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Research report

Changes in cognitive versus somatic symptoms of depression and event-free survival following acute myocardial infarction in the Enhancing Recovery In Coronary Heart Disease (ENRICHD) study

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ABSTRACT

Background: Randomized controlled trials focusing on the effects of antidepressant treatment in cardiac patients have found modest effects on depressive symptoms but not on cardiac outcomes. A secondary analysis was conducted on data from the Enhancing Recovery in Coronary Heart Disease trial to assess whether changes in somatic or cognitive depressive symptoms following acute MI predicted event-free survival and whether the results differed per treatment arm (cognitive behavior therapy or care as usual).

Methods: Patients who met depression criteria and completed the 6th month depression assessment ($n=1254$) were included in this study. Measurements included demographic and clinical data and the Beck Depression Inventory at baseline and 6 months. The primary endpoint was a composite of recurrent MI and mortality over 2.4 years (standard deviation=0.9 years).

Results: Positive changes (per 1 point increase) in somatic depressive symptoms (HR: 0.95; 95% CI: 0.92–0.98; $p=0.001$) but not in cognitive depressive symptoms (HR: 0.98; 95% CI: 0.96–1.01; $p=0.19$) were related to a reduced risk of recurrent MI and mortality after adjustment for baseline depression scores. There was a trend for an interaction effect between changes in somatic depressive symptoms and the intervention ($p=0.08$). After controlling for demographic and clinical variables, the association between changes in somatic depressive symptoms and event-free survival remained significant in the intervention arm (HR: 0.93; 95% CI: 0.88–0.98; $p=0.01$) only.

Limitations: Secondary analyses.

Conclusions: Changes in somatic depressive symptoms, and not cognitive symptoms, were related to improved outcomes in the intervention arm, independent of demographic and clinical variables.

1. Introduction

Depression is associated with morbidity and mortality in patients with coronary heart disease (CHD) and this association appears to be independent from medical variables, including measures of cardiac disease severity (Barth et al., 2004; Meijer et al., 2011). Randomized controlled trials focusing on the effects of antidepressant treatment in cardiac patients have found modest effects on depressive symptoms but not on cardiac outcomes (Glassman et al., 2002; Berkman et al., 2003; van Melle et al., 2007). Further analyses of these studies revealed that patients who did not respond to antidepressant treatment were at increased risk of adverse outcomes (Glassman et al., 2009; Carney et al., 2004; de Jonge et al., 2007). Several recent studies suggest that somatic symptoms of depression (e.g. fatigue, sleep problems), but not cognitive symptoms (e.g. shame, guilt) are related to adverse cardiac prognosis in patients with myocardial infarction (MI) (de Jonge et al., 2006; Martens et al., 2010; Smolderen et al., 2009). Although the association between somatic symptoms of depression and adverse prognosis was partly confounded by somatic health status, somatic symptoms of depression remained predictive of cardiac outcomes after adjustment for measures of disease severity (de Jonge et al., 2006; Martens et al., 2010). No previous studies have focused on the changes in cognitive and somatic depressive symptoms after depression treatment and their potentially differential associations with event-free survival.

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This is a secondary analysis of data from the Enhancing Recovery in Coronary Heart Disease (ENRICHD) trial. We assessed whether somatic and cognitive depressive symptoms improved after cognitive behavior therapy (CBT) and whether changes in somatic or cognitive depressive symptoms following acute MI were related to event-free survival. We also assessed whether these associations differed by treatment arm since an earlier study based on the ENRICHD trial showed that intervention patients whose depression did not improve were at higher risk for late mortality than were patients who responded to treatment (Carney et al., 2004). We hypothesized that positive changes in somatic symptoms of depression are associated with a reduced rate of recurrent MI and all-cause mortality.

2. Methods

2.1. Subjects

Participants were patients recruited within 28 days following an acute MI who met ENRICHD-modified Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) (American Psychiatric Association, 1994) criteria for major depressive disorder, minor depressive disorder with a history of major depressive disorder, or dysthymia using the Depression Interview and Structured Hamilton (DISH) (Freedland et al., 2002). Under these criteria, patients were eligible if depressive symptoms had been present for at least 7 days, provided patients had a history of major depression (The ENRICHD Investigators, 2000; Berkman et al., 2003). Patients admitted between October 1996 and November 1999 to coronary care units at eight ENRICHD clinical trial sites for an MI were screened for eligibility. MI was documented by cardiac enzymes and by chest pain compatible with acute MI, characteristic evolutionary ST–T changes, or new Q waves. Details of the methods and design of the ENRICHD clinical trial are available elsewhere (Berkman et al., 2003; The ENRICHD Investigators, 2000). Briefly, patients were excluded if they:

1. had other life-threatening medical illnesses, cognitive impairment, other major psychiatric disorders, or were at imminent risk of suicide;
2. were too ill or logistically unable to participate;
3. had been taking a non-study antidepressant for less than 21 days; or
4. were exempted by their cardiologist from participating in the study.

For the present analyses, patients included in ENRICHD with low perceived social support but no depression were excluded, as well as patients who had a recurrent MI or died before the assessment of depression outcomes (6 months).

2.2. Procedure

2.2.1. Assessment

Depressive symptoms were measured with the Beck Depression Inventory (BDI), a 21-item self-report measure developed to assess the presence and severity of depressive symptoms (Beck et al., 1961). Each item is rated on a 0–3 scale with higher scores reflecting greater severity. The BDI is a valid and reliable measure of depressive symptoms in cardiac patients (Davidson et al., 2006). For the present study, we used the BDI at the time of randomization and at 6 months post-randomization to calculate difference scores comparable to the time frame of the active treatment arm. Depressive symptoms were defined as cognitive or somatic using the original division proposed by Beck and Steer (1987). Therefore, the items concerning sadness, pessimism, sense of failure, dissatisfaction, guilt, punishment, self-dislike, self-accusations, suicidal ideas, crying, irritability, social withdrawal, and indecisiveness were summed to obtain scores for the cognitive depressive dimension and the items concerning body image change, work difficulty, insomnia, fatigue, loss of appetite, weight loss, somatic preoccupation, and loss of libido were summed to obtain scores for the somatic depressive dimension. This division was chosen because in recent studies in patients with CHD, items divergently loaded on the somatic and cognitive dimension (de Jonge et al., 2006; Martens et al., 2010; Roest et al., 2011). However, a 2 factor solution resembling the original division is found in most cases. Further, significant change in somatic depressive symptoms was defined as a standardized effect size (Cohen's d) ≥ 0.5, which is widely accepted as representing a clinically meaningful improvement in depression (Denollet and Brutsaert, 2001). We assessed whether patients who significantly improved were at decreased risk of adverse outcomes and we compared baseline characteristics of patients who significantly improved with characteristics of patients who did not improve.

2.3. Design and treatment

After written informed consent was obtained, the participants were randomly assigned by an automated system located at the ENRICHD coordinating center within 28 days of their index MI, to receive either the intervention or usual care. Both groups received the American Heart Association's Active Partnership™ health education booklet. The usual care patients received no further contact from study personnel except for follow-up.

The intervention consisted of CBT and was guided by two standard CBT manuals (Beck et al., 1979; Beck, 1995). The Beck Institute for Cognitive Therapy and Research provided the training and quality control for the intervention. The therapists were supervised by clinical investigators at each site and by Beck Institute Personnel. The intervention, training and quality control procedures are described in detail elsewhere (The ENRICHD Investigators, 2001). Participants randomized to the intervention arm who were severely depressed (Hamilton Rating Scale for Depression score >24) at enrollment or who did not show at least a 50% reduction in BDI scores after five weeks of CBT were referred to a study psychiatrist for concurrent pharmacotherapy. For these patients, unless contraindicated, sertraline was initiated at 50 mg per day. Patients who were unable to tolerate or who were unresponsive to sertraline were switched to an alternative antidepressant. The maximum duration of treatment was 6 months of CBT and 12 months of sertraline.

2.4. Endpoints

The primary endpoint for the present analysis was a composite of all-cause mortality and recurrent MI, consistent with the primary endpoint of the ENRICHD randomized trial (Berkman et al., 2003). All-cause mortality was a secondary endpoint. These endpoints were ascertained by follow-up assessments (including a medical history, physical examination and a resting electrocardiograph) and phone calls, routine hospital surveillance, and contacts with the patient's physician. Since this study focused on the effects of changes in depressive symptoms on event-free survival, only deaths and MIs that occurred after the assessment of depression outcomes (6 months) were taken into account, which is consistent with previous studies (Carney et al., 2004; de Jonge et al., 2007). The mean follow-up period was 2.4 years (standard deviation [SD] = 0.9 years).