

Rationale and trial design of a randomized, controlled study on short-term psychotherapy after acute myocardial infarction: the STEP-IN-AMI trial (Short Term Psychotherapy in Acute Myocardial Infarction)

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Objective A number of previous studies addressed the effect of psychological interventions in patients after acute myocardial infarction (AMI), but it is not known whether psychotherapy might be beneficial after medical and interventional therapy of AMI. We designed a randomized, controlled study to assess the effects of a short-term psychotherapy (STP) on the clinical outcomes of patients who underwent an emergency percutaneous coronary intervention after AMI.

Methods One hundred consecutive patients undergoing an emergency percutaneous coronary intervention will be randomized 1 week after AMI to medical therapy (control group, C group) or to medical therapy and STP (STP group). Clinical follow-up visits are scheduled at 6 months, 1 and 5 years, whereas psychometric tests (Self-Evaluation test, Modified Maastricht Questionnaire, Social Support Questionnaire, Recent Life Change Questionnaire, Beck Depression Inventory, the MacNew Heart Disease Health-Related Quality of Life Questionnaire, Type D Personality test) are scheduled 1 week after AMI and at 1 year. The primary outcome measures of the study are the cumulative incidence of new cardiological events (myocardial reinfarction, death, stroke, life-threatening ventricular arrhythmias, and recurrence of angina) and the occurrence

of new medical disorders. Secondary outcome measures are the incidence of rehospitalizations due to cardiological problems, the prevalence of patients with New York Heart Association class \geq II, left ventricular function, as assessed by echocardiography, and mean score of psychometric tests in the two groups at follow-up.

Conclusion Our study has been planned to obtain an insight into how a STP influences clinical outcomes after interventional and medical treatment of AMI. *J Cardiovasc Med* 10:947–952 © 2009 Italian Federation of Cardiology.

Journal of Cardiovascular Medicine 2009, 10:947–952

Keywords: acute myocardial infarction, coronary angioplasty, psychological intervention, psychotherapy

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Received 12 March 2009 Revised 14 May 2009
Accepted 10 June 2009

Introduction

In year 2000, cardiovascular diseases (CVD) accounted for nearly half of all deaths in the developed world and 25% in the developing world, despite improved treatment options and a subsequent decrease in mortality due to cardiac causes in the second half of the twentieth century [1,2]. The estimate for 2030 is that ischemic heart disease will become the world's number one cause of death and disability, the majority of which will be due to acute myocardial infarction (AMI) and late sequelae in survivors [3]. This rise is in part due to the increasing incidence of coronary artery disease (CAD) worldwide but also to an incomplete efficacy of therapies, in spite of the impressive strides in the diagnosis and treatment of AMI. Indeed ST-segment elevation myocardial infarction (STEMI) still causes death in approximately one-

third of patients in the acute phase [4]. At 30 days, mortality is still approximately 9–10% for both STEMI and non-ST-segment elevation myocardial infarction (NSTEMI), whereas the long-term incidence for both mortality and nonfatal events is higher for patients with NSTEMI compared with STEMI and can reach 50% [5,6].

The incomplete efficacy of therapies for ischemic heart disease is due to the intrinsic limitations of any specific treatment, in the presence of a complex multifactorial pathophysiology. In fact, myocardial infarction (MI) is the final, common syndrome resulting from a complex and variable interplay (among different individuals and among different time intervals in the same individual) between coronary vasomotricity, coagulation, endogenous

fibrinolytic, immune and inflammation systems on a variable atherosclerotic and individual predisposition milieu [7,8]. In this multidimensional network, psychosocial factors have been shown to be important predisposing and/or precipitating factors, likely due to a higher frequency of adverse health behaviors and pathophysiological mechanisms, such as neuroendocrine, immune system, coagulation factors and platelet activation [9–13].

In the late 1950s in their pioneering studies, Rosenman *et al.* [14] identified the type A behavior pattern (TABP), a syndrome characterized by competition, hostility and exaggerated commitment to work. The prospective Collaborative Group Study reported that TABP was associated with a two-fold increased risk of CAD and five-fold increased risk of recurrent MI over an 8.5-year follow-up period [14]. However, although TABP continues to receive attention, a series of studies have not been able to confirm a relationship between TABP and CAD risk [15,16].

Subsequently, hostility, a major attribute of TABP, has received considerable attention as a potential critical element in the pathogenesis of this construct. As many as 10 studies assessed the relationship between hostility and CAD in healthy individuals, although with unclear results [11].

Following the visionary studies by Friedman and Rosenman, the research concerning psychosocial factors has grown considerably. Two reviews published by Rozanski *et al.*, the first in 1999 [11] and the second in 2005 [12], reiterated that psychosocial factors contribute significantly to the pathogenesis and expression of CAD. In their opinion, CAD risk is related to five specific psychosocial domains: depression, anxiety, social isolation, chronic life stress and personality factors. With regard to personality factors, some studies [17,18] have investigated whether personality patterns or individual character traits promote the development of CAD.

There is increasing interest in ‘type D’ personality, a new risk marker characterized by a joint tendency toward negative affectivity and social inhibition. Type D is related to adverse health outcome across CVD patient groups, with a two- to five-fold increased risk of adverse prognosis, impaired quality of life, and symptoms of anxiety and depression, independent of traditional biomedical risk factors, including disease severity [19–22]. In the specific setting of AMI, the INTERHEART study [23,24] showed that psychosocial risk factors (i.e. work stress, stress at home, severe financial stress and stressful life events in the past year) came in third after ApoB/ApoA1 ratio and smoking, but before diabetes, as associates of AMI in both sexes and at all ages in all world regions.

On the basis of the numerous epidemiological data collected about the relevance of psychosocial risk factors in the pathogenesis and expression of CAD, a variety of behavioral and psychosocial intervention trials have been implemented in cardiac patients. A first important review of psychological interventions for CAD was published in 2004 [25]. In the latter review, only 36 out of 6535 selected studies met the inclusion criteria (randomized controlled trials of nonpharmacological interventions, administered by trained staff, either single modality interventions or as part of comprehensive cardiac rehabilitation programs, with minimum follow-up of 6 months). Overall, this review showed that psychological interventions had no effect on mortality (both total and cardiac), but did show small reductions in anxiety and depression in patients with CAD. A reduction in the rate of nonfatal MI was observed, although it was considered uncertain because of the poor quality of the trials included, their considerable heterogeneity, and evidence of significant publication bias.

A meta-analysis of the outcome of psychological treatment was published in 2007, including 43 randomized controlled trials if at least one intervention arm permitted the identification of effects attributable to psychological therapy [26]. Overall, psychological therapy of patients suffering from heart disease reduced mortality by 27% and the incidence of recurrent events by 43% (rehospitalization for cardiac emergency and new cardiac procedures, new MI, newly diagnosed arrhythmias, or persistent angina) at long-term follow-up. Successful reduction of distress was necessary for mortality benefits to occur and studies that failed to reduce subjective distress failed to produce significant mortality benefits.

An updated review on depression screening and treatment in patients with CVD was published in 2008 [27]. The investigators reviewed all data sources from inception to 1 May 2008 and selected only six depression treatment trials, comparing depression treatment with placebo or usual care. The authors concluded that depression treatment with drug or cognitive behavioral therapies in patients with CVD is associated with modest improvement in depressive symptoms but no improvement in cardiac outcomes.

Taken together, these studies show that some psychological interventions (like ‘stress management’) may improve prognosis of patients with CAD, but the great heterogeneity of the studies warrants a demonstration in each specific subgroup, such as MI, in which the pathophysiology underlying the clinical manifestations of the diseases is variable. In addition, these studies spanned many years, during which considerable progress has been made in pharmacologic and interventional treatment of CAD, with significant improvement in outcomes, specifically in AMI, wherein the latest treatments may outweigh

the benefit of any further psychological treatment. Therefore, scientific evidence of an additional benefit of psychological intervention with respect to the most updated therapies is still to be obtained. Particularly, to our knowledge, no intervention trial has studied the efficacy of a psychotherapeutic approach after contemporary optimal treatment of MI, encompassing an urgent or emergent revascularization. Moreover, no psychological interventional study has been performed to evaluate the possibility of modifying type D personality and the subsequent clinical cardiological implications.

Therefore, we designed a randomized, controlled trial for the following reasons:

- (1) To assess the contemporary outcomes after a psychotherapy performed in patients who underwent an urgent or emergent interventional treatment for an AMI.
- (2) To seek for any correlation between psychometric variables and cardiological features in the acute phase and in the follow-up, including the quality of life.

Methods

The study is being performed in San Filippo Neri Hospital, Rome, Italy. The protocol was designed between December 2004 and January 2005. Before beginning recruitment, the protocol study was approved by the hospital ethics committee. Recruitment began in June 2005 and is still going on.

Participants

Inclusion criteria

The participants in this study are patients aged 70 years or less, admitted to San Filippo Neri Hospital for AMI and treated with primary or urgent percutaneous coronary intervention (PCI). Primary percutaneous transluminal coronary angioplasty (PTCA) is performed up to 12 h after the beginning of chest pain in case of STEMI, whereas patients with NSTEMI are enrolled if the urgent PTCA is being performed up to 48 h from the beginning of chest pain. Only patients with a complete revascularization are being enrolled in the study. Patients have to be recruited during hospitalization and have to sign an informed consent form prior to the enrollment.

Exclusion criteria

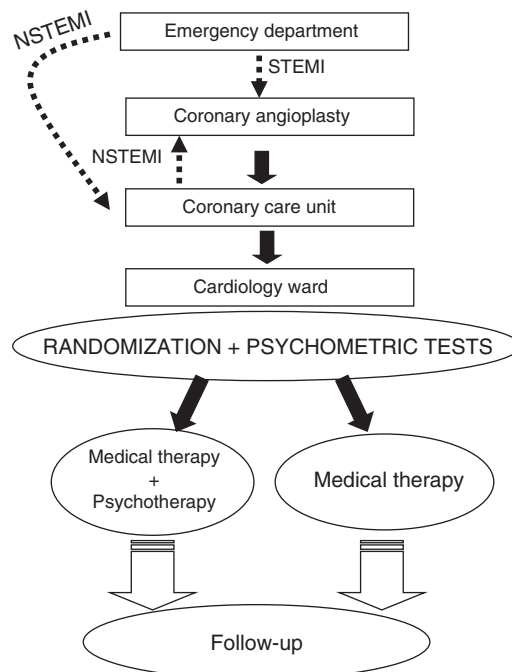
Patients with disability, cognitive impairments, or other life-threatening conditions are excluded from the study.

Study design

Randomization

The study is following the planned randomization scheme 1:1. Randomization is carried out in the first week after the hospitalization, in the cardiology ward, after the patients have been discharged from the intensive care unit (Fig. 1). Given that the inclusion criteria

Fig. 1



Patients with suspected acute myocardial infarction are admitted in the hospital through the emergency department. In case of ST-segment elevation myocardial infarction (STEMI), patients are directly transported to the catheterization laboratory facilities and thereafter to the coronary care unit, whereas non-ST-segment elevation myocardial infarction (NSTEMI) patients are transported to the coronary care unit and, from there, to the catheterization laboratory within 12–24 h and then back to the coronary care unit immediately after the interventional procedure. The informed consent signature and the randomization take place after the patients have been discharged from the coronary care unit to the cardiology ward. The psychological tests are performed in the first days after randomization.

include a wide age interval and that both STEMI and NSTEMI patients are eligible for study participation, the randomization is being performed in blocks according to age and to type/location of the infarction, as follows: patients aged 65 years or less with anterior STEMI; patients aged 66–70 years with anterior STEMI; patients aged 65 years or less with lateral or inferior STEMI; patients aged 66–70 years with lateral or inferior STEMI; patients aged 65 years or less with NSTEMI; and patients aged 66–70 years with NSTEMI. This is done in order to minimize the possible imbalance between the two groups in clinical variables and to avoid the confounding of differences in these variables on outcomes.

For logistic reasons, patients are recruited in blocks of 10 to allow close psychological and medical care in the acute phase and during follow-up. Every block is randomized to usual care (combined pharmacological and interventional therapies) with short-term psychotherapy (STP group); and usual care only (C group). When the target (number of patients) has been reached in a given block, the inclusion stops until the group of patients randomized

to STP has completed the psychotherapy, and then recruitment starts over.

Study management and follow-up

Data are recorded on paper case-report forms and transferred from there into an electronic database, with the principal investigator cross-checking the consistency of data for all patients. Case-report forms have been created to collect patient profile data (risk factors, medical and personal history); medical and clinical data related to hospitalization (administered drugs, echocardiographic data, detailed interventional procedure data); and psychological assessments.

Follow-up is being planned at 6 months, 1 year, and 5 years with a fully comprehensive medical visit, routine blood tests, echocardiography and stress test, or stress myocardial perfusion scintigraphy, being performed by physicians blinded to the randomization. Psychometric assessment is being performed at the 1-year follow-up visit.

Hard copies of original medical records regarding any follow-up event and of all tests are kept in the case-report form by the visiting physician for the final adjudication of events. All the data collected are being peer reviewed at 1-year and 5-year follow-up and clinical adverse events will be adjudicated by a committee composed of three cardiologists blinded to the allocation to study arms.

Psychological assessments

In order to obtain a comprehensive picture of psychologic conditions, the following psychometric tests have been selected:

- (1) Self-Evaluation test: It is used to assess the global level of psychological distress. Patients are asked to estimate retrospectively their distress levels in the preceding 2 weeks on an analogic visual scale. (Indeed previous studies have shown that AMI is often preceded by premonitory symptoms in the 1–2 weeks before the acute event) [28].
- (2) Modified Maastricht Questionnaire: Modified Maastricht Questionnaire adapted from the Maastricht Questionnaire of Apples and Mulder [29,30], is specifically designed to assess levels of vital exhaustion, that is a state characterized by unusual fatigue, increased irritability, and feeling dejected and defeated, in the period preceding its administration. Six items out of the 21 of the original Maastricht Questionnaire were removed to avoid assessing extreme and improbable manifestations of psychological distress (i.e. desire to commit suicide) and two were added in order to better explore manifestations of anxiety [28].
- (3) Social Support Questionnaire: It is used to evaluate each individual's perception of his/her social net-

work, as it explores the presence and importance of three elements in the patient's life (i.e. a particularly important person, family and friends). It consists of 12 items and its score indicates the degree of perceived social isolation [28,31].

- (4) Recent Life Change Questionnaire: It is designed to evaluate the presence and importance of occasional major life events and chronically recurring aggravations in daily life [32]. Patients are asked to indicate which listed events have occurred during the year prior to the evaluation, the outcome of each event (i.e. joyful or painful) and the relevance of each event from an emotional point of view.
- (5) Beck Depression Inventory (BDI): It is used to evaluate the presence of major or minor depression (in accordance with the modified *Diagnostic and statistical manual of mental disorders*, 4th ed., diagnostic criteria) [33,34]. A score between 10 and 15 is considered indicative of mild depression, whereas a score equal or superior to 16 is considered indicative of clinically relevant depression.
- (6) The MacNew Heart Disease Health-Related Quality of Life Questionnaire: It evaluates the quality of life related to three specific domains – emotional, physical, and social – with a score for each domain and a global score [35].
- (7) In a subset of patients, the Type D Scale (DS14), assessing whether a patient has a type D personality disposition, is evaluated [36,37].

Therapies

Medical drug therapy in the acute and chronic phase is being left to the treating physician's discretion and carefully recorded in the case-report form. Pharmacological psychiatric treatments, wherever needed, are not part of this protocol and therefore are being left to the caring psychiatrist's independent decision and are also recorded in the case-report forms. All patients are informed about the importance of modifying their diet, stopping smoking, and engaging in moderate daily exercise. To minimize the possibly etherogenous effects of different psychotherapists, psychotherapy is being performed by one skilled and graduated psychotherapist, with the help of clinical staff – both psychologists and nurses. The psychotherapy uses a humanistic-existential approach, associated with psychodynamic analysis, carried out in individual and group meetings during a 6-month period after the incident AMI. The intervention is being tailored to the specific needs and problems of every patient, with the number of individual sessions ranging from 3 to 11. After the individual sessions, the patients are being admitted to the group sessions (five sessions during the course of 3 months), in which partners are being invited to participate. The group sessions include educational therapy, music-guided breathing and muscular relaxation, comprehension of body signals and elements of oneiric language, and specific attention to partner relationship problems.

All patients have scheduled cardiological controls for the study at 1 and 6 months, 1 year and 5 years. Every patient has the possibility of contacting the hospital researchers in case of any health problems.

Study endpoints and outcome measures

The primary study endpoint is the net cumulative incidence of new cardiological events (i.e. myocardial reinfarction, death, stroke, any revascularization, life-threatening ventricular arrhythmias, and recurrence of typical angina pectoris) and the occurrence of any new medical disorder at 5 years in the study arms. In hospital, myocardial reinfarction is defined as any development of new diagnostic Q waves in at least two contiguous ECG leads and/or any elevation of creatine kinase-myocardial band isoenzyme (CK-MB) levels at least three times the upper level of normal (ULN) within 36 h of the procedure, or at least two times the ULN beyond this time limit. Myocardial reinfarction occurring during follow-up after discharge was defined as recurrence of ST-segment elevation and/or any new significant Q wave and/or the occurrence of any increase in CK-MB levels above the last value, associated with recurrent symptoms. Life-threatening arrhythmias are defined as resuscitated cardiac arrest and/or documented asystole and/or ventricular fibrillation and/or sustained ventricular tachycardia and/or pulseless electrical activity.

The secondary endpoints are the assessment at any follow-up visit of the following outcomes:

- (1) Breakdown analysis for individual outcomes of primary endpoint.
- (2) Incidence of new hospital admissions for cardiologic and/or medical reasons.
- (3) Echocardiographic ejection fraction, ventricular volumes and wall motion score index.
- (4) Prevalence of New York Heart Association (NYHA) class \geq II.
- (5) Rate of automatic implantable cardiac defibrillators (AICD)
- (6) Changes in psychometric tests score
- (7) Change in quality of life.
- (8) Prevalence of type D personality.
- (9) Correlation of psychological descriptors and clinical, laboratory and echocardiographic data.

Statistical analysis

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

Continuous variables for each of the study groups will be reported as mean (standard deviation) or as median [minimum–maximum], as appropriate; categorical variables will be reported as the absolute number and percentage. Continuous variables will be compared using

independent-sample Student's *t*-test or Mann–Whitney *U*-test, where appropriate. Categorical variables will be compared by means of Pearson's χ^2 analysis or Fisher's exact test, where appropriate. Multivariable binary logistic regression analysis will be performed to appraise the independent predictive role of psychometric tests score on both primary and secondary outcomes, selecting variables for the final multivariable model using a backward stepwise algorithm.

On the basis of clinical results reported in previous psychological intervention studies [11,25,26], a 60% incidence of the primary composite endpoint can be expected at 5 years in the control group; hypothesizing a 50% reduction of this incidence in the psychotherapy arm, it will be necessary to randomize 84 patients to achieve statistical significance with an α of 0.05 and a power of 80. Taking into account a lost-to-follow-up, which is difficult to anticipate in a psychological intervention study, it has been decided to enroll 100 patients.

A *P* value of less than 0.05 will be considered statistically significant, with all reported *P* values two-tailed. Statistical analysis will be performed using SPSS version 11.5 (SPSS Inc., Chicago, Illinois, USA).

Enrollment status

Since June 2005, 70 patients have been randomized. The slow rate of inclusion is due to the single psychotherapist approach and to the protocol design (see randomization paragraph), which stops the study inclusion after every 10 enrolled patients until the STP group (composed of five patients) finishes the psychotherapy cycle. So far,

Table 1 Clinical baseline characteristics of the initially randomized patients

	STP group (N=36)	Control group (N=34)	<i>P</i>
No. of risk factors/patient			
AMI	3.1 ± 1.5	3.4 ± 1.4	NS
STEMI	22	24	NS
NSTEMI	8	5	NS
No. of diseased vessels	1.7 ± 0.7	1.7 ± 0.7	NS
Door-to-balloon time (min)	712 ± 749	492 ± 508	NS
PCI on LAD artery			
TIMI flow	20	21	NS
Pre	1.2 ± 1.2	1.1 ± 1.3	NS
Post	2.8 ± 0.5	2.9 ± 0.4	NS
Patients having received drug-eluting stent(s)	17	13	NS
CK-MB max (ng/ml)			
Echocardiogram	124 ± 100	180 ± 126	NS
EF (%)	48 ± 13	52 ± 11	NS
WMSI	1.5 ± 0.4	1.5 ± 0.4	NS
Cardiac rehabilitation	15	16	NS
Number of noncardiac diseases/patient	0.8 ± 1	0.8 ± 1.1	NS

AMI, acute myocardial infarction; CK-MB, creatine kinase-myocardial band isoenzyme; EF, ejection fraction; LAD, left anterior descending; NS, not significant; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; STP, short-term psychotherapy; TIMI, thrombolysis in myocardial infarction; WMSI, wall motion score index.

Table 2 Psychosocial baseline characteristics of the initially randomized patients

Psychological assessment	STP group (N = 36)	Control group (N = 34)	P
Self-Evaluation test	7.1 ± 2.3	6.5 ± 2.7	NS
Modified Maastricht test	74.9 ± 30.7	80.5 ± 40	NS
Recent Life Change test	1.5 ± 6.2	2.4 ± 9.3	NS
Social Support test	25 ± 8.9	22.9 ± 9.4	NS
Beck Depression Inventory test	7.5 ± 6.2	11.5 ± 9.5	NS
MacNew test (global score)	5.2 ± 6.8	4.9 ± 0.9	NS
Type D personality test	60% (3/5 patients)	43% (3/7 patients)	NS

NS, not significant; STP, short-term psychotherapy.

patients included in the study are homogeneous on baseline clinical (Table 1) and psychosocial characteristics (Table 2). Considering the rate of inclusion, the enrollment is expected to be completed by the summer of 2010. The 1-year follow-up of all the patients should then be achieved in 2011, and the complete 5-year follow-up in 2015.

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