Sequential Combination of Cognitive-Behavioral Treatment and Well-Being Therapy in Depressed Patients with Acute Coronary Syndromes: A Randomized Controlled Trial (TREATED-ACS Study)

Sequential combination of cognitive-behavioral treatment and Well-Being Therapy in depressed patients with acute coronary syndromes.

A randomized controlled trial (TREATED-ACS Study)

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Short title: Sequential combination of CBT and WBT in depressed ACS patients

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Abstract

Introduction*:** Randomized controlled trials (RCT) of psychotherapeutic interventions have addressed depression and demoralization associated with Acute Coronary Syndromes (ACS). The present trial introduces psychological well-being, an increasingly recognized factor in cardiovascular health, as a therapeutic target. ***Objective: This study was designed to determine whether the sequential combination of Cognitive-Behavioral Therapy (CBT) and Well-Being Therapy (WBT) may yield more favorable outcomes than an active control group (Clinical Management, CM) and to identify subgroups of patients at greater risk for cardiac negative outcomes. ***Methods*:** This multicenter RCT compared CBT/WBT sequential combination versus CM, with up to 30-month follow-up. One hundred consecutive depressed and/or demoralized patients (out of 740 initially screened by cardiologists after a first episode of ACS) were randomized to CBT/WBT associated with lifestyle suggestions (N= 50) and CM (N= 50). Main outcome measures included severity of depressive symptoms according to the Clinical Interview for Depression, changes in subclinical psychological distress, well-being and biomarkers; medical complications and events. ***Results*:** CBT/WBT sequential combination was associated with a significant improvement in depressive symptoms compared to CM. In both groups, benefits persist at follow-up, even though differences faded. Treatment was also related to significant amelioration of biomarkers (platelet count, HDL, d-dimer), whereas the two groups showed similar frequencies of adverse cardiac events. ***Conclusions*:** Addressing psychological well-being in the psychotherapeutic approach to ACS patients with depressive symptoms was found to entail important clinical benefits. It is argued that lifestyle changes geared to cardiovascular health may be facilitated by a personalized approach that targets well-being.

Trial registration: ClinicalTrials.gov NCT00998400 (October 20, 2009), https://clinicaltrials.gov

Introduction

There is extensive evidence that the presence of depressive symptoms in Acute Coronary Syndromes (ACS) is associated with poor therapeutic adherence, higher frequency of relapses and increased mortality [1]. Mood disturbances may consist of major or minor depressive episodes, chronic depression, and demoralization [1-3], which is characterized by a sense of subjective incompetence [4].

The relationship of depression to ACS has generated the hypothesis that treatment of mood disturbances may yield improved medical and psychological outcomes. A number of randomized controlled trials have indicated the effectiveness of antidepressant drugs compared to placebo in relieving depression, yet a favorable effect on cardiovascular events was not detected [1] or could not be generalized [5]. Similar findings have been reported for the application of Cognitive-Behavioral Therapy (CBT) to ACS [6], pioneered by the ENRICHD trial [7].

Psychotherapeutic approaches, however, have been mainly shifted on the side of psychological dysfunction and have neglected psychological well-being. There is increasing evidence on the role of positive psychological assets on lifestyle and cardiovascular health [8].

In this trial, the sequential use of distress and well-being psychotherapeutic strategies was selected. The first phase of treatment (CBT) was concerned with distress associated with hospitalization and medical events. In the second phase, Well-Being Therapy (WBT), a specific psychotherapeutic approach for modulating psychological well-being [9], was introduced and suggestions for lifestyle modifications geared to cardiovascular health were provided [10]. The sequential combination of CBT and WBT has been found to yield enduring clinical benefits in the setting of psychiatric disorders [9-10], with particular reference to recurrent depression [11].

The aim of the trial was to evaluate the efficacy of the sequential combination of CBT and WBT, compared to clinical management (CM), as to depressive symptoms (primary outcome), psychological distress, well-being, as well as cardiovascular events, biomarkers and mortality

(secondary outcomes), both after treatment and up to 30-month follow-up. The identification of subgroups of patients at greater risk for cardiac negative outcomes was included.

Methods

Sample

Participants were patients hospitalized for a first episode of acute myocardial infarction or unstable angina at the Cardiology Divisions of Maggiore Hospital (Bologna) and Molinette Hospital (Torino). Myocardial infarction was documented by cardiac symptoms (presence of acute chest, epigastric, neck, jaw, or arm pain or discomfort or pressure without apparent non-cardiac source) and signs (acute congestive heart failure or cardiogenic shock in the absence of non-CHD causes), associated with ECG findings (characteristic evolutionary ST-T changes or new Q waves) and/or cardiac biomarkers (blood measures of myocardial necrosis, specifically CK, CK-MB, CK-MBm, or troponin, cTn). Instable angina was documented by cardiac symptoms (chest pain lasting less than 20 minutes) with likely ECG findings (ST-segment depression and abnormal T-wave) in absence of myocardial necrosis biomarkers.

Medically eligible patients underwent a psychological evaluation by two clinical psychologists with expertise in the field of psychosomatic aspects of cardiovascular diseases about 30 days after ACS. Inclusion criteria were: current diagnosis of major/minor depression or dysthymia according to DSM-IV-TR [12] and/or demoralization according to DCPR criteria [13]. The study was approved from the institutional review board of the Ethics Committee in both centers (identifier: Studio CE 09058). Written informed consent was secured from all patients, for both initial psychological evaluation and trial participation, after the procedures ~~were~~ had been fully explained to them. Participants did not receive any compensation. Exclusion criteria included a positive history of bipolar disorder (DSM-IV-TR), major depression with psychotic features, positive history of

substance abuse/dependence during the previous 12 months, suicide risk, current use of antidepressants and/or psychotherapy.

Psychological evaluation was performed in 288 patients with a first episode of ACS and the first 100 depressed and/or demoralized consecutive patients were enrolled (Fig. 1).

Assessment

Medical variables. Data on ACS, traditional cardiac risk factors (smoking habit, hypertension, dyslipidemia, family history of cardiovascular disease, diabetes mellitus, left ventricular ejection fraction < 40), medications and comorbidities were collected from medical records. The cardiologists involved in the study evaluated the patients at intake and once every 6 months to monitor changes in the clinical course of cardiac disease. Data from electrocardiogram, echocardiogram, X-ray, blood pressure and blood samples (cholesterol levels, creatinine, glycosylated hemoglobin, C-reactive protein, coagulation/fibrynolysis biomarkers) were provided at intake. The Global Registry of Acute Coronary Events (GRACE) risk index [14] was calculated during hospital admission for ACS to determine both in-hospital and 6-month post-discharge risk of morbidity and mortality. From the beginning of the psychological treatment and up to 30-month follow-up after the end of the intervention, information about cardiac negative outcomes, such as re-hospitalizations due to cardiac complications, acute myocardial infarction, unstable angina, angioplasty, cardiac surgery, and cardiac mortality after the first ACS, were collected.

Psychological variables. Psychological assessment included both observer-rated and self-reported measures, before the beginning of the interventions (baseline, pre-treatment), at the end (post-treatment), and 3, 6, 12 and 30 months after the end of treatment. The Structured Clinical Interview for DSM-IV-TR, Axis I Disorders [15], was used to investigate the presence of major/minor depression and dysthymia. The Semi-Structured Interview based on the Diagnostic Criteria for Psychosomatic Research (SSI-DCPR) [16] was administered to assess the presence of demoralization [17]. This interview has shown excellent inter-rater reliability, with kappa values ranging from 0.69

to 0.97 [18]. The 20-item change version of the Clinical Interview for Depression (CID) [19-20], a modified version of the Hamilton Rating Scale for Depression [21-22], was used to perform a comprehensive assessment of affective symptoms. It contains 20 items rated on a 7-point *Likert* scale, with specification of each anchor point based on severity, frequency and/or quality of symptoms. The higher the score, the worse the psychological condition. CID has been shown to be a sensitive assessment tool in clinical trials [20]. The Symptom Questionnaire (SQ) [23-24] is a 92-item self-report questionnaire, which yields 4 main scales: "depression", "anxiety", "hostility-irritability" and "somatization". The higher the score, the higher the psychological distress. The Psychological Well-Being scales (PWB) [25-26], an 84-item questionnaire, has been used to evaluate six psychological well-being dimensions (autonomy, environmental mastery, personal growth, positive relations, purpose in life, self-acceptance). Higher scores correspond to greater psychological well-being.

Study design

The study is a two-center randomized controlled trial with a longitudinal and prospective design. Enrolled patients were randomly assigned to either CBT/WBT or CM and assessed at the beginning, the end of CBT/WBT or CM sessions, and subsequent follow-ups up to 30 months after the conclusion of the interventions. Treatment allocation was accomplished through random computerized assignment that allocated 50% of patients to each treatment group, with assignments concealed until the time of group assignment. Patients were assessed by two clinical psychologists, who were blind as to treatment assignment, at pretreatment, post-treatment, and 3, 6, 12 and 30 months after the end of treatment. Both the sequential combination of CBT/WBT and the CM were performed by psychotherapists who had received specific training. Both interventions consisted in 12 weekly, 45-minute sessions. The sequential administration of CBT (8 sessions) and WBT (4 sessions) was based on a written protocol [9-10]. The WBT techniques were used to improve or balance one or more of the six dimensions of psychological well-being (environmental mastery, purpose in life, personal growth, autonomy, self-acceptance and positive relations with others), and were

supplemented with suggestions for lifestyle modification geared to cardiovascular health, including treatment adherence.

CM entails the same amount of time and attention from a professional figure than the experimental group, but specific interventions (such as exposure strategies, diary work and cognitive restructuring) were proscribed [27]. Such form of active control - unlike in previous trials that used treatment as usual[5] - allows to discriminate specific and non-specific ingredients of the psychotherapeutic approach. It consisted of empathic listening, reviewing patients' clinical status and providing opportunities for disclosure of distress and worries, and encouragement of treatment adherence.

Statistical analyses

Data were analyzed by means of SPSS 20.0 (SPSS Inc., Chicago, IL, USA). The quality of data collection was monitored regularly to assure accuracy and completeness. For all tests performed, significance level was set at 0.05, two-tailed. The sample size was estimated using Piface software, which identified a minimum of 16 participants per arm to detect the expected superiority of CBT/WBT on CM [11], with a power of 80% and a significance level of 5%. Thus, with 50 patients per group we expected a "large" effect size (Cohen's d=0.8) [28].

Multivariate ANOVA was used to examine differences in dimensional psychological variables (i.e. CID-20 total score, PWB and SQ scales scores) between patients assigned to CBT/WBT and CM at pre-intervention.

Mixed-model ANOVA (Repeated Measures) was performed to test differences between groups (CBT/WBT or CM) on the CID-20 total score, the PWB scales, and the SQ scale scores at different follow-up evaluations. All analyses were performed by using intention-to-treat (ITT) analysis, where missing values were managed by means of multiple imputations procedure. Greenhouse-Geisser correction was applied when appropriate. All analyses were adjusted for cardiac illness severity (i.e., GRACE index for 6-month probability of cardiac mortality) [14].

Each biomarker was dichotomized around the baseline median of the sample, in order to identify subgroups of patients at higher cardiovascular risk. McNemar test (applied to contingency tables) was used to identify significant changes over time in the frequencies of DSM, DCPR diagnoses and subgroups of patients at higher cardiovascular risk.

Survival analyses (Cox Regression, Kaplan-Meier) to identify cardiac events and mortality that occurred between pre-treatment and 30-month follow-up were performed.

Results

Baseline profile of the sample

The first 100 consecutive depressed and/or demoralized patients one month after ACS were enrolled, yielding 50 patients in each treatment group. The mean age of the sample was 58.8 (SD= 10.5) years (range: from 40 to 84 years). Participants were mainly men (69%), married (69%), employed (58%) and graduated from high school (44%). No significant differences based on group allocation were found (Table 1).

As to the cardiac profile of the sample, ST-Elevation Myocardial Infarction (STEMI) was the most frequent form of ACS (66%) and almost all patients (94%) underwent percutaneous transluminal coronary angioplasty (PTCA), 77% with the application of a single stent, 17% of 2 or more stents. The most frequent cardiovascular risk factors registered at hospital admission were dyslipidemia (58%) and hypertension (52%). No differences concerning ACS-related aspects and GRACE risk scores were found comparing CBT/WBT versus CM (Table 1).

Among the medications prescribed at discharge, the most frequent were statins (96%), beta-blockers (96%), and platelet aggregation inhibitors (96%). Patients allocated to CM were prescribed significantly more frequently beta-blockers, calcium antagonists, and alpha-adrenergic receptor inhibitors compared to the CBT/WBT group (Table 1).The sample presented with a number of medical comorbidities; the most frequent were gastrointestinal (43%) and endocrine diseases (14%).

As to comorbid medical diagnoses and levels of biomarkers assessed at baseline, the two groups did not show any significant difference (Table 1). From the psychological point of view, the most frequent diagnosis was demoralization (91%), followed by minor depression (56%). The two groups did not show any statistical difference, except for PWB "personal growth" scores (F= 4.45; df= 1, 98; p= 0.038) and frequency of depression/demoralization comorbidity (χ^2= 4.86; df= 1; p= 0.028), that were significantly higher among the CBT/WBT patients (Table 1).

Pre/post intervention modifications

Psychological variables. Forty-eight patients completed the CBT/WBT treatment, and 48 patients attended CM sessions. Two patients in each group early dropped-out, mainly for lack of interest or motivation. Forty and 38 patients, respectively, completed follow-up evaluations (Fig. 1).

As to the CID-20 total score, a significant interaction between group allocation and time was found (F= 2.75; df= 3.85; p< 0.05) (Table 2). Significant decreases in symptoms scores from pre- to post-treatment were found in both CBT/WBT (p< 0.001) and CM (p< 0.01) groups. However, the effect sizes for score modifications were strong in the CBT/WBT treatment group (Cohen's d= 1.161 and 1.393, respectively) and weak/medium among CM patients (Cohen's d= 0.492 and 0.589, respectively) (Table 2). Patients allocated to CBT/WBT reported significant lower scores at post-treatment (p= 0.040) compared to CM. Starting from the 3-month follow-up, CID-20 score differences between the two groups were no longer significant. Benefits, however, tended to persist in both groups.

No significant interactions were found between time and group allocation as to SQ and PWB mean scores, except for hostility as assessed by the SQ (F= 3.12; df= 4.29; p< 0.05), with CM group showing significantly higher scores at 6-month follow-up than CBT/WBT (p= 0.039) (Table 2).

Biomarkers. At 3-month post-intervention follow-up, we observed a significant reduction of the frequencies of patients with biomarkers' levels considered to be at risk (below or above the median), only among patients allocated to CBT/WBT group. In particular, we found a significant

decrease of the cases with high platelet count (from 52% to 36%, $p < 0.05$; median= 226 10^3/mmc), lower HDL cholesterol (from 52% to 34%, $p<0.05$; median= 47 mg/dL) and higher D-dimer (from 56% to 40%, $p < 0.05$; median= 0.31 mg/LFEU) in patients assigned to CBT/WBT compared to those receiving CM. No significant decrease in patients with risky levels of biomarkers was observed in the CM group.

Survival analyses

Within 36 months from baseline, 15% of the total sample had an adverse cardiac outcome. As to cardiac morbidity and mortality, we did not find any significant difference between CBT/WBT and CM groups in terms of survival. Indeed, among patients allocated to CBT/WBT, 16% (N= 8) had non-fatal cardiac events and one patient (2%) had a cardiac death (occurring after 18 months from baseline), whereas among CM patients, 10% (N= 5) had non-fatal events and one patient (2%) had a cardiac death (after 36 months from baseline). Nonetheless, CBT/WBT patients displayed most of the negative cardiac outcomes within the first 9 months, with almost half of them (4/9) relapsing during treatment sessions. On the contrary, CM participants were more likely to relapse after a longer period (starting after 8 months from baseline) (Fig. 3).

Stratifying the sample by group allocation, we found that among CBT/WBT patients, both the in-hospital (Wald= 4.235; df= 1; hazard ratio (HR)= 1.040, 95%CI: 1.002–1.079; p= 0.040) and the 6-month post-discharge (Wald= 4.594; df= 1; HR= 1.031, 95%CI: 1.003–1.060; p= 0.032) probabilities of cardiac death, as calculated with GRACE indices, were found to predict worse cardiac prognosis. On the contrary, in the CM group adverse cardiac outcomes were predicted by baseline scores of depression, as assessed by CID (Wald= 5.540; df= 1; HR= 1.204, 95%CI: 1.031–1.404; p= 0.019).

Discussion

As far as we could determine, this is the first RCT demonstrating a significant improvement in depressive symptoms and biomarkers in patients with ACS following sequential CBT/WBT when compared with CM. The study provides new important clinical insights regarding the treatment of depression in the setting of ACS. The sequential combination of CBT/WBT was effective in significantly decreasing depressive symptoms, compared to CM. In both groups, benefits persisted at follow-up, even though differences between them faded (Fig. 2). It is noteworthy the different trend observed in the two groups concerning hostility, since it represents a key variable in the literature on the psychological issues embedded in depressive states [29] and it has been found to play a negative role on cardiac prognosis [30].

Medical outcomes did not differ between the two groups, yet among CBT/WBT patients negative cardiac prognosis was associated with a greater severity of the cardiac illness (as indicated by GRACE indexes and the timing of relapses), whereas in CM group with the severity of baseline depressive symptomatology. Moreover, patients who were assigned to the treatment group displayed significant decreases in the placement according to normative values of platelet count, HDL Cholesterol, and D-dimer. There is evidence that these biomarkers may entail prognostic significance of the occurrence of cardiovascular events [31-33].

The findings are important in view of the methodology that was used. Patients were not assessed during hospitalization, but after one month, when stress linked to hospitalization and the impact of acute illness are likely to subside and the evaluation of depressive symptoms is likely to be more reliable [34]. The impact of the CBT/WBT sequential combination was not compared to treatment as usual, as occurred in other studies [6], but to clinical management, where patients received the non-specific elements of psychotherapy [27, 35]. Indeed, also CM yielded significant improvement in affective symptoms. This indicates that non-specific support after ACS may be important, but specific psychotherapeutic strategies are associated with greater benefits and underlines the need to schedule booster sessions (i.e., WBT or brief CBT) in order to reinforce progresses or address potential obstacles to continuance of positive changes made during the therapy.

WBT is a short-term psychotherapeutic strategy that emphasizes self-observation of psychological well-being, with the use of structured diary, cognitive restructuring of interfering thoughts and/or behaviors and homework assignments [9-10]. The working hypothesis was that lifestyle changes could only be achieved with a personalized approach that targets psychological well-being [9]. Based on examples taken from post-ACS everyday life, patients allocated to CBT/WBT were instructed on how to overcome specific obstacles concerning lifestyle (i.e., specific strategies for medication adherence, scheduling of gradual physical exercises and dietary modification according to specific prescriptions following hospital guidelines). In the phase that immediately follows ACS, interventions that bring the person out of negative functioning and distress may be important, and this was the target of the first phase of psychotherapy (CBT). However, facilitating progression toward restoration of the positive ("There is life after ACS") and appreciation of healthy lifestyle is another target that requires specific interventions (WBT). The results of this investigation confirm previous studies on the role of psychotherapeutic strategies in the setting of ACS [6] and provide a valid alternative/integration to pharmacological strategies, which carry the disadvantages of side effects of antidepressant drugs [36-37], with particular reference to cardiovascular safety [38]. The sequential psychotherapeutic strategy that was used may also be applied after pharmacological treatment of depression, if appropriate, and may have potential in extending therapeutic benefits beyond time of medication administration, as was found to be the case in psychiatric settings [39].

This therapeutic approach may be potentially extended to cardiovascular rehabilitation in view of the suitability of WBT for the rehabilitation process [40] and the adverse prognostic role of unhealthy lifestyle and depressive symptoms in these settings [41-43]. A number of clinical situations (delayed recovery after treatment, discrepancy between cardiovascular status/functioning, presence of psychological comorbidity, problems with lifestyle and risky behavior, presence of stressful circumstances) may be addressed by the sequential strategy we have outlined.

The findings of this investigation targeting psychological well-being in ACS should be seen as preliminary and await proper replication studies. It should also be noted that more than a quarter of

the ACS patients diagnosed with depression and/or demoralization (36/136, 26.5%) refused to join the RCT. This percentage, however, is lower than refusal rates found in the literature on secondary prevention programs, which range from 31.4% [44] to 72.2% [45] among depressed patients. Moreover, about half of the 740 patients initially screened by the cardiologists refused to undergo psychological assessment and almost half of those who agreed refused to join the trial or retreated the initial consent. The results are thus likely to reflect a self-selected population. Nonetheless, they indicate a road to the practice of lifestyle medicine [4446] that is worth perusing.

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Statement of Ethics

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

~~Disclosure Statement~~Conflict of Interest Statement

The authors report no conflict of interest.

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Author contribution

C.R., G.A.D. and G.A.F. conceptualized and designed the study. C.R., S.G., G.A.D. and G.A.F. collected, analyzed and interpreted the data. C.R., S.G. and G.A.F. wrote the first draft of the manuscript. All the Authors critically revised the manuscript for important intellectual content. S. G. performed the statistical analyses. All the Authors provided administrative, technical, or material support. C.R., G.A.D. and G.A.F. supervised the whole process.

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Figure legends

Fig. 1. CONSORT Flow Diagram of the study

Fig. 2. CID-20 total scores at different time points (Intention-To-Treat analysis)

Fig. 3. Survival curves of CBT/WBT group and CM

Fig. 1.

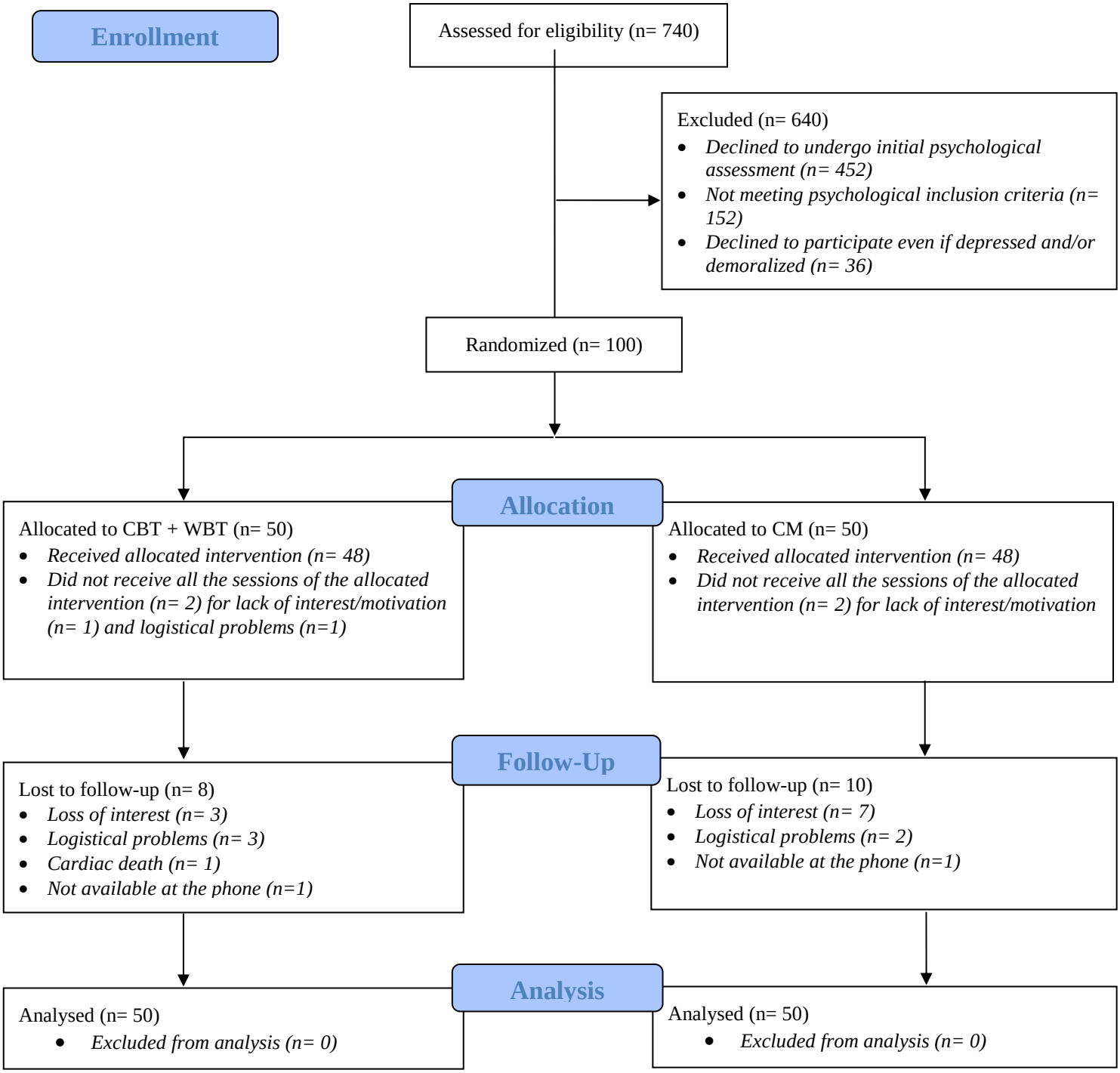

Enrollment
Assessed for eligibility (n= 740)
Excluded (n= 640)
Declined to undergo initial psychological assessment (n= 452)
Not meeting psychological inclusion criteria (n= 152)
Declined to participate even if depressed and/or demoralized (n= 36)
Randomized (n= 100)
Allocation
Allocated to CBT + WBT (n= 50)
Received allocated intervention (n= 48)
Did not receive all the sessions of the allocated intervention (n= 2) for lack of interest/motivation (n= 1) and logistical problems (n=1)
Allocated to CM (n= 50)
Received allocated intervention (n= 48)
Did not receive all the sessions of the allocated intervention (n= 2) for lack of interest/motivation
Follow-Up
Lost to follow-up (n= 8)
Loss of interest (n= 3)
Logistical problems (n= 3)
Cardiac death (n= 1)
Not available at the phone (n=1)
Lost to follow-up (n= 10)
Loss of interest (n= 7)
Logistical problems (n= 2)
Not available at the phone (n=1)
Analysis
Analysed (n= 50)
Excluded from analysis (n= 0)
Analysed (n= 50)
Excluded from analysis (n= 0)

Fig. 2.

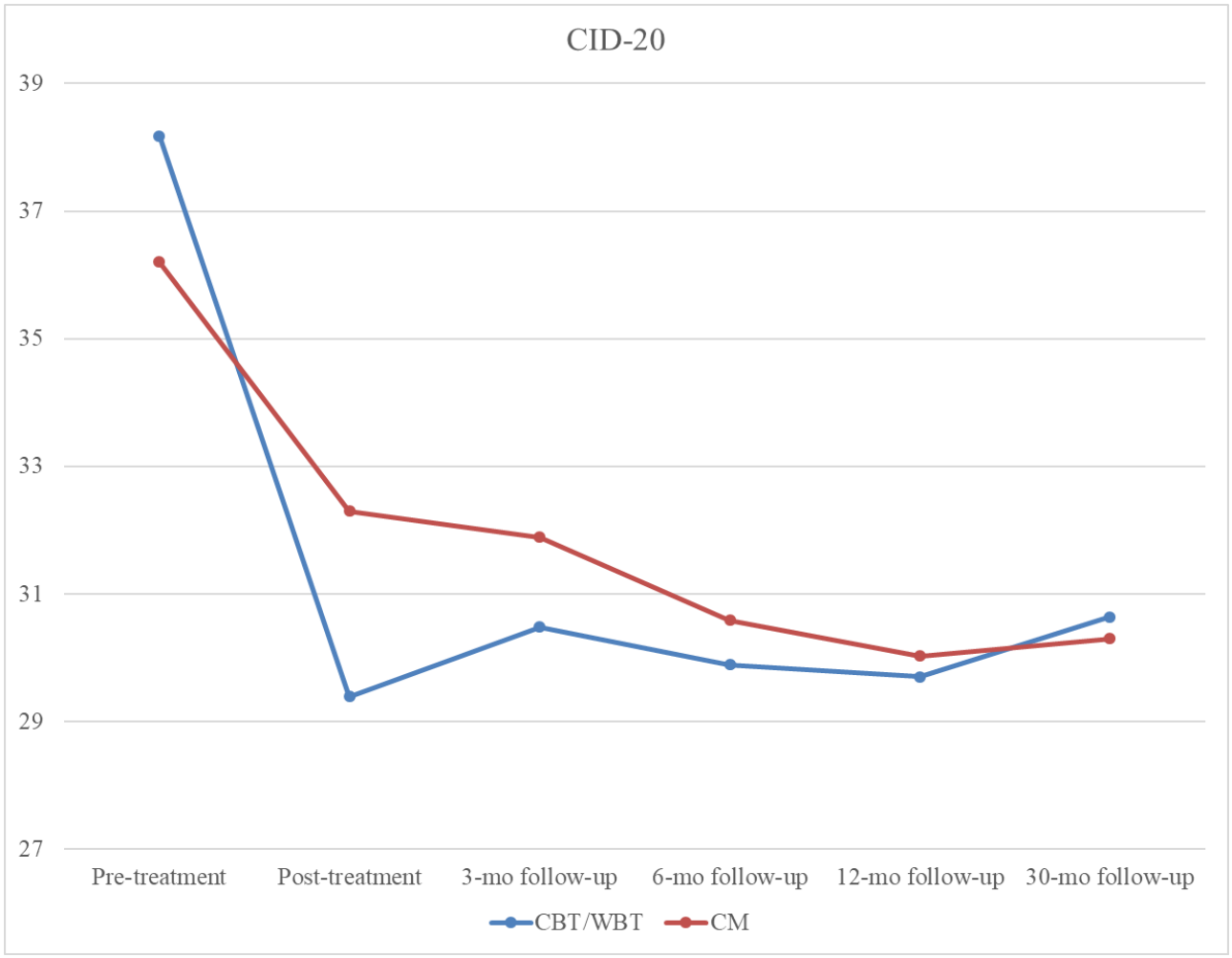
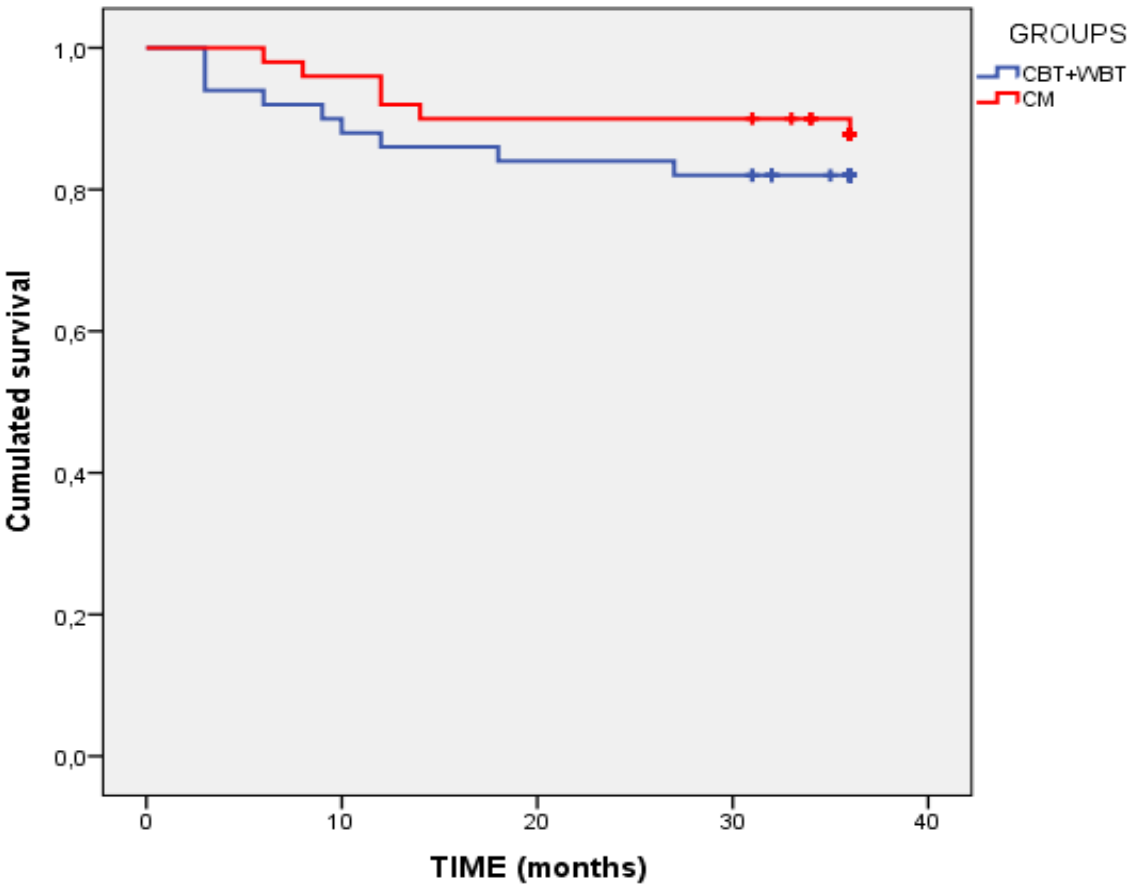

CID-20
39
37
35
33
31
29
27
Pre-treatment
Post-treatment
3-mo follow-up
6-mo follow-up
12-mo follow-up
30-mo follow-up
CBT/WBT
CM

Fig. 3.



LogRank (Mantel-Cox): χ^2= 0.809; df= 1; *p*= 0.368

Table 1. Baseline socio-demographic, medical and psychological profile of the sample.

Variables	CBT/WBT group (n = 50)	CM group (n = 50)
Age, mean (SD), y	57.64 (9.99)	60.02 (10.94)
Sex, No. (%)		
Males	31 (62)	38 (76)
Females	19 (38)	12 (24)
Marital status, No. (%)		
Single	4 (8)	7 (14)
Married	33 (66)	36 (72)
Separated	5 (10)	4 (8)
Divorced	2 (4)	1 (2)
Widow/Widower	6 (12)	2 (4)
Occupation, No. (%)		
Employed	34 (68)	24 (48)
Unemployed	1 (2)	4 (8)
Retired	13 (26)	19 (38)
Homemaker	2 (4)	3 (6)
Education, No. (%)		
Primary School	5 (10)	5 (10)
Middle School	16 (32)	18 (36)
High School	19 (38)	25 (50)
University	8 (16)	1 (2)
Post graduate education	2 (4)	1 (2)
Type of ACS, No. (%)		
STEMI acute myocardial infarction	33 (66)	33 (66)
NSTEMI acute myocardial infarction	14 (28)	13 (26)
Unstable angina	3 (6)	4 (8)
Medical procedure for ACS, No. (%)		
Single PTCA	38 (76)	39 (78)
PTCA with 2 or more stents	9 (18)	8 (16)
None	3 (6)	3 (6)
Drug-eluting Stent (DES), No. (%)	24 (51.1)	18 (38.3)
Cardiovascular (CV) risk factors, No. (%)		
Dyslipidemia	31 (62)	27 (54)
Hypertension	27 (54)	25 (50)
Smoke (current)	22 (44)	20 (40)
Familiarity	17 (34)	11 (22)
Diabetes	10 (20)	9 (18)
LVEF < 40	4 (8)	3 (6)
GRACE Risk index at admission (mortality)		
In-hospital risk, mean (SD), %	3.51 (8.58)	4.56 (7.90)
6-month risk, mean (SD), %	6.60 (11.60)	8.69 (10.57)
GRACE Risk index at admission (mortality + AMI)		
In-hospital risk, mean (SD), %	15.50 (9.85)	16.56 (10.49)
6-month risk, mean (SD), %	25.30 (12.73)	27.50 (15.00)
Medications, No. (%)		
Cholesterol reducers	49 (98)	47 (94)
Beta-blockers *	46 (92)	50 (100)
Platelet aggregation inhibitors	48 (96)	48 (96)
Cardioaspirin	47 (94)	48 (96)
Vasodilators	36 (72)	35 (70)
Angiotensin Converting Enzyme (ACE) inhibitors	31 (62)	35 (70)
Polyunsaturated fatty acids - Omega-3	11 (22)	10 (20)
Anti-hyperglycaemics	6 (12)	8 (16)
Diuretics	6 (12)	5 (10)
Angiotensin receptor blockers	5 (10)	4 (8)
Calcium antagonists *	1 (2)	6 (12)

Alpha-adrenergic receptor inhibitors *	0 (0)	4 (8)
Anti-hyperuricemics	0 (0)	2 (4)
Anti-arrhythmic	1 (2)	0 (0)
Heart rate reducers	0 (0)	1 (2)
7 or more medications, No. (%) *	11 (22)	23 (46)
Medical comorbidities, No. (%)		
Digestive system diseases	18 (36)	25 (50)
Endocrine diseases	9 (18)	5 (10)
Circulatory / cardiac comorbidities	2 (4)	4 (8)
Prostatic and male reproductive system diseases	3 (6)	2 (4)
Urinary system diseases	2 (4)	2 (4)
Orthopedic diseases	1 (2)	3 (6)
Asthma	3 (6)	1 (2)
Chronic obstructive pulmonary disease	2 (4)	1 (2)
Stroke / Aneurysm	2 (4)	1 (2)
Heteroplasia/neoplasia	2 (4)	1 (2)
Hyperuricemia	0 (0)	3 (6)
Glaucoma	1 (2)	0 (0)
Multiple sclerosis	1 (2)	0 (0)
Cluster headache	1 (2)	0 (0)
Cushing disease	1 (2)	0 (0)
Sarcoidosis	1 (2)	0 (0)
Thalassemia	0 (0)	1 (2)
Rheumatoid arthritis	0 (0)	1 (2)
2 or more medical comorbidities, No. (%)	12 (24)	13 (26)
Biomarkers		
Hemoglobin, mean (SD), g/dL	13.91 (1.21)	13.93 (1.33)
Platelet, mean (SD), 10^3/mmc	235.42 (57.64)	232.96 (50.20)
Creatinine, mean (SD), mg/dL	0.94 (1.78)	0.95 (0.20)
Triglycerides, mean (SD), mg/dL	115.96 (52.91)	121.69 (58.68)
HDL-C, mean (SD), mg/dL	51.98 (16.59)	46.51 (12.01)
LDL-C, mean (SD), mg/dL	87.40 (25.48)	93.96 (29.25)
Total-C, mean (SD), mg/dL	156.44 (31.07)	160.90 (37.45)
Glycated Haemoglobin, mean (SD), mmol/mol	41.20 (8.36)	42.97 (10.21)
Fibrinogen, mean (SD), mg/dL	347.84 (66.04)	356.49 (68.28)
D-dimer, mean (SD), mg/LFEU	0.68 (1.39)	0.45 (0.39)
HRV[a], mean (SD), msec	51.10 (27.66)	41.50 (12.29)
C-reactive protein		
BO: mean (SD), mg/dL	0.19 (0.21)	0.39 (0.69)
TO: mean (SD), mg/L	0.28 (0.39)	0.64 (1.16)
Symptom Questionnaire, mean (SD)		
Anxiety	8.60 (4.73)	7.24 (4.67)
Depression	7.92 (4.77)	6.90 (4.87)
Somatization	9.82 (5.65)	7.82 (5.12)
Hostility	4.70 (4.00)	5.34 (4.36)
Psychological Well-Being scales, mean (SD)		
Autonomy	62.20 (9.18)	61.80 (9.25)
Environmental Mastery	55.28 (11.52)	55.32 (10.65)
Personal Growth *	60.48 (9.88)	56.18 (10.50)
Positive Relations with Others	61.26 (13.26)	60.20 (10.68)
Purpose in Life	56.80 (11.51)	56.22 (11.59)
Self-Acceptance	54.48 (11.63)	55.80 (13.68)
20-item Clinical Interview for Depression (CID-20), mean (SD)		
CID-20 Total score	38.18 (8.48)	36.20 (8.57)
Depression (DSM), No. (%)	35 (70)	27 (54)
Major Depression	2 (4)	3 (6)
Minor Depression	32 (64)	24 (48)
Dysthymia	1 (2)	0 (0)
History of Depression (DSM), No. (%)	34 (68)	26 (52)
Demoralization (DCPR), No. (%)	47 (94)	44 (88)
History of Demoralization (DCPR), No. (%)	36 (72)	32 (64)
Comorbidities, No. (%)		

Depression + Demoralization *	32 (64)	21 (42)
Chronicity of Depression/Demoralization, No. (%)		
Current + previous episode of Depression	26 (52)	19 (38)
Current + previous episode of Demoralization	35 (70)	31 (62)

ACS= acute coronary syndrome; AMI= acute myocardial infarction; CV= cardiovascular; DCPR= diagnostic criteria for psychosomatic research; df= degrees of freedom; PTCA= percutaneous transluminal coronary angioplasty;
BO= Bologna; TO= Torino
[a] *assessed only in Torino*
** $p \leq 0.05$*

Table 2. Effects of treatment groups on psychological characteristics. All analyses were adjusted for GRACE index (6-month probability of cardiac mortality).

INTENTION-TO-TREAT (ITT) ANALYSIS											
Variable	Pre-treatment	Post-treatment	3-month follow-up	6-month follow-up	12-month follow-up	30-month follow-up	TIME*GROUP			Cohen's *d**	Within-group scores change *, [a]
CBT/WBT group (n = 50), mean (SD)							*F*	*df*	*p-value*		
PWB Autonomy	62.20 (9.18)	64.58 (9.42)	64.54 (9.24)	64.40 (9.12)	65.50 (8.53)	64.93 (9.67)	0.173	3.846	0.948	-0.26	-2.38 (-5.51, 0.76)
PWB Environmental mastery	55.28 (11.52)	57.33 (12.93)	59.48 (11.32)	58.02 (11.83)	58.36 (12.15)	58.69 (10.97)	0.309	4.353	0.886	-0.17	-2.09 (-5.61, 1.43)
PWB Personal growth	60.48 (9.88)	61.46 (9.92)	61.95 (9.91)	60.79 (9.58)	60.55 (9.54)	59.94 (9.34)	0.982	4.253	0.420	-0.10	-0.93 (-3.91, 2.06)
PWB Positive relations	61.26 (13.26)	61.82 (13.50)	61.88 (12.86)	60.60 (13.08)	61.27 (12.08)	60.48 (11.60)	0.709	4.183	0.592	-0.04	-0.57 (-3.33, 2.19)
PWB Purpose in life	56.80 (11.51)	57.31 (11.21)	58.35 (10.09)	57.88 (10.85)	57.42 (9.81)	57.63 (9.70)	1.104	3.803	0.353	-0.04	-0.49 (-4.14, 3.17)
PWB Self-acceptance	54.48 (11.63)	55.70 (14.36)	57.59 (13.51)	55.83 (14.19)	56.66 (11.92)	56.15 (13.90)	1.593	4.325	0.170	-0.09	1.30 (-4.48, 1.89)
SQ Anxiety	8.60 (4.73)	7.04 (5.23)	6.60 (4.87)	6.67 (4.19)	6.62 (4.51)	6.00 (4.35)	1.008	4.180	0.405	0.31	1.54 (-0.10, 3.19)
SQ Depression	7.92 (4.77)	7.21 (5.42)	6.38 (5.03)	7.06 (5.22)	6.91 (5.08)	5.99 (4.64)	0.605	4.180	0.667	0.14	0.70 (-0.98, 2.37)
SQ Somatization	9.82 (5.65)	8.80 (5.73)	8.67 (5.42)	8.96 (5.02)	9.49 (5.19)	8.17 (5.00)	0.787	3.981	0.534	0.18	1.04 (-0.75, 2.84)
SQ Hostility	4.70 (4.00)	5.19 (4.96)	5.18 (4.46)	4.41 (3.71)	5.32 (4.71)	3.81 (3.37)	3.121	4.288	0.013	-0.11	-0.51 (-1.91, 0.89)
CID-20 Total score	38.18 (8.48)	29.39 (6.55)	30.48 (5.81)	29.89 (5.88)	29.70 (6.51)	30.64 (7.02)	2.748	3.853	0.030	1.16	8.73 (5.39, 12.07)
CM group (n = 50), mean (SD)											
PWB Autonomy	61.80 (9.25)	62.82 (8.77)	63.20 (8.51)	63.21 (9.00)	64.57 (9.34)	63.71 (9.26)				-0.11	-1.02 (-4.16, 2.11)
PWB Environmental mastery	55.32 (10.65)	56.69 (8.81)	57.81 (10.15)	57.51 (8.78)	58.03 (11.19)	58.81 (8.10)				-0.14	-1.33 (-4.85, 2.19)
PWB Personal growth	56.18 (10.50)	56.54 (8.70)	56.67 (9.65)	57.10 (8.90)	57.64 (10.24)	57.00 (8.85)				-0.04	-0.41 (-3.40, 2.57)
PWB Positive relations	60.20 (10.68)	59.90 (10.93)	59.93 (12.13)	58.78 (10.82)	58.95 (11.54)	60.56 (10.78)				0.03	0.31 (-2.45, 3.07)
PWB Purpose in life	56.22 (11.59)	54.97 (9.41)	55.47 (10.32)	55.96 (10.12)	55.63 (10.82)	57.76 (8.16)				0.12	1.23 (-2.42, 4.89)
PWB Self-acceptance	55.80 (13.68)	56.03 (11.52)	57.86 (12.84)	58.32 (12.39)	59.69 (13.38)	59.94 (10.52)				-0.02	-0.15 (-3.34, 3.04)
SQ Anxiety	7.24 (4.67)	6.39 (4.41)	6.13 (4.21)	7.10 (5.14)	6.33 (5.09)	5.69 (4.07)				0.19	0.87 (-0.78, 2.51)
SQ Depression	6.90 (4.87)	5.94 (4.22)	5.83 (4.75)	6.80 (5.45)	6.22 (5.09)	5.83 (4.18)				0.21	0.98 (-0.69, 2.66)
SQ Somatization	7.82 (5.12)	8.24 (4.90)	7.87 (4.58)	8.15 (5.64)	7.90 (5.38)	7.61 (4.72)				-0.08	-0.44 (-2.23, 1.36)
SQ Hostility	5.34 (4.36)	4.12 (3.78)	4.71 (3.92)	6.01 (4.73)	5.17 (4.14)	4.56 (4.11)				0.30	1.24 (-0.16, 2.64)
CID-20 Total score	36.20 (8.57)	32.30 (7.26)	31.89 (7.11)	30.59 (7.28)	30.03 (7.05)	30.30 (6.82)				0.49	3.97 (0.63, 7.31)

CID-20= 20-item change version Clinical Interview for Depression; CBT= Cognitive-Behavioral Therapy; CM= clinical management; df= degrees of freedom; PWB= Psychological Well-Being scales; SD= standard deviation; SQ= Symptom Questionnaire; WBT= Well-Being Therapy

* Pre/Post-treatment scores change; [a] Values are expressed as mean difference (95% confidence interval)