



# Early EPS/ICD strategy in survivors of acute myocardial infarction with severe left ventricular dysfunction on optimal beta-blocker treatment<sup>☆</sup> The BEta-blocker STRategy plus ICD trial

Antonio Raviele<sup>a,\*</sup>, Maria Grazia Bongiorno<sup>b</sup>, Michele Brignole<sup>c</sup>,  
Riccardo Cappato<sup>d</sup>, Alessandro Capucci<sup>e</sup>, Fiorenzo Gaita<sup>f</sup>,  
Michele Gulizia<sup>g</sup>, Salvatore Mangiameli<sup>h</sup>, Annibale Sandro Montenero<sup>i</sup>,  
Roberto F.E. Pedretti<sup>j</sup>, Jorge A. Salerno Uriarte<sup>k</sup>, Sergio Sermasi<sup>l</sup>,  
Seah Nisam<sup>m</sup>, for the BEST+ICD Trial Investigators

<sup>a</sup> Cardiology Division, Ospedale Umberto I, Via Circonvallazione, 50 – 30170 Mestre-Venezia, Italy

<sup>b</sup> Cardiology Division, Ospedale Cisanello, Pisa, Italy

<sup>c</sup> Cardiology Division, Ospedale Civile, Lavagna, Italy

<sup>d</sup> Cardiology Division, Istituto Policlinico S Donato, S Donato Milanese, Italy

<sup>e</sup> Cardiology Division, Ospedale Civile, Piacenza, Italy

<sup>f</sup> Cardiology Division, Ospedale Civile, Asti, Italy

<sup>g</sup> Cardiology Division, Ospedale S Luigi-S Currò, Catania, Italy

<sup>h</sup> Cardiology Division, Ospedale Garibaldi, Catania, Italy

<sup>i</sup> Cardiology Division, Policlinico MultiMedica, Sesto S Giovanni, Italy

<sup>j</sup> Cardiology Division, IRCCS Fondazione S Maugeri, Tradate, Italy

<sup>k</sup> Cardiology Division, Università dell'Insubria, Ospedale di Circolo, Varese, Italy

<sup>l</sup> Cardiology Division, Ospedale degli Infermi, Rimini, Italy

<sup>m</sup> Guidant Corporation Europe, Brussels, Belgium

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## KEYWORDS

defibrillation;  
electrophysiology;

**Abstract Aims** This multicentre prospective randomised trial was undertaken to evaluate the usefulness of an electrophysiological study (EPS)–guided/implantable cardioverter defibrillator (ICD) strategy in patients at high risk of sudden death (SD)

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\* Corresponding author. Tel.: +39 041 2607201; fax: +39 041 2607235.

E-mail address: araviele@tin.it (A. Raviele).

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early after myocardial infarction (MI). Previous studies have shown the benefits of such a strategy only in high-risk patients late after MI.

**Methods and results** We enrolled 143 survivors of acute MI (<1 month) with left ventricular ejection fraction  $\leq 35\%$  and either frequent ( $\geq 10/h$ ) premature ventricular complexes (PVCs), or depressed heart rate variability (SDNN  $< 70$  ms) or abnormal signal-averaged ECG, who were able to tolerate optimised beta-blocker therapy ( $68 \pm 40$  mg/day of metoprolol). Of these, 138 were randomised, in a 2:3 ratio, to two therapeutic strategies: conventional (CONV) strategy ( $n = 59$ ) or EPS-guided/ICD strategy ( $n = 79$ ). The latter resulted in ICD implantation in 24 inducible patients and in CONV therapy in the remaining 55. During a mean follow-up of  $540 \pm 378$  days, 26 patients (19%) died: nine (6.5%) SD, nine (6.5%) non-SD, and four (3%) non-cardiac death; in four patients (3%) the cause of death was unknown. The actuarial overall mortality for the CONV and EPS-guided/ICD arms was 18% vs 14% after 1 year and 29.5% vs 20% after 2 years, respectively ( $P = 0.3$  and  $0.2$ ).

**Conclusions** Despite optimal therapy, mortality remains significant in high-risk patients following MI. Although there is a trend in favour of EPS-guided/ICD, our data are insufficient to demonstrate a survival benefit of this strategy early after MI. © 2005 The European Society of Cardiology. Published by Elsevier Ltd. All rights reserved.

## Introduction

Many studies have shown that total mortality and sudden death (SD) after acute myocardial infarction (MI) have significantly decreased in recent years, as a result of modern therapy [1]. Nevertheless, there is a subgroup of patients with recent MI which remains at high risk of dying in the first months or years after hospital discharge (overall mortality  $\geq 20\%$  at 2 years) [2]. SD due to the occurrence of sustained ventricular arrhythmia is the main contributor to total mortality in these high-risk post-MI patients, accounting for about 40% of all deaths [3]. It is therefore crucial to identify and protect patients with recent MI who are prone to serious ventricular arrhythmias during follow-up, in order to reduce both SD and all-cause mortality.

Researchers have identified several factors predictive of life-threatening ventricular arrhythmias in the post-MI period, such as low left ventricular ejection fraction (LVEF) [4], frequent and/or repetitive ventricular premature complexes (PVCs) [5], ventricular late potentials [6], decreased heart rate variability (HRV) [7], decreased baroreflex sensitivity, QT prolongation or dispersion, T-wave alternans, and inducibility of sustained ventricular arrhythmias during electrophysiological study (EPS) [8,9]. However, the real importance of these factors is still debated. Of the currently available antiarrhythmic therapies, only beta-blockers [10,11] and implantable cardioverter defibrillators (ICD) [12–14] have proved to

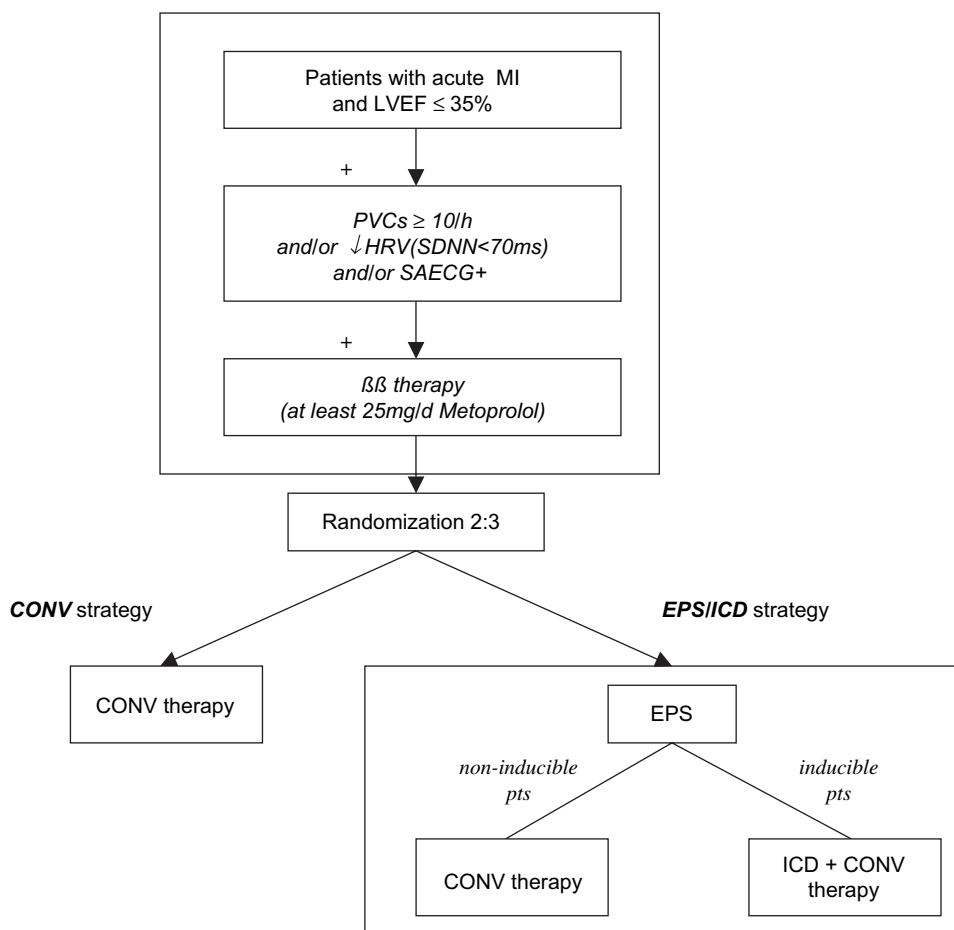
be highly effective in decreasing both SD and total mortality after MI. However, despite the clear evidence of their benefit, beta-blockers, even today, are relatively underused in post-MI patients [15]. Moreover, data on the prophylactic use of ICDs come from studies, such as MADIT, MUSTT and MADIT II, all performed in patients late after MI [12–14]. Therefore, the best risk stratification and the value of using ICDs prophylactically in patients with recent MI, optimally treated with beta-blockers, are not yet known. The BEST + ICD trial was planned and carried out in order to answer this question.

## Methods

The BEST + ICD trial is a double-arm observational randomised investigation, promoted by the Italian Association of Arrhythmology and Cardiac Pacing – AIAC to determine whether, in high-risk post-MI patients treated with beta-blockers at the maximum tolerated dosage, EPS-guided therapy – including the prophylactic implantation of ICD in inducible patients (EPS/ICD strategy) – is able to improve survival in comparison with conventional therapy (CONV strategy).

## Trial design, inclusion and exclusion criteria

The trial design is depicted in Fig. 1 and was described in detail in a previous report [16]. The



**Figure 1** Patient enrolment cascade. MI = myocardial infarction; LVEF = left ventricular ejection fraction; PVCs = premature ventricular complexes; HRV = heart rate variability; SDNN = standard deviation of normal QRS complex intervals; SAECG = signal-averaged electrocardiogram;  $\beta\beta$  = beta-blocker; CONV = conventional; EPS = electrophysiological study; ICD = implantable cardioverter defibrillator.

study protocol was approved by the ethics committee of each participating centre.

To be included in the study, patients who had survived an acute MI (5–30 days before enrolment) had to have an LVEF  $\leq 35\%$  on two-dimensional echocardiography, and one or more of the following additional non-invasive risk factors: a number of PVCs  $\geq 10/h$ ; a reduced HRV with standard deviation of normal QRS complex intervals – SDNN  $< 70$  ms, during 24-h Holter monitoring; positive signal-averaged electrocardiogram (defined as presence of  $\geq 2$  of the following criteria: filtered QRS complex duration  $> 114$  ms, root mean square voltage of the terminal 40 ms of the QRS complex  $< 20 \mu V$ , and duration of low amplitude signal  $< 40 \mu V > 38$  ms). Moreover, they had to be on and to tolerate therapy with metoprolol at a dosage of at least 25 mg/day; if possible, this dosage was increased during the run-in phase to a maximum of 200 mg/day or to a maximum tolerated dosage. We chose metoprolol as beta-blocking agent because

at the time the BEST + ICD trial was planned no data had been published on other beta-blockers in the post-infarction period.

The following conditions, besides contraindications or intolerance to metoprolol, constituted exclusion criteria from the study: (1) history of sustained ventricular arrhythmias associated or not associated with the acute MI (with the exception of primary ventricular fibrillation – VF); (2) non-sustained ventricular tachycardia (VT) ( $\geq 3$  consecutive beats) during 24-h Holter monitoring (MADIT screening was recommended for these patients); (3) residual myocardial ischaemia for which early myocardial revascularization (percutaneous transluminal coronary angioplasty – PTCA or coronary artery bypass grafting – CABG) was needed; (4) cardiogenic shock, severe hypotension, NYHA functional class IV; (5) life expectancy  $< 1$  year; (6) irreversible brain damage; (7) refusal or inability of the patient to participate in the study; (8) participation in other trials;

(9) long distance from the patient's residence to the referring centre, or other factors that made follow-up impossible.

After giving informed written consent, all eligible patients underwent administration of metoprolol and all the other drugs currently considered effective in post-MI patients, such as aspirin, angiotensin converting enzyme inhibitors, statins, etc. They were then randomised, in a 2:3 ratio, to two different therapeutic strategies: CONV strategy or EPS/ICD strategy (Fig. 1). Unlike those randomised to CONV strategy, patients randomised to EPS/ICD strategy were further stratified by means of EPS; those in whom a sustained ventricular arrhythmia was inducible on programmed ventricular stimulation were subsequently implanted with an ICD. Non-inducible patients did not receive an ICD and were treated as the patients assigned to CONV strategy.

### EPS protocol and ICD implantation

Immediately after randomisation, programmed ventricular stimulation was performed according to a stimulation protocol that included up to three extrastimuli using three different drive cycle lengths (600, 460, and 375 ms) from two right ventricular sites (apex and outflow tract). The coupling interval was never shortened to less than 200 ms. EPS was considered positive if sustained monomorphic VT ( $> 30$  s or requiring interruption because of haemodynamic compromise) or polymorphic VT  $> 120$  bpm or VF was induced. We anticipated a 35% induction rate of sustained ventricular arrhythmias in our patient population.

### Patient follow-up and study end-points

After hospital discharge, patients were followed up every 4 months. In accordance with the study protocol, the administration of any antiarrhythmic drug, including amiodarone, to prevent ventricular arrhythmias and SD after MI was not allowed. Antiarrhythmic drugs were permitted only for the treatment of supraventricular arrhythmias, when clinically indicated. At each follow-up visit, a patient history was taken and current therapy recorded, with particular focus on beta-blocker therapy and prescribed dose; in addition, baseline examination, standard 12-lead ECG and ICD follow-up were performed in patients implanted with an ICD.

The primary end-point of the BEST + ICD trial was all-cause mortality. Secondary end-points were SD, non-SD, non-cardiac death, resuscitated cardiac arrest, non-fatal sustained VT and appropriate and inappropriate shocks from the ICD in

implanted patients. SD was defined as occurring within 1 h of the onset of symptoms or during sleep if death was not witnessed and the patient had been seen in a healthy state before going to bed the previous night.

### Mortality expectations and sample size

We estimated a 20% two-year all-cause mortality in the CONV strategy arm vs 14% in the EPS/ICD-treated patients, which corresponds to a 30% reduction in mortality. Assuming a 3% cross-over from control to EPS-guided therapy and 0.3% per month loss of patients to follow-up, we calculated (with an  $\alpha$  error of 0.05 and a study power of 90%) a sample size of 1200 patients, 480 of whom would have to be randomised to the CONV strategy and 720 to EPS/ICD strategy. We anticipated having to screen approximately 14,000 patients with acute MI to reach the sample size.

### Statistical analysis

Data were analysed on the basis of "intention-to-treat" analysis. Student's *t*-test or non-parametric tests for quantitative variables, and the chi-square test or Fisher test for qualitative variables, were used to verify the real balance of the randomised groups. The survival analysis was performed using Kaplan–Meier curves. A two-tailed *P* value  $< 0.05$  was required for statistical significance.

### Log book

Most participating centres established a log book to record the data on all patients with acute MI admitted to the Coronary Care Unit (CCU) during the recruitment period.

## Results

### Screening log

A screening log was kept in 45 participating centres on patients with acute MI admitted to the CCU from July 1998 to February 2003. Fifteen thousand five hundred and seven patients were registered. The value of LVEF during CCU stay was available for 10,724 patients; of these, 1190 (11.1%) had an LVEF  $\leq 35\%$  and 781 (7.3%) an LVEF  $\leq 30\%$ .

Reasons for exclusion are known for 1124 patients with LVEF  $\leq 35\%$ . Beta-blocker therapy was contraindicated or not tolerated in 17.7% of the patients. The second greatest cause of exclusion

**Table 1** Causes of exclusion in 1124 patients with LVEF  $\leq$  35%

Cause of exclusion	%
Beta-blocker intolerance or contraindication	17.7
Revascularisation <sup>a</sup>	16.3
Non-sustained VT	7.0
Cardiogenic shock	5.3
Death during run-in period	5.6
Severe cerebral damage or life expectancy < 1 year	6.2
Other medical reasons	1.9
Reasons other than medical (consent refusal, age over 80, geographical, etc.)	40.0

LVEF = left ventricular ejection fraction; VT = ventricular tachycardia.

<sup>a</sup> Before the November 1, 1999 amendment, which established that primary and rescue percutaneous transluminal coronary angioplasty were not exclusion criteria.

was the need for early mechanical or surgical revascularisation, which accounted for 16.3% of cases. Other causes of exclusion are reported in Table 1.

One thousand and sixty patients with acute MI and LVEF  $\leq$  35% underwent additional non-invasive risk stratification. At least one risk factor was found in 975 (92%) patients.

### Patient flow and clinical characteristics

One hundred and forty three patients were randomised (in 32 centres) to the CONV ( $n = 60$ ) or EPS/ICD arm ( $n = 83$ ). No follow-up data could be obtained for five patients (one in CONV arm and four in EPS/ICD arm). Therefore, 138 patients (59 CONV and 79 EPS/ICD) were finally analysed. This number is substantially lower than the target calculated for the sample size and led to the early interruption of the study after the first interim analysis was performed in January 2003. The main reasons for trial termination were the lower than expected recruitment rate and the contemporary publication of MADIT II results [14].

The clinical characteristics of the randomised patients are listed in Table 2. No statistically significant differences were found between the two study arms for any of the parameters examined. In 80 of the 138 randomised patients, the three additional non-invasive risk factors were evaluated: in 43 patients (54%) only one risk factor was detected; in 29 (36%) two risk factors, and in eight (10%) three risk factors.

One patient initially randomised to the CONV arm had an episode of non-sustained VT soon after enrolment, underwent EPS and received an ICD. On the basis of the "intention-to-treat" principle, this patient was analysed in the CONV arm.

### Results of EPS

Of the 79 patients randomised to EPS/ICD, three did not undergo EPS (one refused to consent to the procedure, one had worsening of angina and underwent surgical revascularization, and one had occurrence of refractory heart failure). Thus, only 76 patients underwent EPS. A sustained ventricular arrhythmia was induced in 24 patients (32%). All these patients underwent ICD implantation. The remaining 52 non-inducible patients (68%) were treated with optimal medical therapy exactly like the patients allocated to the CONV arm. The type of induced arrhythmia was monomorphic sustained VT in 18 patients (75%), polymorphic sustained VT in one patient (4%) and VF in five patients (21%). The sustained ventricular arrhythmia was induced by means of two extrastimuli in 11 patients (46%) and three extrastimuli in 13 patients (54%). The mean ( $\pm$  SD) cycle length of induced monomorphic sustained VT was  $448 \pm 115$  ms. The induced arrhythmia was interrupted by anti-tachycardia pacing in six patients (25%) and by electrical cardioversion in 16 patients (67%); in two patients (8%) the induced arrhythmia reverted spontaneously 30 s after the onset.

Arrhythmia inducibility on EPS was not associated with the presence of any of the additional non-invasive risk factors.

### ICD implantation and therapy on discharge

All 24 inducible patients underwent ICD implantation within 3 days after EPS. No deaths occurred in this period of time. None of the 24 patients who received an ICD had implantation-related complications.

The therapy on discharge is reported in Table 3. No differences were found between the two study arms with regard to any of the drug classes examined. In particular, the mean dosage of metoprolol was  $67.2 \pm 35.9$  mg/day in the CONV arm and  $68.6 \pm 43.5$  mg/day in the EPS/ICD arm ( $P = 0.8$ ).

### Follow-up data

The mean duration ( $\pm$  SD) of follow-up was  $540 \pm 403$  days. During this period there were no substantial changes in the therapy in either study

**Table 2** Clinical and demographic characteristics of the study population

	CONV (n = 59)	EPS/ICD (n = 79)	All (n = 138)	P value
Male sex (%)	72.9	69.6	71.0	0.6761
Age (years)	66.3 ± 10.5	66.5 ± 9.0	66.5 ± 9.6	0.8939
Previous MI (%)	30.5	41.0	36.5	0.2055
Previous revascularization (%)	6.8	11.4	9.4	0.3588
History of HF (%)	13.8	8.9	10.9	0.3610
HF in CCU (%)	56.1	47.4	51.1	0.3176
Serum creatinine (mg/dl)	1.5 ± 0.9	1.3 ± 0.5	1.4 ± 0.7	0.2343
Systolic blood pressure (mmHg) <sup>a</sup>	120 ± 18	119 ± 15	119 ± 16	0.8220
Heart rate (BPM) <sup>a</sup>	71 ± 13	73 ± 12	72 ± 12	0.2480
LVEF (%)	31.4 ± 4.2	30.8 ± 4.0	31.1 ± 4.1	0.4464
PVC ≥ 10/h (%) <sup>b</sup>	57.9	47.4	51.9	0.2297
SDNN < 70 ms (%) <sup>c</sup>	58.8	65.8	62.9	0.4318
Positive SAECG (%) <sup>d</sup>	55.6	59.2	57.6	0.7380
Anterior acute MI (%)	59.3	62.0	60.9	0.7475
QRS > 120 ms (%)	35.3	33.3	34.1	0.8518
QRS > 150 ms (%)	8.8	11.8	10.6	0.6659
LBBB in CCU (%)	3.4	8.9	6.5	0.3003 <sup>^</sup>
AF in CCU (%)	24.6	19.2	21.5	0.4564
Thrombolytics (%)	30.5	44.3	38.4	0.0993
Primary PTCA (%)	15.3	15.2	15.2	0.9917
Rescue PTCA (%)	8.5	10.1	9.4	0.7424

CONV = conventional strategy; EPS/ICD = electrophysiological study/implantable cardioverter defibrillator strategy; MI = myocardial infarction; HF = heart failure; CCU = coronary care unit; LVEF = left ventricular ejection fraction; PVC = premature ventricular complexes; SDNN = standard deviation of normal QRS complex intervals; SAECG = signal-averaged electrocardiogram; LBBB = left bundle branch block; AF = atrial fibrillation; PTCA = percutaneous transluminal coronary angioplasty.

<sup>a</sup> On baseline examination.

<sup>b</sup> Calculated for 135 patients.

<sup>c</sup> Calculated for 124 patients.

<sup>d</sup> Calculated for 85 patients.

group (Table 3); the mean dosage of metoprolol at the last follow-up visit was 63.1 ± 52.1 mg/day in the CONV arm and 63.1 ± 48.4 mg/day in the EPS/ICD arm ( $P = 1$ ).

Considering the 24 patients implanted with an ICD, the mean dosage of metoprolol was 82.7 ± 54.7 mg/day at discharge and 86.1 ± 33.3 mg/day at the last follow-up.

### Mortality

During follow-up, 26 patients (19%) died: nine (6.5%) SD, nine (6.5%) non-SD, and four (3%) non-cardiac deaths. In four patients (3%) the cause of death was unknown. There were no statistically significant differences between the two study groups, either in total mortality (13 patients in CONV arm [22%] vs 13 patients in EPS/ICD arm [16%],  $P = 0.4$ ), or in SD (five patients in CONV arm [9%] vs four patients in EPS/ICD arm [5%],  $P = 0.5$ ).

The Kaplan–Meier estimates of overall mortality and SD mortality are reported in Fig. 2A and B. For all patients, actuarial overall mortality was 14% after 1 year and 24% after 2 years. The corresponding values for the CONV and EPS/ICD arms were 18% and 11% after 1 year ( $P = 0.3$ ) and

29.5% and 20% after 2 years ( $P = 0.2$ ), respectively. For all patients, actuarial SD mortality was 5% after 1 year and 9% after 2 years. The corresponding values for the CONV and EPS/ICD arms were 8% and 3% after 1 year ( $P = 0.2$ ) and 11% and 7.5% after 2 years ( $P = 0.4$ ), respectively.

Of the 24 patients with ICDs, five (21%) died during a mean (±SD) follow-up of 566 ± 379 days. Of these, one (4%) suffered SD and three (12.5%) non-SD; in one patient (4%) the cause of death was unknown. Among the 52 non-inducible patients, overall mortality was lower (15%, during a mean [±SD] follow-up of 597 ± 392 days) and SD mortality was higher (6%) than among the inducible patients. We also calculated the Kaplan–Meier estimates for overall survival and SD survival of the 24 ICD patients vs the remaining 114 patients who received only CONV therapy. There were no statistically significant differences between the two study groups (Fig. 3A and B).

### ICD intervention and arrhythmic events

The device intervened in five (21%) patients; two of these underwent both appropriate and inappropriate ICD therapy, one had only appropriate

**Table 3** Therapy on discharge and at the last follow-up examination

	CONV (n = 56) (%)	EPS/ICD (n = 67) (%)	All (n = 123) (%)	P value
<b>Therapy on discharge</b>				
Ace-inhibitors	86	78	81	0.2511
Digoxin	27	30	29	0.7075
Diuretics	79	81	80	0.7810
Aspirin	84	79	81	0.4944
Other antiplatelet/anticoagulant agents	23	18	20	0.4667
Nitrates	88	97	93	0.0778 <sup>a</sup>
Calcium channel blockers	11	6	8	0.5098 <sup>a</sup>
Statins	27	18	22	0.2363
Amiodarone	7	6	7	1 <sup>a</sup>
<b>Therapy at last follow-up</b>				
	CONV (n = 59) (%)	EPS/ICD (n = 79) (%)	All (n = 138) (%)	
Ace-inhibitors	78	79	78	0.9422
Digoxin	36	29	32	0.4191
Diuretics	85	84	84	0.8487
Aspirin	81	83	82	0.8540
Other antiplatelet/anticoagulant agents	32	24	28	0.2888
Nitrates	80	77	78	0.7304
Calcium channel blockers	14	8	10	0.2509
Statins	24	25	25	0.8304
Amiodarone	12	11	12	0.9317

CONV = conventional strategy; EPS/ICD = electrophysiological study/implantable cardioverter defibrillator strategy.

<sup>a</sup> Fisher exact test.

therapy and two had only inappropriate therapy. In total, the therapy delivered was appropriate in three cases (12.5%) and inappropriate in four (16.5%). When appropriate, the cause of ICD intervention was sustained VT in all cases; intervention consisted of anti-tachycardia pacing in two cases and of DC shock in 1 case. When inappropriate, the cause of ICD intervention was paroxysmal atrial fibrillation in three cases (12.5%) and paroxysmal atrial tachycardia in one case (4%).

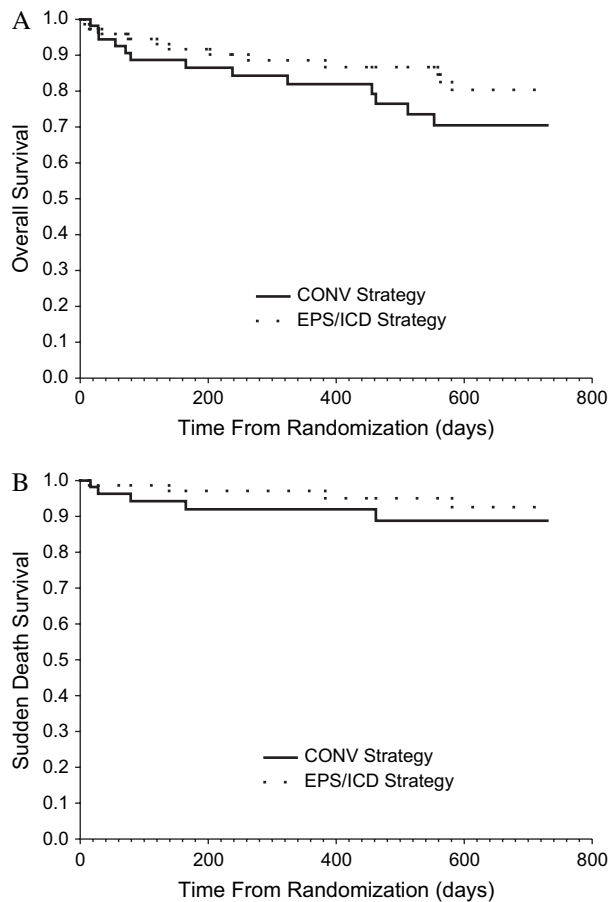
No episodes of resuscitated cardiac arrest or symptomatic sustained VT occurred in CONV arm patients or in non-inducible EPS/ICD arm patients.

## Discussion

### Main finding

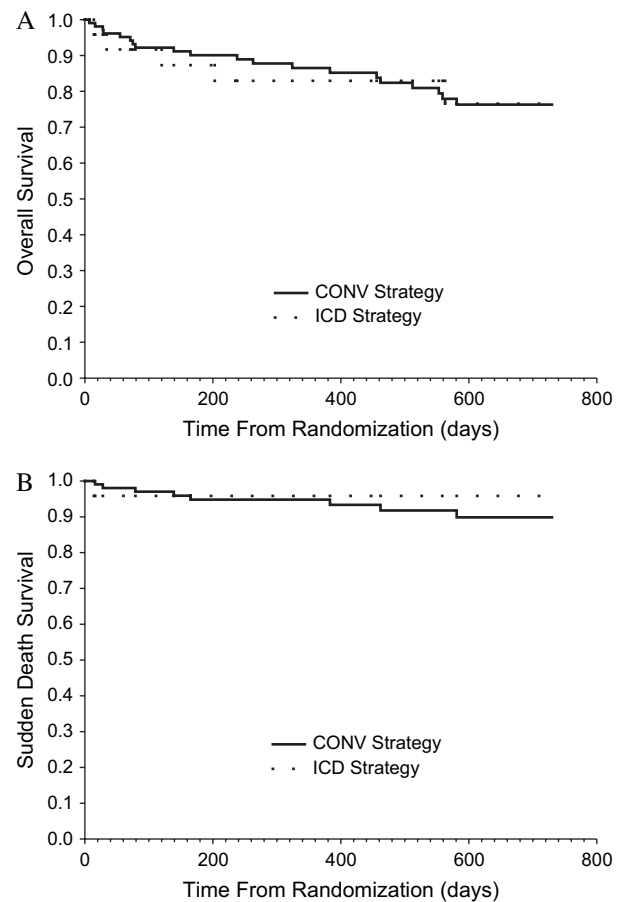
Our study showed a trend in favour of EPS/ICD vs CONV strategy in a population of high-risk survivors following acute MI. However, despite screening over 15,000 patients, we encountered difficulties in enrolment that obliged us to end the study with only 12% of the target population randomised. Our data are therefore insufficient to prove or disprove our hypothesised survival benefit.

The unique feature of the BEST + ICD trial is that, in contrast to all previously reported post-MI studies, 100% of the patients were on beta-blockers. Another important aspect is that until now no randomised study has evaluated the usefulness of a combined strategy based on non-invasive and invasive risk stratification and subsequent implantation of an ICD in high-risk patients early after acute MI. Moreover, in the BEST + ICD trial, we found that the overall mortality of survivors of an acute MI remains high (16% at 1 year and 24% at 2 years), even when they are treated with optimal medical therapy. This indicates that the population we selected for the trial truly constitutes a high-risk subgroup of patients with recent MI, who deserve to be identified and efficaciously protected by preventive measures. Finally, the results of the BEST + ICD trial are consistent with those found in two recent studies: a sub-analysis of the MADIT II trial [14] and the DINAMIT study [18]. The first revealed that the benefit of ICD therapy improves as a function of time post-MI; in particular, in MADIT II, patients enrolled 1–17 months after MI (the period of time for which our patients were followed up) had a lower, and not statistically significant, benefit from ICD therapy when compared with patients enrolled in subsequent periods, which demonstrated increased hazard ratios in



**Figure 2** Kaplan–Meier estimates of overall survival (panel A) and sudden death survival (panel B) for the conventional (CONV) strategy arm and for the electrophysiological study/implantable cardioverter defibrillator (EPS/ICD) strategy arm.

favour of ICD therapy. The second, the DINAMIT trial, showed no benefit of ICD implantation over conventional therapy in a group of high-risk patients with recent MI similar to our study population (LVEF  $\leq 35\%$ , reduced HRV or elevated heart rate, MI initiated  $< 40$  days before). We can therefore speculate that, at later times after the index MI, our patients might also have shown a better outcome. Thus, despite its non-significant results, the BEST + ICD trial may be considered an important



**Figure 3** Kaplan–Meier estimates of overall survival (panel A) and sudden death survival (panel B) for the 24 inducible patients who received an implantable cardioverter defibrillator (ICD) and for the remaining 114 patients who received only conventional (CONV) therapy.

pilot study, which should stimulate further trials involving a greater number of patients and a longer follow-up to assess the real value of EPS/ICD therapy in high-risk survivors of acute MI.

### Reasons for low recruitment rate and new epidemiological findings

The most striking epidemiological feature of the BEST + ICD trial is probably the far lower

**Table 4** Exclusion due to recent developments in therapy (see [Methods](#))

Development	Expected % (before 1997)	Observed % (1999–2002)
Systolic function preservation (LVEF $> 35\%$ )	81	89.1
No additional risk factor	20	8
PTCA during run-in period	7	16.3
Non-sustained VT	20	7
Beta-blocker contraindication or intolerance	23	17.7

LVEF = left ventricular ejection fraction; PTCA = percutaneous transluminary coronary angioplasty; VT = ventricular tachycardia.



incidence (11.1%) of severely depressed LVEF than that consistently reported in the literature at the time the trial was planned (Table 4) [16]. This certainly reflects the recent great advances in early post-MI management [1], which have successfully prevented excessive left ventricular deterioration in many patients. This far lower number of patients with severely depressed LVEF was one of the main obstacles to achieving our target in patient randomisation. Another important factor was the higher percentage of acute percutaneous transluminal coronary angioplasties (16.3% vs the 7% which had been calculated at the time of study design) [16]. On the other hand, fewer patients were excluded because of non-sustained VT (7% vs 20%) or beta-blocker intolerance (17.7% vs 23%) or presented with no additional risk factors (8% vs 20%). All this provides further confirmation of the current good standard of treatment of acute MI in the hospitals participating in the study.

### Minor findings

Considering that currently approximately 11% of survivors of an acute MI have an LVEF  $\leq$  35%, and that half of these were excluded in the BEST + ICD trial for various reasons (absence of additional non-invasive risk factors, co-morbidity, etc.), we can assume that the proportion of patients following recent MI who are potential candidates for EPS/ICD strategy is about 5% of the whole population of patients. This represents a large number of patients in absolute terms. Moreover, according to our data, more than 7% of survivors of an acute MI have an LVEF  $\leq$  30% and, thus, theoretically meet the MADIT II criteria for ICD implantation [14], provided that these criteria can be applied to the early phase of acute MI.

In our study, more than 90% of patients with LVEF  $\leq$  35% had at least one of the following additional non-invasive risk factors: high hourly rate of PVC, reduced HRV, and ventricular late potentials. On the basis of this finding, doubts may be raised about the clinical usefulness of non-invasive testing in addition to LVEF assessment in selecting post-MI patients eligible for EPS or ICD implantation. This is in contrast with the conclusions of previous studies [7,9,12,13,21] but is in accordance with the MADIT II strategy [14].

In our patients with recent MI, we found a rate of induction of sustained ventricular arrhythmias by programmed electrical stimulation (32%) comparable with that reported in previous studies [8,13]. However, VF was observed in only 7% of the patients who underwent EPS (corresponding to 21% of the

inducible patients), a value lower than that reported in the literature [8]. It, therefore, seems that optimal treatment with beta-blockers is unable to reduce the rate of induction of sustained ventricular arrhythmias, but probably contributes to minimising the most life-threatening forms. The well-known anti-fibrillatory effect of beta-blockers [20] may also explain the lack of intervention of ICD for VF during the follow-up. However, as demonstrated in the MADIT II sub-study [17], the risk apparently increases with time after MI.

Overall mortality during follow-up was higher in inducible patients than in non-inducible patients (21% vs 15%), thus confirming that inducibility is an important indicator of a worse prognosis [8,9,19,20,22]. However, the excess in mortality in our inducible patients was exclusively due to an increased incidence of non-SD and non-cardiac death, whereas SD mortality was lower (4% vs 6%), in accordance with DINAMIT results [18]. The most likely explanation for this is that ICD implantation in inducible patients and the intervention of the device for sustained VT in three of them may have avoided some arrhythmic deaths, thereby allowing a greater proportion of patients to die from progressive heart failure or other causes.

### Conclusion

Our study showed a trend, but was inadequately powered to determine whether the EPS + ICD strategy should be implemented soon after MI or delayed until a later phase. This important question remains to be answered by future studies.

### Appendix A

*Steering Committee:* MG Bongiorno, Pisa (Italy); M Brignole, Lavagna (Italy); R Cappato, S. Donato Milanese (Italy); A Capucci, Piacenza (Italy); F Gaita, Asti (Italy); M Gulizia, Catania (Italy); S Mangiameli (Chairman), Catania (Italy); AS Montenero, Milano (Italy); RFE Pedretti, Tradate (Italy); A Raviele (Chairman), Mestre (Italy); JA Salerno, Varese (Italy); S Sermasi, Rimini (Italy).

*Writing Committee:* F Barbieri, Milano (Italy); M Brignole, Lavagna (Italy); M Gulizia, Catania (Italy); AS Montenero, Milano (Italy); S Nisam, Brussels (Belgium); RFE Pedretti, Tradate (Italy); G Raciti, Milano (Italy); A Raviele, Mestre (Italy).

*Data and Safety Monitoring Board:* H Klein, Magdeburg (Germany); P Rizzon, Bari (Italy).

*Clinical Advisory Board:* M Chiariello, Napoli (Italy), S Nisam, Brussels (Belgium).

*Monitoring and data analysis:* Quintiles srl, Milan (Italy); L Calvano, F Forini, T Usari.

*Participating centres:* The following centres and investigators participated in the BEST + ICD trial (the numbers in brackets indicate the number of patients enrolled) Italy: Ospedale Umberto I°, Mestre – A Raviele, P Della Valentina (48); Ospedale Civile, Piacenza – A. Capucci (11); Presidio Ospedaliero, Rovigo – F Zanon (10); Ospedali Riuniti, Lavagna – M Brignole (6); Ospedale Ferrarotto, Catania – V Calvi (6); Ospedale Garibaldi, Catania – S Mangiameli (6); Ospedale S Gerardo, Monza – A Vincenti (6); Ospedale di Circolo, Varese – NF Forgiore (5); Ospedale Santa Croce e Carle, Cuneo – C Bruna (5); Arcispedale S Maria Nuova, Reggio Emilia – C Menozzi (4); Ospedale Maggiore della Carità, Novara – E Occhetta (4); Ospedale SS Annunziata, Taranto – N Baldi (3); Ospedale Ca' Foncello, Treviso – R Mantovan (3); Ospedale Celesia, Rivarolo – S Setti (3); Ospedale Maggiore, Bologna – D Bracchetti (2); Ospedale S Andrea, Vercelli – M Gronda (2); Ospedale degli Infermi, Rimini – S Sermasi (2); Ospedale Sant'Andrea, La Spezia – D Bernabò (1); Ospedale. S Spirito, Roma – V Ceci (1); Casa Sollievo della Sofferenza, S Giovanni Rotondo – R Fanelli (1); Ospedale Civile, Asti – F Gaita (1); Ospedale Bolognini, Seriate – P Giani (1); Ospedale Civile, Legnago – D Igidbashian (1); Ospedale S Croce, Moncalieri – M Marcolongo (1); Ospedale S Maria, Terni – AS Montenero (1); Presidio Ospedaliero, Monfalcone – T Morgera (1); Ospedale Generale, Gorizia – G Nicotra (1); Ospedale Morgagni, Forlì – A Pettini (1); Ospedale dei Poveri Infermi, Borgosesia – G Rognoni (1); Ospedale S Maria degli Angeli, Pordenone – F Zardo (1).

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