Post Myocardial Infarction Risk Stratification for Sudden Cardiac Death in Patients with Preserved Ejection Fraction (PRESERVE EF) Study

Clinicaltrials.gov identifier: NCT02124018

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Methods

Trial oversight: The PRESERVE EF study is a multicenter, prospective, observational cohort study (clinicaltrials.gov identifier NCT02124018) with seven Cardiology departments in Greece actively participating. Study protocol was approved by all institutions' ethics committees and was endorsed by the Hellenic Society of Cardiology with an anonymized online database created and maintained in its servers(1).

Patients: Post-angiographically proven MI patients, at least 40 days after the event (90 days after surgery if they underwent coronary artery bypass grafting)(2, 3), with LVEF≥40% (also assessed after 40 or 90 days, respectively from the index event), either revascularized or not – but without any evidence of active ischemia (following negative myocardial scintigraphy/exercise treadmill test/stress echocardiography in the previous 6 months), on optimal tolerated medical therapy, were enrolled. Exclusion criteria were: (1) Presence of a secondary prevention indication for ICD implantation, (2) Presence of a permanent pacemaker, due to potential effects on NIRF acquisition following pacemaker dependency and cardiac memory(4), (3) Persistent, long-standing persistent and permanent atrial fibrillation, (4) Neurological symptoms (presyncope or syncope) within the last 6 months, (5) Patients with systemic illnesses (cancer, liver failure, end-stage renal disease, rheumatic diseases and thyroid dysfunction), (6) Administration of antiarrhythmic medication other than β-blockers, (7) Age ≥80 or ≤18 years old.

All patients provided written informed consent.

Study protocol: A two-step stratification algorithm was implemented(1). Upon the first step of the algorithm, an ambulatory 24-hour, as well as signal-averaged electrocardiogram recordings were obtained and evaluated for the presence of the following NIRFs(1, 5-8): (1) >30 premature ventricular complexes/hour on 24-hour electrocardiography, (2) presence of non-sustained ventricular tachycardia on 24-hour electrocardiography, (3) 2/3 positive criteria for late potentials, either conventional or modified(8), (4) QTc derived from 24-hour electrocardiography >440ms (men) or >450ms (women)(6) according to the Fridericia formula from a signal recorded in 3 pseudo-orthogonal leads, (5) Ambulatory T-wave alternans ≥65μV in two Holter channels(5), (6) Standard deviation of normal RR intervals ≤75ms on the 24-hour electrocardiography, (7) Deceleration capacity ≤4.5ms and heart rate turbulence onset ≥0% and heart rate turbulence slope ≤2.5ms(7).

In the presence of at least one NIRF, patients underwent invasive PVS and were classified as inducible if sustained monomorphic ventricular tachycardia or ventricular flutter or polymorphic ventricular tachycardia were induced. The arrhythmia induced was defined as sustained monomorphic ventricular tachycardia when a uniform morphology of QRS complexes with a rate between 120-220bpm was observed, while persisting for ≥30 seconds (or shorter, if termination was necessary due to hemodynamic instability). Faster rates of regular monomorphic ventricular tachycardia (≥220bpm) not permitting QRS complexes to be readily distinguished from T waves and without deterioration towards fibrillation, were defined as ventricular flutter, but they were included in the monomorphic category. Polymorphic ventricular tachycardia was defined if constantly changing morphologies and axis were present, eventually degenerating into fibrillation. See "Appendix" for PVS protocol details.

Patients with paroxysmal atrial fibrillation were evaluated for NIRF presence and submitted to PVS while on sinus, with same stimulation protocol implemented in all cases.

Risk level groups: After completion of the study protocol, patients were stratified into three groups:

- Group 1 –No NIRFs present – no invasive PVS performed
- Group 2 – At least one NIRF present – noninducible upon PVS
- Group 3 – At least one NIRF present AND inducible upon PVS.

An ICD was offered only to Group 3 patients.

Patients declining PVS were considered not to have completed stratification and were not included in the protocol performance and survival analyses, yet were followed up as scheduled for the occurrence of any events. Patients completing the protocol but declining an offered ICD were fully included in all analyses.

ICD programming: In accordance with trials favouring prolonged detection intervals at higher rates for the avoidance of treatment of self-terminating arrhythmic events(9), ventricular tachycardia therapy cycle length was set to 330msec and number of intervals to detect to 32. Fibrillation therapy cycle length was set to 270msec and number of intervals to detect to 18/24. In devices with time programming, the same cycle lengths were used but intervals were set to 7sec for CLs in the 270-330msec range and to 2.5sec for CLs<270msec.

Ventricular tachycardia therapy consisted of several attempts of antitachycardia pacing, followed by cardioversion at progressively increasing energy. High-energy shocks were administered to terminate ventricular fibrillation. In 32 cases dual-chamber ICDs were inserted, while in the remaining 5 a single-chamber device was chosen by both the primary and implanting physicians, after excluding the presence of bradyarrhythmic aberration on the electrophysiological study.

Follow up: Implanted patients were followed up every three months, and nonimplanted patients every six months. Events included cardiac (sudden and nonsudden) and non-cardiac death. Acute coronary syndromes and/or repeat revascularization events were also recorded. All device activation were adjudicated independently by two electrophysiologists (D.T. and P.A.). In case of discrepancy, a third electrophysiologist (K.A.G.) reviewed the event.

Outcomes: The primary endpoint of the study was the occurrence of MAEs, namely either SCD/clinical ventricular tachycardia/fibrillation or/and appropriate ICD activation. SCD was defined as death occurring within one hour of symptom onset if no evidence of alternative causes was present. Death was considered nonsudden cardiac if occurring in the context of heart failure deterioration. All other deaths were classified as noncardiac. The secondary endpoint was total mortality.

Statistics: The primary goal of the study was to assess the proposed two-step PVS-inclusive risk stratification algorithm's ability to identify a subpopulation of post-myocardial infarction patients with left ventricular ejection fraction≥40% at risk for MAEs. To that end, the study was designed to have a statistical power of 80% for detecting free from primary endpoint occurrence survival curve divergence at the 0.05 significance level(1). All continuous variables were checked for normality of distribution, using the Shapiro-Wilk test. Regarding those with normal distribution, Student's t-test was used for all comparisons. In case of non-normality, the Mann-Whitney U-test was used. In cases of categorical variables Fisher's exact test was used. Binary logistic regression was used to compare the odds ratio between groups with different number of NIRFs regarding inducibility. Kaplan-Meier curves were used to visualize survival free from primary endpoint occurrence and the logrank test was applied to assess the presence of statistically significant differences. A two-sided p-value of ≤0.05 was considered statistically significant in all cases.

Power analysis(1): Due to the paucity of data regarding PVS yield in similar population cohorts, it was necessary to use metrics derived from noninvasive indices included in this Study as well. After setting the type I error probability for a two sided test at 5% and the power of our study at 80%, SDNN was found to be the variable that required the largest sample (a ratio of high SDNN patients/controls to low SDNN patients/exposed equal to 12 was anticipated). The anticipated accrual/mean follow up intervals were 2 and 3 years, respectively. Relative risk (based on SDNN performance) of control subjects relative to exposed subjects was equal to 0.65. Based on the above, 66 exposed subjects and 792 control subjects would need to be studied to be able to reject with a probability of 80% the null hypothesis that the exposed and control survival curves are equal.

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