Long-Term Arrhythmia-Free Survival in Patients With Severe Left Ventricular Dysfunction and No Inducible Ventricular Tachycardia After Myocardial Infarction

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Background—A negative electrophysiology study (EPS) may delineate a subgroup of patients with severely impaired left ventricular ejection fraction (LVEF) whose care can be safely managed long-term without an implantable cardioverter-defibrillator.

Methods and Results—Consecutive patients treated with primary percutaneous coronary intervention for ST-segment-elevation myocardial infarction underwent early (median 4 days) LVEF assessment. Patients with LVEF $\leq$40% underwent EPS. A prophylactic implantable cardioverter-defibrillator was implanted for a positive (inducible monomorphic ventricular tachycardia) but not a negative (no inducible ventricular tachycardia or inducible ventricular fibrillation/flutter) EPS result. Patients who would have become eligible for a late primary prevention implantable cardioverter-defibrillator with LVEF $\leq$30% or $\leq$35% with New York Heart Association class II/III heart failure were included and analyzed according to EPS result. Patients with LVEF $>$40%, ineligible for EPS, were followed up as control subjects (n=1286). The primary end point was survival free of death or arrhythmia (resuscitated cardiac arrest or sustained ventricular tachycardia/ventricular fibrillation). EPS performed in 128 patients with LVEF $\leq$30% or with LVEF $\leq$35% and heart failure was negative in 63% (n=80) and positive in 37% (n=48). Implantable-cardioverter defibrillators were implanted in <0.1%, 4%, and 90% of control, EPS-negative, and EPS-positive patients, respectively. The distribution of time to death or arrhythmia was comparable in control patients and EPS-negative patients with LVEF $\leq$30% or with LVEF $\leq$35% and heart failure (P=0.738), who both differed significantly from EPS-positive patients (P<$0.001$). At 3 years, 91.8±3.2%, 93.4±1.0%, and 62.7±7.5% of control, EPS-negative, and EPS-positive patients were free of death or arrhythmia, respectively.

Conclusions—Revascularized patients with ST-segment-elevation myocardial infarction with severely impaired left ventricular function but no inducible ventricular tachycardia have a favorable long-term prognosis without the protection of an implantable cardioverter-defibrillator. (Circulation. 2014;129:848-854.)

Key Words: death, sudden ■ electrophysiology ■ myocardial infarction ■ tachycardia

Impaired left ventricular ejection fraction (LVEF) is one of the strongest predictors of death or arrhythmia postmyocardial infarction (MI). Randomized trials have demonstrated that post-MI patients with impaired LVEF derive a mortality benefit with implantation of a prophylactic implantable cardioverter-defibrillator (ICD) for prevention of sudden cardiac death (SCD).1,2 This mortality benefit is seen only in the chronic stage, with no randomized trial yet showing a benefit of early post-MI (within 40 days) ICD implantation.3,4 Current guidelines therefore limit prophylactic ICDs to patients who are $>$40 days post-MI with either LVEF $\leq$30% or LVEF $\leq$35% in the presence of New York Heart Association class II/III heart failure (HF).5 However, this risk-stratification method for prevention of SCD is limited by the poor specificity of impaired LVEF for arrhythmic versus nonarrhythmic cardiac death.6 In addition, although the rate of SCD has declined in the era of early revascularization for MI, it remains concerningly elevated in the first 40 days.7-9 Inducible ventricular tachycardia (VT) at electrophysiological study (EPS) demonstrates the presence of a substrate for reentrant tachyarrhythmia and consistently predicts arrhythmia in observational and randomized studies.10-16 The potential utility of EPS to guide early ICD implantation after MI has been demonstrated.17,18

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Although EPS has been shown to select patients at high risk of future tachyarrhythmia, concern still surrounds its negative predictive value. We aimed to demonstrate that early post-MI patients with severe left ventricular (LV) dysfunction and a negative EPS (no inducible VT) can be safely managed long-term without the protection of an ICD.

Methods

Consecutive patients with ST-segment–elevation myocardial infarction (STEMI) treated with primary percutaneous coronary intervention at a single tertiary center from 2004 to 2011 were prospectively recruited. The study was approved by an institutional review committee, and subjects gave their written informed consent. Patients presented directly to the intervention-capable Westmead Hospital (Sydney, Australia) or were referred by 3 associated district hospitals. All patients in the study had angiographically confirmed STEMI. No patients received thrombolytic therapy. Patients with STEMI underwent inpatient assessment of LV function at day 3 or later after MI with gated heart pool scan or transthoracic echocardiogram where gated heart pool scan was not available. After early revascularization, optimal medical therapy, including β-blockers, angiotensin-converting enzyme inhibitors, statins, and antiplatelet therapy, was begun for patients with LV dysfunction. According to hospital protocol, patients with LVEF ≤40% were eligible for EPS as a risk-stratification test to identify patients at risk of SCD. Previous research conducted at our institution analyzing the predictive value of EPS after STEMI had prospectively recruited patients from 1999 to 2008, with ~40% of these patients included in the present study. In the present study, patients were included if they had an EPS performed with LVEF ≤30% (irrespective of the presence of HF) or an EPS performed with LVEF 31% to 35% (only if HF New York Heart Association class II or III was also present). Patients with LVEF >40% who were not eligible for EPS were followed up as the control group.

Electrophysiological Study

Programmed stimulation was performed at twice diastolic threshold at the right ventricular apex (single site) using a programmable stimulator. A drive train (S1S1) of 8 beats at 400 ms was followed by up to 4 extrastimuli. Stimuli were rectangular pulses of 2 ms duration at twice diastolic threshold with a 3-second delay between each drive train. The initial extrastimulus was delivered at a coupling interval of 300 ms and then decreased in 10-ms steps to ventricular refractoriness. If the earliest possible extrastimulus (eg, S1S2) failed to induce VT, that extrastimulus was delivered 10 ms outside the ventricular effective refractory period and an additional extrastimulus added (eg, S2S3) at a coupling interval of 300 ms. The additional extrastimulus was decreased in 10-ms steps in the same manner. Additional extrastimuli were added in a similar manner (always starting with a coupling interval of 300 ms) until either VT or ventricular fibrillation (VF) was induced or refractoriness of the fourth extrastimulus was reached. There was no set lower limit for the shortest permissible extrastimulus coupling interval. The programmed stimulation was repeated a second time from the same site, using the same protocol, if the initial induction was negative for VT. Isoprenaline infusion was not used to facilitate VT induction. Patients with sustained monomorphic VT cycle length ≥200 ms with ≤4 extrastimuli were considered inducible (positive EPS). Inducible VT had to be ≥20 seconds in duration if hemodynamically tolerated or ≥210 seconds in duration if hemodynamically unstable. Patients with no arrhythmia induced or inducible VF or ventricular flutter (cycle length <200 ms) were considered to have a negative EPS. The predictive value of this approach has been discussed in detail previously.15–22 PredischARGE ICD implantation was recommended for EPS-positive patients. EPS-negative patients were discharged without an ICD and according to study protocol did not undergo ICD implantation >40 days after MI irrespective of persistent LV dysfunction.

ICD Implantation and Programming

All devices were preprogrammed or subsectorial systems, with the manufacturer and type determined by the hospital device-acquisition process. Device detection and therapy were programmed as follows: VF required 18 of 24 R-R intervals with cycle length ≤250 ms. Therapy was a single antitachycardia pacing burst during charging (8 pulses per burst) followed by ≤6 shocks. VT required 16 consecutive beats with cycle length 251 to 360 ms and 12 consecutive beats with cycle length 251 to 360 ms for redetection. Initial therapy for VT was ≤3 ATP bursts (8 pulses per burst) followed by ≤6 shocks. Ventricular arrhythmia that did not reach the set number of detection intervals was classified as nonsustained. Discriminators for supraventricular tachycardia were standardized on the basis of arrhythmia onset, stability, and ventriculoatrial dissociation. To reduce unnecessary right ventricular pacing, backup pacing was set at 40 bpm VVI for single-chamber devices and AAI-DDD for devices with an atrial lead.

End Points and Follow-Up

The primary end point was a combination of all-cause death and arrhythmia. The secondary end point was the first arrhythmic event (arrhythmia defined as SCD, resuscitated cardiac arrest, and ECG-documented sustained VT or VF). Cause of death was determined by 2 local investigators on the basis of information obtained from witnesses, family members, death certificates provided by the state registry of births and deaths, hospital medical records, rhythm strips, and autopsy reports. A third independent investigator adjudicated if their opinions differed. SCD was strictly defined on the basis of a modified Hinkle and Thaler system as death that occurred “suddenly and unexpectedly” in a patient in otherwise stable condition, inclusive of witnessed instantaneous death (with or without documentation of arrhythmia), unwitnessed death if the patient had been seen within 24 hours before death (in the absence of another clear cause of death), death caused by incessant ventricular tachyarrhythmia, deaths considered a sequel to cardiac arrest, and death resulting from proarrhythmia of antiarrhythmic drugs. Resuscitated cardiac arrest was defined as a sudden circulatory arrest that required cardiopulmonary resuscitation, with the most likely cause a tachyarrhythmia (with or without documented VT or VF), from which the patient regained consciousness. Ventricular tachyarrhythmia was defined as ECG-documented VT or VF in patients without an ICD, or ICD-detected VT or VF that required treatment to terminate (antitachycardia pacing or shock). Cardiac mortality included both sudden and nonsudden cardiac deaths, with nonsudden cardiac deaths defined as death attributable to MI, HF, or another cardiovascular cause. HF was defined as symptoms or signs consistent with congestive HF (either clinical or radiographic evidence) that required treatment with decongestive therapy (diuretics or inotropes), intra-aortic balloon pump, or invasive/noninvasive ventilation. Only HF during the index STEMI admission was assessed. All patients were followed up by the study investigators throughout their time in the hospital and by telephone contact at 1, 3, and 6 months after discharge and at 6-month intervals thereafter. Patients with an ICD were also followed up in the ICD clinic, with electrograms of device detections or activations analyzed by the study investigators.

Statistical Analysis

SPSS for Windows (release 21.0) was used to analyze the results. Patients were analyzed according to study group assignment. All analyses were exploratory, and 2-tailed tests with a significance level of 5% were used throughout. No adjustment has been made for multiple comparisons. False-positive findings are therefore possible, and any statistically significant results need to be confirmed in further independent studies. The χ² or Fisher exact tests were used as appropriate to test for an association between categorical variables. ANOVA or Kruskal-Wallis equivalent was used to test for differences in the distribution of continuous variables between groups. Kaplan–Meier curves were used to illustrate the cumulative distribution of
the primary end point by time after infarction. Tarone-Ware tests were used to look for differences in survival distribution between the groups.

**Results**

A total 1910 STEMI patients were taken to the cardiac catheterization laboratory for primary percutaneous coronary intervention. Of these patients, 188 (9.8%) did not undergo early LVEF assessment. The reasons for this included inpatient death before LVEF assessment (n=94; 50%), patient refusal or discharge before LVEF assessment (n=54; 29%), transfer back to a peripheral hospital (n=20; 11%), and transfer to another treating specialty (n=20; 11%). Early LVEF assessment was performed in 1722 patients a median of 4 days after STEMI by gated heart pool scan in 87% (n=1506), transthoracic echocardiogram in 12% (n=212), and sestamibi scan or transoesophageal echocardiogram in <1% (n=4). Patients with LVEF >40% made up 75% (n=1286) of STEMI patients and formed the control group. Of the total cohort, 10% of patients had LVEF ≤30% (n=172), whereas 8% had LVEF 31% to 35% (n=136), of which 38% (n=51) had concomitant New York Heart Association class II/III HF. EPS was performed at a median of 8 days after STEMI (lower quartile, 6–11 days) in 57% of patients (n=128) with LVEF ≤30% or ≤35% and HF (n=223). It was not performed in all patients because of either in-hospital death before EPS (n=39; 41%), secondary indication for ICD (n=9; 9%), patient refusal (n=5; 5%), or patient deemed inappropriate for ICD implantation because of limited life expectancy (old age, significant comorbidities or malignancy; n=42; 44%). Among patients with LVEF ≤30% or ≤35% and HF, the EPS was negative in 63% (n=80) and positive for inducible VT in 37% (n=48). The baseline characteristics according to the 3 study groups are shown in Table 1.

**ICD Implantation**

A predischarge ICD was implanted early (median 13 days) after STEMI in 43 of 48 patients with LVEF ≤30% or ≤35% and HF and a positive EPS (90%). An ICD was not implanted in 5 patients with a positive EPS because of patient refusal (n=2) or because the patient was not covered by health insurance (n=3). A predischarge ICD was implanted in 3 of 80 patients (4%) with a negative EPS (protocol violations) by the treating physicians on the basis of impaired LVEF alone. A predischarge ICD was implanted in <0.1% of control patients (LVEF >40%) because of a secondary indication (n=1).

**Table 1. Baseline Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>LVEF ≤30% or ≤35% Plus HF</th>
<th>Control</th>
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<td></td>
<td>EPS Negative (n=80)</td>
<td>EPS Positive (n=48)</td>
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<tr>
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<td>57±12</td>
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<tr>
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<td>Clopidogrel or prasugrel</td>
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</tr>
<tr>
<td>LVEF, %</td>
<td>27±5</td>
<td>26±6</td>
</tr>
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</table>

Values are percentages or mean±SD. ACE-I indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CABG, coronary artery bypass grafting; EPS, electrophysiology study; HF, heart failure; IHD, ischemic heart disease; LAD, left anterior descending coronary; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; STEMI, ST-segment–elevation myocardial infarction; and TIMI, Thrombolysis in Myocardial Infarction.

*EPS-negative vs EPS-positive patients;
†EPS-negative vs control patients.
Primary Outcome
Median follow-up for all patients was 32 months (lower quartile to upper quartile, 24–50 months). Median follow-up for EPS-negative patients with LVEF ≤30% or ≤35% and HF was 42 months (lower quartile to upper quartile, 24–61 months). The Kaplan–Meier estimated survival free of death or arrhythmia is shown in Figure 1, with no significant difference between patients in the control group (LVEF >40%) and those with LVEF ≤30% or LVEF ≤35% and HF who were EPS negative (P=0.738). At 3 years, 93.4±1% of patients with LVEF ≤30% or LVEF ≤35% and HF and a negative EPS and 91.8±3.2% of control patients (LVEF >40%) were free of death or arrhythmia. The Kaplan–Meier survival plot inclusive of EPS-positive patients is shown in Figure 2, with EPS-positive patients having a significantly lower survival free of arrhythmia or death than control (P<0.001) patients. At 3 years, 62.7±7.5% of EPS-positive patients were free of arrhythmia or death.

Secondary Outcomes
Over the follow-up period, arrhythmia occurred in <1% of control patients (n=6; LVEF >40%), 2.5% of EPS-negative patients (n=2), and 33% of EPS-positive patients (n=16; 5 SCD in an EPS-positive patient without an ICD because of protocol violation). Two-year arrhythmic event rates were 1% for EPS-negative (n=1) and 24% for EPS-positive patients (n=11). The sensitivity and specificity of EPS at 2 years were therefore 92% and 68%, respectively. There was no significant difference in the Kaplan–Meier estimated total mortality in control, EPS-negative, and EPS-positive patients, respectively (P=0.451). At 3 years, the total mortality was 6.5±1%, 6.8±2.9%, and 14.6±5.5% in control, EPS-negative, and EPS-positive patients, respectively. Death and arrhythmia outcomes are expanded in Table 2. Inappropriate ICD activations (all attributable to supraventricular tachycardia) occurred in 11% of patients with an ICD (5/47), with 1 patient receiving an inappropriate shock.

Discussion
Post-MI patients with severe LV dysfunction have low long-term rates of arrhythmia or death if no VT is induced at electrophysiology testing. Patients with LVEF >40% were followed up as a control group given the well-established low risk of SCD or arrhythmia in this population.12,14,24 We found that EPS-negative patients with severe LV dysfunction had a similarly good long-term prognosis as patients with preserved LVEF. It is well accepted that the presence of inducible monomorphic VT at EPS selects patients at high risk for spontaneous tachyarrhythmia; however, a predominant concern with EPS as a risk-stratification tool for prevention of SCD is its negative predictive value. Results from the Multicenter Automatic Defibrillator Implantation Trial II (MADIT II) suggested that EPS added little prognostic information, because those investigators found patients late after MI with LVEF ≤30% experienced sudden death even if EPS testing was negative.1 The more recent CARISA (Cardiac Arrhythmias and Risk Stratification After Acute Myocardial Infarction) and ABCD (Alternans Before Cardioverter Defibrillator) trials found that although EPS had the highest specificity, its sensitivity

![Figure 1](link-to-image)

**Figure 1.** Kaplan–Meier survival free of death or arrhythmia (cardiac arrest or ventricular tachycardia [VT]/ventricular fibrillation) for patients with severe left ventricular dysfunction but a negative electrophysiology study (no inducible VT) compared with control (left ventricular ejection fraction >40%). EP−ve indicates negative electrophysiology study; HF, heart failure; and MI, myocardial infarction.

![Figure 2](link-to-image)

**Figure 2.** Kaplan–Meier survival free of death or arrhythmia in patients with severe left ventricular dysfunction and a negative (no inducible ventricular tachycardia [VT]) vs positive (inducible VT) electrophysiology study. A, Arrhythmia is inclusive of implantable cardioverter-defibrillator–treated VT events. B, Arrhythmia is exclusive of implantable cardioverter-defibrillator–treated VT events. EP+ve indicates positive electrophysiology study; EP−ve, negative electrophysiology study; HF, heart failure; and MI, myocardial infarction.
was comparable to noninvasive modalities such as microvolt T-wave alternans and heart rate variability. However, the negative predictability of EPS appears critically dependent on the VT induction protocol used. The MADIT II study performed EPS through the ICD device in a proportion of patients, which would have considerably restricted its predictive ability. The ABCD and CARISMA investigators used an EPS protocol of up to 3 extrastimuli and included not only sustained monomorphic VT as a positive result but also VF or polymorphic VT. Inducible VF or ventricular flutter cycle length <200 ms has been shown to be a nonpredictive result.\textsuperscript{12,25} We have demonstrated previously that a VT induction protocol that contains 4 extrastimuli, with inducible monomorphic VT cycle length >200 ms classified as a positive result, best identifies nearly all patients at high risk for ventricular fibrillation and heart rate variability. However, the negative predictability of EPS appears critically dependent on the VT induction protocol used. The MADIT II study performed EPS through the ICD device in a proportion of patients, which would have considerably restricted its predictive ability. The ABCD and CARISMA investigators used an EPS protocol of up to 3 extrastimuli and included not only sustained monomorphic VT as a positive result but also VF or polymorphic VT. Inducible VF or ventricular flutter cycle length <200 ms has been shown to be a nonpredictive result.\textsuperscript{12,25} We have demonstrated previously that a VT induction protocol that contains 4 extrastimuli, with inducible monomorphic VT cycle length >200 ms classified as a positive result, best identifies nearly all patients at high risk for arrhythmia.\textsuperscript{12,19–22,26,27} The present study, which used such a VT induction protocol, strongly suggests that patients with a negative EPS have very low rates of death or arrhythmia despite having severe LV dysfunction and no ICD.

The evidence supporting post-MI ICD implantation for primary prevention has largely come from randomized trials that used LVEF as the sole selection tool.\textsuperscript{13} However, LVEF used alone has low specificity for arrhythmic versus nonarrhythmic deaths\textsuperscript{5} and limited sensitivity, whereby a large proportion of SCDs occur above the LVEF cutoff.\textsuperscript{7} MADIT-II and the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT), which used LVEF alone, found a large number of patients (11 and 14, respectively) required treatment with a defibrillator to save 1 life.\textsuperscript{28} The risks of ICD implantation, such as multiple or inappropriate shocks and quality of life deterioration, must be weighed against potential survival benefits. In addition, ICDs are expensive, and a cost-benefit ratio should be considered. In comparison, in the Multicenter Unsustained Tachycardia Trial (MUSTT) and the Multicenter Automatic Defibrillator Implantation Trial (MADIT), in which EPS was used in addition to LVEF, only 4 and 5 patients, respectively, required treatment with an ICD to save 1 life.\textsuperscript{11} Our findings suggest that within the subgroup of post-MI patients with LVEF ≤35%, low-risk patients exist who would derive little benefit from an ICD. Restricting ICD implantation in this group through the additional use of EPS could allow a substantial cost benefit without a sacrifice in population life expectancy.

Depressed LV function is a strong predictor of mortality. In randomized ICD trials, the mortality in patients with LVEF ≤30% was high, with 1-year mortality ranging from 6.8% to 19%.\textsuperscript{1,2,11} Studies assessing mortality and arrhythmia in the cohort of patients treated exclusively with primary percutaneous coronary intervention are limited. In 2007, Ottervanger et al\textsuperscript{8} described a much lower rate of death after primary percutaneous coronary intervention for STEMI of 5.8% at 1 year; however, they excluded all deaths within 1 month, and LVEF was measured later after MI. Sudden death was the most common cause of death (40%). Total mortality in the present study in patients with LVEF ≤30% or with LVEF ≤35% and HF who survived to undergo EPS-guided ICD implantation was low (10% at 3 years). This likely reflects the improved mortality in the era of early revascularization for STEMI, optimal medical management, and targeted ICD implantation.

**Study Limitations**

The main limitation of the present study was its observational nature. Because ICDs were not implanted in EPS-negative patients, there was an unavoidable bias in the detection of arrhythmic events in EPS-positive patients. ICD-detected VT/
VF overestimates SCD by 2- to 4-fold, which limits any comparison in arrhythmic events of overall EPS-positive with overall EPS-negative patients (although the very low SCD rate of <1% in the EPS-negative group is reassuring). However, the primary aim of the present study, to compare survival in EPS-negative and control patients (LVEF >40%), was not influenced by this bias, because neither group received ICDs, as per our study protocol. Although we have demonstrated that there was no significant difference between EPS-negative patients with impaired LVEF and control patients (LVEF >40%), we have not proven these groups are equivalent. To demonstrate a statistically significant equivalence to within 1% in survival free of arrhythmia or death between EPS-negative and control patients, several thousand patients would be needed in each arm of the study. Confirmation of an EPS-guided strategy for primary prevention of SCD requires a large, multicenter, randomized, controlled trial.

Disclosures
None.

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**CLINICAL PERSPECTIVE**

Left ventricular ejection fraction (LVEF) ≤30% or ≤35% in the presence of New York Heart Association class II/III heart failure is the recommended criterion to select a patient for a primary prevention implantable cardioverter-defibrillator after myocardial infarction (MI). However, impaired LVEF used alone as a risk stratification tool is limited by poor specificity for arrhythmic versus nonarrhythmic cardiac death, with a survival benefit seen only in the chronic phase after MI. Although sudden cardiac death incidence has declined in the era of early revascularization for MI, it remains significantly elevated in the first 40 days. This study assessed the utility of an electrophysiology study (EPS) to guide implantation of an implantable cardioverter-defibrillator early after MI. Consecutive patients treated with primary percutaneous coronary intervention for ST-segment-elevation MI underwent early LVEF assessment with EPS performed if LVEF ≤40%. Patients were prospectively followed up with a primary end point of death or arrhythmia (sudden cardiac death, resuscitated cardiac arrest, or ventricular tachycardia/ventricular fibrillation). Patients with LVEF ≤30% or ≤35% and heart failure who were EPS negative (n=80) were compared with control patients (LVEF >40%, n=1286). We found that EPS-negative patients with severe left ventricular dysfunction had a similar long-term survival free of death or arrhythmia as patients with preserved LVEF. Although the use of EPS early after MI remains controversial, this study has important implications for future trials assessing EPS as a risk-stratification tool for prevention of sudden cardiac death. A negative EPS may delineate a subgroup of patients early after MI with impaired LVEF who can be managed safely long-term without a defibrillator.

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