

Original Research

Post Myocardial Infarction Risk Stratification for Sudden Cardiac Death in Patients with Preserved Ejection Fraction: PRESERVE-EF Study Design

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The estimated yearly incidence of sudden cardiac death (SCD) in European countries is 1 per 1000 inhabitants.¹ Despite improvements in the treatment of myocardial infarction (MI), a large proportion of SCD cases occur in survivors of a previous MI, mostly as a result of ventricular tachyarrhythmias.² Towards primary prevention of SCD in this setting, current guidelines recommend the use of an implantable cardioverter defibrillator (ICD) in post-MI patients with left ventricular ejection fraction (LVEF) $\leq 35\%$.³

Nowadays, the percentage of eligible post-MI patients for ICD implantation has radically decreased, mainly as a result of the implementation of primary percutaneous coronary intervention (PCI). Specifically, while in the 70s and 80s 1/3 of post-MI patients had LVEF $< 40\%$, nowadays this percentage is around 15%.⁴ Although the risk for SCD is relatively lower in post-MI patients with preserved LVEF, the absolute number of SCD victims with-

in this highly prevalent population is significantly high.⁵

This has been confirmed in registries of patients who experienced SCD: in the Maastricht Circulatory Arrest Registry, 51% of SCD victims with echocardiography available during the study period had an LVEF $> 40\%$.⁶ Similar results were derived from the Oregon Sudden Unexpected Death Study, where LVEF $> 35\%$ was present in 70% of SCD victims in whom an LVEF measurement was available before cardiac arrest.⁷ Analyzing data from 2130 acute MI survivors, 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 $\leq 35\%$).⁸

An additional finding that shows the limited sensitivity of LVEF for SCD prediction is the estimation of LVEF in cardiac arrest survivors implanted with an ICD in the setting of secondary prevention. Mean LVEF in the AVID, CASH and CIDS trials was 32%, 45%, and 34%, respec-

tively, indicating that at least 50% of these patients would not have been enrolled in the primary prevention trials.⁹⁻¹¹ There are recent reports supporting the equally protective role of ICDs in post-MI patients with either decreased or preserved LVEF.^{12,13}

Based on the above, and taking into consideration that the main mode of death is SCD in post-MI patients with preserved LVEF, rather than pump failure, it is of utmost importance to identify a risk stratification model for these patients. This article presents an overview of the ongoing PRESERVE-EF study design (post myocardial infarction risk stratification for sudden cardiac death in patients with preserved ejection fraction), which will assess the prevalence and the prognostic value of noninvasive indexes and programmed ventricular stimulation (PVS) for SCD in post-MI patients with LVEF > 40%.

Methods

Study population

PRESERVE-EF is a multicenter, prospective, long-term observational cohort study (clinicaltrials.gov identifier NCT02124018) of post-MI revascularized patients with LVEF > 40% at 40 days until 3 years after MI. The study is being conducted at 7 centers in Greece:

1. Hippokraton Hospital of Athens, First Cardiology Division, University of Athens
2. Hippokraton Hospital of Athens, State Cardiology Department
3. Attikon Hospital, Second Cardiology Division, University of Athens
4. Evangelismos Hospital, Second State Cardiology Department, Athens
5. University Hospital of Heraklion, Department of Cardiology, University of Crete
6. University Hospital of Ioannina, Cardiology Division, University of Ioannina
7. Hippokraton Hospital of Thessaloniki, Third Cardiology Division, Aristotle University Medical School, Thessaloniki

The ethics review board at each institution approved the protocol. Enrollment started in April 2014. All patients provide written, informed consent. The study population includes primary prevention post-MI patients, aged between 18 and 80 years, divided into two categories:

1. Asymptomatic patients with revascularized MI (remaining stenoses in non-culprit vessels < 70%)

at 40 days post-MI (when LVEF > 40% will be reassessed);

2. Asymptomatic patients late (until 3 years) after MI (initially STEMI-NSTEMI and at discharge Q-non Q) with LVEF > 40% immediately after a negative stress test or a coronary catheterization examination negative for stenoses. In the case of preceding revascularization (PCI or coronary artery bypass grafting [CABG]), the risk stratification process will take place at least 1 month after PCI and 3 months after CABG.

Patients are excluded if they have a secondary prevention indication for ICD implantation (episodes of sustained ventricular tachycardia [VT] or aborted SCD 48 hours after the acute MI phase), a permanent pacemaker or a preexisting class I indication for pacemaker implantation, chronic atrial fibrillation, or episodes of syncope within the last 6 months. Patients with systematic illnesses (cancer, liver failure, end-stage renal disease, rheumatic diseases and thyroid dysfunction) as well as those taking antiarrhythmic drugs other than b-blockers are also excluded from the present study.

Study protocol

Phase A: noninvasive tests in the whole study population

On enrollment, each patient has a comprehensive history taken and undergoes a thorough cardiovascular physical examination. Emphasis will be placed on the recording of risk factors (hypertension, diabetes, dyslipidemia, current smoking status, family history for coronary artery disease and SCD) and coronary artery disease history (type of MI, number of diseased vessels, revascularized vessels and mode of revascularization). A laboratory workup will help to assess the presence of any exclusion criteria.

All 12-lead electrocardiograms (ECGs) are obtained at a paper speed of 25 mm/s (sensitivity 10 mV/cm). Echocardiographic studies are performed according to the recommendations of the American Society of Echocardiography.¹⁴ All participants also undergo a 24-h digital ambulatory ECG recording followed by a 45-min high-resolution digital ECG recording. A GE Healthcare GETEMED CardioDay Holter system is used in all patients (recorder CardioMem CM4000 and software CardioDay v. 2.4, GE Healthcare, Fairfield, CT, USA).

Based on the results of noninvasive parameters, patients are classified into high or low risk. Subse-

quently, high-risk patients are selected for phase B. Specifically, high-risk patients are those who fulfill at least one of the following criteria:

- >30 premature ventricular complexes (PVCs)/hour on 24-h Holter monitoring (HM)
- presence of non-sustained VT (NSVT) on HM
- 2/3 positive criteria for late potentials (LPs), either conventional or modified, obtained through the 45-min high-resolution digital ECG recording
- QTc derived from HM >440 ms (men) or >450 ms (women)
- Ambulatory T wave alternans (TWA) $\geq 65 \mu\text{V}$
- SDNN <75 ms on the 24-h HM
- Deceleration capacity ≤ 4.5 ms and heart rate turbulence (HRT) onset $\geq 0\%$ and HRT slope ≤ 2.5 ms

Rationale for selection of non-invasive criteria

All the above noninvasive markers for risk stratification may identify the arrhythmic substrate, reflecting different patterns of arrhythmogenicity:¹⁵

1) Presence of positive LPs, NSVT and >30 PVCs/h reflect myocardial substrate lesions and post-infarction fibrosis

The presence of abnormal electric activity due to depolarization delay developed in areas of fibrosis and scars around the infarcted myocardial zones, namely LPs, can be revealed and quantified with the signal-averaged ECG through short-term high-resolution digital ECG recording. According to the established criteria, the presence of a slow conducting current can be accepted as real LPs when at least two of the following three criteria are fulfilled: 1) a filtered QRS complex >114 ms (fQRS>114 ms); 2) a low-amplitude signal voltage <40 μV in the terminal QRS complex lasting >38 ms (LAS>38 ms); and 3) a signal <20 μV in the last 40 ms of the filtered QRS complex (RMS<20 μV).¹⁶ In the case of patients with intraventricular conduction delay or bundle branch block (standard QRS duration ≥ 120 ms) modified LP criteria will be used.¹⁷

NSVT is defined as a sequence of at least 3 ventricular premature beats at a rate of >100 beats/minute that is self-terminated in less than 30 s. In the case of frequent PVCs as a selection criterion, 12-lead ECG morphology will be analyzed in order to assess the PVCs' origin.

2) Increased QTc derived from Holter monitoring and ambulatory T wave alternans reflect abnormal repolarization

The automatic measurement of QT duration is performed every 30 averaged beats. Corrected QT intervals are labeled as QTc. As correction formulas, Fridericia is selected. This mean QTc value (HM) carries more accurate information about the heart's repolarization status, reflecting the entire 24-h period, and is a more potent arrhythmia risk stratifier compared with the QTc interval that was derived from the 12-lead ECG.¹⁸

T wave alternans (TWA) is measured by the modified moving average (MMA) method using a commercial system (GE Healthcare GETEMED CardioDay Holter system). TWA was analyzed in three channel records (V₁, V₃, V₅) from routine 24-h Holter ECG recordings without an exercise protocol. The MMA algorithm separates odd and even beats into separate bins and creates median templates for both the odd and even complexes every 10 s. The templates are superimposed, and the difference between the odd and even median complexes at any point is defined as the MMA-TWA value. These templates of superimposed complexes can be examined visually to verify MMA-TWA presence and magnitude. The maximal MMA-TWA voltage at a heart rate <120 beats/min is derived automatically in 2 leads. After that, manual editing is performed by 2 cardiologists if the data are not available because of noise or artifacts. In this study, the greater maximal voltage of MMA-TWA has been chosen for assessment. MMA-TWA is determined as positive when the voltage is >65 μV in at least 2 leads.¹⁹

3) Decreased heart rate variability (SDNN <75 ms) and decreased deceleration capacity along with impaired HRT reflect impaired autonomic nervous system function

The standard deviation of the normal-to-normal RR intervals is computed from 24-hour HM and is expressed in ms:

$$SDNN = \sqrt{\sum_{i=1}^N \frac{(NN_i - \overline{NN})^2}{N}}$$

where NN_i is a normal RR interval, N is the total number of such intervals, and \overline{NN} is the mean value of all these intervals.

Deceleration capacity (DC) is an integral measure of all deceleration-related oscillation observed over 24-hour HM. The computation of DC is based on a novel signal-processing algorithm capable of extracting periodic components out of non-stationary biological signals. DC is considered abnormal if it is ≤ 4.5 ms.²⁰

HRT was measured automatically using an algorithm applied to 24-h HM. (GE Healthcare GETEMED CardioDay Holter system). HRT parameters included turbulence onset (TO) and turbulence slope (TS). TO is calculated as: $TO = 100 \times ((RR1 + RR2) - (RR-2 + RR-1)) / (RR-2 + RR-1)$, where RR-2 and RR-1 are the two RR intervals immediately preceding the PVC coupling interval, and RR1 and RR2 are the two RR intervals immediately after the compensatory pause. TO is determined for each individual PVC, followed by the determination of the average value of all individual measurements. Positive values for TO indicate deceleration, negative values indicate acceleration of the sinus rhythm.

TS is defined as the maximum positive regression slope assessed over any 5 consecutive sinus rhythm RR intervals within the first 15 sinus rhythm RR intervals after the PVC. The TS calculations are based on the averaged tachogram and are expressed in ms per RR interval. HRT values are usually classified into three categories:²¹

- HRT Category 0: both TO and TS are normal (TO < 0% and TS > 2.5 ms/RR interval);
- HRT Category 1: either TO or TS is abnormal;
- HRT Category 2: both TO and TS are abnormal.

Phase B: selected high risk patients for PVS

As mentioned above, patients on antiarrhythmic drugs other than β -blockers are excluded from the present study. All selected high-risk patients will undergo PVS using a standardized stimulation protocol consisting of up to triple extrastimuli (S2S3S4) delivered at two paced cycle lengths (550 ms and 400 ms) at the right ventricular apex and at the right ventricular outflow tract. Extrastimuli are applied after a six-beat drive train with a 2-s interdrive pause. Ventricular extrastimuli are introduced beginning late in diastole and move progressively earlier in 10-ms steps until either ventricular refractoriness or a coupling interval of 200 ms is reached.

The arrhythmia induced is defined as sustained monomorphic VT when it shows a uniform morphology of QRS complexes with a rate between 120-220

bpm, while persisting for ≥ 30 seconds (or shorter, if termination was necessary due to hemodynamic instability). Faster rates of regular unimorphic VT (≥ 220 bpm) not permitting QRS complexes to be readily distinguished from T waves and without deterioration towards ventricular fibrillation (VF), were defined as ventricular flutter, but they are included in the monomorphic VT category. Polymorphic VT is defined if constantly changing morphologies and axes are present, leading eventually to VF.²²

The role of PVS in the risk stratification process of post-MI patients

A plethora of data regarding the role of PVS in the risk stratification of patients with ischemic heart disease have been derived from large ICD clinical trials; however, they have been focused on patients with depressed systolic function. A MADIT II sub-study suggested no role for PVS in post-MI patients with decreased LVEF, since inducibility was predictive only of VT, but not of VF, while non-inducible patients had a considerable VT event rate.²³ Based on this study's results, a narrow definition of inducibility, including only monomorphic VT induction, improved the correlation of inducibility with the subsequent occurrence of VT.²³ The MUSTT investigators reported a significantly higher rate of arrhythmic death and cardiac arrest in inducible compared to non-inducible patients, although the 2-year negative predictive value of PVS was suboptimal (88%).²⁴ When the incidence of arrhythmic arrest and VF causing ICD shock is taken into account, an even higher negative predictive value has been exhibited in ischemic patients with LVEF $\leq 40\%$.²⁵ Notably, recent data suggested that early ICD implantation limited to patients with inducible VT achieved low overall mortality in patients with impaired LVEF after primary PCI for ST-elevation myocardial infarction.²⁶

Preliminary results have been derived from the long-term follow up of post-MI patients with preserved EF in the First Cardiology Division, University of Athens Medical School.¹³ According to our study protocol, we enrolled asymptomatic patients (n=24) either with ≥ 1 episodes of NSVT or an average of ≥ 30 premature ventricular complexes/hour on 24-hour Holter monitoring, as well as post-MI patients with syncope (n=25) and presyncope (n=20). All these patients had LVEF > 40%. Sustained monomorphic VT was induced in 23/69 (33.3%) post-MI patients and an ICD was implanted in all of them. None of the

non-inducible patients experienced SCD or syncope during the follow-up period. Appropriate ICD activation occurred in 12/23 post-MI patients and the mean time to the first ICD activation was 25.4 months.

Device implantation and programming

All post-MI patients with induced sustained monomorphic VT will undergo left-sided dual chamber ICD implantation, without periprocedural defibrillation threshold testing. Patients with induced VF and/or polymorphic VT degenerating into VF will be approached according to the discretion of the performing electrophysiology team regarding the need for ICD implantation. The ICD lead will be positioned at the right ventricular apex but programmed for minimal ventricular pacing.

All devices will be programmed in three consecutive zones: a VT monitoring zone (140-179 bpm), a VT zone (180-220 bpm with a detection interval of 32 beats, or 7 s in devices that are programmed by time), and a VF zone (>220 bpm with a detection interval of 18/24, or 2.5 s in devices with time programming). Supraventricular tachycardia discriminators will be activated in all cases (supraventricular tachycardia limit 200 bpm).

In the VT zone, an initial attempt will be made to terminate VTs by 3 bursts of anti-tachycardia pacing (ATP) (8 pulses per ATP and ATP pacing at 86% of the VT cycle length) followed by 3 ramp ATP runs and, if the arrhythmia continues, by low energy cardioversion and subsequently defibrillator shocks. In the case of VF, maximal energy device shocks will be the initial therapy and ATP will be activated during charging.

Follow up

Patients' enrollment will last for 2 years and patients will be subsequently followed up for 3 years. Patients without an ICD will be regularly followed up in the outpatient arrhythmia clinic every six months. Implanted patients will be routinely followed up every 3-6 months, or urgently if shocks occur. The ICD will be interrogated for device performance metrics and recorded arrhythmic events. All stored electrograms from delivered ICD therapies will be collected and adjudicated by 2 clinical cardiac electrophysiologists. For every recorded event, each electrophysiologist independently determines the rhythm at the time of initial detection and after therapy delivery. If there is disagreement with the diagnosed rhythm at the time

of initial detection, the episode is then reviewed by a third electrophysiologist for final adjudication. Patients who miss their scheduled visits or are unable to return to the enrolling center for follow-up will be contacted by phone. During these phone interviews, current health status and medication use will be updated as well as any interim cardiovascular-related events. Every effort will be made to obtain source documentation of pertinent hospitalizations.

The cause of death is determined as SCD (defined as the occurrence of death within one hour after symptom onset) or death due to progressively deteriorating heart failure. Other possible non-cardiac causes of death will also be recorded. The major endpoints of the study are the incidence of cardiac death and SCD, as well as successful and appropriate first ICD activation for implanted patients or sustained ventricular arrhythmia/aborted SCD in non-implanted patients. The time to first appropriate ICD therapy delivery will also be recorded in implanted patients.

Data selection

An electronic Case Report Form will be available from the online database at the site of Hellenic Cardiological Society. Additionally, baseline 12-lead ECG, 24-hour HM, and 45-minutes high-resolution ECG monitoring, as well as the 12-lead ECG of the induced VT will be stored in electronic form.

Statistical analysis

Patients are considered part of the cohort after successful completion of Phase A. In the time-to-event analysis for appropriate ICD activation, patients are censored at the time of death or at the last date of contact among those still alive. In the time-to-event analysis for cardiac death and SCD, follow up is censored at the last date of contact or the date of death. The Kaplan–Meier method will be used to estimate the cumulative incidence of these events. Incidence rates for a given event will be calculated by taking the ratio of the total number of events and the total number of person-years of follow up contributed by cohort participants. Hazard ratios of study outcomes adjusted for other participant characteristics will be estimated using proportional hazards regression models.

Power analysis

Based on the design of our study, and given that the main

hypothesis is going to be tested at the univariate level using the log-rank test, we conducted a sample size estimation using the Schoenfeld and Richter approach (Schoenfeld DA, Richter JR. Nomograms for calculating the number of patients needed for a clinical trial with survival as an endpoint. *Biometrics* 1982; 38: 163-170) and the PS software (Version 3.0.43, Vanderbilt University).

We calculated the required sample for a given effect, according to the tested variable, setting the type I error probability for a two sided test at 5% and the power of our study at 80%. We successively tested all the noninvasive variables for risk stratification that are going to be applied in the whole study population and we knew their distribution in a post MI population from previous studies. SDNN was the variable that required the largest sample. Specifically, we expect a ratio of high SDNN patients (controls) to low SDNN patients (exposed) equal to 12. Given an accrual interval of 2 years and additional follow up after the accrual interval of 3 years, a median event-free time in the control group from previous studies of approximately 2.8 years and a true hazard ratio (relative risk) of control subjects relative to exposed subjects equal to 0.65, we will need to study 66 exposed subjects and 792 control subjects to be able to reject with a probability of 80% the null hypothesis that the exposed and control survival curves are equal.

Consequently, we are planning to recruit 1000 subjects in our study in order to have the additional power to conduct multivariate modeling of the main hypothesis using proportional hazards models, to manage the expected lost information due to follow-up losses, given the non-interventional design of our study, and to test all the secondary hypotheses.

Rationale for the study performance – future perspectives

A severely impaired LVEF has been considered the main risk stratifier for the future development of malignant ventricular arrhythmias in the post-MI population, based on the findings of the landmark primary prevention ICD trials.³ In the era of primary PCI, only a minority of post-MI patients are eligible for ICD implantation on the grounds of a low LVEF.⁴ Although the risk for SCD is relatively lower in post-MI patients with preserved compared to those with impaired LVEF, the absolute number of SCD victims within the preserved LVEF population is significantly high, necessitating the development of a different risk stratification approach.⁵

In this setting, the ongoing REFINE-ICD (NCT00673842) and VIP-HF (NCT01989299) studies will evaluate the efficacy of ICD implantation in heart failure patients with preserved LVEF and noninvasively derived arrhythmic indexes. A number of noninvasively derived electrocardiographic variables, such as ventricular ectopic activity, LPs, TWA, Holter-derived repolarization abnormalities, and autonomic disturbance indices could be used in order to identify high-risk asymptomatic patients with preserved LV function.^{15-21,27-29} Towards this direction, we will investigate both the negative and positive predictive value of all available noninvasive risk factors, along with PVS, for the incidence of SCD and its surrogate. We hypothesize that there is a higher likelihood of interrupting a truly malignant ventricular tachyarrhythmia event, as the underlying mechanism of the cardiac arrest, at early stages of heart failure with less severe systolic dysfunction and a higher risk profile (based on our selected criteria), than at advanced stages with severely depressed LVEF. In the latter stages, a common mechanism of cardiac arrest is pulseless electrical activity that does not respond to the ICD therapy. Based on this hypothesis, we expect a much more promising ICD benefit in patients at early stages of heart failure with a relatively well preserved LVEF, when the potential for significant survival prolongation after terminating an unexpected life threatening “electrical accident” is indeed more realistic. Living still in an era of technological and logistical difficulties, we cannot apply this revolutionary ICD therapy in all coronary disease patients. However, there is accumulating evidence that we can identify a small proportion of such post-MI patients who are at risk for major arrhythmic events. Whether these patients could be effectively protected by an ICD remains largely unknown. We hope that PRESERVE-EF might provide conclusive answers to the above and will constitute the base for a subsequent large randomized trial.

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