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## One-year results of the randomized, controlled, short-term psychotherapy in acute myocardial infarction (STEP-IN-AMI) trial

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### ABSTRACT

**Background:** Previous studies on cognitive and interpersonal interventions have yielded inconsistent results in ischemic heart disease patients.

**Methods:** 101 patients aged  $\leq 70$  years, and enrolled one week after complete revascularization with urgent/emergent angioplasty for an AMI, were randomized to standard cardiological therapy plus short-term humanistic–existential psychotherapy (STP) versus standard cardiological therapy only.

Primary composite end point was: one-year incidence of new cardiological events (re-infarction, death, stroke, revascularization, life-threatening ventricular arrhythmias, and the recurrence of typical and clinically significant angina) and of clinically significant new comorbidities. Secondary end points were: rates for individual components of the primary outcome, incidence of re-hospitalizations for cardiological problems, New York Heart Association class, and psychometric test scores at follow-up.

**Results:** 94 patients were analyzed at one year. The two treatment groups were similar across all baseline characteristics. At follow-up, STP patients had had a lower incidence of the primary endpoint, relative to controls (21/49 vs. 35/45 patients;  $p = 0.0006$ , respectively; NNT = 3); this benefit was attributable to the lower incidence of recurrent angina and of new comorbidities in the STP group (14/49 vs. 22/45 patients,  $p = 0.04$ , NNT = 5; and 5/49 vs. 25/45,  $p < 0.0001$ , NNT = 3, respectively). Patients undergoing STP also had statistically fewer re-hospitalizations, a better NYHA class, higher quality of life, and lower depression scores.

**Conclusion:** Adding STP to cardiological therapy improves cardiological symptoms, quality of life, and psychological and medical outcomes one year post AMI, while reducing the need for re-hospitalizations. Larger studies remain necessary to confirm the generalizability of these results.

**Clinical trial registration:** ClinicalTrials.gov: NCT00769366

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### 1. Introduction

Psychosocial issues have been shown to be critical predisposing and/or precipitating factors for acute myocardial infarction [1], likely due to both a higher frequency of adverse health behaviors and to specific pathophysiological mechanisms involving coagulation factors and platelet activation, as well as the neuroendocrine and immune systems [2–4].

On this basis, a variety of randomized behavioral and psychosocial intervention trials have been performed in cardiac patients to assess for possible effects on medical and psychological prognosis. However, across the numerous meta-analyses that have been published on the subject, the results have been inconsistent and conclusions controversial [5–9]. Principally, the heterogeneity between previous studies concerning diverse approaches to interventions – procedural, medicinal and psychotherapeutic – outlines the need to consider different classes of approach separately. Concerning psychotherapy, several methods have been tested, chiefly behavioral, cognitive and interpersonal therapy; they have proven to be effective at improving psychological symptoms [10–13], but there is uncertainty about their efficacy in terms of medical and cardiac prognosis. Assessments of humanistic–existential psychotherapy approaches remain missing, but this therapy is more difficult to standardize across different psychotherapists because of its specific characteristics.

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<sup>2</sup> Each individual author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

From a cardiological perspective, enrolling heterogeneous classes of cardiac patient (lumping together different patterns of non-ischemic and ischemic heart disease, including infarcted and non-infarcted, or unstable and stable patients) has also been a concern in individual trials [14,15], while the study of selected patients with acute myocardial infarction, the first cause of cardiac morbidity and mortality, remain unaddressed. To address these shortfalls, we performed, for the first time, a randomized, controlled study to preliminarily assess the efficacy of an original short-term psychotherapy (STP), highly standardized by being delivered by a single operator, in a selected population of patients with recent myocardial infarction treated with an urgent or emergent percutaneous coronary intervention. As STP, we utilized a form of humanistic–existential psychotherapy derived from the ontopsychological approach [16] and adapted to the setting of cardiac patients.

2. Methods

The STEP-IN-AMI trial is an open label, superiority, 1:1 randomized controlled trial of a non-pharmacological intervention. The report for this study has been written in compliance with the extension of the CONSORT statement for randomized trials of non-pharmacologic interventions [17]. A detailed description of the final STEP IN AMI trial protocol has been published elsewhere [18], though the design is recapitulated in Fig. 1, in accordance with a previously described method [19].

The study was approved by the local ethics committee of our institution, and all subjects provided signed informed consent before taking part.

In brief, 101 patients aged ≤70 years and admitted to our hospital for AMI were randomized either to receive or not to receive additional short-term psychotherapy on top of standard contemporary treatment for AMI. The AMI had to be treated in the acute phase with primary or urgent PCI of the culprit lesion, within 12 h of the onset of an ST elevation-associated MI (STEMI, primary PTCA), or within 48 h in patients with a non-STEMI (urgent PTCA). In cases of multi-vessel disease, complete revascularization had to be achieved before discharge from hospital. The study was performed at our institution, a tertiary hospital with high annual volumes of percutaneous coronary interventions. In order to obtain a comprehensive picture of psychological conditions, the following psychometric tests were administered to all patients at enrollment and after one year: 1) *Self evaluation test*, assessing global level of psychological distress over the preceding two weeks [20]; 2) *Modified Maastricht Questionnaire*, specifically assessing levels of vital exhaustion [19,21]; 3) *Social Support Questionnaire*, evaluating each individual's perception of his/her social network [20,22]; 4) *Recent Life Change Questionnaire*, evaluating the presence and importance of occasional major life events and chronically recurring aggravations in daily life [23]; 5) *Beck Depression Inventory (BDI)*, evaluating for symptoms of major or minor depression [24,25], where a score between 10 and 15 was considered indicative of mild depression, and a score equal or superior to 16 was considered indicative of clinically relevant depression; and 6) *The MacNew Heart Disease Health-Related Quality of Life Questionnaire*, assessing the patient's quality of life related to three specific domains – emotional, physical and social – as well as providing a global QOL score [26]. All data were collected using specific case-report forms and peer-reviewed at one-year follow-up, with clinical adverse events adjudicated by a committee composed of three cardiologists (CP, VP, and FP) blinded to study arm allocation.

2.1. Randomization and interventions

The STEP-IN-AMI trial was initially designed and approved by the local ethics committee in 2004, at which time the intention was to enroll 240 patients. However, because a single psychotherapist was used to perform all psychotherapy, the rate of subject inclusion was too slow to allow for completion of the study at that scale. Consequently, the protocol was amended after the start of randomization, reducing the number of subjects; since then, the latest version of the study protocol has been published [18]. Based upon previous studies, a 60% incidence of the primary composite endpoint was expected in the control group; therefore, hypothesizing a 50% reduction in this incidence within the psychotherapy arm – it was sufficient to randomize 84 patients to achieve statistical significance with 95% confidence and 80% power. Taking into account losses to follow-up, which were difficult to anticipate in a psychological intervention study, it ultimately was decided to randomize 100 patients.

To minimize potential imbalance between the two groups and resultant confounding that might affect outcomes, randomization was performed in blocks (according to patient age, and the type and location of the infarction) within one week after discharge from the intensive care unit. To avoid introducing imbalances in the study blocks, the initial randomization scheme based upon 240 patients was not altered after the study was resized. In order to conceal the sequence of allocation, individual allocation to treatment was reported in case-report forms, which were sealed in envelopes and subdivided into different boxes according to randomization blocks. At the time of randomization, the relevant envelope was then given to the attending physician and the case-report form could then be unsealed revealing treatment allocation.

The choice of drug therapy in the acute and chronic phases was left to the treating physician's discretion. Administration of psycho-active drugs was not part of the protocol; but, in patients already being treated, psychiatric drugs were not discontinued after enrollment.

To maximize standardization of therapy, psychotherapy was performed by a single skilled and licensed psychotherapist (AR), with the help of clinical staff, both psychologists and nurses. We utilized STP, derived from the ontopsychological method and specifically adapted by the psychotherapist herself to the context of research in the field of cardiac psychology. We developed a standardized, basic model of STP that could be reproduced and delivered easily within the context of the Italian national health care system. The ontopsychological method [16] is a complex and original synthesis derived from psychoanalysis, analytical psychology and humanistic–existential methods, as elaborated by Abraham Maslow [27]. With this approach, the human being is considered a complex system consisting of a unity of psyche and body, where anything happening in the body may influence the psyche and vice versa, as demonstrated by several studies in the field of psycho-neuro-endocrine-immunology [28–31]. With this view, a psychotherapeutic intervention must improve global health to be considered effective.

Psychotherapy was delivered initially in individual and then group sessions over a 6-month period after the incident AMI. Individual meetings focused on personal history, as emotionally lived by the patient, and on understanding basic expression of the unconscious dimension, through the interpretation of body and oneiric language. The number of individual meetings was tailored to the specific needs and problems of each patient, ranging from 3 to 11 meetings over a 3-month period. The shortest cycle, which was 3 sessions, involved a 31-year old man, who exhibited great resistance to the analysis; whereas the longest cycle of 11 sessions occurred with a 56-year old man with clinically relevant depression and two suicide attempts.

Over the duration of this brief course of treatment, the psychotherapist helps the patient to gain insights and elaborate on conflicts that need to be resolved, as well as on dysfunctional behaviors and interpersonal relationships. After the initial interviews, aimed at focusing on and overcoming main conflicts in the patient's life, the psychotherapist helps the patient to gain insights into his/her body sensations. Generally, cardiac patients

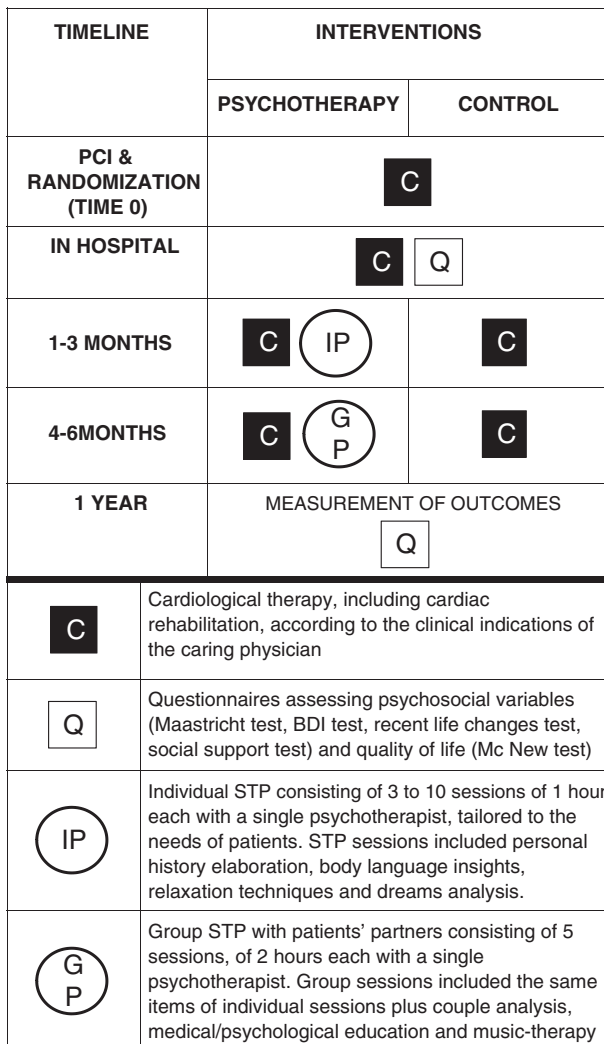


Fig. 1. Study design.

report a distorted and partial perception of their body, their body often perceived as foreign. The psychotherapist guides the patient to acquire full contact with his/her body, starting from the visceral zone, with the help of abdominal breathing and relaxation techniques. In the final phase of the individual meetings and whenever possible, the psychotherapist guides the patient into deeper insights through dream analysis. Generally, patients who have suffered a recent myocardial infarction report having experienced nightmares, often starting several months or even years before the acute event; or, alternatively, finding it impossible to remember dreams (often, patients only recall a few dreams from their childhood and/or adolescence). As the psychotherapist helps the patient to contact the central positive nucleus of their unconscious (the “*In Se*”), their nightmares cease and/or the patient resumes remembering dreams related to their real-life problems. This reflects inner changes orchestrated by the patient.

The psychotherapeutic work done during the individual sessions is reiterated during group sessions, where the analysis and goals achieved in the individual sessions can be reinforced via exchanges between group members. Group sessions to which partners are invited entail educational cardiological therapy (which includes a broader explanation of myocardial infarction and atherosclerotic processes, while accentuating the importance of cardiac risk factor prevention/reduction and lifestyle changes); music-guided breathing and muscular relaxation; comprehension of body signals; elements of oneiric language; and attention to specific partner/relationship issues. In this study, five group sessions were delivered over a 3-month period.

The aim of all these processes was to stabilize the pathology and promote global well-being within each patient.

All patients were invited to participate in a cardiac rehabilitation program; those who refused the program received educational training and lifestyle change recommendations.

## 2.2. Outcomes and follow-up

For all patients, clinical follow-up was performed at six months and one year, and reported on the case-report forms.

Based upon a previous meta-analysis on the subject [5] and taking into account potential systemic effects of psychotherapy that might not be necessarily confined to cardiovascular outcomes, as explained before, we chose a primary study endpoint consisting of the net cumulative incidence of new cardiological events (i.e., myocardial re-infarction, death, stroke, any revascularization procedure, life-threatening ventricular arrhythmias, and recurrence of typical angina pectoris) and the occurrence of any clinically significant new co-morbidity at one and five year in both study arms. This report focuses on the outcomes at one year.

Secondary endpoints at follow-up were: breakdown analysis of individual outcomes of the primary endpoint; the incidence of new hospital admissions for cardiological and/or medical reasons; ejection fraction as measured by echocardiography; ventricular volumes and wall motion score index; prevalence of NYHA class  $\geq$  II; changes in psychometric test scores; changes in quality of life scores; and correlations between psychological descriptors and clinical variables.

Major adverse cardiological and cerebrovascular events (MACCE) were defined as death, stroke, myocardial re-infarction, or any revascularization procedure.

Recurrence of angina was defined as the recurrence of typical, severe chest pain during effort or at rest, significantly and objectively affecting normal daily activities (e.g., work capacity impairment, inability to cope, severe exercise limitations) and warranting an increase in baseline cardiological therapy and/or requiring hospitalization.

In order to include possible non-cardiovascular, systemic effects of psychotherapy, comorbidities were defined as any new non-cardiological condition significantly impairing normal daily activities, requiring hospitalization, or needing specific and permanent drug treatment.

According to these a priori definitions, the clinical adverse-event committee adjudicated endpoints on an individual basis at case-report form data review after one-year follow-up and after database locking. At that time, the following new-onset non-cardiological events were adjudicated: major depression, generalized anxiety disorder, acute hepatitis, arterial hypertension, renal failure, type II diabetes mellitus, acute bronchial asthma, severe lumbago, hip arthritis, respiratory failure, cancer, herpes zoster resulting in severe pain, renal colic with and without calculi, a bladder stone with severe hematuria, an inguinal hernia requiring urgent surgical repair, severely hemorrhagic hemorrhoids, intermittent claudication of the lower legs, severe perianal abscess requiring hospitalization, viral pleuro-pericarditis, thorax basalioma, and global transient amnesia with ischemic brain lesions detected on magnetic resonance imaging (MRI).

## 2.3. Statistical analysis

Unless otherwise specified, all study data were analyzed on an intention-to treat basis.

Continuous variables for each of the study groups are reported as means (standard deviations or 95% confidence intervals) or as medians [lower quartile-upper quartile], as appropriate; categorical variables are reported as absolute numbers and percentages. Continuous unpaired variables were compared using independent-sample Student's *t* or Mann-Whitney *U* tests, as appropriate. Continuous paired variables were compared using paired Student's *t* or Wilcoxon tests, as appropriate. Categorical variables were compared by Pearson's chi-square analysis or Fisher's exact test, again, as appropriate. Multivariable binary logistic regression analysis was performed to appraise the independent predictive role of psychometric test scores on the primary outcome; variable selection for the final multivariable model was performed using a backward stepwise algorithm with statistical significance fixed at  $p < 0.10$ , while including other variables

deemed to be clinically significant and/or potentially conditioning outcomes. Survival free from the primary endpoints in the two study groups was analyzed via semi-parametric Cox proportional hazards ratios. Proportional hazards assumptions were tested by inspecting log-minus-log curves. A *p* value  $< 0.05$  was considered statistically significant, with all inferential tests 2-tailed. Statistical analysis was performed using SPSS version 11.5 (SPSS Inc., Chicago, Illinois).

## 3. Results

Enrollment was begun in June 2005 and ended in January 2011, as per the designed protocol [11] which, in order to allow for management of the study by a single psychotherapist, suspended study recruitment after each group of ten patients were enrolled, until each subgroup of five patients randomized to STP had finished its psychotherapy cycle. Therefore, pooling together all enrollment phases and excluding the phases of psychotherapy in which enrollment was stopped, actual enrollment lasted 18 months, overall.

Study flow is summarized in Fig. 2. Due to the randomization scheme (see Methods), a slight imbalance between groups was present after 101 patients were enrolled, with 54 assigned to the STP and 47 to the control group.

Among the patients initially randomized to the STP group, five patients refused to continue the study before undergoing psychotherapy, leaving 49. Among these 49 patients who actually began the study, four patients completed individual sessions but discontinued the STP before group sessions; these four were analyzed on an intention-to-treat basis. Average attendance rate of individual sessions was 95% and of group sessions 85%.

In the control group, one of the 47 patients died before the study started and another subject refused to continue immediately after randomization (lost to follow-up) and before psychological tests, leaving 45 controls available for analysis. Among these, one patient asked to begin psychotherapy before the end of the study, but again

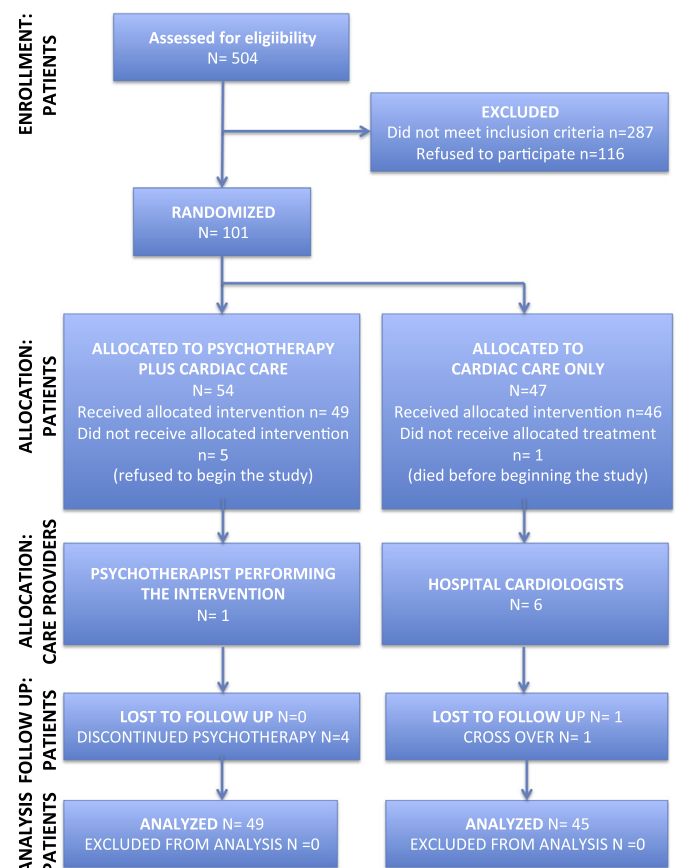


Fig. 2. Study flow chart.

**Table 1**  
Baseline characteristics of patients.

	Psychotherapy (n = 49)	Traditional (n = 45)	p
Age	55 ± 9	55 ± 8	0.78
Female	4/45	6/45	0.50
BMI	26 [25–30]	27 [25–31]	0.40
Ejection fraction	51 ± 9	54 ± 10	0.17
Post-MI cardiological rehabilitation	21/49	22/45	0.56
Risk factors			
Active smoking	30/49	30/45	0.58
Hypercholesterolemia	29/47	23/44	0.58
Family history of CADD	37/47	33/45	0.54
Arterial hypertension	24/49	29/45	0.13
Diabetes mellitus	13/48	12/45	0.96
Nr. of active medical disease	0.9 ± 1	0.9 ± 1	0.70
AMI & angio characteristics			
STEMI	38/49	35/45	0.98
Symptom-to-balloon time (STEMI)	300 [165–540]	240 [150–360]	0.15
Anterior MI (STEMI)	22/38	24/35	0.34
Rescue PCI (STEMI)	7/38	11/38	0.28
Peak CK-MB (STEMI)	155 ± 109	188 ± 117	0.24
Nr. of diseased vessels	1.9 ± 0.9	1.7 ± 0.9	0.43
Drug therapy			
Aspirin	48/49 (98%)	43/49 (96%)	0.11
B- blockers	47/49 (96%)	40/45 (89%)	0.37
ACE-inhibitors or ARB	37/49 (76%)	40/45 (89%)	0.09
Statins	47/49 (96%)	45/45 (100%)	0.54
Clopidogrel	49/49 (100%)	45/45 (100%)	1
Diuretics	6/49 (12%)	14/45 (31%)	<b>0.04</b>
Calcium-antagonists	1/49 (2%)	6/45 (13%)	0.09
Nitrates	14/49 (29%)	14/45 (31%)	0.79
Psycho-active drugs	1/49 (2%)	-	
Psychological tests			
Maastricht	72 ± 32	72 ± 37	0.97
Life events	3 [–1–7]	3 [–2–7]	0.57
BDI	7 [3–11]	8 [5–14]	0.09
BDI > 10 – n (%)	16 (33%)	22 (49%)	0.20
BDI > 15 – n (%)	6 (12%)	9 (20%)	0.31
Social support	19 [16–31]	21 [16–28]	0.95
Stress	7 [4–8]	6 [6–8]	0.27
MacNew global	5 [5,6]	5 [5,6]	0.34
MacNew emotional	6 [5,6]	5 [4–6]	0.25
MacNew physical	5 [5,6]	5 [5,6]	0.91
MacNew social	5 [5,6]	5 [5,6]	0.28
Duration of psychotherapy (days)	223 ± 291	NA	NA

BMI: body mass index; MI: myocardial infarction; CAD: coronary artery disease; AMI: acute myocardial infarction; STEMI: ST-elevated myocardial infarction; CK-MB: MB iso-form of creatininkinase; ACE: aiotensin-II converting enzyme; ARB: angiotensin-II receptor blocker; BDI: Beck depression inventory score; NA: not applicable.

was analyzed on an intention-to-treat basis, resulting in a comparison of 49 STP-treated patients and 45 controls, 94 subjects overall.

Patient characteristics at enrollment are summarized in Table 1. The two groups were balanced in terms of demographics, as well as in clinical, angiographic and psychometric characteristics. Only 22 controls and 21 subjects in the STP group accepted to attend the proposed cardiac rehabilitation program. Pharmacological therapy at discharge was similar in the two groups, except for nitrates which were more frequently prescribed in the control group.

### 3.1. Medical outcomes

At one year, patients randomized to STP on top of standard cardiological therapy had a significantly lower incidence of the composite primary endpoint, relative to patients undergoing cardiological therapy only (43% vs. 78%,  $p = 0.0006$ ), equaling a 35% absolute risk reduction and a number needed to treat (NNT) of three (95%CI: 1.9 to 6.1) (Table 2). This was confirmed by Cox survival analysis (Fig. 3), whereby the survival curves of the two groups steadily and significantly diverged throughout the first year of follow-up ( $p = 0.004$ ).

However, no deaths or strokes occurred after one year, with the ensuing MACCE similar in the two groups and largely driven by new

revascularizations (Table 2 and Fig. 4A,  $p = 0.82$ ). Based upon this, whatever benefit observed in the STP group appeared to be attributable to the lower recurrence of typical angina (NNT = 5; 95%CI: 2.5 to 100.4) (Table 2; Fig. 4B,  $p = 0.04$ ) and to the lower incidence of new comorbidities versus controls (NNT = 3; 95%CI: 1.6 to 3.2) (Table 2; Fig. 4C,  $p = 0.001$ ). Of note, although not statistically significant, three episodes of life-threatening arrhythmias occurred in the cardiological therapy only group, while none occurred in those receiving STP (Table 2).

Consistent with primary outcome findings, in patients randomized to STP, the re-hospitalization rate was significantly lower at one year relative to controls (Table 2). Moreover, psychotherapy subjects experienced a better average NYHA class than their counterparts, despite similar mean ejection fractions and wall motion score-indices at follow up in the two groups. The prevalence of patients on therapy with the different classes of drugs was similar between the two groups at one year (Table 2). However during follow-up, 35/45 (78%) patients of the control group needed an increase in doses of diuretics or betablockers or vasoactive drugs (nitrates and/or calcium-antagonists and/or ace-inhibitors and/or angiotensin-receptor blockers), as compared to 15/49 (31%) in the psychotherapy group ( $p < 0.0001$ ). No patient receiving STP required psychiatric drugs during the first year follow-up, whereas three controls were administered psychiatric treatment for major depression and generalized anxiety disorder.

### 3.2. Psychological and quality-of-life outcomes

At one year, those who were randomized to STP exhibited a significantly lower BDI depression score than controls, consistent with a marked trend toward a lower prevalence of depression overall (patients with a BDI score > 10) and a statistically significant lower prevalence of severe depression (i.e., patients with a BDI score > 15) in the STP group (Table 2). This appeared to be due both to improved BDI scores in the STP group and to worsening BDI scores in controls relative to baseline.

All other psychological test scores were similar in the two groups.

The STP patients experienced statistically better quality of life in the physical domain, and trended toward enhanced quality of life in the social domain and globally.

### 3.3. Subgroup analysis and outcome predictors

On unadjusted subgroup analysis (Table 3), the reduction in primary endpoint incidence with STP on top of cardiological treatment was statistically significant in patients who did not undergo a rehabilitation program, in patients with STEMI as their index event, and in younger patients. Benefit from STP also was irrespective of baseline depression score, although patients with higher scores had a lower relative risk of primary events with psychotherapy than patients with lower scores. Albeit not statistically significant, a marked trend toward better outcomes with psychotherapy also was observed in patients who participated in a cardiac rehabilitation program, whereas STP seemed not to produce any reduction in the risk of primary outcomes in patients with NSTEMI or in patients more than 58 years old.

Upon multivariate analysis (Fig. 5), the only independent predictors of the primary outcome were 'being randomized to STP' and 'having a life-event score > 10 at enrollment'.

## 4. Discussion

In our one-year analysis of the STEP-IN AMI trial, we demonstrated that adding short-term psychotherapy (STP) on top of standard cardiological care early after an acute myocardial infarction treated with urgent/emergent PCI yields a striking reduction in the incidence of a primary composite cardiological and medical endpoint, such that only three subjects need to be treated before one less event is noted. Interestingly, an average 92% reduction in the risk of occurrence of the primary

**Table 2**  
One year results in study groups.

	Psychotherapy (n = 49)	Traditional (n = 45)	p
Primary endpoint			
Incident proportion (%) (Nr. of events)	21/49 (43%) (33)	35/45 (78%) (78)	<b>0.0006</b>
Reinfarction	2/49 (4%) (2)	3/45 (7%) (3)	0.67
Death	–	–	–
Stroke	–	–	–
Revascularization	9/49 (18%) (12)	12/45 (27%) (12)	0.33
MACCE	11/49 (22%) (14)	15/45 (33%) (15)	0.24
Life-threatening ventricular arrhythmia	0/49 (0%) (0)	2/45 (4%) (3)	0.23
Recurrence of typical angina	14/49 (29%) (14)	22/45 (49%) (23)	<b>0.04</b>
New comorbidities	5/49 (10%) (5)	25/45 (56%) (37)	<b>&lt;0.0001</b>
Rehospitalizations nr.	37	56	
Average total rehospitalizations – mean (95%CI)	0.77 (0.53–0.98)	1.2 (0.92–1.57)	<b>0.02</b>
Cardiology driven – mean (95%CI)	0.69 (0.48–0.90)	1.0 (0.71–1.38)	0.14
Medically driven – mean (95%CI)	0.08 (0.002–0.16)	0.2 (0.05–0.35)	0.25
NYHA class	1.0 ± 0.1	1.3 ± 0.8	<b>0.01</b>
NYHA class ≥ 2 (pts)	1/49 (2%)	8/45 (18%)	<b>0.01</b>
Ejection fraction			
Overall	56 ± 10	56 ± 12	0.82
STEMI	55 ± 11	55 ± 12	0.92
NSTEMI	58 ± 8	60 ± 10	0.61
WMSI			
Overall	1.40 ± 0.32	1.43 ± 0.37	0.72
STEMI	1.43 ± 0.33	1.47 ± 0.39	0.66
NSTEMI	1.32 ± 0.27	1.27 ± 0.28	0.71
Drug therapy at 1 year follow up			
Aspirin	44/49 (90%)	43/45 (95%)	0.29
B-blockers	44/49 (90%)	40/45 (89%)	0.89
ACE-inhibitors or ARB	39/49 (80%)	38/45 (84%)	0.54
Statins	46/49 (94%)	45/45 (100%)	0.24
Clopidogrel	46/49 (94%)	45/45 (100%)	0.24
Diuretics	9/49 (18%)	16/45 (35%)	0.06
Calcium-antagonists	2/49 (4%)	6/45 (13%)	0.27
Nitrates	15/49 (31%)	20/45 (44%)	0.11
Psycho-active drugs	1/49 (2%)	2/45 (4%)	0.93
Psychological tests			
Stress	5 [3–8]	5 [3–7]	0.85
Maastricht	56.45 [46.97–79.25]	59.7 [43.4–101.3]	0.32
Life events	1 [–3–4]	2 [–1.5–5]	0.38
BDI	6 [3–8]	8 [5–14]	<b>0.03</b>
BDI > 10 – n (%)	7 (14%)	12 (27%)	0.05
BDI > 15 – n (%)	2 (4%)	9 (20%)	<b>0.01</b>
Social support	22 [18–30.5]	19.5 [15.7–31.2]	0.30
MacNew global	6.07 [5.48–6.39]	5.67 [4.89–6.31]	0.07
MacNew emotional	5.79 [5.36–6.35]	5.79 [5–6.32]	0.38
MacNew physical	6.23 [5.7–6.53]	5.69 [4.85–6.29]	<b>0.03</b>
MacNew social	6.15 [5.69–6.61]	5.86 [5–6.46]	0.06

MACCE: major adverse cardio-vascular events, NYHA: New York Heart Association; STEMI: ST-elevated myocardial infarction; NSTEMI: non-ST-elevated myocardial infarction; WMSI: wall motion score-index; ACE: angiotensin converting-enzyme; ARB: angiotensin receptor blocker; BDI: Beck depression inventory score.

endpoint with psychotherapy still was present after controlling for potential confounders, including baseline depression state and attendance in a cardiac rehabilitation program. Indeed, upon multivariate analysis, only psychotherapy and a life-event score > 10 emerged as independent predictors of the primary outcome.

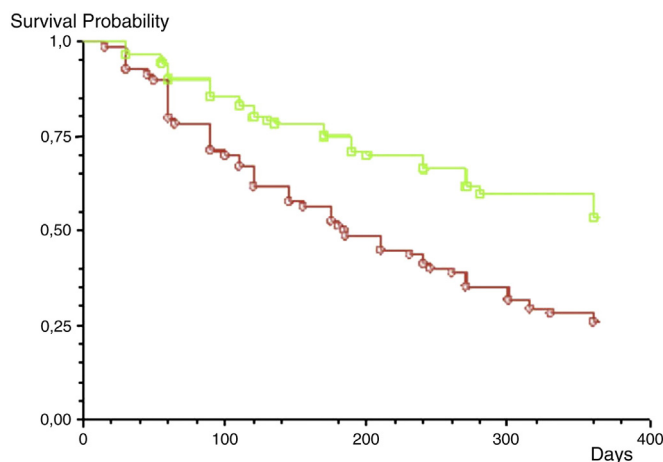
As possible consequences of these findings, with psychotherapy we observed statistically significant reductions in the re-hospitalization rate and depression score, as well as improved quality of life at one year.

We believe that this is the first study completed on a carefully selected population within one week of a myocardial infarction treated with standard contemporary interventional and medical therapy, in which psychotherapy was standardized by being administered by a single psychotherapist, and data were reviewed by an independent events committee. Moreover, an original and new short-term psychotherapy program synthesized from onto-psychological methods was tested for the first time in ischemic heart disease.

Previous meta-analyses in this subject area [5–9] have failed to identify any significant effects of different psychotherapeutic approaches on cardiologic end-points, though efficacy at reducing psychological symptoms has been evident. However, these meta-analyses suffered from considerable heterogeneity within the analyzed trials, particularly

in terms of patient selection criteria and psychotherapeutic approach. Our study, which addressed the limitations of previous studies, provides evidence that the benefits at one-year produced by short-term STP after AMI treated with primary or urgent PTCA are attributable to a lower angina recurrence rate and to a lower incidence of new non-cardiological disorders; but we observed no effect on MACCE. This improvement in cardiologic symptoms is consistent with the need for lower drugs dosage and better functional class experienced by patients at one-year follow-up, relative to those who did not receive psychotherapy, despite similar ejection fractions and wall motion score indices in the two groups. The reason of the mismatch between functional class and systolic ventricular function in the control group is unclear and could be hypothetically due to a different perception of symptoms during follow-up and/or to a different diastolic function at one year, as compared to the STP group. However these parameters were not systematically assessed in our study.

Whether this benefit, observed only in cardiologic symptoms, was due to the relatively short-term follow-up is yet to be clarified. Indeed, in a recent report evaluating the efficacy of cognitive behavioral therapy after up to 8 years of follow-up in a more heterogeneous population of ischemic patients, a 41% reduction in recurrent cardiovascular events



**Fig. 3.** Plot of cumulative event-free survival from the primary endpoint. Patients randomized to STP (green line) experienced statistically significant prolongation of event-free survival versus controls (red line) ( $p = 0.004$ ). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

was observed with psychotherapy [15]. Furthermore, specific effects related to the type and duration of psychotherapy, and the time of therapy initiation post MI [5,9] cannot be ruled out. An additional possible explanation for the lack of any effect on MACCE is that patients received cardiological therapy in line with recent guidelines, while previous studies obviously could not. Improving outcomes with the most recent pharmacologic and interventional therapies in both randomization arms may have outweighed any positive effects conveyed by psychotherapy in previous studies. This conjecture is supported by the low ensuing cardiovascular risk of the study population at randomization, after a complete and timely revascularization (the average post-AMI ejection fraction was 53%). This being said, adequately dimensioned studies to assess the effects of psychotherapy on MACCE are needed to clarify this issue.

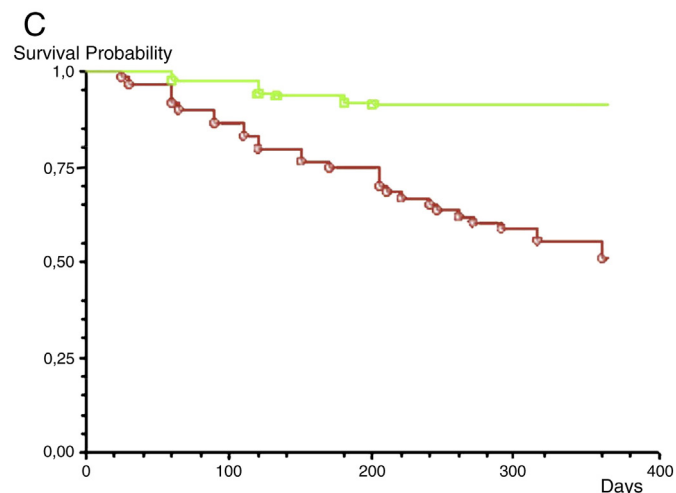
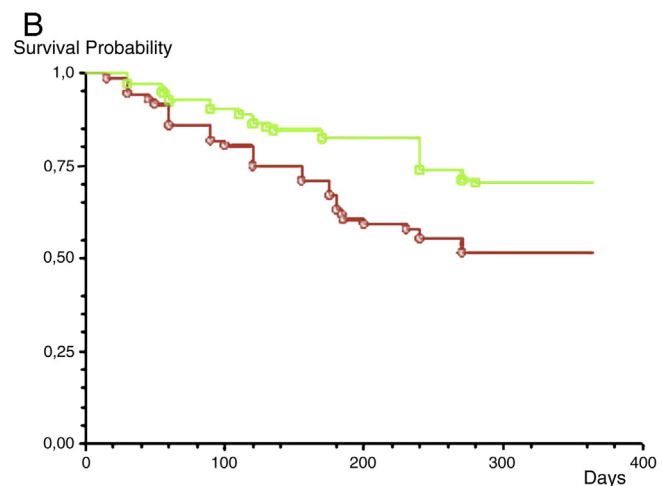
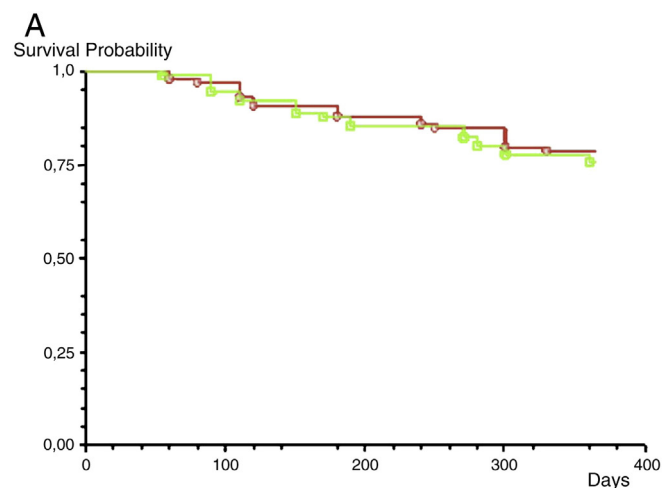
Our STP group also experienced statistically better quality of life in the physical domain, and trended toward enhanced quality of life in both the social domain and globally. This result is consistent with the specific psychological methodology, which focused a great part of its analysis on the comprehension of body signals, with a sensation of improved physical wellness noted by participants during the psychotherapy sessions. Moreover, the trend toward enhanced quality of life in the social domain and globally may be related to the wide range of issues treated during the psychotherapy sessions and the continuous enhancement of the positive personal and social resources of the patient.

Our study also detected that STP post AMI reduces new-onset, clinically significant comorbidities. This finding supports the systemic effects of psychotherapy and may be regarded consistent with a previous meta-analysis that indicated a trend in the reduction of all-cause mortality after psychotherapy performed for cardiac disease [5].

Finally, if the results of this study will be confirmed in larger series, the costs of the implementation of extensive psychotherapy programs in all post-AMI patients may be a barrier to their widespread introduction. However, the statistically significant 34% relative reduction in all-cause re-hospitalizations after STP psychotherapy in our study, the improvement in quality of life, the need for lower doses of drugs and the independent effect on outcome with small NNTs relative to standard cardiological care, may be relevant from a cost/effectiveness perspective in the management of post-MI patients.

## 5. Limitations of the study

Interpretation of the results of this study should also consider its limitations.



**Fig. 4.** Plot of cumulative event-free survival from MACCE (A), angina (B) and new comorbidities (C) in the STP group (green line) versus controls (red line). A. Patients randomized to STP and controls had similar survival free from MACE ( $p = 0.82$ ). B. Patients randomized to STP had longer survival free from angina than controls ( $p = 0.04$ ). C. Patients randomized to STP had longer survival free from new comorbidities than controls ( $p = 0.001$ ). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

The study was designed to achieve a high internal validity, often not sufficiently achieved in previous studies. Thereby – to obtain a homogenous study population – only patients with recent myocardial infarction were selected who had been completely re-vascularized by coronary angioplasty. Moreover, for the same purpose, a single

**Table 3**

Unadjusted subgroup analysis for the probability of reducing the occurrence of primary outcome with STP.

	NR. OF PTS	OR	95% CI	ARR	NNT
BDI ≥ 10	38	7.5	1.7–33.0	44%	2.3
BDI < 10	56	3.4	1.05–11.34	28%	3.5
Rehabilitation	43	3.5	0.99–12.2	–	–
No rehabilitation	51	7.7	1.85–31.91	40%	2.5
STEMI	73	5.7	2.14–15.60	37%	2.7
NSTEMI	21	5.1	0.46–56.90	–	–
EF ≥ 50%	61	2.9	1.00–8.58	42%	2.4
EF < 50%	33	8.7	1.76–42.61	55%	1.8
Age ≥ 58 years	35	4.7	0.63–59.25	–	–
Age < 58 years	59	4.1	1.37–12.14	34%	3.0

OR: odds ratio; CI: confidence intervals; ARR: absolute-risk reduction; RRR: relative-risk reduction; STP: short-term psychotherapy; BDI: Beck depression inventory score; STEMI: ST-segment-elevated myocardial infarction; NSTEMI: non-ST-segment-elevated myocardial infarction; EF: ejection fraction.

psychotherapist was used as care provider in the psychotherapy arm to control and standardize methodology (used for the first time in ischemic heart disease) and to ensure a homogenous experience with psychotherapy. These characteristics, although enhancing internal validity, limit the external validity of the study. External validity is even more limited by the slow enrollment rate and, hence, by the small number of patients. Therefore, the generalizability of the results remains to be assessed in different populations and with different psychotherapists in future studies.

Moreover, albeit only used for secondary outcomes and using only a stepwise (backward) variable selection technique for regression, multivariate analysis performed on non-parametric data and on a small sample should be only considered exploratory.

The choice of a complex composite primary end-point, including “hard” and “soft” endpoints and non-cardiological outcomes, may seem problematic. However, a study addressing psychotherapy outcomes has different characteristics than studies considering medical interventions. In fact, psychotherapy is a systemic therapy, potentially acting at many levels with a broader range of effects than expected with usual cardiologic therapies, therefore the outcomes in these studies should be wider than what we are used to consider in classical pharmacologic intervention trials. As a consequence of enlarging the range of effects, we observed a high incidence of primary outcome in the study population, which may seem odd if one still considers them as purely cardiologic endpoints. However, the observed incidence in this study was largely driven by recurrent clinically relevant angina

and non-cardiological endpoints. The value of this finding is confirmed by the ensuing re-hospitalization rate, which was lower in the psychotherapy than usual care arm.

**6. Conclusions**

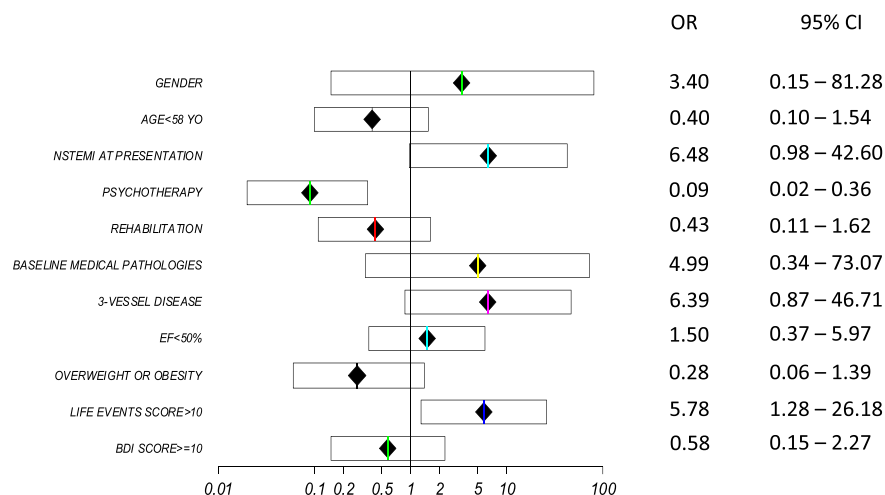
In conclusion, early results of the STEP-IN-AMI trial indicate improved medical and psychological outcomes one year after MI, translating a in a lower re-hospitalization rate and in a lower dosage of drugs, with short-term ontopsychological psychotherapy, which adds to the benefits of standard cardiologic treatment and may translate into overall cost savings. Five-year follow-up is underway to assess longer-term outcomes, while larger studies remain necessary to confirm the generalizability of our results.

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**Fig. 5.** Multivariate analysis of primary endpoint predictors. On logistic regression analysis, the only significant predictors of the primary endpoint were “being randomized to STP” (psychotherapy) and “having a life events score > 10 at baseline”.

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