Internal and Emergency Medicine

DEPRESSIVE SYMPTOMS, FUNCTIONAL MEASURES AND LONG-TERM OUTCOMES OF HIGH-RISK ST-ELEVATED MYOCARDIAL INFARCTION PATIENTS TREATED BY PRIMARY ANGIOPLASTY.

--Manuscript Draft--

Manuscript Number:	IAEM-D-15-00222R2
Full Title:	DEPRESSIVE SYMPTOMS, FUNCTIONAL MEASURES AND LONG-TERM OUTCOMES OF HIGH-RISK ST-ELEVATED MYOCARDIAL INFARCTION PATIENTS TREATED BY PRIMARY ANGIOPLASTY.
Article Type:	ORIGINAL
Section/Category:	IM - ORIGINAL
Keywords:	depression; Beck inventory; Physical fitness; myocardial infarction; prognosis.
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Abstract:	Background Presence of major depressive symptoms is usually considered a negative long-term prognostic factor after an acute myocardial infarction (AMI). However, most of the supporting research was conducted before the era of immediate reperfusion by percutaneous coronary intervention. Aims of this study were to evaluate if depression still retains long-term prognostic significance in our era of immediate coronary reperfusion, and to study possible correlations with clinical parameters of physical performance. Methods and Results In 184 patients with recent ST-elevated AMI (STEMI), treated by immediate reperfusion, moderate or severe depressive symptoms (evaluated by Beck Depression Inventory version I) were present in 10% of cases. Physical performance was evaluated by two 6-minute walk tests and by a symptom-limited cardiopulmonary

	exercise test: somatic/affective (but not cognitive/affective) symptoms of depression and perceived quality of life (evaluated by the EuroQoL questionnaire) were worse in patients with lower levels of physical performance. Follow-up was performed after a median of 29 months by means of telephone interviews; 32 major adverse cardiovascular events (MACE) occurred. Presence of 3 vessels disease and low left ventricle ejection fraction were correlated with greater incidence of MACE; only somatic/affective (but not cognitive/affective) symptoms of depression correlated with long-term outcomes. Conclusions In patients with recent STEMI treated by immediate reperfusion, somatic/affective but not cognitive/affective symptoms of depression showed prognostic value on long-term MACE. Depression symptoms were not predictors "per se" of adverse prognosis, but seem to express an underlying worse cardiac efficiency, clinically reflected by poorer physical performance.
Response to Reviewers:	AUTHORS' ANSWERS TO REVIEWERS' COMMENTS DEPRESSIVE SYMPTOMS, FUNCTIONAL MEASURES AND LONG-TERM OUTCOMES OF HIGH-RISK ST-ELEVATED MYOCARDIAL INFARCTION PATIENTS TREATED BY PRIMARY ANGIOPLASTY. Note: All the changes made to the paper have been underlined in yellow in the manuscript, here following Reviewer's comment #1: ... how many of your AMI did not have 3 RF ... Authors' answer: We understand the doubt of the reviewer. Three (or more) risk factors are very often present in AMI patients. Anyway, all the AMI patients that had been admitted to our residential Cardiac Rehabilitation (CR) responded to the routines in use in Italy at the time of data collection, that have been formalized in 2011 as recommendations of a national Joint Committee (ANMCO-IACPR/GICR Consensus, G Ital Cardiol (Rome). 2011 Mar;12(3):219-229); in such recommendations, (besides clinically complicated cases) patients are admitted to CR if their risk factors are particularly "out-of-control" and need intensive multifaceted intervention. (For instance: persistence smoking habit, elevated cholesterol levels, poorly controlled insulin-dependent diabetes, sedentary/aged patients...). The related reference has been added, in the paragraph Materials and Methods. Reviewer's comment #2: ... cognitive/affective v. somatic/affective symptomatology ... highlight this and break it out into a table or box. Authors' answer: According to the Reviewer's suggestion, a Box has been added, with the Beck's Inventory split into two columns according to cognitive vs somatic symptoms. Reviewer's comment #3: ... suicidal ideation, sadness, ... put this in the discussion, as many providers are more likely to key into these manifestations ... ... PCPs should specifically inquire about the somatic symptoms as they are more predictive of long term results. Authors' answer: We agree with the suggestion, and have included a sentence in Discussion (page 13, line 19). Reviewer's comment #4: ... the study was approved by the Ethics Committee - is that the same as your institutional review board? Authors' answer: A first approval to the study was given by the Institutional Review Board (type of activity, type of questions to the patients, privacy, use of data), but the final approval was given by the Ethical Committee, that is a Committee of upper level located at the Provincial Directorate of Health, Belluno (Italy). To such Committe (that includes provincial Director of Health, pharmacologist, lawyer, doctors appointed to ethics issues), all details of the larger study (of which the present paper reports psychological data) on long-term results of AMI patients submitted to CR have been presented; written approval was obtained. Reviewer's comment #5: ...separate analysis regarding the types of MI (inferior, ...) and outcome and patients with somatic/affective symptoms and relation to exercise tolerance? ...to see if the type of MI impacted the analysis. Authors' answer: Thank you for your observations. Analysis had been done, but the

	results had not been included in the original manuscript, because there was no statistical difference in the occurrence of MACE between patients with anterior vs inferior AMI. Following your suggestion, a short statement about this has been included in the manuscript at page 10 line 9. Patients with higher Beck somatic/affective scores performed in a worse way at 6MWT and reached lower W-max at final CPET (but not lower peak-VO2 or percentage of expected peak-VO2); this was already stated in the manuscript, in the last paragraph of page 1, line 27 (see underlined sentences). Patients with anterior AMI presented statistically lower LVEF; this has been added at page 11, line 14. Reviewer's comment #6: ...large range regarding follow-up 28±16 months... Authors' answer: As the Reviewer pointed out, expressing the period of follow-up a mean±SD is misleading; the ample SD is mainly due to some patients that have been followed-up for as much as 54 months. The 95% CI of the period of follow-up was 25.5-30.8 months, that is at least 2 years. We changed the sentence at page 9, including only the median time of follow-up and its 95%C.I. Thank you for your observation. Reviewer's comment #7: ...32 did not complete Beck Inventory out of 220 ... ... same number as MACE. Authors' answer: The 32 patients with MACE at follow-up are not the same as the 32 patients that did not have BDI-1 score (these last ones have been excluded from analysis). It is a pure coincidence of numbers. Reviewer's comment #8: ...none of the later category (patients with moderate-severe depressive symptoms) was placed on antidepressants... ... You touched briefly the ENRICHD study and your opinion that the decreased exercise tolerance/physical limitations was responsible for the symptoms (somatic) Authors' answer: That's exactly what we are thinking, and what we try and communicate with the paper. Evaluation of depressive symptoms by BDI-1 scores in patients in the early post-STEMI period is biased by the weigh of pure somatic symptoms in the Beck inventory; in this phase, BDI-1 scores do not correspond to real depressive symptoms, while they are linked to physical limitations, that often are transient or may partly during CR or afterwards. As already reported by Zuidersma et al (Ref 48), implementation of an antidepressant treatment strategy does not seem to reduce the risk of cardiovascular morbidity and mortality; same concepts have been expressed also by other Authors, such as Shapiro et al (Ref 49). Also the ENRICHD study (Ref 50), in which cognitive (!) behaviour therapy was performed in a group of patients, did not report any significant differences in outcomes between patients treated by usual care and patients that received cognitive behaviour therapy. We have to say that anyway all our patients received a comprehensive CR intervention, that - as reported in Materials and Methods - included also individual and group counselling meetings. We slightly modified the paragraph of Conclusions (some terms here and there) to try and make our conclusions clearer. Reviewer's comment #9: Not having the patient's previous psychiatric history is also a significant limitation ... ...previous medications... ...illicit drug abuse and alcohol abuse? Authors' answer: Lack of knowledge about presence of depressive symptoms prior to STEM is a limitation that is already reported in the § Limitations. Anyway, medical history taken at initial hospital admission (to CCU9 and repeated by our team at admission to CR confirmed that no patient was taking major antidepressant drugs at the time of hospital admission. None of our patients was drug-addict. In spite of being mainly living in an area of Italy with one of the greatest (and best!) production of wines in the world, our patients use to drink one or two glasses of wine / day, but none of them presented signs of alcohol abuse (history, clinical and laboratory); none presented abstinence during initial hospital admission. We added a sentence to the § Limitations to clear the aspect of drugs use or alcohol. Reviewer's comment #10: Did you analyze gender, to see if men vs women had more somatic/affective vs cognitive/affective? Could be an interesting subanalysis. Authors' answer: After your interesting suggestion, we performed an analysis of possible correlation between sex and degree of cognitive/affective or somatic/affective symptoms. It seems that a greater number of women present higher (upper quartile)

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June 17th, 2016

To
the Editor in Chief
of ***Internal and Emergency Medicine***

Dear Editor,
I am pleased to resubmit to your kind attention the manuscript **"Depressive symptoms, functional measures and long-term outcomes of high-risk ST-elevated myocardial infarction patients treated by primary angioplasty"** (manuscript number: IAEM-D-15-00222R1), after the revision according to Reviewer's suggestions.

Following the precious suggestions given by the Reviewer, the manuscript has been partially modified. All the modifications are highlighted in yellow in the copy of the manuscript in Annex to this letter.
In Annex, please also find detailed answers to each of the Reviewer's comments.

We hope that now the manuscript could reach the standards for acceptance for publication in your esteemed Journal.

On behalf of my Colleagues, I confirm what already stated at the time of previous submission:

1- the manuscript has not been published previously and it is not under consideration for publication elsewhere;
2- all Authors participated in the preparation of the paper (conception of the work, follow-up of the patients, collection and interpretation of the results, revision of the manuscript);
3- each author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation;
4- all Authors are in agreement with the content of the manuscript and approve the submission;
5- no Author has any type of relationship with companies or relevant entities that make products pertinent to the paper.

Hoping to receive from you positive news, I present my best regards.

Leonida Compostella, MD
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AUTHORS' ANSWERS TO REVIEWERS' COMMENTS

DEPRESSIVE SYMPTOMS, FUNCTIONAL MEASURES AND LONG-TERM OUTCOMES OF HIGH-RISK ST-ELEVATED MYOCARDIAL INFARCTION PATIENTS TREATED BY PRIMARY ANGIOPLASTY.

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Short Title: Compostella - Depression and outcomes after STEMI

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Statement: Each one of the above mentioned authors takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

Source of funding: This work was not supported by grant.

Conflicts of interest: No Author has any conflict of interest to declare.

Word count: 8595 (total); text only 4734

Number of Tables: 2 (1 Table + 1 Box)

Number of figures: 3

Abstract

Background

Presence of major depressive symptoms is usually considered a negative long-term prognostic factor after an acute myocardial infarction (AMI). However, most of the supporting research was conducted before the era of immediate reperfusion by percutaneous coronary intervention. Aims of this study were to evaluate if depression still retains long-term prognostic significance in our era of immediate coronary reperfusion, and to study possible correlations with clinical parameters of physical performance.

Methods and Results

In 184 patients with recent ST-elevated AMI (STEMI), treated by immediate reperfusion, moderate or severe depressive symptoms (evaluated by Beck Depression Inventory version I) were present in 10% of cases. Physical performance was evaluated by two 6-minute walk tests and by a symptom-limited cardiopulmonary exercise test: somatic/affective (but not cognitive/affective) symptoms of depression and perceived quality of life (evaluated by the EuroQoL questionnaire) were worse in patients with lower levels of physical performance. Follow-up was performed after a median of 29 months by means of telephone interviews; 32 major adverse cardiovascular events (MACE) occurred. Presence of 3 vessels disease and low left ventricle ejection fraction were correlated with greater incidence of MACE; only somatic/affective (but not cognitive/affective) symptoms of depression correlated with long-term outcomes.

Conclusions

In patients with recent STEMI treated by immediate reperfusion, somatic/affective but not cognitive/affective symptoms of depression showed prognostic value on long-term MACE. Depression symptoms were not predictors "per se" of adverse prognosis, but seem to express an underlying worse cardiac efficiency, clinically reflected by poorer physical performance.

Keywords: depression, Beck inventory, physical fitness, myocardial infarction, prognosis.

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List of Acronyms

%-VO_2 = percentage of expected peak Oxygen uptake

6MWT = 6-minute Walk Test

ACE = Angiotensin Converting Enzyme

AMI = Acute Myocardial Infarction

AT-II = Angiotensin II receptor type 2

BDI-I = Beck Depression Inventory, version 1

CABG = Coronary Artery By-pass Graft

CPET = Cardio-Pulmonary Exercise Test

CR = Cardiac Rehabilitation

ECG = Electrocardiogram

EQ-5D-3L = European QoL questionnaire 5D-3L

EQ-VS = European QoL questionnaire Visual Scale

MACE = Major Adverse Cardiovascular Events

MRI = Magnetic Resonance Imaging

PCI = Percutaneous Coronary Intervention

peak-VO_2 = peak Oxygen uptake

QoL = Quality of Life

STEMI = ST-elevated Myocardial Infarction

W-max = maximum sustained workload at CPET, in Watt

In the last 25 years, along with improvements of intensive treatment of patients with acute myocardial infarction (AMI), numerous prospective studies, systematic reviews and meta-analyses have been conducted that show a robust association between depression (major depression or elevated depressive symptoms) and increased morbidity and mortality after AMI. Consequently, major depression has been recently proposed as risk factor for poor prognosis among patients with acute coronary syndromes.[1]

However, it must be said that the majority of the studies showing a correlation between depression and clinical outcomes after an AMI have been conducted before the era of immediate reperfusion by percutaneous coronary intervention (PCI). Among 32 studies included in the recent review by Lichtman JH et al,[1] only half reported the treatment performed in the acute phase of the infarction, with primary PCI performed mostly in a modest proportion of patients (widely variable from 0 to 76 percent of cases).[2-3] Different treatments in the acute phase of myocardial infarction could have influenced initial clinical conditions and patients' health perception, that could not be the same as in today's patients.

Furthermore, nowadays an increasing number of post-AMI patients are admitted to a cycle of cardiac rehabilitation (CR),[4] mainly based on exercise training. Besides positive effects on all-cause and cardiovascular mortality,[5] CR may exert some positive effects also on depressive mood of post-AMI patients.[6-9]

Thus, the complex interrelationship between depression, physical fitness and exercise-based rehabilitation, and the influence of these factors on patients' long-term survival constitute a changing scenario.

Aims of this study were: 1- to assess the prevalence of depressive symptoms in patients admitted to CR after a complicated ST-elevated myocardial infarction (STEMI) treated by primary PCI, 2- to evaluate if depression still maintains a prognostic value in the era of immediate reperfusion in patients submitted to CR, 3- to estimate possible relationship between depression and physical fitness.

Materials and Methods

Design of the Study

We retrospectively reviewed the clinical files of 262 consecutive patients admitted to our CR unit for a period of residential, exercise-based rehabilitation, 16 ± 10 days (95% CI 15 - 18) after a complicated STEMI. All patients had undergone coronary angiography at initial admission to the Intensive Coronary Care Unit, during the first 6 hours from beginning of AMI symptoms: 94% of them underwent PCI of the culprit coronary artery, while only a small percentage of them (6%) was not revascularized due to unfavourable coronary anatomy and were put on optimal medical therapy. Patients were selected by the submitting centre and sent to our CR program if they suffered a complicated AMI (cardiogenic shock or pulmonary edema, episode of cardiac arrest, complex ventricular arrhythmias), or if they had

incomplete revascularization (because of unfavourable coronary anatomy or technical failure), or had at least 3 major cardiovascular risk factors.[10] Low risk patients followed an out-patient CR program in another centre and were not considered for this study.

Echo- or cardiac MRI- documented intracavitary thrombosis, extreme thinning or suspected rupture of the ventricular wall and/or intra-myocardial bleeding were exclusion criteria from admittance to CR; history of previous myocardial infarction was an exclusion criteria for the present study.

The following clinical variables were recorded for each patient: age, gender, body mass index, cardiovascular risk factors, site of infarction, culprit coronary artery vessel, number of diseased coronary artery vessels (defined as presence of diameter stenosis > 50%), history of previous PCI or coronary or valvular surgery, presence of ancillary diseases (renal failure, thyroid dysfunction, known diabetes or abnormal glucose metabolism, pulmonary diseases, history or presence of neoplastic diseases, carotid and peripheral vascular disease) and drug therapy. During stay in CR, all patients without previous diagnosis of diabetes underwent an oral glucose tolerance test to identify subclinical abnormal glucose metabolism. Left ventricular ejection fraction (LVEF) was measured before discharge by 2-D echocardiography, following the Simpson method.

Depressive symptoms evaluation

During the CR period, patients were carefully evaluated by a trained psychologist; symptoms of depression were assessed using a self-report questionnaire, the Beck Depression Inventory version 1 (BDI-I).

The BDI-I is a 21-item self-report measure, developed to assess the presence and severity of depressive symptoms;[11] each of the 21 items represents an aspect of depression clinical presentation and is rated on a 0-3-point scale of symptom severity. Scores on items 1–10 and 12–14 (sadness, pessimism, sense of failure, self-dissatisfaction, guilt, punishment, self-dislike, self-accusations, suicidal ideas, crying, social withdrawal, indecisiveness, body image change) may be summed to calculate cognitive/affective symptom scores. Items 11 and 15–21 (irritability, work difficulty, insomnia, fatigability, loss of appetite, weight loss, somatic preoccupation, loss of libido) may be summed to calculate somatic/affective symptom scores. BDI-I scores of 10-15 are indicative of mild symptoms of depression, 16-23 moderate depression, and 24-63 severe depression. In this study, we analysed separately the total BDI-I score and the scores for somatic/affective and cognitive/affective symptoms (see Box 1).

Perceived quality of life

To assess the impact of the most frequent physical symptoms of the disease and its treatments on the perceived quality of life (QoL), the European QoL questionnaire 5D-3L (EQ-5D-3L) was administered to our study patients during the CR period.

The EQ-5D-3L is a descriptive system of health-related QoL states that captures the respondent's situation at the time of completion. It consists of five questions on five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression); each dimension can take one of three levels of responses, recording three levels of severity (no problems/some or moderate problems/extreme problems).[12] The questionnaire is integrated with a visual analogue scale (EQ-VS), that records the respondent's self-rated health on a vertical scale, where the endpoints are labelled "Best imaginable health state" and "Worst imaginable health state". In our study, this information was used as a quantitative measure of health status as judged by the individual respondents.

Cardiac Rehabilitation

The training consisted of a low-medium intensity exercise protocol developed in 3 sets of exercises, 6 days a week for an average of 2 weeks: 30 min of respiratory training, followed by an aerobic session on a stationary bike (or with an arm-ergometer for those patients who were not able to cycle) in the morning and 30 min of callisthenic exercises in the afternoon. Each session was supervised by a physician and a physiotherapist and all patients were ECG monitored by a telemetry system. Aerobic training was performed using a constant work rate modality, without exceeding 70% of the maximal predicted peak heart rate for each patient.[13] Each aerobic session lasted 10 minutes at the beginning, with a 5 minutes progressive increase to reach a 30 min target; the exercise prescription and evaluation of exercise intensity was carefully derived from the subjective rating of perceived exertion, using a category ratio Borg scale.

Individual and group counselling meetings and nutritional evaluation were also performed for all patients.

Physical evaluation

Physical performance of the patients was assessed by two different methods: two six-minute walk tests (6MWT), performed at admission (6MWT-in) and at the end of the rehabilitative period (6MWT-out), and a symptom-limited cardiopulmonary exercise test (CPET) performed on the day before discharge from CR.

The 6MWTs were performed in a 30 m long, unobstructed indoor corridor, according to the American Thoracic Society recommendations.[14]

The CPET was performed on a computer-driven cycle ergometer (Cardiovit CS-200 Ergo-Spiro, Schiller AG, Baar, CH; Ergoselect 100 ergometer, Ergoline GmbH, Bitz, D). A progressive ramp protocol of 6 to 10 W/min was used, until subjective exhaustion or appearance of clinical or electrocardiographic criteria for termination.[15] Expired gas was

collected by means of a tightly fitting face mask and continuously analyzed during the exercise test (Schiller Ganshor CS-200 Power Cube). Peak oxygen consumption (peak-VO_2) was expressed relative to body weight, and as a percentage of the expected based on age, sex and body mass (%-VO_2). Peak exercise capacity was expressed in Watt as maximum sustained workload (W-max).

End Points and Follow-Up

At the time of follow-up, the clinical status of the patients was assessed by telephone interviews, performed by a doctor or a trained team nurse. In case of clinical events, detailed information was obtained from the patient or his/her relatives. The primary end point of the study was the occurrence of major adverse cardiovascular events (MACE), defined as death (all-cause mortality, cardiac mortality), or readmission for a new AMI, new revascularization, episodes of heart failure or stroke.

Statistical analysis

Continuous variables were expressed as a mean ± standard deviation and compared using an unpaired Student t-test; categorical variables were expressed as frequencies and percentages and were compared between groups by Pearson's chi-squared test (χ^2). The relationships between continuous variables were evaluated by Spearman's correlation coefficient. Event free survival curves were calculated by the Kaplan-Meier method and groups were compared with a log-rank test. A Cox regression multivariate analysis was performed to determine the influence of different factors (age>65 years, sex, time from event to CR, site of STEMI, signs of heart failure, number of vessels with critical lesions, incomplete revascularization, NYHA functional class, EF<40%, known diabetes, chronic renal failure, physical performance parameters, depression and quality of life parameters) on MACE. All reported probability values are two-tailed and the significance level was set at 0.05. Statistical analyses were performed using SPSS 18 software package (SPSS Inc, Chicago, IL,USA).

Statement

During CR hospitalization, all the participants have been informed about the procedures they were undergoing; a written consent was obtained from all patients before performance of CPET. The usual diagnostic and follow-up routine for CR were applied; no special test or treatment was performed. The research was conducted in accordance with the ethical guidelines of the 1975 Declaration of Helsinki. This study is part of a larger follow-up study on AMI patients admitted to CR; approval of the Provincial Ethics Committee (Provincial Directorate of Health, Belluno, Italy) was obtained for the main research.

RESULTS

General Findings

During the study period (January 2008 to June 2012), 262 patients had been directly transferred from the Cardiology Department to our CR unit, for intensive in-hospital rehabilitation on average 16 days (95% CI: 14.9-17.9) after a first complicated STEMI. No fatal events occurred during the CR stay (median duration 14.5 days; 95% CI: 14.1-14.9 days), although 3 patients had to be transferred back to the Intensive Care Unit because of complications before completing the rehabilitation protocol; thus, they dropped out of the study.

According to inclusion and exclusion criteria as reported in the patients selection flowchart represented in Fig. 1, a final group of 188 patients was suitable for the follow-up study.

STEMI was anterior in 121 cases (64%), inferior in 65 patients (35%) and in other segments in the remaining 2 cases; 71 (38%) patients were affected by a single vessel disease, while 60 (32%) presented a two vessels disease and 57 (30%) a three vessels disease. Approximately 4% of patients had history of previous CABG (7 patients) and 7% previous elective PCI (14 patients).

Primary PCI was successful in 173 patients (92% of the study cases). In only 15 patients (8% of the study group) the primary revascularization attempt failed due to unfavourable coronary anatomy; these patients were thus submitted to medical therapy. Of the 173 primary PCI patients, 61 (32%) had been immediately treated also on non-culprit coronary lesions; 8 (4%) received further elective percutaneous revascularization during the initial stay in the Cardiology Department. Overall, at the time of transferral to the CR unit, 113 patients (60%) had a complete revascularization, while 75 patients (40%) had still an incomplete revascularization.

All patients were discharged from CR on aspirin and 93% were also receiving a second antiplatelet agent; 13% were receiving oral anticoagulation; other therapy included β-blockers (92%), Ca-antagonists (8%), ACE-inhibitors (87%) or AT-II-antagonists (8%), statins (98%) and diuretics (36%).

Clinical characteristics and follow-up

At the time of follow-up, at a median of 28.8 months (95% CI: 25.5-30.8) after the acute event, it was not possible to trace a total of 4 patients (2.1%).

Among the 184 followed-up patients, MACE occurred in 32 cases and consisted of 6 deaths (3.2%) and 7 cases of new non fatal AMI (3.8%), 3 strokes (1.6%), 6 cases of successful elective revascularization (3.2%: 3 CABG, 3 elective PCI), and 10 hospital readmissions for heart failure (5.4%).

The main characteristics of the 184 followed-up patients with and without MACE are summarized in Table I.

At multivariate analysis, age and LVEF <40% were the only clinical characteristics that were significantly correlated with long-term prognosis (p = 0.039 and p = 0.044, respectively). Patients that presented a greater myocardial damage, as indicated by a lower LVEF (<40%), had a greater number of MACE in the follow-up, than patients with less compromised LVEF (χ^2 5.305, p = 0.021).

Patients with a 3-vessel disease had an incidence of MACE during the period of follow-up (12 MACE on a total of 54 patients, 22%) that was similar to that of patients with less diffuse coronary disease (18 MACE among a total of 130 cases, 14%) (χ^2 = 1.96, p = 0.161); no significant correlation was found with other clinical characteristics, such as sex (p = 0.354), number of vessels treated during the primary PCI (p = 0.767), history of incomplete revascularization (p = 0.132), site of myocardial infarction (p=0.444) or presence of signs of heart failure during initial admission (p = 0.801).

At follow-up, no patients reported having used any major antidepressant drug since the index event.

Depressive symptoms, perceived QoL and outcome

Depressive symptoms during CR were identified by BDI-I ≥ 10 in one out of four patients (25% of cases) but only 3 patients (1.6%) were classified has having severe symptoms of depression (BDI-I ≥ 25) and other 19 (8.5%) as having moderate depressive symptoms.

In the whole group of patients, mean BDI-I scores were similar between the group of patients that presented MACE during the period of follow-up and those without MACE. Although patients with higher depression scores showed a tendency for a greater incidence of MACE (MACE in 14% of patients with BDI-I ≤ 9; 18% in BDI-I 10-15; 24% in BDI-I 16-23; no MACE among the 2 patients with BDI-I ≥ 24), the Pearson's chi-square showed no significant correlation (χ^2 = 1.333; p = 0.721), perhaps due to the small number of events recorded.

The Kaplan-Meier cumulative MACE-free survival curves, stratified according to BDI-I scores <16 versus ≥16 (Fig. 2A), confirmed that no significant difference was found between the two groups of patients without symptoms or with mild symptoms of depression in comparison to patients with moderate or severe symptoms of depression (p = 0.827).

The findings were different when observing the relationship between somatic/affective scores of the BDI-I questionnaire (question 11 and 15-21) and MACE. Somatic/affective symptoms accounted for widely variable percentages of the total score of the BDI-I questionnaire, ranging from 0 to 100% (mean percentage of scores 64±30%; median 62.5%; 95% CI: 58-70). Patients that presented somatic/affective scores in the upper quartile (a score ≥6 in our cases) during the period of CR suffered a significantly greater number of events during follow-up: 10 out of 30 patients (33%) suffered MACE during follow-up, while only 5 MACE occurred among 73 cases (7%) with somatic/affective scores in the other three quartiles (χ^2 11.99; p < 0.001). In fig. 2B, the Kaplan-Meier cumulative MACE-free survival curve for patients in the upper quartile of somatic/affective BDI-I scores indicates significantly different outcomes in

comparison to patients in the lower quartiles (p = 0.007). By the contrary, no significant correlation was found between cognitive/affective symptoms of depression during CR and long-term MACE: among 36 patients in the upper quartile of cognitive/affective score (in our cases ≥5), 6 patients (17%) suffered MACE during follow-up, while there were 6 cases of MACE among 66 patients (9%) in the lower quartiles of cognitive/affective score (χ^2 1.29, p = 0.2564).

As regards perceived quality of life during CR, it was worse in the subgroup of patients that during follow-up presented MACE, as indicated by the results of EQ-VS; at Cox regression analysis, EQ-VS was the only psychological variable that maintained a significant correlation with MACE-free survival (p = 0.013). Lower values of perceived quality of life as reported by EQ-VS were also correlated with higher depressive symptoms as indicated by higher values of BDI-I (Spearman ρ -0.472; p < 0.001); at separate analysis of somatic/affective and cognitive/affective symptoms, both components presented a significant inverse correlation with EQ-VS (somatic/affective symptoms: ρ -0.374, p < 0.001; cognitive/affective symptoms: ρ -0.344, p < 0.001)

Functional measures and outcome

Patients that suffered an anterior AMI presented lower LVEF in comparison to patients with inferior AMI (45±9% vs 52±7%; p=0.000). A significant correlation was evident between LVEF and functional measures: patients with higher values of LVEF were able to walk longer distances both at admission to CR (ρ 0.196, p = 0.009) and at discharge (ρ 0.215, p = 0.004), as well as to reach higher levels of effort at pre-discharge CPET (W-max: ρ 0.306, p <0.001; peak-VO_2: ρ 0.340, p < 0.001).

Anyway, no clear correlation was evident between functional parameters and long-term outcomes: although all functional parameters studied with pre-discharge 6MWT and CPET were lower in the group that subsequently developed MACE than in group without MACE, the differences were not statistically significant. In particular, patients in the lowest quartile of peak-VO_2 (as percentage of predicted) at pre-discharge CPET did not show worse long-term outcomes in comparison to patients in the higher quartiles of peak-VO_2 (χ^2 0.13, p = 0.723). These results were confirmed by multivariate Cox regression analysis (p = 0.816).

Functional measures and depressive symptoms/perceived QoL

Patients with lower physical performance at pre-discharge CPET (lower peak-VO_2 and lower peak effort) presented values of BDI-I significantly higher than patients with better functional measures (respectively: ρ -0.214, p = 0.007; ρ -0.261, p < 0.001); at separate analysis of cognitive/affective and somatic/affective components of BDI-I, only somatic/affective scores correlated inversely with peak-VO_2 (ρ -0.200, p = 0.033) and peak effort (ρ -0.272, p = 0.003).

Similarly, higher depressive symptoms (higher BDI-I scores) were found in patients that walked shorter distance both at admission and at pre-discharge 6 minute walk test (for 6MWT-in: ρ -0.205, p = 0.006; for 6MWT-out: ρ -0.191, p = 0.011); the separate analysis of the components of BDI-I allowed to identify that somatic/affective symptoms correlated with the distance walked at 6MWT, both at admission (ρ -0.189, p = 0.039) and at discharge from CR (ρ -0.229, p = 0.012), while cognitive/affective symptoms did not (respectively: ρ -0.175, p = 0.057, and ρ -0.126, p = 0.170).

Patients with better physical fitness presented a better perception of the quality of their lives, as indicated by a positive correlation of most performance parameters with the EQ-VS (6MWT-in: ρ 0.318, p < 0.001; 6MWT-out: ρ 0.384, p < 0.001; peak-VO_2: ρ 0.233, p = 0.003; W-max: ρ 0.296, p < 0.001).

Patients in which revascularization during the initial phase of AMI was not successful did not show higher degrees of depressive symptoms in comparison to the other patients (χ^2 11.051, p = 0.995).

DISCUSSION

Almost all our patients with a recent, first episode of complicated STEMI have been treated with successful primary angioplasty in the initial phase of the disease. This constitutes the main difference between our study population and that of the majority of previous studies investigating depression in the post-acute phase of myocardial infarction, many of which have been conducted before the era of immediate reperfusion.[1]

In spite of our patients having experienced various kinds of major complications in the acute phase of STEMI, during an average follow-up period of 28 months major adverse cardiovascular events (MACE: a composite of mortality and nonfatal events, defined as cardiovascular and all-cause death, new AMI, new coronary revascularization, episodes of heart failure, episodes of stroke) appeared in a relatively low percentage of cases (17%), with only 3% overall mortality and 4% new myocardial infarctions. Such MACE incidence is slightly lower than that of 21% that can be extrapolated from 13 previous AMI studies (conducted mainly before the era of immediate reperfusion) included in the recent review by Lichtman et al.[1]

Depressive symptoms (as identified by a BDI-I score ≥10) during the post-STEMI CR period were present in one out of four patients (25%), but only around 11% of the patients have been classified as presenting major depression (moderate or severe symptoms, with a BDI-I score ≥16). In literature, BDI-I scores ≥10 are reported in variable percentages, on average between 30% to 35% of STEMI patients;[16-17] higher scores of BDI-I are reported with percentages not dissimilar from our ones.

In previous studies, BDI-I scores ≥10 have been often associated with poor prognosis in myocardial infarction patients,[18-19] although there was no universal agreement on the prognostic role of depression on mortality.[20] By the contrary, among the patients of our study, long-term cumulative MACE-free survival was not influenced by depressive symptoms present during a CR period, shortly after an AMI. It must be observed that in order to assess presence and severity of depressive symptoms our patients have been tested with the Beck Depression Inventory in its first version (BDI-I), as it was the most widely applied instrument used in previous works. However, BDI-I includes not only cognitive/affective symptoms, but also somatic/affective symptoms (items 11 and 15-21), that could be transiently high in the post-acute phase of a myocardial infarction: they can introduce a measurement bias, inflating the BDI-I total score.[21]

In 1996 a revised version of BDI, the BDI-II, has been proposed, in which the weight of somatic/affective symptoms has been modulated.[22] Nevertheless, among the studies of post-AMI depression and cardiovascular outcomes, to our best knowledge only two studies used the BDI-II:[23-24] although finding a trend towards higher incidence of cardiac complications in depressed compared to non-depressed patients, neither study found a statistically significant relationship between symptoms of depression and cardiovascular prognosis. Other studies aimed at verifying if somatic/affective and cognitive/affective symptoms of Beck Inventory could carry different prognostic significance: all studies reported that somatic/affective symptoms, but not cognitive/affective symptoms, predicted negative cardiovascular outcomes in post-AMI patients.[25-29]

Also our data confirm absence of correlation between cognitive/affective symptoms of depression and outcomes, while somatic/affective symptoms were significantly linked to worse long-term outcomes. Thus, we may suggest to focus analysis to the somatic/affective component of BDI-1 when the aim is to extract some predictivity about long-term outcomes; otherwise, search for evidence of depressive symptoms should be probably better performed with specific interrogation of patients on major cognitive/affective symptoms (such as suicidal ideation, sadness, pessimism).

Furthermore, in our study higher somatic/affective symptoms of depression were correlated with objective measures of poorer physical performance (lower peak effort sustained at CPET, shorter distance walked during a 6MWT); similarly, in patients with worse performance parameters, poorer ratings of perceived QoL were also recorded. So, the presence of a limited physical fitness during the post-acute phase of a STEMI seems to be the underlying factor for both worse depressive symptoms and poorer perception of QoL.

The deterioration of heart function caused by myocardial necrosis (measurable by reduced LVEF) is connected to more frequent long-term MACEs among our patients, as it is already widely known.[30-32] A poor heart function (reduced LVEF) correlates also with lower effort capacity; the perception of an impaired body integrity may have lead to the

increase of the somatic/affective symptoms reported by BDI-I and to a poor rating of the perspective of the future quality of life.[33]

In the same time, in post-AMI patients with a reduced LVEF a significant activation of the neurohormonal system is known to be present, together with a negative left ventricular remodelling process. Both cardiac remodelling and abnormal cardiovascular autonomic response[17, 34-36] are closely associated with higher risk of morbidity and mortality in post-AMI patients. The dysregulation of the autonomic nervous system and serious myocardial remodelling have also been considered as plausible links between depression and negative outcomes in coronary heart patients.[37-38]

All our patients underwent a cycle of intensive comprehensive exercise-based CR during the first month after the acute event, and have been educated to try and maintain a regular physical exercise after hospital discharge. It is known that exercise training improves long-term outcomes and quality of life after an AMI;[39] thus, the period of comprehensive cardiac rehabilitation may have contributed to the relatively few events recorded during the follow-up of our patients, at least in the group of patients with less diffuse coronary disease. CR may also improve depressive symptoms: after formal CR exercise training programs, prevalence of depressive symptoms is reported to reduce by more than 50%.[6-9] Intensive exercise training is effective for improving cardiac autonomic modulation,[40-41] even though there is no general agreement on the topic.[42] In addition, the inflammatory process, that is known to be activated after an AMI, may be involved in increasing the risk of depression in coronary heart disease patients; exercise (and exercise-based CR) may contribute in reducing both pro-inflammatory status and depressive symptoms in post-AMI patients.[43]

It must be underlined that almost all our patients received an effective revascularization in the first few hours of AMI; thus, it may be hypothesized that the small number of MACE and the better long-term survival of our patients may be mainly attributed to the effects of the timely reperfusion strategy, with consequent reduction of infarct size, salvage of more heart muscle, and improvement of cardiac autonomic function,[44] as well as to the multiple pharmacological therapy used.[45]

In Fig. 3, we try and outline our concept of the relationship between myocardial damage, physical performance, perceived quality of life, depressive symptoms and long-term outcome.

Limitations of the study

Criteria of exclusion from the study were history of a previous myocardial infarction and presence of a non-ST elevated myocardial infarction; no data about depressive symptoms of these patients are thus available.

All our STEMI patients suffered major complications during the initial phase of their disease, before transferral to CR; such patients could have presented degrees of depressive symptoms that may not be generalized to the other complicated or uncomplicated STEMI patients.

We had no data that could help distinguish between pre-STEMI and post-STEMI depressive symptoms; presence of a pre-STEMI depression could have biased the results of our study. Anyway, none of our patients was taking major antidepressant drugs at the time of hospital admission; by medical history and clinical and laboratory examination, no patient resulted to be an illicit drugs user or an alcohol addict.

Symptoms of depression have been assessed by BDI-I, as it was the tool most widely used in previous studies on prevalence of depression after an AMI. This tool is nowadays considered not ideal for use in the context of AMI; its limitations have already been described in Discussion.

The total number of patients observed in our study is relatively small; as late cardiac mortality in STEMI patients treated with early PCI is known to be quite low,[46] a much larger patient sample could have helped to reveal possible differences of the outcomes linked to depression. Anyway, it must be said that a relevant proportion of previous studies analyzing composite outcomes in post-AMI depressed patients included population samples sizes similar to our study.[1]

Conclusions

In conclusion, in our group of complicated STEMI patients treated with primary PCI we can confirm what already reported in a few papers in literature:[25-29] somatic/affective but not cognitive/affective symptoms of depression are associated with worse long-term prognosis. This somatic component of depressive symptoms is linked to varying levels of physical limitations, associated with the severity of the myocardial damage caused by the infarction.

In STEMI patients treated with primary PCI, we assume that physical impairment (with the associated feeling of limitation) is the underlying reason for the worse symptoms of depression evaluated by BDI-1. In our opinion, such "depressive" symptoms are not predictors "per se" of adverse cardiovascular prognosis in STEMI patients, but seem to be a manifestation of an underlying poorer cardiac efficiency, clinically reflected by a limited physical performance.[47] If so, treating depressive symptoms may not allow a modification of long-term prognosis of primary-PCI STEMI patients,[48-49] as already observed in the original ENRICHD Study,[50] even though anti-depressive treatment may potentially give a positive contribution reducing the sympathetic hyperactivity that is present in depressed patients.[51] By the other side, therapeutic measures aimed at improving physical fitness (i.e. comprehensive exercise-based cardiac rehabilitation programs)[6] could in the same time alleviate depressive symptoms and improve long-term survival.

Further studies with larger populations are needed to confirm our results and to test interventions that could effectively lead to better long-term outcomes of STEMI patients.

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Table I – Main data of patients with and without MACE

	No MACE (n = 154)	**MACE (n = 30)**	**p***	**p#**
Age, years	60.5 ± 11.7	66.5 ± 12.3	0.012	
Gender				
Male, n (%)	124 (80)	24 (80)		0.948
Female, n (%)	30 (20)	6 (20)		
Cardiovascular Risk Factors				
Known diabetes, n (%)	26 (17)	12 (40)		0.003
Abnormal glucose metabolism, n (%)	56 (36)	8 (27)		0.298
Hypertension, n (%)	97 (63)	23 (77)		0.202
Smoking habit, n (%)	60 (39)	11 (37)		0.856
Family history, n (%)	89 (58)	12 (40)		0.088
Total cholesterol at discharge, mg/dl	123.0 ± 26.2	120.5 ± 26.0	0.643	
BMI	27.0 ± 3.9	27.1 ± 3.8	0.907	
STEMI characteristic				
Anterior, n (%)	100 (65)	19 (63)		0.831
Inferior, n (%)	54 (35)	10 (33)		0.818
Coronary vessels with critical lesions, n	1.9 ± 0.8	2.0 ± 0.9	0.462	
Coronary arteries treated by PCI, n	1.3 ± 0.7	1.2 ± 0.7	0.433	
Incomplete revascularization, n (%)	57 (37)	16 (53)		0.095
Time before CR, days	16.4 ± 10.2	16.9 ± 11.8	0.815	
LVEF, %	48.0 ± 9.1	44.9 ± 9.3	0.089	
LVEF <40%, n (%)	28 (18)	11 (37)		0.023
Depressive symptoms				
BDI-I	6.7 ± 6.1	8.7 ± 5.5	0.094	
BDI-I-somatic/affective	3.8 ± 3.0	5.4 ± 2.6	0.037	
BDI-I-cognitive/affective	2.6 ± 3.7	4.0 ± 4.0	0.142	
Perceived QoL				
EQ-5D-3L (EQ-VS)	73.5 ± 17.7	63.9 ± 19.2	0.008	
Physical evaluation				
6MWT-in, m	449.0 ± 113.0	379.8 ± 115.2	0.005	
6MWT-out, m	513.0 ± 119.0	420.6 ± 125.2	0.013	
Peak-VO_2, ml/kg/min	18.7 ± 5.3	17.0 ± 4.9	0.152	
%-VO_2, %	71.3 ± 19.8	72.2 ± 18.4	0.839	
W-max, W	84.8 ± 32.1	72.9 ± 21.7	0.089	

Footnote of Table I

MACE: major adverse cardiovascular events at follow-up; p*: level of significance from unpaired t tests; p#: level of significance from chi-square tests; STEMI: ST-elevated myocardial infarction; PCI: percutaneous coronary intervention; CR: cardiac rehabilitation; LVEF: left ventricle ejection fraction; BDI-I: Beck Depression Inventory version I; QoL: quality of life; EQ-5D-3L (EQ-VS): Euro quality of life, 5 dimensions, 3 levels, Visual Scale; 6MWT-in: 6 minute walk test at admission; 6-MWT-out: 6 minute walk test at discharge; peak-VO_2: peak oxygen uptake; %-VO_2: peak oxygen uptake expressed as percentage of expected; W-max: peak exercise capacity, in Watt.

Fig. 1 – Flowchart of patient selection

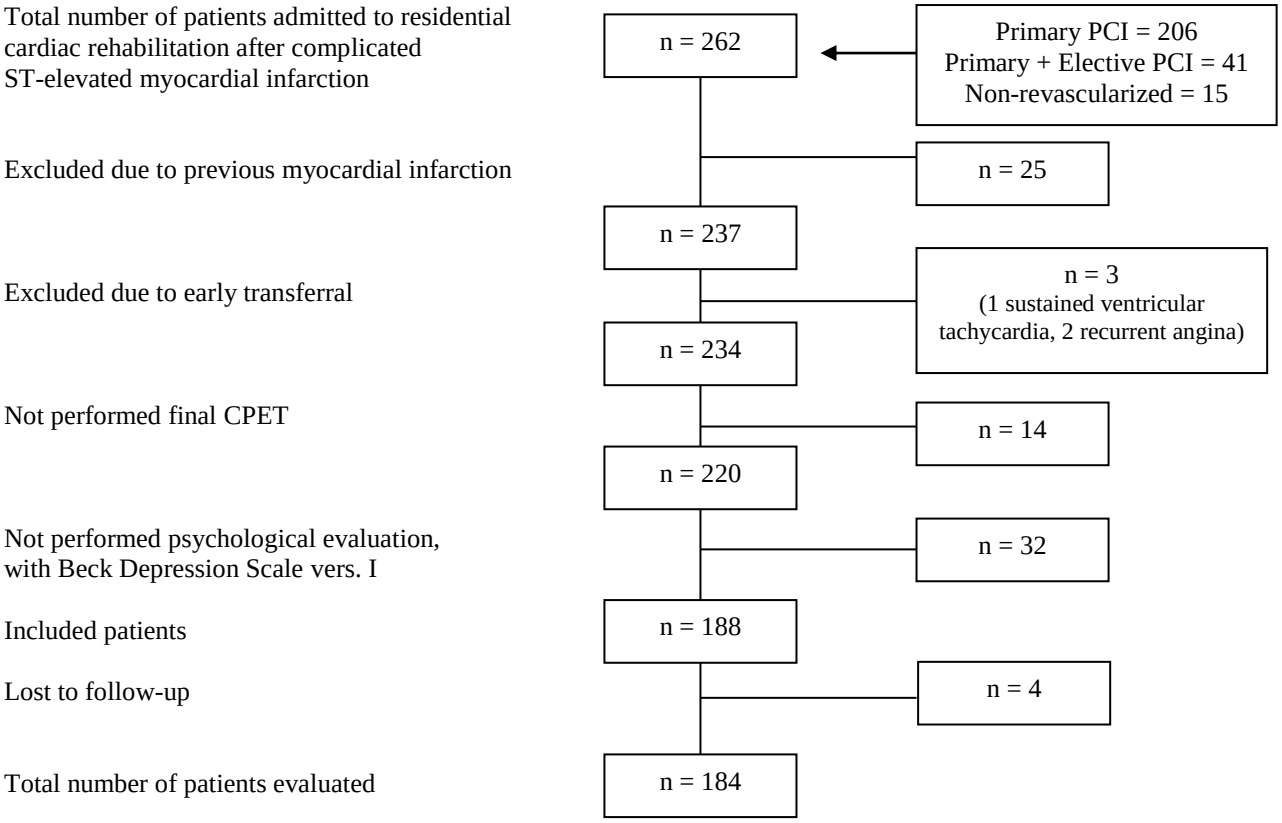
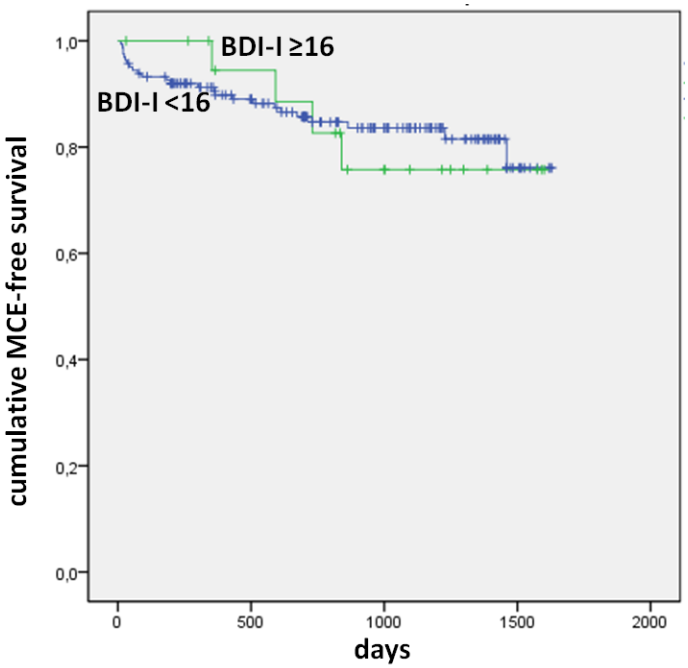


Fig. 2 - Kaplan-Meier cumulative MACE-free survival curves, for patients stratified according to BDI-I scores ≥16 versus <16 (A) and according to somatic/affective symptoms of BDI-I ≥6 versus <6 (B).

A



B

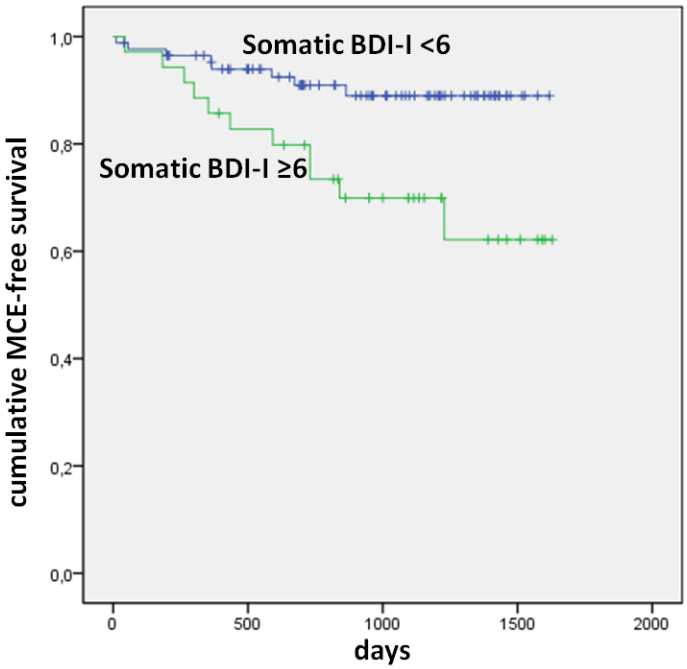
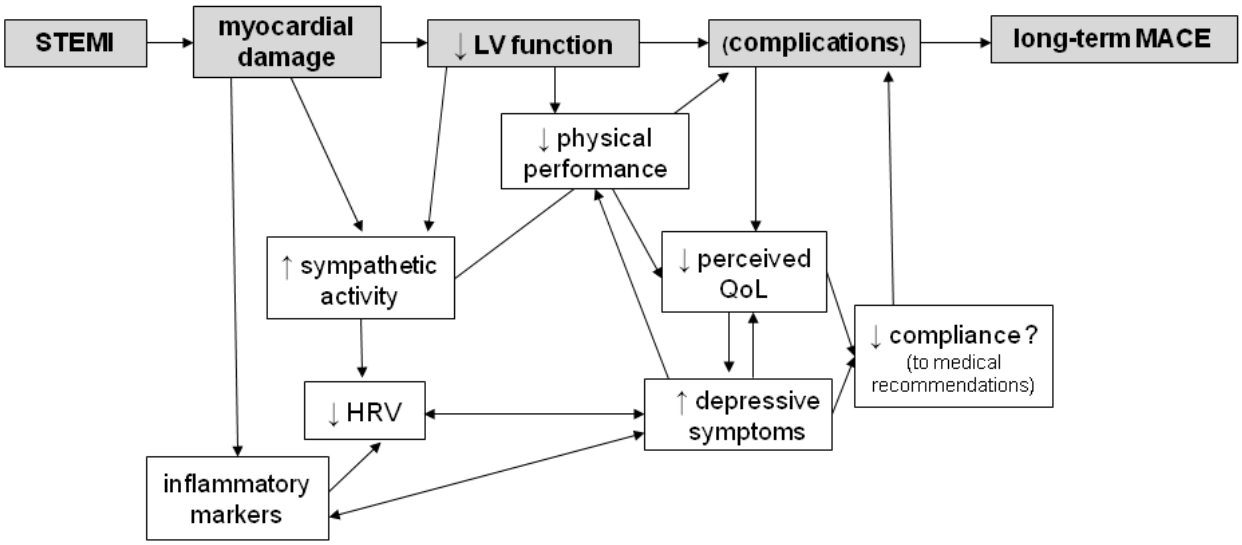


Fig. 3 - Hypothesis of relationship between myocardial damage, physical performance, perceived quality of life, depressive symptoms and long-term outcome



Box 1 - Beck's Depression Inventory, version 1

		Cognitive/affective symptoms			Somatic/affective symptoms
Item	Score		Item	Score	
1	0	I do not feel sad.	11	0	I am no more irritated by things than I ever was.
	1	I feel sad.		1	I am slightly more irritated now than usual.
	2	I am sad all the time and I can't snap out of it.		2	I am quite annoyed or irritated a good deal of the time.
	3	I am so sad and unhappy that I can't stand it.		3	I feel irritated all the time.
2	0	I am not particularly discouraged about the future.	15	0	I can work about as well as before.
	1	I feel discouraged about the future.		1	It takes an extra effort to get started at doing something.
	2	I feel I have nothing to look forward to.		2	I have to push myself very hard to do anything.
	3	I feel the future is hopeless and that things cannot improve.		3	I can't do any work at all.
3	0	I do not feel like a failure.	16	0	I can sleep as well as usual.
	1	I feel I have failed more than the average person.		1	I don't sleep as well as I used to.
	2	As I look back on my life, all I can see is a lot of failures.		2	I wake up 1-2 hours earlier than usual and find it hard to get back to sleep.
	3	I feel I am a complete failure as a person.		3	I wake up several hours earlier than I used to and cannot get back to sleep.
4	0	I get as much satisfaction out of things as I used to.	17	0	I don't get more tired than usual.
	1	I don't enjoy things the way I used to.		1	I get tired more easily than I used to.
	2	I don't get real satisfaction out of anything anymore.		2	I get tired from doing almost anything.
	3	I am dissatisfied or bored with everything.		3	I am too tired to do anything.
5	0	I don't feel particularly guilty	18	0	My appetite is no worse than usual.
	1	I feel guilty a good part of the time.		1	My appetite is not as good as it used to be.
	2	I feel quite guilty most of the time.		2	My appetite is much worse now.
	3	I feel guilty all of the time.		3	I have no appetite at all anymore.
6	0	I don't feel I am being punished.	19	0	I haven't lost much weight, if any, lately.
	1	I feel I may be punished.		1	I have lost more than five pounds.
	2	I expect to be punished.		2	I have lost more than ten pounds.
	3	I feel I am being punished.		3	I have lost more than fifteen pounds.
7	0	I don't feel disappointed in myself.	20	0	I am no more worried about my health than usual.
	1	I am disappointed in myself.		1	I am worried about physical problems like aches, pains, upset stomach, or constipation.
	2	I am disgusted with myself.		2	I am very worried about physical problems and it's hard to think of much else.
	3	I hate myself.		3	I am so worried about my physical problems that I cannot think of anything else.
8	0	I don't feel I am any worse than anybody else.	21	0	I have not noticed any recent change in my interest in sex.
	1	I am critical of myself for my weaknesses or mistakes.		1	I am less interested in sex than I used to be.
	2	I blame myself all the time for my faults.		2	I have almost no interest in sex.
	3	I blame myself for everything bad that happens.		3	I have lost interest in sex completely.
9	0	I don't have any thoughts of killing myself.			

	1 2 3	I have thoughts of killing myself, but I would not carry them out. I would like to kill myself. I would kill myself if I had the chance.			
10	0 1 2 3	I don't cry any more than usual. I cry more now than I used to. I cry all the time now. I used to be able to cry, but now I can't cry even though I want to.			
12	0 1 2 3	I have not lost interest in other people. I am less interested in other people than I used to be. I have lost most of my interest in other people. I have lost all of my interest in other people.			
13	0 1 2 3	I make decisions about as well as I ever could. I put off making decisions more than I used to. I have greater difficulty in making decisions more than I used to. I can't make decisions at all anymore.			
14	0 1 2 3	I don't feel that I look any worse than I used to. I am worried that I am looking old or unattractive. I feel there are permanent changes in my appearance that make me look unattractive I believe that I look ugly.			

DEPRESSIVE SYMPTOMS, FUNCTIONAL MEASURES AND LONG-TERM OUTCOMES OF HIGH-RISK ST-ELEVATED MYOCARDIAL INFARCTION PATIENTS TREATED BY PRIMARY ANGIOPLASTY.

Short Title: Compostella - Depression and outcomes after STEMI

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Statement: Each one of the above mentioned authors takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

Source of funding: This work was not supported by grant.

Conflicts of interest: No Author has any conflict of interest to declare.

Word count: 8595 (total); text only 4734

Number of Tables: 2 (1 Table + 1 Box)

Number of figures: 3

Abstract

Background

Presence of major depressive symptoms is usually considered a negative long-term prognostic factor after an acute myocardial infarction (AMI). However, most of the supporting research was conducted before the era of immediate reperfusion by percutaneous coronary intervention. Aims of this study were to evaluate if depression still retains long-term prognostic significance in our era of immediate coronary reperfusion, and to study possible correlations with clinical parameters of physical performance.

Methods and Results

In 184 patients with recent ST-elevated AMI (STEMI), treated by immediate reperfusion, moderate or severe depressive symptoms (evaluated by Beck Depression Inventory version I) were present in 10% of cases. Physical performance was evaluated by two 6-minute walk tests and by a symptom-limited cardiopulmonary exercise test: somatic/affective (but not cognitive/affective) symptoms of depression and perceived quality of life (evaluated by the EuroQoL questionnaire) were worse in patients with lower levels of physical performance. Follow-up was performed after a median of 29 months by means of telephone interviews; 32 major adverse cardiovascular events (MACE) occurred. Presence of 3 vessels disease and low left ventricle ejection fraction were correlated with greater incidence of MACE; only somatic/affective (but not cognitive/affective) symptoms of depression correlated with long-term outcomes.

Conclusions

In patients with recent STEMI treated by immediate reperfusion, somatic/affective but not cognitive/affective symptoms of depression showed prognostic value on long-term MACE. Depression symptoms were not predictors "per se" of adverse prognosis, but seem to express an underlying worse cardiac efficiency, clinically reflected by poorer physical performance.

Keywords: depression, Beck inventory, physical fitness, myocardial infarction, prognosis.

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List of Acronyms

%-VO_2 = percentage of expected peak Oxygen uptake

6MWT = 6-minute Walk Test

ACE = Angiotensin Converting Enzyme

AMI = Acute Myocardial Infarction

AT-II = Angiotensin II receptor type 2

BDI-I = Beck Depression Inventory, version 1

CABG = Coronary Artery By-pass Graft

CPET = Cardio-Pulmonary Exercise Test

CR = Cardiac Rehabilitation

ECG = Electrocardiogram

EQ-5D-3L = European QoL questionnaire 5D-3L

EQ-VS = European QoL questionnaire Visual Scale

MACE = Major Adverse Cardiovascular Events

MRI = Magnetic Resonance Imaging

PCI = Percutaneous Coronary Intervention

peak-VO_2 = peak Oxygen uptake

QoL = Quality of Life

STEMI = ST-elevated Myocardial Infarction

W-max = maximum sustained workload at CPET, in Watt

In the last 25 years, along with improvements of intensive treatment of patients with acute myocardial infarction (AMI), numerous prospective studies, systematic reviews and meta-analyses have been conducted that show a robust association between depression (major depression or elevated depressive symptoms) and increased morbidity and mortality after AMI. Consequently, major depression has been recently proposed as risk factor for poor prognosis among patients with acute coronary syndromes.[1]

However, it must be said that the majority of the studies showing a correlation between depression and clinical outcomes after an AMI have been conducted before the era of immediate reperfusion by percutaneous coronary intervention (PCI). Among 32 studies included in the recent review by Lichtman JH et al,[1] only half reported the treatment performed in the acute phase of the infarction, with primary PCI performed mostly in a modest proportion of patients (widely variable from 0 to 76 percent of cases).[2-3] Different treatments in the acute phase of myocardial infarction could have influenced initial clinical conditions and patients' health perception, that could not be the same as in today's patients.

Furthermore, nowadays an increasing number of post-AMI patients are admitted to a cycle of cardiac rehabilitation (CR),[4] mainly based on exercise training. Besides positive effects on all-cause and cardiovascular mortality,[5] CR may exert some positive effects also on depressive mood of post-AMI patients.[6-9]

Thus, the complex interrelationship between depression, physical fitness and exercise-based rehabilitation, and the influence of these factors on patients' long-term survival constitute a changing scenario.

Aims of this study were: 1- to assess the prevalence of depressive symptoms in patients admitted to CR after a complicated ST-elevated myocardial infarction (STEMI) treated by primary PCI, 2- to evaluate if depression still maintains a prognostic value in the era of immediate reperfusion in patients submitted to CR, 3- to estimate possible relationship between depression and physical fitness.

Materials and Methods

Design of the Study

We retrospectively reviewed the clinical files of 262 consecutive patients admitted to our CR unit for a period of residential, exercise-based rehabilitation, 16 ± 10 days (95% CI 15 - 18) after a complicated STEMI. All patients had undergone coronary angiography at initial admission to the Intensive Coronary Care Unit, during the first 6 hours from beginning of AMI symptoms: 94% of them underwent PCI of the culprit coronary artery, while only a small percentage of them (6%) was not revascularized due to unfavourable coronary anatomy and were put on optimal medical therapy. Patients were selected by the submitting centre and sent to our CR program if they suffered a complicated AMI (cardiogenic shock or pulmonary edema, episode of cardiac arrest, complex ventricular arrhythmias), or if they had

incomplete revascularization (because of unfavourable coronary anatomy or technical failure), or had at least 3 major cardiovascular risk factors.[10] Low risk patients followed an out-patient CR program in another centre and were not considered for this study.

Echo- or cardiac MRI- documented intracavitary thrombosis, extreme thinning or suspected rupture of the ventricular wall and/or intra-myocardial bleeding were exclusion criteria from admittance to CR; history of previous myocardial infarction was an exclusion criteria for the present study.

The following clinical variables were recorded for each patient: age, gender, body mass index, cardiovascular risk factors, site of infarction, culprit coronary artery vessel, number of diseased coronary artery vessels (defined as presence of diameter stenosis > 50%), history of previous PCI or coronary or valvular surgery, presence of ancillary diseases (renal failure, thyroid dysfunction, known diabetes or abnormal glucose metabolism, pulmonary diseases, history or presence of neoplastic diseases, carotid and peripheral vascular disease) and drug therapy. During stay in CR, all patients without previous diagnosis of diabetes underwent an oral glucose tolerance test to identify subclinical abnormal glucose metabolism. Left ventricular ejection fraction (LVEF) was measured before discharge by 2-D echocardiography, following the Simpson method.

Depressive symptoms evaluation

During the CR period, patients were carefully evaluated by a trained psychologist; symptoms of depression were assessed using a self-report questionnaire, the Beck Depression Inventory version 1 (BDI-I).

The BDI-I is a 21-item self-report measure, developed to assess the presence and severity of depressive symptoms;[11] each of the 21 items represents an aspect of depression clinical presentation and is rated on a 0-3-point scale of symptom severity. Scores on items 1–10 and 12–14 (sadness, pessimism, sense of failure, self-dissatisfaction, guilt, punishment, self-dislike, self-accusations, suicidal ideas, crying, social withdrawal, indecisiveness, body image change) may be summed to calculate cognitive/affective symptom scores. Items 11 and 15–21 (irritability, work difficulty, insomnia, fatigability, loss of appetite, weight loss, somatic preoccupation, loss of libido) may be summed to calculate somatic/affective symptom scores. BDI-I scores of 10-15 are indicative of mild symptoms of depression, 16-23 moderate depression, and 24-63 severe depression. In this study, we analysed separately the total BDI-I score and the scores for somatic/affective and cognitive/affective symptoms (see Box 1).

Perceived quality of life

To assess the impact of the most frequent physical symptoms of the disease and its treatments on the perceived quality of life (QoL), the European QoL questionnaire 5D-3L (EQ-5D-3L) was administered to our study patients during the CR period.

The EQ-5D-3L is a descriptive system of health-related QoL states that captures the respondent's situation at the time of completion. It consists of five questions on five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression); each dimension can take one of three levels of responses, recording three levels of severity (no problems/some or moderate problems/extreme problems).[12] The questionnaire is integrated with a visual analogue scale (EQ-VS), that records the respondent's self-rated health on a vertical scale, where the endpoints are labelled "Best imaginable health state" and "Worst imaginable health state". In our study, this information was used as a quantitative measure of health status as judged by the individual respondents.

Cardiac Rehabilitation

The training consisted of a low-medium intensity exercise protocol developed in 3 sets of exercises, 6 days a week for an average of 2 weeks: 30 min of respiratory training, followed by an aerobic session on a stationary bike (or with an arm-ergometer for those patients who were not able to cycle) in the morning and 30 min of callisthenic exercises in the afternoon. Each session was supervised by a physician and a physiotherapist and all patients were ECG monitored by a telemetry system. Aerobic training was performed using a constant work rate modality, without exceeding 70% of the maximal predicted peak heart rate for each patient.[13] Each aerobic session lasted 10 minutes at the beginning, with a 5 minutes progressive increase to reach a 30 min target; the exercise prescription and evaluation of exercise intensity was carefully derived from the subjective rating of perceived exertion, using a category ratio Borg scale.

Individual and group counselling meetings and nutritional evaluation were also performed for all patients.

Physical evaluation

Physical performance of the patients was assessed by two different methods: two six-minute walk tests (6MWT), performed at admission (6MWT-in) and at the end of the rehabilitative period (6MWT-out), and a symptom-limited cardiopulmonary exercise test (CPET) performed on the day before discharge from CR.

The 6MWTs were performed in a 30 m long, unobstructed indoor corridor, according to the American Thoracic Society recommendations.[14]

The CPET was performed on a computer-driven cycle ergometer (Cardiovit CS-200 Ergo-Spiro, Schiller AG, Baar, CH; Ergoselect 100 ergometer, Ergoline GmbH, Bitz, D). A progressive ramp protocol of 6 to 10 W/min was used, until subjective exhaustion or appearance of clinical or electrocardiographic criteria for termination.[15] Expired gas was

collected by means of a tightly fitting face mask and continuously analyzed during the exercise test (Schiller Ganshor CS-200 Power Cube). Peak oxygen consumption (peak-VO_2) was expressed relative to body weight, and as a percentage of the expected based on age, sex and body mass (%-VO_2). Peak exercise capacity was expressed in Watt as maximum sustained workload (W-max).

End Points and Follow-Up

At the time of follow-up, the clinical status of the patients was assessed by telephone interviews, performed by a doctor or a trained team nurse. In case of clinical events, detailed information was obtained from the patient or his/her relatives. The primary end point of the study was the occurrence of major adverse cardiovascular events (MACE), defined as death (all-cause mortality, cardiac mortality), or readmission for a new AMI, new revascularization, episodes of heart failure or stroke.

Statistical analysis

Continuous variables were expressed as a mean ± standard deviation and compared using an unpaired Student t-test; categorical variables were expressed as frequencies and percentages and were compared between groups by Pearson's chi-squared test (χ^2). The relationships between continuous variables were evaluated by Spearman's correlation coefficient. Event free survival curves were calculated by the Kaplan-Meier method and groups were compared with a log-rank test. A Cox regression multivariate analysis was performed to determine the influence of different factors (age>65 years, sex, time from event to CR, site of STEMI, signs of heart failure, number of vessels with critical lesions, incomplete revascularization, NYHA functional class, EF<40%, known diabetes, chronic renal failure, physical performance parameters, depression and quality of life parameters) on MACE. All reported probability values are two-tailed and the significance level was set at 0.05. Statistical analyses were performed using SPSS 18 software package (SPSS Inc, Chicago, IL,USA).

Statement

During CR hospitalization, all the participants have been informed about the procedures they were undergoing; a written consent was obtained from all patients before performance of CPET. The usual diagnostic and follow-up routine for CR were applied; no special test or treatment was performed. The research was conducted in accordance with the ethical guidelines of the 1975 Declaration of Helsinki. This study is part of a larger follow-up study on AMI patients admitted to CR; approval of the Provincial Ethics Committee (Provincial Directorate of Health, Belluno, Italy) was obtained for the main research.

RESULTS

General Findings

During the study period (January 2008 to June 2012), 262 patients had been directly transferred from the Cardiology Department to our CR unit, for intensive in-hospital rehabilitation on average 16 days (95% CI: 14.9-17.9) after a first complicated STEMI. No fatal events occurred during the CR stay (median duration 14.5 days; 95% CI: 14.1-14.9 days), although 3 patients had to be transferred back to the Intensive Care Unit because of complications before completing the rehabilitation protocol; thus, they dropped out of the study.

According to inclusion and exclusion criteria as reported in the patients selection flowchart represented in Fig. 1, a final group of 188 patients was suitable for the follow-up study.

STEMI was anterior in 121 cases (64%), inferior in 65 patients (35%) and in other segments in the remaining 2 cases; 71 (38%) patients were affected by a single vessel disease, while 60 (32%) presented a two vessels disease and 57 (30%) a three vessels disease. Approximately 4% of patients had history of previous CABG (7 patients) and 7% previous elective PCI (14 patients).

Primary PCI was successful in 173 patients (92% of the study cases). In only 15 patients (8% of the study group) the primary revascularization attempt failed due to unfavourable coronary anatomy; these patients were thus submitted to medical therapy. Of the 173 primary PCI patients, 61 (32%) had been immediately treated also on non-culprit coronary lesions; 8 (4%) received further elective percutaneous revascularization during the initial stay in the Cardiology Department. Overall, at the time of transferral to the CR unit, 113 patients (60%) had a complete revascularization, while 75 patients (40%) had still an incomplete revascularization.

All patients were discharged from CR on aspirin and 93% were also receiving a second antiplatelet agent; 13% were receiving oral anticoagulation; other therapy included β-blockers (92%), Ca-antagonists (8%), ACE-inhibitors (87%) or AT-II-antagonists (8%), statins (98%) and diuretics (36%).

Clinical characteristics and follow-up

At the time of follow-up, at a median of 28.8 months (95% CI: 25.5-30.8) after the acute event, it was not possible to trace a total of 4 patients (2.1%).

Among the 184 followed-up patients, MACE occurred in 32 cases and consisted of 6 deaths (3.2%) and 7 cases of new non fatal AMI (3.8%), 3 strokes (1.6%), 6 cases of successful elective revascularization (3.2%: 3 CABG, 3 elective PCI), and 10 hospital readmissions for heart failure (5.4%).

The main characteristics of the 184 followed-up patients with and without MACE are summarized in Table I.

At multivariate analysis, age and LVEF <40% were the only clinical characteristics that were significantly correlated with long-term prognosis (p = 0.039 and p = 0.044, respectively). Patients that presented a greater myocardial damage, as indicated by a lower LVEF (<40%), had a greater number of MACE in the follow-up, than patients with less compromised LVEF (χ^2 5.305, p = 0.021).

Patients with a 3-vessel disease had an incidence of MACE during the period of follow-up (12 MACE on a total of 54 patients, 22%) that was similar to that of patients with less diffuse coronary disease (18 MACE among a total of 130 cases, 14%) (χ^2 = 1.96, p = 0.161); no significant correlation was found with other clinical characteristics, such as sex (p = 0.354), number of vessels treated during the primary PCI (p = 0.767), history of incomplete revascularization (p = 0.132), site of myocardial infarction (p=0.444) or presence of signs of heart failure during initial admission (p = 0.801).

At follow-up, no patients reported having used any major antidepressant drug since the index event.

Depressive symptoms, perceived QoL and outcome

Depressive symptoms during CR were identified by BDI-I ≥ 10 in one out of four patients (25% of cases) but only 3 patients (1.6%) were classified has having severe symptoms of depression (BDI-I ≥ 25) and other 19 (8.5%) as having moderate depressive symptoms.

In the whole group of patients, mean BDI-I scores were similar between the group of patients that presented MACE during the period of follow-up and those without MACE. Although patients with higher depression scores showed a tendency for a greater incidence of MACE (MACE in 14% of patients with BDI-I ≤ 9; 18% in BDI-I 10-15; 24% in BDI-I 16-23; no MACE among the 2 patients with BDI-I ≥ 24), the Pearson's chi-square showed no significant correlation (χ^2 = 1.333; p = 0.721), perhaps due to the small number of events recorded.

The Kaplan-Meier cumulative MACE-free survival curves, stratified according to BDI-I scores <16 versus ≥16 (Fig. 2A), confirmed that no significant difference was found between the two groups of patients without symptoms or with mild symptoms of depression in comparison to patients with moderate or severe symptoms of depression (p = 0.827).

The findings were different when observing the relationship between somatic/affective scores of the BDI-I questionnaire (question 11 and 15-21) and MACE. Somatic/affective symptoms accounted for widely variable percentages of the total score of the BDI-I questionnaire, ranging from 0 to 100% (mean percentage of scores 64±30%; median 62.5%; 95% CI: 58-70). Patients that presented somatic/affective scores in the upper quartile (a score ≥6 in our cases) during the period of CR suffered a significantly greater number of events during follow-up: 10 out of 30 patients (33%) suffered MACE during follow-up, while only 5 MACE occurred among 73 cases (7%) with somatic/affective scores in the other three quartiles (χ^2 11.99; p < 0.001). In fig. 2B, the Kaplan-Meier cumulative MACE-free survival curve for patients in the upper quartile of somatic/affective BDI-I scores indicates significantly different outcomes in

comparison to patients in the lower quartiles (p = 0.007). By the contrary, no significant correlation was found between cognitive/affective symptoms of depression during CR and long-term MACE: among 36 patients in the upper quartile of cognitive/affective score (in our cases ≥5), 6 patients (17%) suffered MACE during follow-up, while there were 6 cases of MACE among 66 patients (9%) in the lower quartiles of cognitive/affective score (χ^2 1.29, p = 0.2564).

As regards perceived quality of life during CR, it was worse in the subgroup of patients that during follow-up presented MACE, as indicated by the results of EQ-VS; at Cox regression analysis, EQ-VS was the only psychological variable that maintained a significant correlation with MACE-free survival (p = 0.013). Lower values of perceived quality of life as reported by EQ-VS were also correlated with higher depressive symptoms as indicated by higher values of BDI-I (Spearman ρ -0.472; p < 0.001); at separate analysis of somatic/affective and cognitive/affective symptoms, both components presented a significant inverse correlation with EQ-VS (somatic/affective symptoms: ρ -0.374, p < 0.001; cognitive/affective symptoms: ρ -0.344, p < 0.001)

Functional measures and outcome

Patients that suffered an anterior AMI presented lower LVEF in comparison to patients with inferior AMI (45±9% vs 52±7%; p=0.000). A significant correlation was evident between LVEF and functional measures: patients with higher values of LVEF were able to walk longer distances both at admission to CR (ρ 0.196, p = 0.009) and at discharge (ρ 0.215, p = 0.004), as well as to reach higher levels of effort at pre-discharge CPET (W-max: ρ 0.306, p <0.001; peak-VO_2: ρ 0.340, p < 0.001).

Anyway, no clear correlation was evident between functional parameters and long-term outcomes: although all functional parameters studied with pre-discharge 6MWT and CPET were lower in the group that subsequently developed MACE than in group without MACE, the differences were not statistically significant. In particular, patients in the lowest quartile of peak-VO_2 (as percentage of predicted) at pre-discharge CPET did not show worse long-term outcomes in comparison to patients in the higher quartiles of peak-VO_2 (χ^2 0.13, p = 0.723). These results were confirmed by multivariate Cox regression analysis (p = 0.816).

Functional measures and depressive symptoms/perceived QoL

Patients with lower physical performance at pre-discharge CPET (lower peak-VO_2 and lower peak effort) presented values of BDI-I significantly higher than patients with better functional measures (respectively: ρ -0.214, p = 0.007; ρ -0.261, p < 0.001); at separate analysis of cognitive/affective and somatic/affective components of BDI-I, only somatic/affective scores correlated inversely with peak-VO_2 (ρ -0.200, p = 0.033) and peak effort (ρ -0.272, p = 0.003).

Similarly, higher depressive symptoms (higher BDI-I scores) were found in patients that walked shorter distance both at admission and at pre-discharge 6 minute walk test (for 6MWT-in: ρ -0.205, p = 0.006; for 6MWT-out: ρ -0.191, p = 0.011); the separate analysis of the components of BDI-I allowed to identify that somatic/affective symptoms correlated with the distance walked at 6MWT, both at admission (ρ -0.189, p = 0.039) and at discharge from CR (ρ -0.229, p = 0.012), while cognitive/affective symptoms did not (respectively: ρ -0.175, p = 0.057, and ρ -0.126, p = 0.170).

Patients with better physical fitness presented a better perception of the quality of their lives, as indicated by a positive correlation of most performance parameters with the EQ-VS (6MWT-in: ρ 0.318, p < 0.001; 6MWT-out: ρ 0.384, p < 0.001; peak-VO_2: ρ 0.233, p = 0.003; W-max: ρ 0.296, p < 0.001).

Patients in which revascularization during the initial phase of AMI was not successful did not show higher degrees of depressive symptoms in comparison to the other patients (χ^2 11.051, p = 0.995).

DISCUSSION

Almost all our patients with a recent, first episode of complicated STEMI have been treated with successful primary angioplasty in the initial phase of the disease. This constitutes the main difference between our study population and that of the majority of previous studies investigating depression in the post-acute phase of myocardial infarction, many of which have been conducted before the era of immediate reperfusion.[1]

In spite of our patients having experienced various kinds of major complications in the acute phase of STEMI, during an average follow-up period of 28 months major adverse cardiovascular events (MACE: a composite of mortality and nonfatal events, defined as cardiovascular and all-cause death, new AMI, new coronary revascularization, episodes of heart failure, episodes of stroke) appeared in a relatively low percentage of cases (17%), with only 3% overall mortality and 4% new myocardial infarctions. Such MACE incidence is slightly lower than that of 21% that can be extrapolated from 13 previous AMI studies (conducted mainly before the era of immediate reperfusion) included in the recent review by Lichtman et al.[1]

Depressive symptoms (as identified by a BDI-I score ≥10) during the post-STEMI CR period were present in one out of four patients (25%), but only around 11% of the patients have been classified as presenting major depression (moderate or severe symptoms, with a BDI-I score ≥16). In literature, BDI-I scores ≥10 are reported in variable percentages, on average between 30% to 35% of STEMI patients;[16-17] higher scores of BDI-I are reported with percentages not dissimilar from our ones.

In previous studies, BDI-I scores ≥10 have been often associated with poor prognosis in myocardial infarction patients,[18-19] although there was no universal agreement on the prognostic role of depression on mortality.[20] By the contrary, among the patients of our study, long-term cumulative MACE-free survival was not influenced by depressive symptoms present during a CR period, shortly after an AMI. It must be observed that in order to assess presence and severity of depressive symptoms our patients have been tested with the Beck Depression Inventory in its first version (BDI-I), as it was the most widely applied instrument used in previous works. However, BDI-I includes not only cognitive/affective symptoms, but also somatic/affective symptoms (items 11 and 15-21), that could be transiently high in the post-acute phase of a myocardial infarction: they can introduce a measurement bias, inflating the BDI-I total score.[21]

In 1996 a revised version of BDI, the BDI-II, has been proposed, in which the weight of somatic/affective symptoms has been modulated.[22] Nevertheless, among the studies of post-AMI depression and cardiovascular outcomes, to our best knowledge only two studies used the BDI-II:[23-24] although finding a trend towards higher incidence of cardiac complications in depressed compared to non-depressed patients, neither study found a statistically significant relationship between symptoms of depression and cardiovascular prognosis. Other studies aimed at verifying if somatic/affective and cognitive/affective symptoms of Beck Inventory could carry different prognostic significance: all studies reported that somatic/affective symptoms, but not cognitive/affective symptoms, predicted negative cardiovascular outcomes in post-AMI patients.[25-29]

Also our data confirm absence of correlation between cognitive/affective symptoms of depression and outcomes, while somatic/affective symptoms were significantly linked to worse long-term outcomes. Thus, we may suggest to focus analysis to the somatic/affective component of BDI-1 when the aim is to extract some predictivity about long-term outcomes; otherwise, search for evidence of depressive symptoms should be probably better performed with specific interrogation of patients on major cognitive/affective symptoms (such as suicidal ideation, sadness, pessimism).

Furthermore, in our study higher somatic/affective symptoms of depression were correlated with objective measures of poorer physical performance (lower peak effort sustained at CPET, shorter distance walked during a 6MWT); similarly, in patients with worse performance parameters, poorer ratings of perceived QoL were also recorded. So, the presence of a limited physical fitness during the post-acute phase of a STEMI seems to be the underlying factor for both worse depressive symptoms and poorer perception of QoL.

The deterioration of heart function caused by myocardial necrosis (measurable by reduced LVEF) is connected to more frequent long-term MACEs among our patients, as it is already widely known.[30-32] A poor heart function (reduced LVEF) correlates also with lower effort capacity; the perception of an impaired body integrity may have lead to the

increase of the somatic/affective symptoms reported by BDI-I and to a poor rating of the perspective of the future quality of life.[33]

In the same time, in post-AMI patients with a reduced LVEF a significant activation of the neurohormonal system is known to be present, together with a negative left ventricular remodelling process. Both cardiac remodelling and abnormal cardiovascular autonomic response[17, 34-36] are closely associated with higher risk of morbidity and mortality in post-AMI patients. The dysregulation of the autonomic nervous system and serious myocardial remodelling have also been considered as plausible links between depression and negative outcomes in coronary heart patients.[37-38]

All our patients underwent a cycle of intensive comprehensive exercise-based CR during the first month after the acute event, and have been educated to try and maintain a regular physical exercise after hospital discharge. It is known that exercise training improves long-term outcomes and quality of life after an AMI;[39] thus, the period of comprehensive cardiac rehabilitation may have contributed to the relatively few events recorded during the follow-up of our patients, at least in the group of patients with less diffuse coronary disease. CR may also improve depressive symptoms: after formal CR exercise training programs, prevalence of depressive symptoms is reported to reduce by more than 50%.[6-9] Intensive exercise training is effective for improving cardiac autonomic modulation,[40-41] even though there is no general agreement on the topic.[42] In addition, the inflammatory process, that is known to be activated after an AMI, may be involved in increasing the risk of depression in coronary heart disease patients; exercise (and exercise-based CR) may contribute in reducing both pro-inflammatory status and depressive symptoms in post-AMI patients.[43]

It must be underlined that almost all our patients received an effective revascularization in the first few hours of AMI; thus, it may be hypothesized that the small number of MACE and the better long-term survival of our patients may be mainly attributed to the effects of the timely reperfusion strategy, with consequent reduction of infarct size, salvage of more heart muscle, and improvement of cardiac autonomic function,[44] as well as to the multiple pharmacological therapy used.[45]

In Fig. 3, we try and outline our concept of the relationship between myocardial damage, physical performance, perceived quality of life, depressive symptoms and long-term outcome.

Limitations of the study

Criteria of exclusion from the study were history of a previous myocardial infarction and presence of a non-ST elevated myocardial infarction; no data about depressive symptoms of these patients are thus available.

All our STEMI patients suffered major complications during the initial phase of their disease, before transferral to CR; such patients could have presented degrees of depressive symptoms that may not be generalized to the other complicated or uncomplicated STEMI patients.

We had no data that could help distinguish between pre-STEMI and post-STEMI depressive symptoms; presence of a pre-STEMI depression could have biased the results of our study. Anyway, none of our patients was taking major antidepressant drugs at the time of hospital admission; by medical history and clinical and laboratory examination, no patient resulted to be an illicit drugs user or an alcohol addict.

Symptoms of depression have been assessed by BDI-I, as it was the tool most widely used in previous studies on prevalence of depression after an AMI. This tool is nowadays considered not ideal for use in the context of AMI; its limitations have already been described in Discussion.

The total number of patients observed in our study is relatively small; as late cardiac mortality in STEMI patients treated with early PCI is known to be quite low,[46] a much larger patient sample could have helped to reveal possible differences of the outcomes linked to depression. Anyway, it must be said that a relevant proportion of previous studies analyzing composite outcomes in post-AMI depressed patients included population samples sizes similar to our study.[1]

Conclusions

In conclusion, in our group of complicated STEMI patients treated with primary PCI we can confirm what already reported in a few papers in literature:[25-29] somatic/affective but not cognitive/affective symptoms of depression are associated with worse long-term prognosis. This somatic component of depressive symptoms is linked to varying levels of physical limitations, associated with the severity of the myocardial damage caused by the infarction.

In STEMI patients treated with primary PCI, we assume that physical impairment (with the associated feeling of limitation) is the underlying reason for the worse symptoms of depression evaluated by BDI-1. In our opinion, such "depressive" symptoms are not predictors "per se" of adverse cardiovascular prognosis in STEMI patients, but seem to be a manifestation of an underlying poorer cardiac efficiency, clinically reflected by a limited physical performance.[47] If so, treating depressive symptoms may not allow a modification of long-term prognosis of primary-PCI STEMI patients,[48-49] as already observed in the original ENRICHD Study,[50] even though anti-depressive treatment may potentially give a positive contribution reducing the sympathetic hyperactivity that is present in depressed patients.[51] By the other side, therapeutic measures aimed at improving physical fitness (i.e. comprehensive exercise-based cardiac rehabilitation programs)[6] could in the same time alleviate depressive symptoms and improve long-term survival.

Further studies with larger populations are needed to confirm our results and to test interventions that could effectively lead to better long-term outcomes of STEMI patients.

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Table I – Main data of patients with and without MACE

	No MACE (n = 154)	MACE (n = 30)	p*	p#
Age, years	60.5 ± 11.7	66.5 ± 12.3	0.012	
Gender				
Male, n (%)	124 (80)	24 (80)		0.948
Female, n (%)	30 (20)	6 (20)		
Cardiovascular Risk Factors				
Known diabetes, n (%)	26 (17)	12 (40)		0.003
Abnormal glucose metabolism, n (%)	56 (36)	8 (27)		0.298
Hypertension, n (%)	97 (63)	23 (77)		0.202
Smoking habit, n (%)	60 (39)	11 (37)		0.856
Family history, n (%)	89 (58)	12 (40)		0.088
Total cholesterol at discharge, mg/dl	123.0 ± 26.2	120.5 ± 26.0	0.643	
BMI	27.0 ± 3.9	27.1 ± 3.8	0.907	
STEMI characteristic				
Anterior, n (%)	100 (65)	19 (63)		0.831
Inferior, n (%)	54 (35)	10 (33)		0.818
Coronary vessels with critical lesions, n	1.9 ± 0.8	2.0 ± 0.9	0.462	
Coronary arteries treated by PCI, n	1.3 ± 0.7	1.2 ± 0.7	0.433	
Incomplete revascularization, n (%)	57 (37)	16 (53)		0.095
Time before CR, days	16.4 ± 10.2	16.9 ± 11.8	0.815	
LVEF, %	48.0 ± 9.1	44.9 ± 9.3	0.089	
LVEF <40%, n (%)	28 (18)	11 (37)		0.023
Depressive symptoms				
BDI-I	6.7 ± 6.1	8.7 ± 5.5	0.094	
BDI-I-somatic/affective	3.8 ± 3.0	5.4 ± 2.6	0.037	
BDI-I-cognitive/affective	2.6 ± 3.7	4.0 ± 4.0	0.142	
Perceived QoL				
EQ-5D-3L (EQ-VS)	73.5 ± 17.7	63.9 ± 19.2	0.008	
Physical evaluation				
6MWT-in, m	449.0 ± 113.0	379.8 ± 115.2	0.005	
6MWT-out, m	513.0 ± 119.0	420.6 ± 125.2	0.013	
Peak-VO_2, ml/kg/min	18.7 ± 5.3	17.0 ± 4.9	0.152	
%-VO_2, %	71.3 ± 19.8	72.2 ± 18.4	0.839	
W-max, W	84.8 ± 32.1	72.9 ± 21.7	0.089	

Footnote of Table I

MACE: major adverse cardiovascular events at follow-up; p*: level of significance from unpaired t tests; p#: level of significance from chi-square tests; STEMI: ST-elevated myocardial infarction; PCI: percutaneous coronary intervention; CR: cardiac rehabilitation; LVEF: left ventricle ejection fraction; BDI-I: Beck Depression Inventory version I; QoL: quality of life; EQ-5D-3L (EQ-VS): Euro quality of life, 5 dimensions, 3 levels, Visual Scale; 6MWT-in: 6 minute walk test at admission; 6-MWT-out: 6 minute walk test at discharge; peak-VO_2: peak oxygen uptake; %-VO_2: peak oxygen uptake expressed as percentage of expected; W-max: peak exercise capacity, in Watt.

Fig. 1 – Flowchart of patient selection

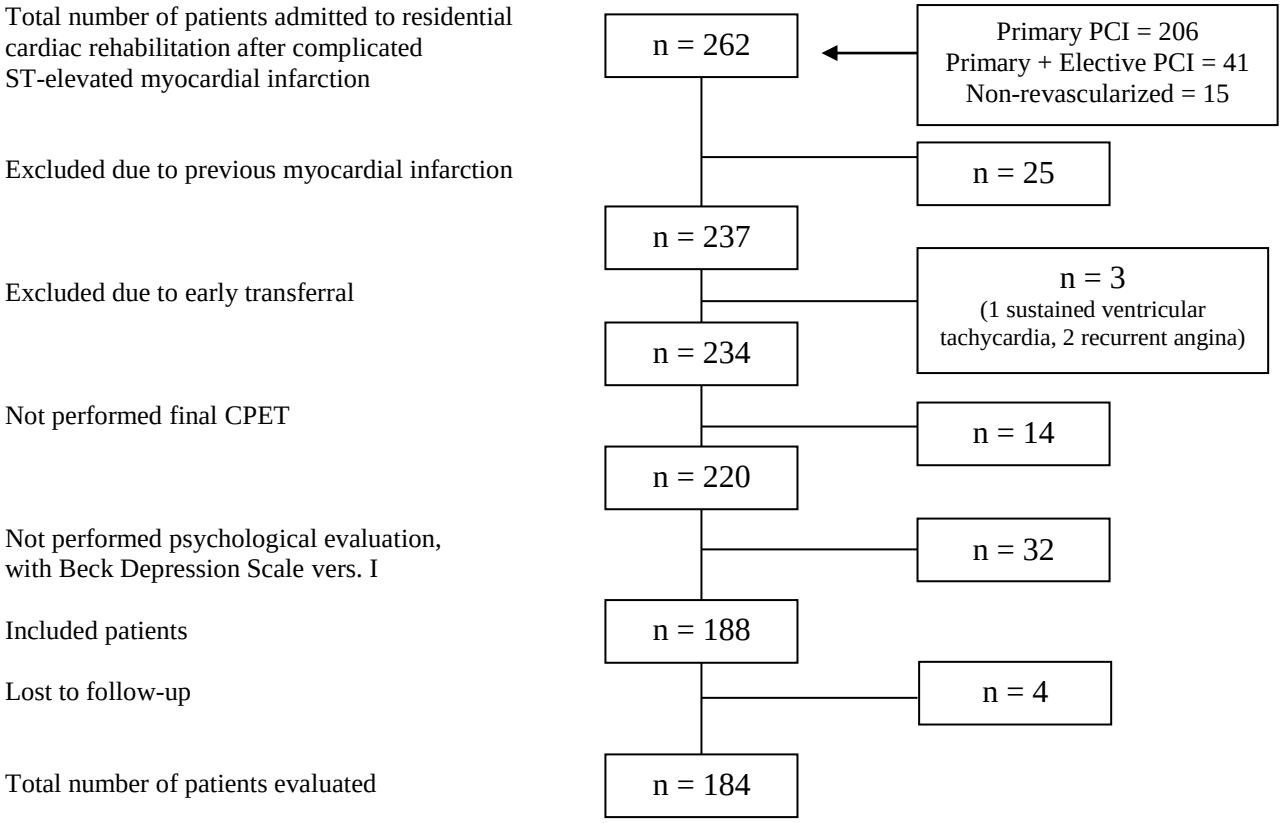
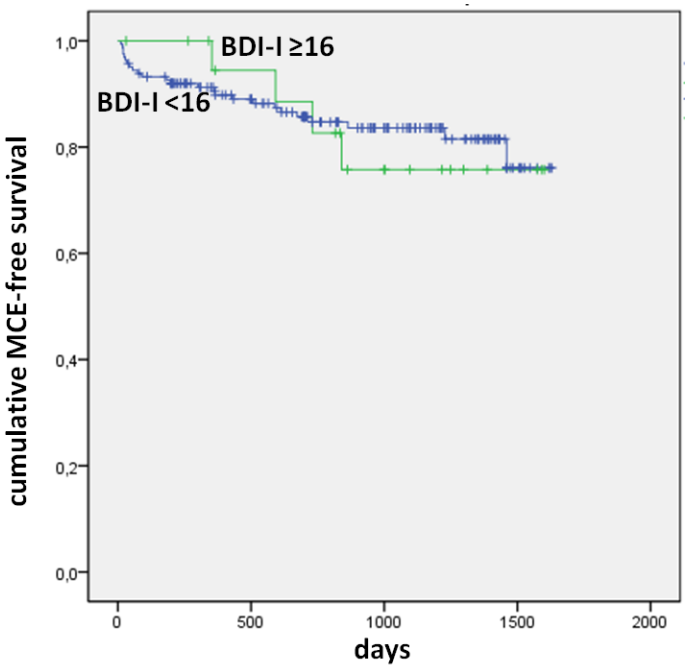


Fig. 2 - Kaplan-Meier cumulative MACE-free survival curves, for patients stratified according to BDI-I scores ≥16 versus <16 (A) and according to somatic/affective symptoms of BDI-I ≥6 versus <6 (B).

A



B

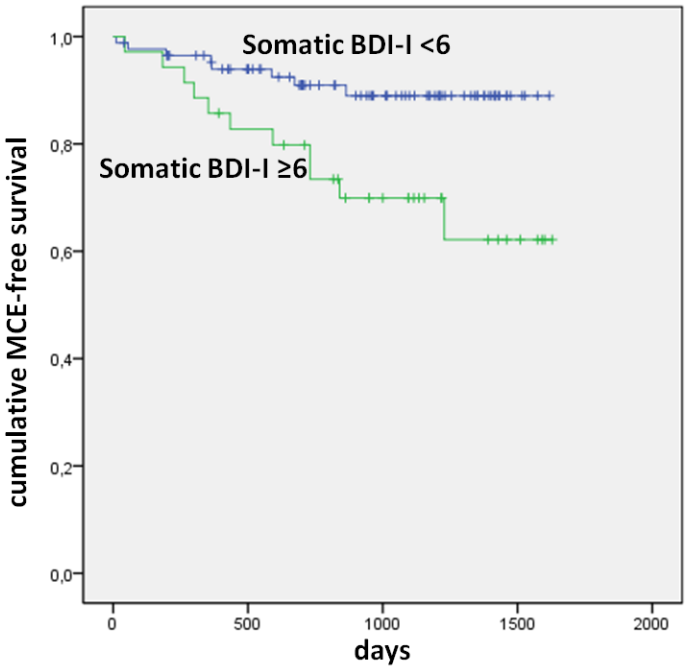
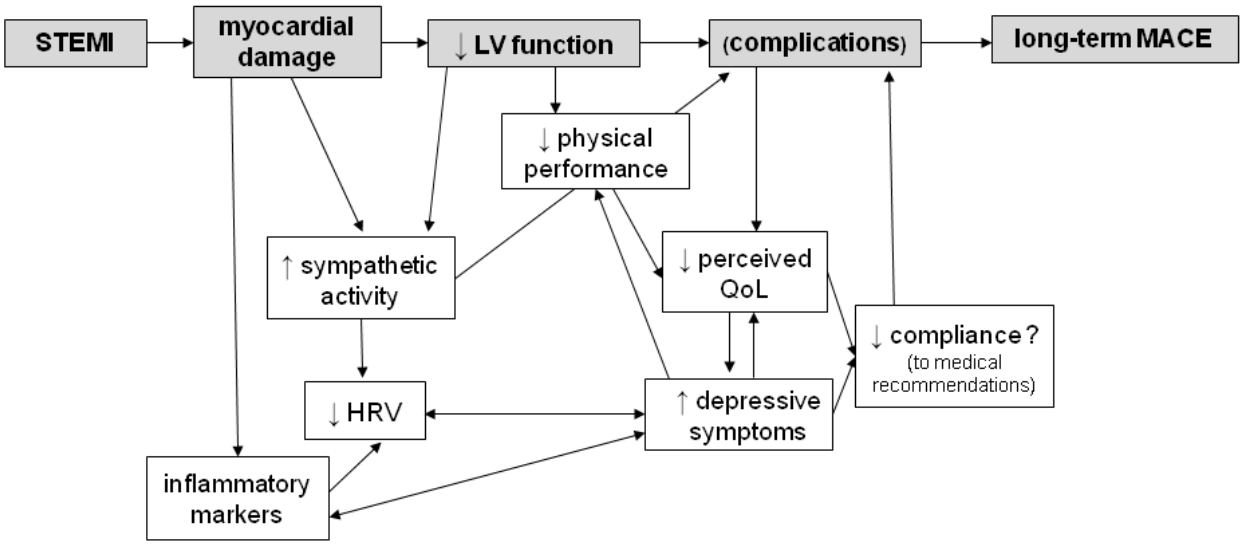


Fig. 3 - Hypothesis of relationship between myocardial damage, physical performance, perceived quality of life, depressive symptoms and long-term outcome



Box 1 - Beck's Depression Inventory, version 1

		Cognitive/affective symptoms			Somatic/affective symptoms
Item	Score		Item	Score	
1	0	I do not feel sad.	11	0	I am no more irritated by things than I ever was.
	1	I feel sad.		1	I am slightly more irritated now than usual.
	2	I am sad all the time and I can't snap out of it.		2	I am quite annoyed or irritated a good deal of the time.
	3	I am so sad and unhappy that I can't stand it.		3	I feel irritated all the time.
2	0	I am not particularly discouraged about the future.	15	0	I can work about as well as before.
	1	I feel discouraged about the future.		1	It takes an extra effort to get started at doing something.
	2	I feel I have nothing to look forward to.		2	I have to push myself very hard to do anything.
	3	I feel the future is hopeless and that things cannot improve.		3	I can't do any work at all.
3	0	I do not feel like a failure.	16	0	I can sleep as well as usual.
	1	I feel I have failed more than the average person.		1	I don't sleep as well as I used to.
	2	As I look back on my life, all I can see is a lot of failures.		2	I wake up 1-2 hours earlier than usual and find it hard to get back to sleep.
	3	I feel I am a complete failure as a person.		3	I wake up several hours earlier than I used to and cannot get back to sleep.
4	0	I get as much satisfaction out of things as I used to.	17	0	I don't get more tired than usual.
	1	I don't enjoy things the way I used to.		1	I get tired more easily than I used to.
	2	I don't get real satisfaction out of anything anymore.		2	I get tired from doing almost anything.
	3	I am dissatisfied or bored with everything.		3	I am too tired to do anything.
5	0	I don't feel particularly guilty	18	0	My appetite is no worse than usual.
	1	I feel guilty a good part of the time.		1	My appetite is not as good as it used to be.
	2	I feel quite guilty most of the time.		2	My appetite is much worse now.
	3	I feel guilty all of the time.		3	I have no appetite at all anymore.
6	0	I don't feel I am being punished.	19	0	I haven't lost much weight, if any, lately.
	1	I feel I may be punished.		1	I have lost more than five pounds.
	2	I expect to be punished.		2	I have lost more than ten pounds.
	3	I feel I am being punished.		3	I have lost more than fifteen pounds.
7	0	I don't feel disappointed in myself.	20	0	I am no more worried about my health than usual.
	1	I am disappointed in myself.		1	I am worried about physical problems like aches, pains, upset stomach, or constipation.
	2	I am disgusted with myself.			
	3	I hate myself.		2	I am very worried about physical problems and it's hard to think of much else.
				3	I am so worried about my physical problems that I cannot think of anything else.
8	0	I don't feel I am any worse than anybody else.	21	0	I have not noticed any recent change in my interest in sex.
	1	I am critical of myself for my weaknesses or mistakes.		1	I am less interested in sex than I used to be.
	2	I blame myself all the time for my faults.		2	I have almost no interest in sex.
	3	I blame myself for everything bad that happens.		3	I have lost interest in sex completely.
9	0	I don't have any thoughts of killing myself.			
	1	I have thoughts of killing myself, but I would not carry them out.			
	2	I would like to kill myself.			
	3	I would kill myself if I had the chance.			
10	0	I don't cry any more than usual.			

	1 2 3	I cry more now than I used to. I cry all the time now. I used to be able to cry, but now I can't cry even though I want to.			
12	0 1 2 3	I have not lost interest in other people. I am less interested in other people than I used to be. I have lost most of my interest in other people. I have lost all of my interest in other people.			
13	0 1 2 3	I make decisions about as well as I ever could. I put off making decisions more than I used to. I have greater difficulty in making decisions more than I used to. I can't make decisions at all anymore.			
14	0 1 2 3	I don't feel that I look any worse than I used to. I am worried that I am looking old or unattractive. I feel there are permanent changes in my appearance that make me look unattractive I believe that I look ugly.			

Figure 2A

Click here to download Figure fig2A KaplanMeier BW.tif

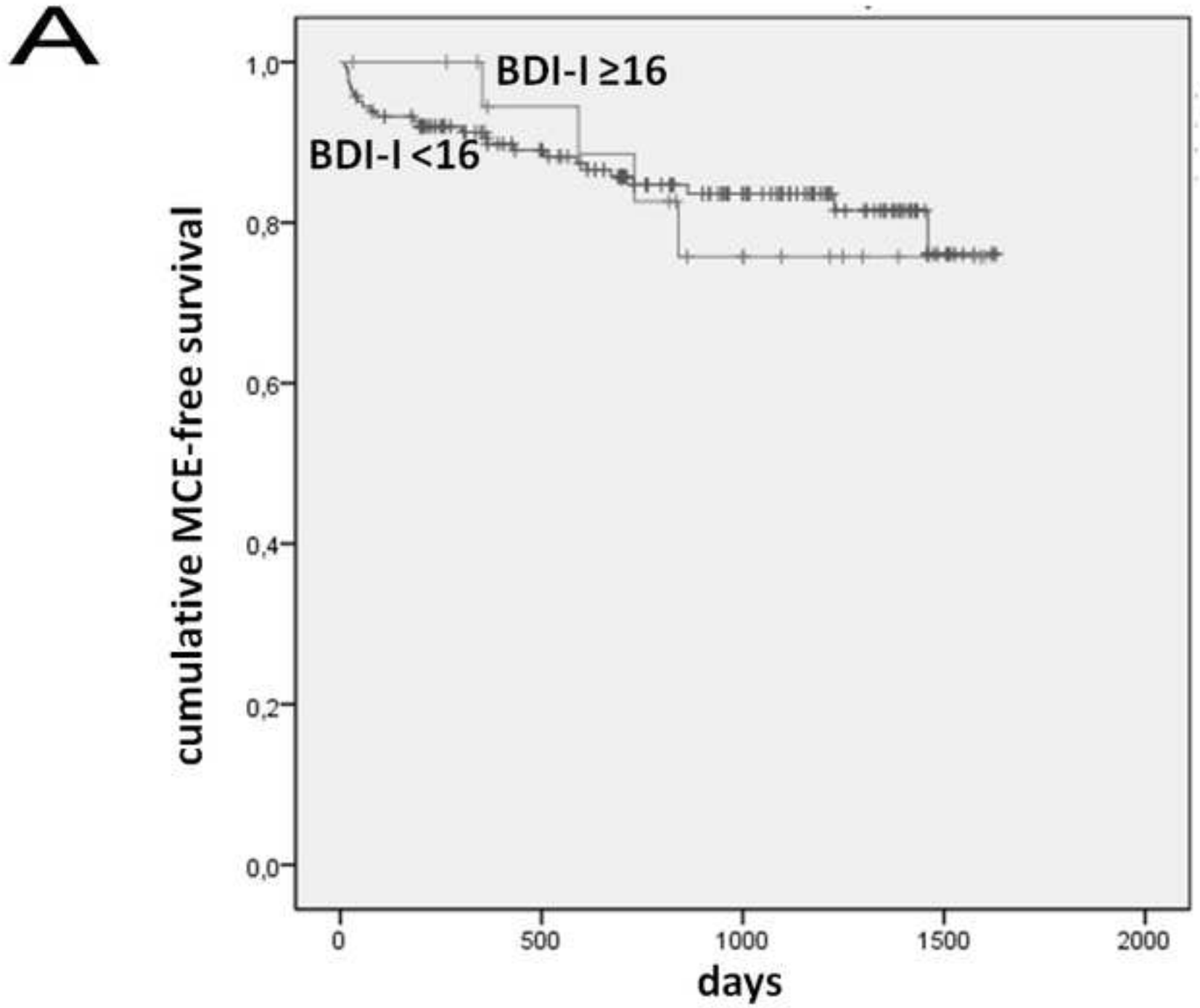


Figure 2B

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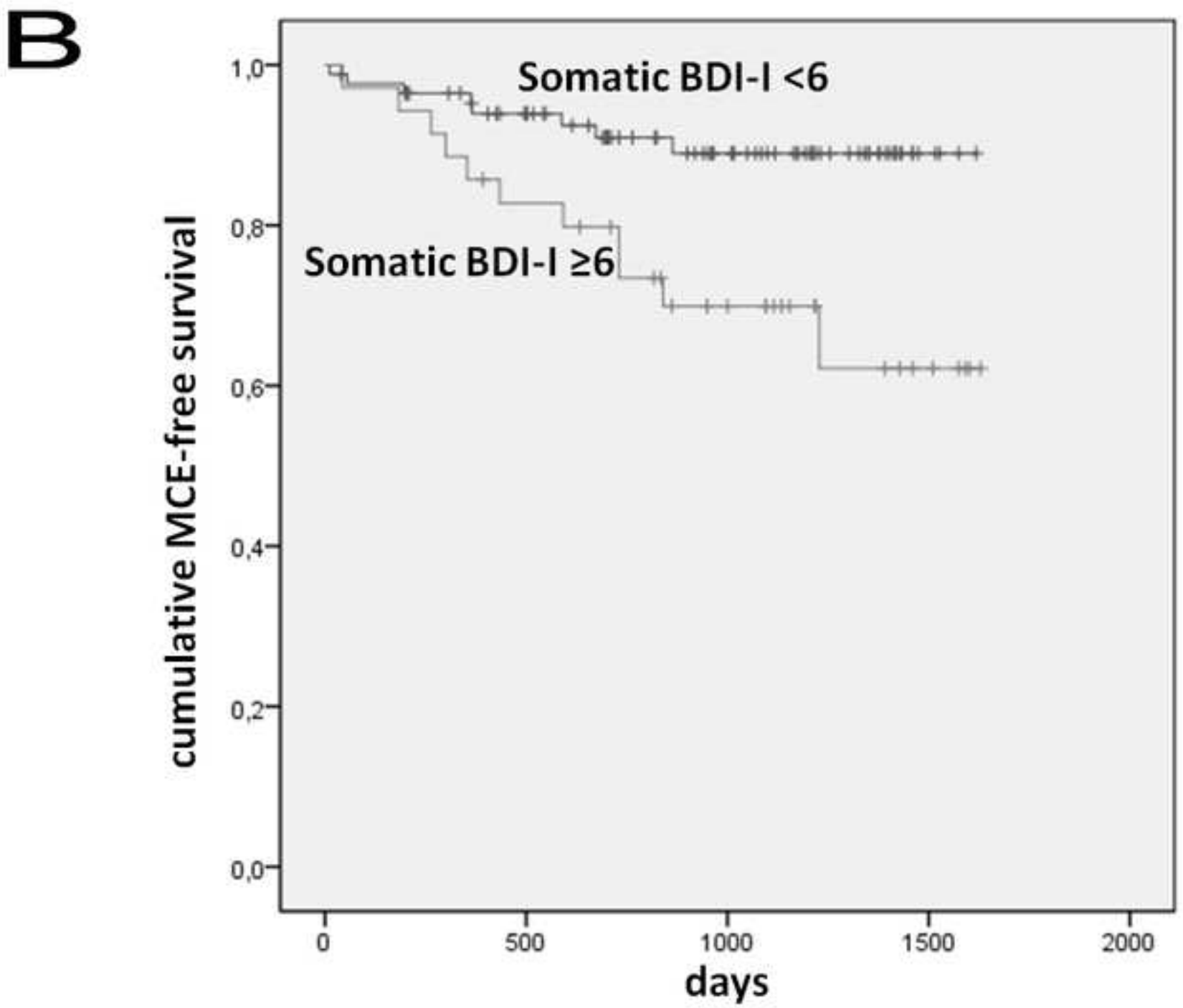
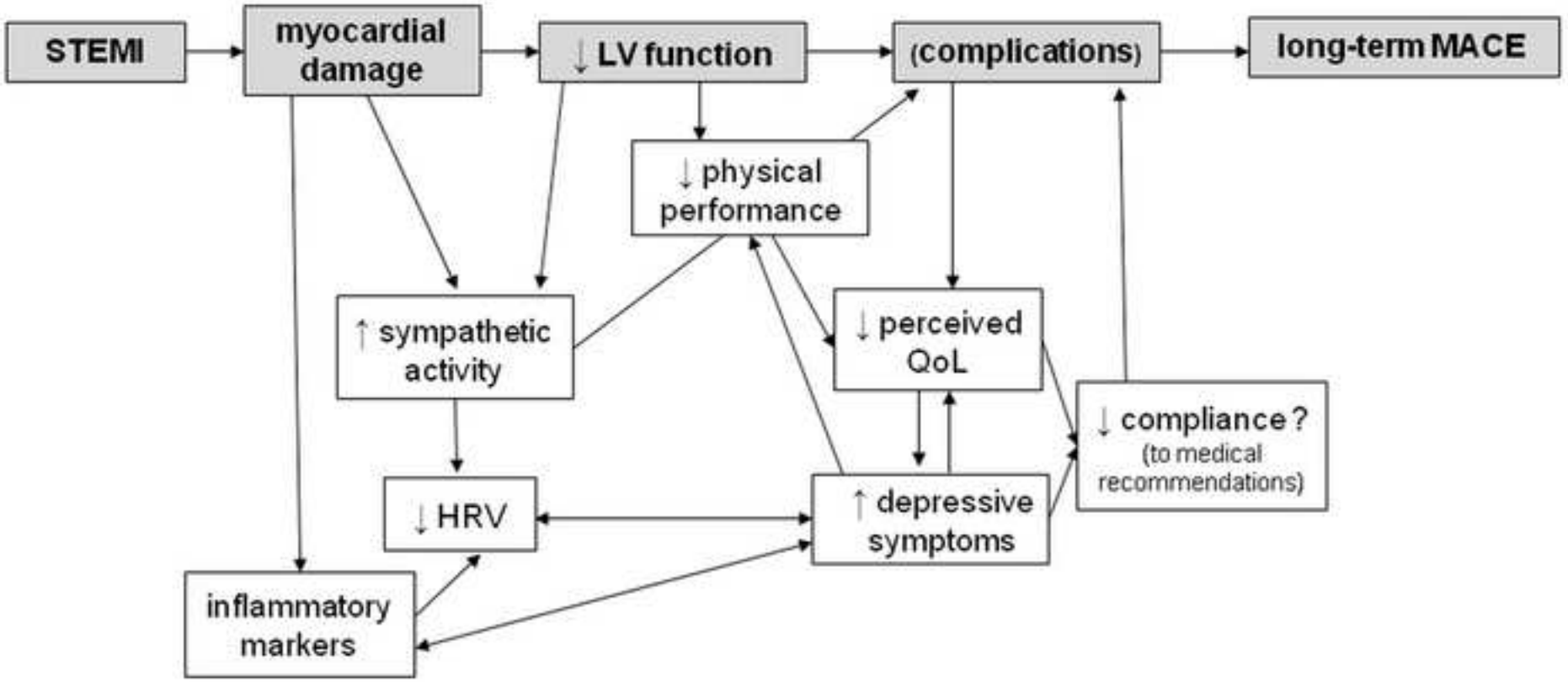


Figure 3



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