stable functional and clinical conditions are present.

**Conclusion**

Both non-invasive and invasive testing may be used for prognostic evaluation of patients with heart diseases. The optimal way to use them in the risk stratification for sudden cardiac death will depend in part on the goals of screening. At present risk markers perform better at identifying low-risk patients who may not need an ICD, because all tests have a high negative predictive accuracy. In our opinion an EP test should not be performed and an ICD should not be implanted in post-MI patients with moderate left ventricular dysfunction (LVEF 30-40%) with a preserved autonomic balance and without non-sustained VT. In MADIT II-like patients EP testing does not seem necessary and an ICD could not be implanted only in patients with a negative TWA test. Most of the available data refer to patients with ischemic cardiomyopathy but preliminary data on TWA suggest its usefulness in patients with non-ischemic cardiomyopathy too, although a large definitive study has not yet been completed in this important population.

**References**


