CLINICAL RESEARCH STUDY

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Short-TErm Psychotherapy IN Acute Myocardial Infarction (STEP-IN-AMI) Trial: Final Results

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ABSTRACT

PURPOSE: The purpose of this research was to assess whether short-term psychotherapy enhances long-term clinical outcomes in patients with a recent acute myocardial infarction (AMI).

METHODS: Patients ≤70 years old were randomized within 1 week of their AMI to short-term ontopsychological psychotherapy plus routine medical therapy vs routine medical therapy only. The primary composite outcome was defined as the combined incidence of new cardiovascular events (re-infarction, death, stroke, revascularization, life-threatening ventricular arrhythmias, and the recurrence of clinically significant angina) and clinically significant new comorbidities. Secondary outcome measures were: rates for individual components of the primary composite outcome; the rate of re-hospitalization for cardiovascular problems; and New York Heart Association functional class.

RESULTS: Ninety-four patients were analyzed, translating into 425 patient-years. The 2 treatment groups were similar across baseline characteristics. At 5-year follow-up, psychotherapy patients had a lower incidence of primary outcome, relative to controls (77/223 vs 98/202 patient-years, respectively; $P = .035$; absolute risk reduction = 19%, number needed to treat = 8); this benefit was attributable to the lower incidence of new comorbidities and clinically significant angina in the psychotherapy group. Gains in the primary outcome, relative to controls, among psychotherapy patients occurred in the first year and subsequently remained stable over the following 4 years.

CONCLUSIONS: Adding short-term ontopsychological psychotherapy to routine secondary prevention of myocardial infarction improves clinical outcomes overall up to 5 years post AMI. Studying time trends may aid in better targeting of psychological interventions during follow-up. Larger studies remain necessary to confirm these results.

TRIAL REGISTRATION: www.ClinicalTrial.gov NCT00769366

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KEYWORDS: Acute myocardial infarction; Ontopsychological psychotherapy; Randomized study; Secondary prevention

INTRODUCTION

Psychosocial factors play an important role in atherosclerosis[1] and ischemic heart disease.[2-4] On this basis, several psychotherapeutic and ancillary psychological interventions have been proposed for ischemic cardiac syndromes; however, their effectiveness at improving ischemic patients' prognosis remains questionable.[5,6] Among the main limitations of the available evidence, including many studies performed within the last few decades, have been the use of now-outdated medical therapies[5] and the heterogeneity of patient characteristics and psychological interventions. Therefore, we performed a randomized trial to assess the effectiveness, in terms of reducing cardiovascular events and other medical comorbidities, of standardized administration of an ontopsychological short-term psychotherapy (STP) program, in carefully characterized patients with a recent acute myocardial infarction (AMI) who also

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were treated with routine, contemporary treatments for their AMI. We have already reported the results of a preliminary 1-year analysis, which revealed a statistically significant reduction in a short-term composite outcome, including both cardiovascular and noncardiovascular events, after STP plus routine medical therapy, relative to routine medical therapy alone. This trial was dimensioned for results assessment through 5 years;[7] so here, we provide the results of the main follow-up with a final and comprehensive analysis of the long-term effects.

CLINICAL SIGNIFICANCE

- Psychotherapy has been proposed for improving prognosis in ischemic cardiac syndromes but its effectiveness remains controversial.
- In this high internal validity randomized study, short-term ontopsychological psychotherapy on top of routine medical therapy significantly and stably improved cardiological and medical outcomes throughout 5 years after an acute myocardial infarction.
- Mind–body relationship opens new avenues of treatment by integrating effective psychological and medical therapies to improve patients' outcomes after acute myocardial infarction.

METHODS

The Short-TErm Psychotherapy IN Acute Myocardial Infarction (STEP-IN-AMI) trial was an open label, superiority, 1:1 randomized controlled trial of a nonpharmacological intervention: short-term psychotherapy. This report was written in compliance with the CONSORT statement,[8] with the study's design detailed in Figure 1.[9]

The study was performed at a tertiary hospital and approved by the local ethics committee. All subjects provided signed informed consent prior to taking part. Due to logistical constraints, a first version of the protocol was amended after the start of randomization, reducing the number of patients that needed to be enrolled. Since then, a final, detailed version of the study protocol has been published.[10]

In brief, 101 patients aged ≤70 years and admitted to our hospital for an AMI were randomized to either receive or not receive ontopsychological STP on top of standard contemporary medical treatment for their AMI.

To obtain a comprehensive picture of baseline psychological conditions, psychometric tests were administered to all patients at enrollment (for details, see the Supplementary materials, available online).[11-17]

All data were collected using specific case-report forms and peer-reviewed at 1- and 5-year follow-up, with adverse clinical events adjudicated by a committee composed of 3 cardiologists blinded to study arm allocation. The authors declare that the main supporting data are available within the article (and its online supplementary files). Further data that support the findings of this study are available from the corresponding author upon reasonable request.

Randomization and Interventions

Patients were randomly assigned, in a 1:1 ratio, to routine medical therapy alone or to routine medical therapy plus STP. To achieve this, a random sequence was generated, in blocks (according to patient age and infarction characteristics), by an online tool at (http://www1.assumption.edu/users/avadum/applets/applets.html). The randomization codes were indicated in case-report forms, which were placed in sealed envelopes to be opened by the attending physician at the time of randomization, within 1 week after discharge from the intensive care unit.

Standard medical care. All patients underwent a percutaneous cardiac intervention to revascularize the culprit lesion in the acute phase; and, in cases of multivessel disease, complete revascularization prior to discharge from hospital. The choice of drug therapy in the acute and chronic phases was left to the treating physician's discretion. All patients were invited to participate in a cardiac rehabilitation program; those who refused this program received educational training.

Psychotherapy. To maximize the study's internal validity, psychotherapy was administered by a single psychotherapist, with the help of clinical staff, both psychologists and nurses.

We developed a standardized, basic model of STP that could be easily reproduced and delivered within the national health care system. We utilized, for the first time, ontopsychological psychotherapy specifically adapted to the context of research in the field of cardiac psychology, by the psychotherapist herself. Further details of the STP intervention administered are provided in the Supplementary materials and elsewhere.[7,10,18]

Outcomes and Follow-Up

A long-term 5-year follow-up was chosen as a primary analysis of the study in order to describe the temporal effects of a short-term psychological intervention performed early after an AMI. Therefore, clinical follow-up was performed every year up to 5 years after enrollment.

Moreover, as psychotherapy may have effects not limited to the cardiovascular system, a broad-definition primary composite outcome was adopted, which consisted of the cumulative incidence of new cardiovascular events AND the occurrence of any clinically significant new noncardiovascular comorbidity. Cardiovascular events were defined as: major adverse cardiological and cerebrovascular events (myocardial re-infarction, death, stroke, any revascularization procedure) PLUS life-threatening ventricular arrhythmias and recurrence of typical angina pectoris. 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 (eg, work capacity

TABLE 1 – GENERAL LAYOUT OF THE STUDY

TIME LINE	INTERVENTIONS	
	PSYCHOTHERAPY	CONTROL
PCI & RANDOMIZATION (TIME 0)	C	
IN HOSPITAL	C Q	
1-3 MONTHS	C IP	C
4-6 MONTHS	C GP	C
1 YEAR	C Q MEASUREMENT OF OUTCOMES	
2 through 5 YEARS	C MEASUREMENT OF OUTCOMES	

C	Cardiological therapy, including cardiac rehabilitation, according to the clinical indications of the caring physician
Q	Questionnaires assessing psychosocial variables (Maastricht test, BDI test, recent life changes test, social support test) and quality of life (Mc New test)
IP	Individual short-term psychotherapy.
GP	Group short-term psychotherapy

Figure 1 Design of the Study.

impairment, inability to cope, severe exercise limitations) and warranting an increase in baseline pharmacological therapy or requiring hospitalization. Clinically significant new noncardiovascular comorbidities were defined as any new, noncardiovascular condition significantly impairing normal daily activities, requiring hospitalization, or requiring specific and permanent drug treatment.

According to these a priori definitions, the clinical adverse-event committee, blinded to treatment allocation, adjudicated endpoints on an individual basis at the time of the case-report form data review. A list of adjudicated new comorbidities can be found in the Supplementary materials (available online).

Secondary endpoints that we examined at 5-year follow-up were the incidence of individual outcomes within the primary composite outcome (eg, each component of cardiovascular events, each component of major adverse cardiological and cerebrovascular events, each new noncardiovascular event); the incidence of new hospital admissions for cardiological or other medical reasons; and the prevalence of New York Heart Association (NYHA) functional class ≥II. We also examined for correlations between baseline characteristics and the various clinical outcomes of interest, and, as a post hoc analysis, the correlation between the number of events and the number of psychotherapy sessions.

Quality-of-life measures and psychometric testing were performed at baseline and after 1 year only; their analysis has been previously published.[7]

Statistical Analysis

A detailed description of statistical methods is provided in the Supplementary materials.

According to sample sizing,[10] it was decided to enroll 100 patients.

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

Event rates were expressed as proportional incidences and as person−time incidence rates. Continuous variables for each of the study groups are reported as means (with standard deviations or 95% confidence intervals) or as medians [lower quartile-upper quartile], as appropriate; while 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, and continuous paired variables were compared using paired Student's t or Wilcoxon tests, as appropriate. Categorical variables were compared by Pearson's chi-squared analysis or Fisher's exact test, as appropriate. The outcome incidences within each study group over long-term follow-up were compared with Friedman's test.

Survival-analysis was performed using Cox proportional hazards ratios. Multivariable binary logistic regression analysis was performed to appraise the independent predictive role of baseline characteristics on the primary composite outcome. Spearman's rank correlation test was performed to assess the correlation between the number of events and the number of psychotherapeutic sessions.

A P value $< .05$ was considered statistically significant, with all inferential tests 2-tailed. Statistical analysis was performed using the statistical software program SPSS, version 11.5 (SPSS Inc., Chicago, Ill).

RESULTS

Study flow is depicted in Figure 2. A detailed report of study flow can be found in the Supplementary materials (available online). The average follow-up duration was 4.6 years, equaling 223 patient-years in the STP group and in 202 patient-years in controls, representing 92% and 90% complete follow-up, respectively.

At enrollment, the 2 treatment groups were balanced, in terms of baseline characteristics and in-hospital treatments, except for diuretics, which were more frequently prescribed among controls (Table 1). The duration of psychotherapy in the STP group was 223 ± 291 days.

Comparison of the Primary Composite Outcome Between the Study Groups

After 5 years of follow-up, patients randomized to receive STP plus standard routine medical therapy had a significantly

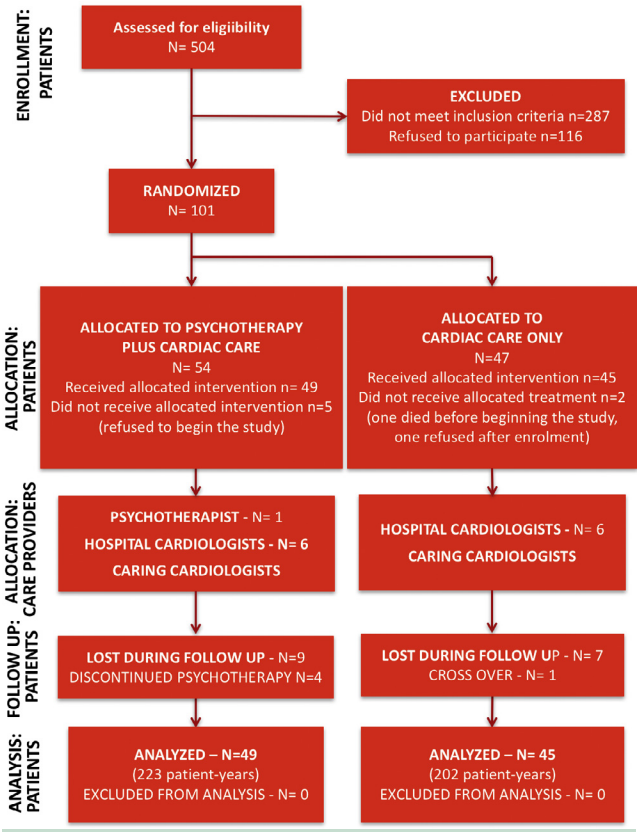

Figure 2 Study flow.

lower incidence of the primary composite outcome, relative to patients undergoing routine medical therapy only, equaling a 14% (95% confidence interval [CI], 5%-23%) absolute risk reduction (ARR) in proportional incidence, and generating a number needed to treat (NNT) of 8 (95% CI, 4-21) (Table 2). Supplementary Table 1 (available online) displays the number of events and results in terms of events per 100 patient-years.

Comparison of Secondary Outcomes Between Study Groups

Table 2 shows a breakdown of individual secondary endpoints in the 2 study groups. Supplementary Table 1 (available online) displays more details on outcome frequencies.

The STP group had a lower incidence of new noncardiovascular events (ARR 17% [95% CI, 9%-25%], NNT = 6 [95% CI, 4-11]) and of typical angina than controls (ARR 10% [95% CI, 2%-18%], NNT = 11 [95% CI, 6-42]). Psychotherapy-treated subjects also achieved a better NYHA functional class than their counterparts. The re-hospitalization rate was similar in the 2 groups.

Supplementary Table 2 (available online) provides the yearly incidence of outcomes.

Survival Analysis

As previously published, improvement in the primary outcome incidence experienced by the STP group was observed during the first year. In this new analysis of outcomes up to 5 years, beyond the first year the 2 groups had a similar yearly incidence of the primary outcome (Table 2), as confirmed by Cox survival analysis (risk ratio [RR] 0.47; 95% CI, 0.29-0.75; Figure 3).

Table 1 Baseline Characteristics of Patients

	Psychotherapy (n = 49)	Traditional (n = 45)	*P* Value
Age	55 ± 9	55 ± 8	.78
Female	4/45	6/45	.50
Body mass index	26 [25-30]	27 [25-31]	.40
Ejection fraction	51 ± 9	54 ± 10	.17
Post-MI cardiological rehabilitation	21/49	22/45	.56
Risk factors			
Active smoking	30/49	30/45	.58
Hypercholesterolemia	29/47	23/44	.58
Family history of CAD	37/47	33/45	.54
Arterial hypertension	24/49	29/45	.13
Diabetes mellitus	13/48	12/45	.96
No. of active medical disease	0.9 ± 1	0.9 ± 1	.70
AMI & angio characteristics			
STEMI	38/49	35/45	.98
Symptom-to-balloon time (STEMI)	300 [165-540]	240 [150-360]	.15
Anterior MI (STEMI)	22/38	24/35	.34
Rescue PCI (STEMI)	7/38	11/38	.28
Peak CK-MB (STEMI)	155 ± 109	188 ± 117	.24
Nr. of diseased vessels	1.9 ± 0.9	1.7 ± 0.9	.43
Drug therapy			
Aspirin	48/49 (98%)	43/49 (96%)	.11
B-blockers	47/49 (96%)	40/45 (89%)	.37
ACE-inhibitors or ARB	37/49 (76%)	40/45 (89%)	.09
Statins	47/49 (96%)	45/45 (100%)	.54
Clopidogrel	49/49 (100%)	45/45 (100%)	1
Diuretics	6/49 (12%)	14/45 (31%)	.04
Calcium-antagonists	1/49 (2%)	6/45 (13%)	.09
Nitrates	14/49 (29%)	14/45 (31%)	.79
Psycho-active drugs	1/49 (2%)	–	
Psychological tests			
Maastricht	72 ± 32	72 ± 37	.97
Life events	3 [−1-7]	3 [−2-7]	.57
BDI	7 [3-11]	8 [5-14]	.09
BDI >10, n (%)	16 (33%)	22 (49%)	.20
BDI >15, n (%)	6 (12%)	9 (20%)	.31
Social support	19 [16-31]	21 [16-28]	.95
Stress	7 [4-8]	6 [6-8]	.27
Mc New global	5 [5-6]	5 [5-6]	.34
Mc New emotional	6 [5-6]	5 [4-6]	.25
Mc New physical	5 [5-6]	5 [5-6]	.91
Mc New social	5 [5-6]	5 [5-6]	.28
Duration of psycho-therapy (days)	223 ± 291	NA	NA

ACE = angiotensin-II converting enzyme; AMI = acute myocardial infarction; ARB = angiotensin-II receptor blocker; BDI = Beck Depression Inventory score; CAD = coronary artery disease; CK-MB = MB isoform of creatine kinase; MI = myocardial infarction; NA = not applicable; PCI = percutaneous coronary intervention; STEMI = ST-elevated myocardial infarction.

Table 2 Cumulative 5-Year Results in Study Groups

	Psychotherapy Pts = 49 Patient-Years = 223	Traditional Pts = 45 Patient-Years = 202	*P* Value
Primary composite endpoint			
Proportional incidence	77/223 (35%)	98/202 (49%)	.031
Cardiovascular events			
Reinfarction	8/224 (4%)	4/202 (2%)	.322
Death	1/224 (0.5%)	2/202 (1%)	.932
Stroke	—	—	—
Revascularization	26/223 (12%)	16/202 (8%)	.197
Major adverse cardiac and cerebrovascular events	29/223 (13%)	17/202 (8%)	.126
Life-threatening ventricular arrhythmia	3/223 (1%)	6/202 (3%)	.410
Recurrence of typical angina	33/223 (15%)	50/202 (25%)	.01
New noncardiovascular events	37/223 (17%)	68/202 (34%)	< .0001
Re-hospitalizations			
Total	83/223 (37%)	79/202 (39%)	.689
Cardiovascular	65/223 (29%)	62/202 (31%)	.728
Noncardiovascular	28/223 (13%)	24/202 (12%)	.832
NYHA class			
Mean ± SD	1.0 ± 0.2	1.26 ± 0.6	.005
NYHA class ≥2 (no. of pts)	4/49 (8%)	14/45 (31%)	.01

NYHA = New York Heart Association; SD = standard deviation.

Patients in the STP group had statistically nonsignificantly longer angina-free survival than controls (Figure 3B, RR 0.62; 95% CI, 0.35-1.09), but statistically longer comorbidity-free survival vs controls (Figure 3C, RR 0.33; 95% CI, 0.20-0.55). There was no intergroup difference in major adverse cardiological and cardiovascular events-free survival (Figure 3D, RR 0.92; 95% CI, 0.46-1.83).

Correlations and Multivariable Analysis

Upon prespecified multivariable analysis (Figure 4), the only independent predictor of primary composite outcome incidence was "being randomized to STP".

No correlation was found between the number of psychotherapy sessions and the number of primary outcome events ($P = .09$, $P = .41$, respectively).

Analysis of the Trends of Change Over Follow-Up Within Each Study Group

The evolution of each group through final follow-up is summarized in Supplementary Table 2 (available online). During follow-up, both the STP and control groups experienced statistically significant improvement in the rates of revascularization, major adverse cardiological and cerebrovascular events, new comorbidities, and both overall and cardiovascular rehospitalization. However, only patients in the STP group had a statistically significant improvement in NYHA class over the course of follow-up; it remained unchanged in controls. Interestingly, controls experienced a statistically significant improvement in primary composite outcome incidence throughout follow-up, whereas STP patients experienced improvement only during the first year. However, as rendered evident by comparing the 2 groups, the improvement in the control group was insufficient to match the relative improvement experienced by the STP group over the first year.

There were no statistically significant variations in drug prescriptions within the 2 groups over the course of follow-up.

DISCUSSION

A previous preliminary analysis of the STEP-IN-AMI trial data showed a significant reduction in the incidence of a primary composite outcome consisting of cardiovascular and noncardiovascular outcomes in the psychotherapy (STP) group after 1 year.[7] However, the study was dimensioned for outcome measures at 5 years.[10] Now, after 5 years of follow-up, we can finally demonstrate that the combination of ontopsychological STP added to standard medical care yields a statistically significant reduction in primary composite outcome incidence relative to patients undergoing routine medical therapy only. Moreover, just 8 treated patients needed to be treated with STP to prevent one primary outcome event per year. In this final analysis, we also see that the overall advantages observed with STP were greatest within the first year, after which they remained constant over the final 4 years. Upon multivariable analysis, only psychotherapy emerged as an independent predictor of the primary composite outcome long term, with an 80% reduction in odds for the primary outcome after controlling for confounders. These final results identify a positive and independent effect of psychotherapy on long-term post-AMI outcomes, and add to the preliminary 1-year results important new evidence demonstrating both the durability and stability of these advantages throughout 5 years of follow-up.

Two recent updated meta-analyses involving more than 9000 patients suggest that psychotherapy might be

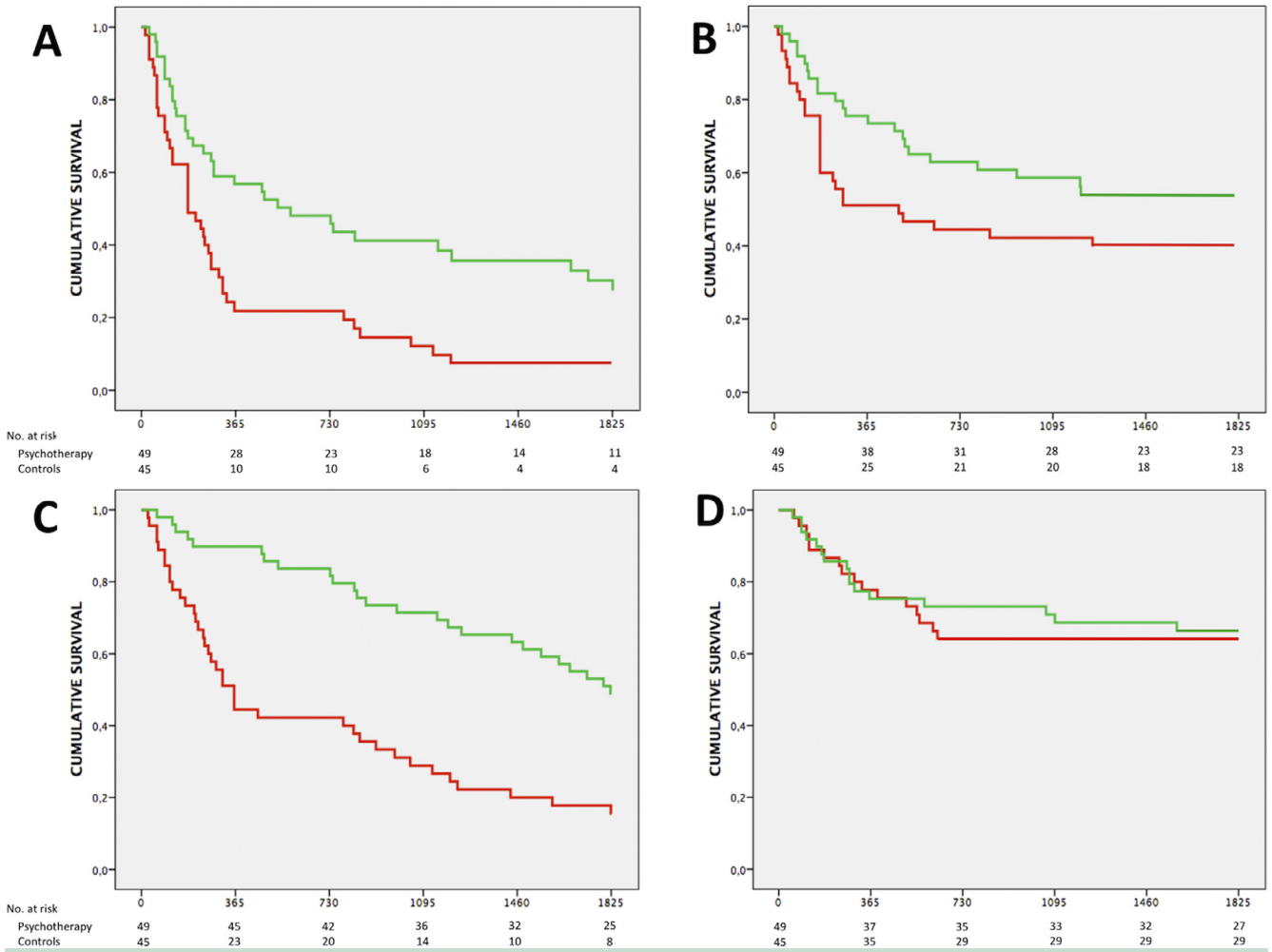

Figure 3 Plot of cumulative event-free survival from the primary endpoint **(A)**, angina **(B)**, new comorbidities **(C)**, and major adverse cardiac and cerebrovascular events **(D)**, in those receiving short-term psychotherapy (green line) vs controls (red line).
(**A**) Patients randomized to receive short-term psychotherapy (STP) experienced statistically significant prolongation of event-free survival vs controls ($\chi^2 = 10.2$; $P = .001$).
(**B**) Patients randomized to receive STP had nonsignificantly longer survival free from angina than controls ($\chi^2 = 2.8$; $P = .089$).
(**C**) Patients randomized to receive STP had statistically longer survival free from new comorbidities than controls ($\chi^2 = 18.4$; $P < .0001$).
(**D**) Patients randomized to receive STP and controls experienced similar survival free from major adverse cardiac and cerebrovascular events (myocardial re-infarction, death, stroke, any revascularization procedure) ($\chi^2 = 0.1$, $P = .807$).

associated with reduced morbidity in patients with ischemic heart disease.[5,6] However, these meta-analyses were judged to suffer from low-quality evidence. Nevertheless, the STEP-IN-AMI trial credibly supports these findings by addressing a number of the limitations that studies included in these meta-analyses had. It does this by strict selection criteria for subjects, randomizing patients within 1 week of their myocardial infarction, employing the most contemporary standard medical therapies, providing standardized administration of psychotherapy by a single psychotherapist, using a blinded review of data by an independent events committee, and enjoying over 90% follow-up at 5 years. One meta-analysis also suggested reduced mortality with psychotherapy in ischemic heart disease patients[5]; however, our study was not dimensioned for this purpose.

Even though our study was not specifically dimensioned to allow for intergroup comparisons of secondary outcome measures, we nonetheless observed that the reduced incidence of primary outcome events was driven by reductions in the recurrence of clinically significant angina and incidence of new noncardiovascular comorbid conditions. This psychotherapy-linked improvement in angina could be explained by favorable changes affecting the neurally mediated control of coronary blood flow; by autonomic efferent inhibitory stimuli on pain pathways; or via the central orchestration of pain perception.[19-23] Moreover, psychotherapy patients experienced a statistically significant improvement in NYHA functional class throughout follow-up, whereas control patients did not. This resulted in an overall statistically significant better NYHA score in the psychotherapy vs nonpsychotherapy

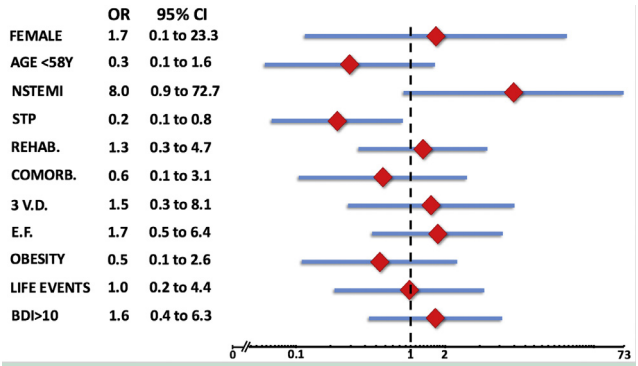

Figure 4 Multivariable analysis of primary endpoint predictors. On logistic regression analysis, the only significant predictor of the primary endpoint (a composite score of cardiovascular and noncardiovascular event) was "being randomized to short-term psychotherapy (STP)."

group. This benefit, at 1 year, was observed in the presence of similar ventricular systolic function; therefore, it potentially was due to a positive effect of psychotherapy on diastolic function or ventricular remodeling, either through direct psychoneural influences or mediated by inflammation and immune processes.[24-29] Additionally, psychotherapy may have influenced perceptions rather than actual instances of dyspnea.

The reduced incidence of new comorbidities could be due to a systemic effect of psychotherapy, because the psychotherapeutic intervention that was administered was a multilevel intervention with both single and group sessions, and entailed psychological and educational discussions, and body relaxation techniques.

The independent effect of short-term psychotherapy on outcomes, requiring small NNTs relative to routine medical care alone, and the broad effect of psychotherapy—which was not limited to cardiovascular outcomes, but also to systemic health status, reducing new-onset clinically significant comorbidities—might also improve the cost-effectiveness of post-myocardial infarction patient management. This being said, this study was performed using short-term psychotherapy only during the first 6 months after AMI, which may have contributed to the major effects being limited to the first-year post randomization. Whether the primary outcome would improve further over time with a more prolonged course of psychotherapy or additional sessions after 1 year remains to be investigated, as well as the impact of such on subsequent costs.

In conclusion, this principal analysis of STEP-IN-AMI trial data indicates that administering short-term ontopsychological psychotherapy on top of contemporary routine medical treatment stably improves a primary composite endpoint of cardiovascular and noncardiovascular events throughout 5 years of follow-up, post AMI, even when the therapy is limited to 6 months of administration early after the AMI. Larger trials remain necessary to confirm our results and to identify possible further psychotherapeutic strategies in post-myocardial infarction patients, given the time trends observed in this study, which could further improve patients' prognosis long term.

Limitations of the Study

This study has general limitations, which have been discussed in greater detail elsewhere.[7] In brief, the STEP-IN-AMI trial was designed to achieve high internal validity, but this feature intrinsically limits its external validity. Moreover, multivariable analysis in a small study should only be considered exploratory. The choice of a composite primary outcome, which includes both "hard" and "soft" endpoints and noncardiovascular outcomes, is unusual in medical studies, but reflects the need to detect the potentially disparate levels of action of psychotherapy. Specific limitations of our 5-year analysis include the lack of any quality of life assessment or psychometric testing beyond the first year.

Finally, the STEP-IN-AMI trial, despite being designed to address a number of limitations of previous studies, was not powered to assess differences in the major adverse cardiological and cerebrovascular events alone, having a 67% post hoc probability of a false-negative finding.

For all these reasons, further studies are needed to more conclusively address these issues.

SUPPLEMENTARY MATERIAL

Supplementary material accompanying this article can be found in the online version at https://doi.org/10.1016/j.amjmed.2018.12.025.

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SUPPLEMENTARY MATERIALS

The Ontopsychological Short-Term Psychotherapy

The ontopsychological method is a complex and original approach, in part derived from psychoanalysis, analytical psychology, and the humanistic-existential approach, as initially elaborated by Abraham Maslow.[1] With the ontopsychological approach, the human being is considered a complex system that consists of the union 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 psychoneuroendocrinoimmunology. With this view, a psychotherapeutic intervention must improve not only psychological symptoms, quality of life, and cardiac prognosis (the main endpoints considered for previous psychological interventions in patients with ischemic heart disease), but also a patient's global health to be considered effective in cardiac patients.

For the current study, psychotherapy was delivered initially in individual sessions, tailored to the specific needs of each patient (range: 3-11 sessions), and then in group sessions over an overall 6-month period. The duration of each psychotherapy session was approximately 60 minutes for individual sessions and 120 minutes for group sessions.

Several specific adaptations have been made to the field of cardiac psychology. Firstly, this methodology has been used generally on a private basis, and it has been delivered freely for the first time in the field of research in cardiac psychology. This may have had consequences in the psychotherapy efficacy and deliverability. Secondly, psychometric tests have been used for the first time in ontopsychological psychotherapy. Thirdly, the psychotherapeutic setting, an important issue in psychotherapy, should, in ontopsychology, consist of a comfortable office with a desk or small table, one or more windows, a plant, and 2 armchairs opposite each other at a distance of about 2 m. However, for the purpose of this study, it has been necessary to use the existing public hospital facilities, which were generally different from what is required. Fourthly, while individual psychotherapy sessions were similar to the classic ontopsychological method applied to psychosomatics, in the group meetings some innovations have been introduced. If desired by the patients, the partners were also invited to participate in group sessions. Moreover, a sequence of 5 sessions has been specifically standardized for this program. In the first session we introduced educational cardiology, including a broader explanation of myocardial infarction and the atherosclerotic process, while accentuating the importance of cardiac risk factors' prevention and lifestyle changes and an explanation about the role of psychosocial risk factors. Also, in the sessions in which the relaxation technique was performed, it was accompanied by melodic music, carefully selected by the therapist to promote sensitivity throughout one's entire body while reducing the threshold for rationality. In the STEP-IN-AMI trial, Celtic pieces, classical music, and selections of ontoart music (a modern, experimental form of music) were used. The music acts by distracting one's consciousness, reducing one's super-ego, and enabling one to appreciate bodily sensations with total abandon. Finally, while in the classic ontopsychological approach, dream analysis is generally performed in the individual meetings, oneiric material was also analyzed in STEP-IN-AMI group meetings.

Psychometric Tests

Self-evaluation test assesses the global level of psychological distress over the preceding 2 weeks;

Modified Maastricht Questionnaire assesses levels of vital exhaustion;

Social Support Questionnaire evaluates each individual's perception of his/her social network;

Recent Life Change Questionnaire evaluates the presence and importance of occasional major life events and chronically recurring aggravations in daily life;

Beck Depression Inventory (BDI) evaluates symptoms of major or minor depression, where a score between 10 and 15 is considered indicative of mild depression, and a score $\geq$16 is considered indicative of clinically relevant depression;

The MacNew Heart Disease Health-Related Quality of Life Questionnaire assesses the patient's quality of life related to 3 specific domains—emotional, physical, and social—as well as providing a global quality-of-life score.

Adjudicated Comorbidities

Neurological and psychiatric diseases: major depression, generalized anxiety disorder, global transient amnesia, peripheral neuropathies, syncope;

Blood, circulatory, and blood vessels diseases: new arterial (carotid or peripheral) stenosis, new onset of arterial hypertension, hypertensive retinal abnormalities, aortic aneurisms, thrombocytopenia;

Genitourinary diseases: renal failure, nephrotic syndrome, post-ureteral stenosis, hematuria, prostate hypertrophy, non-pharmacological sexual impotence, renal colic with and without calculi, a bladder stone with severe hematuria;

Respiratory diseases: acute respiratory failure, acute bronchial asthma, chronic obstructive pulmonary disease, restrictive lung disease;

Metabolic and endocrine diseases: type II diabetes mellitus, hypercholesterolemia, hyperuricemia, thyroid nodules or goiter, hypothyroidism;

Gastrointestinal diseases: gallbladder, inguinal hernia, perianal abscess and fistula, rectal polyposis, severely hemorrhagic hemorrhoids, acute esophagitis requiring hospitalization, gastritis, acute pancreatitis, intestinal polyposis;

Orthopedic diseases: joint arthritis, spinal hernia, severe lumbago, a road accident with multiple bone fractures;

Neoplastic disease: cancer, skin basaliomas;

Infectious diseases: acute hepatitis, flu requiring hospitalization, mandibular sinusitis, parotitis, viral pleuropericarditis;

Degenerative disease: cataract.

Statistical Analysis

Based upon previous studies,[10] a 60% incidence of the primary composite outcome was expected in the control group at 5-year follow-up; hypothesizing a 50% reduction in this composite incidence within the psychotherapy arm—a sample size calculation resulted in 84 patients required overall (42 per treatment arm) to achieve statistical significance with 95% confidence and 80% power. Taking losses to follow-up into account, which was difficult to anticipate in a psychological intervention study, it ultimately was decided to enroll and randomize 100 patients.

For analysis, event rates were expressed as proportional incidences (number of patients with a new primary endpoint during each year of follow-up, divided by the number of patient-years of follow-up) and as person−time incidence rates (events per 100 patient-years).

Continuous unpaired variables were compared using independent-sample Student's *t* or Mann-Whitney *U* tests, depending upon data distribution (normal vs nonnormal). Continuous paired variables were compared using paired Student's *t* or Wilcoxon tests, again based upon the normality of data distribution. Categorical variables were compared by Pearson's chi-squared analysis or Fisher's exact test, based upon data cell numbers. The outcome incidences within each study group over long-term follow-up were compared with Friedman's test.

Multivariable binary logistic regression analysis was performed to appraise the independent predictive role of psychometric test scores on the primary composite outcome, with independent variable selection for the final multivariable model performed using a backward stepwise algorithm with statistical significance fixed at $P < .10$. For this, we included independent variables deemed to be clinically significant or potentially conditioning outcomes, particularly on the basis of our (published) first-year results. Survival-free endpoints (eg, percentage without any primary outcome or each secondary outcome at each end-of-year data-collection point) were compared between the 2 study groups using semi-parametric Cox proportional hazards ratios. Proportional hazards assumptions were tested by inspecting log-minus-log curves.

Study Flow

Given the need to complete each psychotherapy group session with 10 patients prior to enrolling further patients, patients were enrolled over a prolonged time span, from June 2005 to January 2011. However, the sum of all the actual active enrollment phases was only 18 months.

The slight imbalance in the number of randomized patients between groups was due to the randomization scheme (see Methods).

Among the patients initially randomized to the STP group, 5 refused to continue the study prior to undergoing psychotherapy, leaving 49. Among these 49 patients who actually began the study, 4 completed individual sessions but discontinued early the STP prior to group sessions; these 4 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, 2 patients exited the study even prior to undergoing the psychological tests, one because of death and the other because of delayed refusal, leaving 45 subjects for analysis. Among these, one patient crossed over to psychotherapy, but was analyzed on an intention-to-treat basis, resulting in a comparison of 49 STP-treated patients and 45 controls; 94 subjects overall.

In the following 5 years, 2 patients in the control group died during the second year after randomization and one patient from STP group during the fifth year. The number lost to follow-up was similar in the STP group (9 patients) and in controls (7 patients). However, these patients exited the study after an average of 2.3 years in the control group and of 2.6 years in the STP group.

Supplementary Reference

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Supplementary Table 1 Cumulative 5-Year Results in Study Groups

	Psychotherapy Pts = 49 Patient-Years = 223	Traditional Pts = 45 Patient-Years = 202
Primary endpoint		
Events x 100 patient-years (95% CI)	52.9 (41.9-64.0)	91.1 (75.5-106.7)
(absolute no. of events)	(120)	(184)
Cardiovascular events		
Reinfarction	3.6 (1.1-6.0) (8)	2.0 (0-3.9) (4)
Death	0.45 (0-1.3) (1)	1.0 (0-2.4) (2)
Stroke	—	—
Revascularization	11.7 (7.4-15.9) (26)	7.9 (4.2-11.7) (19)
Major adverse cardiac and cerebrovascular events	15.7 (10.0-21.4) (35)	9.9 (5.1-14.7) (23)
Life-threatening ventricular arrhythmia	1.3 (0-2.9) (4)	3.5 (0.6-6.4) (8)
Recurrence of typical angina	15.2 (10.3-20.2) (36)	24.2 (18.8-30.8) (51)
New noncardiovascular events	20.6 (13.9-27.4) (46)	49.5 (38.5-60.5) (100)
Rehospitalizations		
Total	48.0 (38.4-57.6) (107)	57.4 (45.3-69.5) (116)
Cardiovascular	33.6 (25.8-41.4) (75)	42.1 (31.3-52.9) (85)
Noncardiovascular	14.3 (9.1-19.6) (32)	15.3 (9.0-21.7) (31)

CI = confidence interval; CVE = cardiovascular events; MACCE = major adverse cardiovascular events.

Supplementary Table 2 Yearly Incidence of Outcomes in Study Groups

	2nd Year			3rd Year			4th Year			5th Year		
	Psycho	Control	*P* Value	Psycho	Control	*P* Value	Psycho	Control	*P* Value	Psycho	Control	*P* Value
Primary endpoint												
Incident proportion (%)	20/47 (43%)	19/43 (44%)	1.000	10/45 (22%)	15/40 (38%)	.347	13/42 (31%)	17/38 (45%)	.298	13/40 (33%)	13/36 (36%)	.929
(No. of events)	(27)	(36)		(18)	(24)		(21)	(24)		(21)	(22)	
Events x 100 patient-years	57.4	83.7	.449	40.0	60.0	.148	50.0	63.2	.344	52.5	61.1	
(95% CI)	(36.2-78.7)	(50.5-116.9)		(14.0-66.0)	(32.1-87.9)		(23.9-76.1)	(36.1-90.2)		(25.3-79.7)	(27.7-94.5)	.827
Reinfarction	3/47 (6%) (3)	1/43 (2%) (1)	.674	2/45 (4%) (2)	—	.527	—	—	—	1/40 (3%) (1)	—	1.000
Death	—	2/43 (5%) (2)	.436	—	—	—	—	—	—	1/40 (3%) (1)	—	1.000
Stroke	—	—	—	—	—	—	—	—	—	—	—	
Revascularization	6/47 (13%) (6)	6/43 (14%) (6)	1.000	6/45 (13%) (6)	—	.049	1/42 (2%) (1)	—	1.000	1/40 (3%) (1)	1/36 (3%) (1)	1.000
MACCE	7/47 (15%) (9)	6/43 (14%) (7)	1.000	6/45 (13%) (8)	—	.049	1/42 (2%) (1)	—	1.000	3/40 (8%) (3)	1/36 (3%) (1)	1.000
Life-threatening ventricular arrhythmia	—	3/43 (7%) (4)	.105	—	1/40 (3%) (1)	.471	2/42 (5%) (2)	—	.495	1/40 (3%) (2)	—	1.000
Recurrence of typical angina	9/47 (19%) (9)	9/43 (21%) (9)	1.000	6/45 (13%) (7)	4/40 (10%) (4)	.890	4/42 (10%) (4)	9/38 (24%) (9)	.158	2/40 (5%) (2)	6/36 (17%) (6)	.200
New comorbidities	7/47 (15%) (9)	11/43 (26%) (14)	.316	3/45 (7%) (3)	12/40 (30%) (19)	.011	11/42 (26%) (14)	11/38 (29%) (15)	.980	11/40 (28%) (15)	9/36 (25%) (15)	1.000
	19.2 (5.0-33.3)	57.4 (36.2-78.7)	.212	6.7 (0-14.0)	47.5 (22.2-72.8)	.004	33.3 (13.7-53.0)	39.5 (16.6-62.3)	.794	37.5 (15.7-59.3)	41.7 (14.2-69.1)	.853
Rehospitalizations	17/47 (36%) (19)	17/43 (40%) (27)	1.000	15/45 (33%) (16)	9/40 (23%) (10)	.386	12/42 (29%) (16)	7/38 (18%) (11)	.422	11/40 (28%) (19)	11/36 (31%) (12)	.968
	40.4 (23.9-56.9)	62.8 (35.9-89.7)	.423	35.6 (20.1-51.0)	25.0 (9.71-40.3)	.288	38.1 (17.0-59.2)	29.0 (6.9-51.0)	.310	47.5 (17.7-77.3)	33.3 (15.9-50.8)	.985
Cardiovascular mean (95% CI)	14/19 (74%)	19/27 (70%)	1.000	12/16 (75%)	5/10 (50%)	.379	7/16 (50%)	8/11 (73%)	.239	9/19(52%)	6/12 (50%)	1.000
Noncardiovascular mean (95% CI)	5/19 (26%)	9/27 (30%)	.854	4/16 (25%)	5/10 (50%)	.379	9/16 (50%)	3/11 (27%)	.274	10/19 (48%)	6/12 (50%)	1.000
NYHA Class - mean	1.0 ± 0.2	1.3 ± 0.5	.002	1.0 ± 0	1.2 ± 0.6	.004	1.1 ± 0.7	1.2 ± 0.5	.249	1.0 ± 0.2	1.2 ± 0.5	.008
NYHA class ≥2 (pts)	2/47 (6%)	12/43 (31%)	.005	—	7/40 (17%)	.011	3/44 (4%)	6/38 (15%)	.592	0/43 (4%)	6/36 (17%)	.018
Drug therapy												

Supplementary Table 2 (*Continued*)

	2nd Year			3rd Year			4th Year			5th Year		
	Psycho	Control	*P* Value	Psycho	Control	*P* Value	Psycho	Control	*P* Value	Psycho	Control	*P* Value
Aspirin	43/47 (91%)	41/43 (95%)	.756	41/45 (91%)	39/40 (98%)	.431	38/42 (90%)	37/38 (97%)	.362	37/40 (92%)	34/36 (94%)	1.000
B-blockers	39/47 (83%)	37/43 (86%)	.912	38/45 (84%)	34/40 (85%)	1.000	35/42 (83%)	31/38 (82%)	1.000	36/40 (90%)	28/36 (78%)	.273
ACE inhibitors or ARB	38/47 (81%)	36/43 (84%)	.936	37/45 (82%)	34/40 (85%)	.959	35/42 (83%)	32/38 (84%)	1.000	33/40 (82%)	28/36 (78%)	.820
Statins	42/47 (89%)	43/43 (100%)	.057	40/45 (89%)	38/40 (95%)	.530	38/42 (90%)	34/38 (89%)	1.000	38/40 (95%)	34/36 (95%)	1.000
Clopidogrel	4/47 (8%)	2/43 (5%)	.756	4/45 (9%)	4/40 (10%)	1.000	5/42 (12%)	4/38 (11%)	1.000	8/40 (20%)	4/36 (11%)	.456
Diuretics	11/47 (23%)	12/43 (28%)	.805	12/45 (27%)	11/40 (27%)	1.000	10/42 (24%)	10/38 (26%)	1.000	11/40 (28%)	10/36 (28%)	1.000
Calcium-antagonists	2/47 (4%)	8/43 (19%)	.068	3/45 (7%)	6/40 (15%)	.372	2/42 (5%)	6/38 (16%)	.205	5/40 (13%)	4/36 (11%)	1.000
Nitrates	17/47 (36%)	19/43 (44%)	.575	13/45 (29%)	19/40 (47%)	.123	12/42 (29%)	17/38 (45%)	.204	8/40 (20%)	10/36 (28%)	.599
Psychoactive drugs	1/47 (2%)	2/43 (5%)	.604	1/45 (2%)	2/40 (5%)	.599	1/42 (2%)	2/38 (5%)	.602	1/40 (2%)	2/36 (6%)	.600

ACE = angiotensin-converting enzyme; CI = confidence interval; MACCE = major adverse cardiac and cerebrovascular events; NYHA = New York Heart Association.

Supplementary Table 3 Statistical Analysis of the Variations of Outcomes Within the Study Groups (Friedman's Test)

	Psychotherapy n = 49	Traditional n = 45
Primary endpoint	.296	< .001
Reinfarction	.406	.092
Death	NA	NA
Stroke	—	—
Revascularization	< .001	< .001
Major adverse cardiac and cerebrovascular events	.001	< .001
Life-threatening ventricular arrhythmias	.171	.134
Recurrence of typical angina	.187	< .001
New noncardiovascular events	.034	.02
Rehospitalizations		
Total	.002	< .001
Cardiological	< .001	< .001
Medical	.414	.555
NYHA class	0.04	0.05
Drug therapy	0.122	0.381

NA = not applicable; NYHA = New York Heart Association.