Symptom Dimensions of Anxiety Following Myocardial Infarction

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Symptom dimensions of anxiety following myocardial infarction: associations with depressive symptoms and prognosis

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Abstract

Objective

Differential associations of symptom dimensions with prognosis in myocardial infarction (MI) patients have been shown for depression, but no studies have focused on anxiety dimensions. The aim of this study was to assess the association between somatic and psychological symptoms of anxiety following acute MI with adverse prognosis and to assess the overlap between anxiety and depression dimensions.

Methods

Patients (n=418) were assessed on demographic and clinical variables. The Hamilton Anxiety and Depression Rating Scales were used to measure anxiety and depression 2 months post-MI. Mean follow-up period was 3.8 years and the endpoint consisted of all-cause mortality and recurrent MI.

Results

After adjustment for demographic and clinical variables, somatic anxiety was significantly associated with recurrent MI and mortality (HR: 1.32; 95% CI: 1.03-1.69; p=0.03), while a trend was shown for an association between psychological anxiety and outcome (HR: 1.29; 95% CI: 0.99-1.67; p=0.06). The total anxiety score of the HARS was the strongest predictor of recurrent MI and mortality (HR: 1.38; 95% CI: 1.07-1.78; p=0.02). The HARS and the HDRS were highly correlated (r=0.86; p<0.01). Dimensions consisting of psychological distress (HR: 1.29; 95% CI: 1.02-1.63; p=0.03) and cardiopulmonary/autonomic symptoms (HR: 1.36; 95% CI: 1.06-1.75; p=0.02) also predicted outcome in adjusted analyses.

Conclusions

Anxiety was associated with adverse prognosis in MI patients with significant associations for somatic anxiety and total anxiety. When combining anxiety and depression items, psychological distress and cardiopulmonary/autonomic symptoms predicted recurrent MI and mortality. Future

research might better focus on dimensions of anxiety and depression simultaneously in MI patients.

Key words: Anxiety, depression, dimensions, myocardial infarction, mortality

Introduction

Anxiety and depression after acute myocardial infarction (MI) are associated with negative outcomes like worse quality of life, increased health care consumption, and higher rates of cardiac events and mortality [Lane *et al.* 2001; Strik *et al.* 2003; Barth *et al.* 2004; van Melle *et al.* 2004]. A meta-analysis on the relationship between anxiety and cardiac prognosis showed that post-MI anxiety was associated with a 36% increased risk of cardiac morbidity and mortality [Roest *et al.* 2010]. However, this meta-analysis did not adjust for measures of cardiac disease severity [Roest *et al.* 2010].

Recently, there has been wide interest in the potential differential associations of symptom dimensions of depression with cardiac prognosis in patients with coronary heart disease (CHD). It has been suggested that depression in patients with CHD consists of two different symptom clusters of depression, a cognitive/affective and a somatic cluster which partly differ in etiology, expression of symptoms, and association with prognosis [Ormel and de Jonge 2011]. The etiology of cognitive/affective depressive symptoms might be characterized by known risk factors of depression, including vulnerability factors and stressful life events [Ormel and de Jonge 2011]. This theory is supported by the finding that aspects of cognitive vulnerability, namely locus of control and explicit self-depressive associations, were more strongly related to changes in cognitive/affective as compared to somatic symptoms of depression in participants of the Netherlands study of depression and anxiety [Struijs *et al.* 2013]. Somatic depressive symptoms on the other hand might be a result of physiological mechanisms also related to cardiovascular disease, such as hypothalamus-pituitary-adrenal (HPA) axis dysregulation autonomic nervous system dysfunction, and increased inflammation [Ormel and de Jonge 2011; Poole *et al.* 2011]. A recent study found some support for the role of inflammatory markers, namely white blood cell count, in the development of somatic depressive symptoms following

acute coronary syndrome (ACS), although the pattern of findings was inconsistent [Steptoe *et al.* 2013].

Several studies showed that somatic depressive symptoms were stronger predictors of cardiac events as compared to cognitive/affective depressive symptoms in different patient groups [De Jonge *et al.* 2006; Schiffer *et al.* 2009; Smolderen *et al.* 2009; Martens *et al.* 2010*b*; Hoen *et al.* 2010*b*; Roest *et al.* 2011].Yet, not all studies have shown the differential importance of somatic depressive symptoms [Barefoot *et al.* 2000; Frasure-Smith and Lespérance 2003]. In addition, in two studies in patients treated with coronary artery bypass graft surgery (CAGB) only cognitive/affective symptoms predicted cardiac mortality [Connerney *et al.* 2010] and cardiovascular events [Tully *et al.* 2011].

The extent to which the association between somatic depressive symptoms and adverse cardiac outcomes can be attributed to somatic complaints related to cardiac disease severity has been the object of debate [De Jonge *et al.* 2006; Martens *et al.* 2010*b*; Roest *et al.* 2011]. Complaints from cardiovascular or medical diseases and somatic depressive symptoms can intertwine and symptoms can be mistakenly interpreted as depressive symptoms. Indeed, depression has been found to be significantly related to severity of left ventricular dysfunction in MI patients [van Melle *et al.* 2005], although other studies did not find associations between depression and measures of cardiac disease severity, including left ventricular ejection fraction (LVEF) [Kronish *et al.* 2009; Lett *et al.* 2008]. However, a relationship between somatic depressive symptoms and LVEF has been shown as well [De Jonge *et al.* 2006; Martens *et al.* 2010*b*].

To our knowledge, no studies assessed whether there are subtypes of anxiety in patients with CHD or studied the potential differential associations of symptom dimensions of anxiety with prognosis. Therefore, the objective of the present study was to assess the association of somatic and psychological symptoms of anxiety following acute MI with i) LVEF at baseline, and ii)

recurrent MI and mortality at follow-up. We hypothesized that somatic, and not psychological, symptoms of anxiety would be related to LVEF. Secondly, we hypothesized that cardiac disease severity does not fully explain the association between somatic anxiety symptoms and prognosis and that after controlling for cardiac risk factors somatic anxiety symptoms would be more strongly related to adverse outcome as compared to psychological anxiety symptoms. In addition, because anxiety and depression are closely associated in psychiatric [Watson 2005] and MI patients [Denollet *et al.* 2006] we assessed the overlap between somatic and psychological symptoms of anxiety and depression in the prediction of adverse outcome.

Methods

Patient population and procedure

Between May 2003 and May 2006 acute MI-patients (n=477) were recruited during hospitalization from four hospitals in The Netherlands (Catharina Hospital, Eindhoven; St. Anna Hospital, Geldrop; St. Elisabeth Hospital and Tweesteden Hospital, Tilburg). Details of this study have been described elsewhere [Martens *et al.* 2010*b*]. Previous publications on this study examined amongst others the association of (dimensions of) depression with prognosis [Denollet *et al.* 2010; Martens *et al.* 2010*b*] but did not assess the association of anxiety with adverse cardiac outcomes. Prior to this study we performed an update of the outcome variables and therefore this study reports on a longer follow-up period. Criteria for diagnosis of MI were: troponin I levels more than twice the upper limit, with typical ischemic symptoms (e.g. chest pain) lasting for more than ten minutes or electrocardiogram evidence of ST segment elevation or new pathological Q-waves. Exclusion criteria were: severe medical co-morbidities that increased the likelihood of early death (e.g. malignant cancer); significant cognitive impairment (e.g. dementia); serious psychiatric disorders other than mood, anxiety or personality disorders

(e.g. schizophrenia); and no command of the Dutch language. Medical ethics committees of the participating hospitals approved the study protocol and written informed consent was obtained from all patients after complete description of the study.

Demographic and clinical characteristics

Demographic variables included age, gender, partner status, and classified education level. Clinical variables were obtained from the patients' medical record and included cardiac history (previous MI, percutaneous coronary intervention [PCI], or CABG prior to index MI), LVEF, medical co-morbidity (history of diabetes, renal insufficiency, chronic obstructive pulmonary disease [COPD], and arthritis), multi-vessel disease, anterior location of index MI, participation in cardiac rehabilitation after index MI, smoking status (self-report), body mass index (BMI), hypercholesterolemia (total cholesterol > 6.50 mmol/l), hypertension (systolic blood pressure > 140 mmHg and diastolic blood pressure > 90 mmHg) and systolic and diastolic blood pressure. The following medications prescribed at discharge were also noted: beta-blockers, angiotensin-converting enzyme inhibitors, anti-coagulants, statins, aspirin, diuretics, and selective serotonin reuptake inhibitors (SSRIs).

Anxiety and depressive symptoms

Two months after hospital admission for acute MI, patients were assessed for anxiety and depressive symptoms using the Hamilton Anxiety Rating Scale (HARS) and the Hamilton Depression Rating Scale (HDRS). The HARS [Hamilton 1959; Maier *et al.* 1988] and HDRS [Hamilton, 1960] are psychiatric interviews which are widely used in research and in clinical trials assessing the efficacy of treatment for anxiety and depressive disorders.

The HARS contains 14 items and each item is scored on a scale of 0 (not present) to 4 (severe). Reliability and validity of this scale are sufficient [Maier *et al.* 1988]. A HARS score ≥

18 indicates clinically significant levels of anxiety [Goodman *et al.* 2005]. The HARS contains two subscales measuring psychological (i.e. items 1-6, and 14) and somatic (i.e. items 7-13) anxiety [Maier *et al.* 1988]. We tested whether we could replicate this underlying structure in our sample since most studies using the HARS were performed in psychiatric samples. In addition, we tested whether the HARS is an appropriate measure to assess anxiety in our sample. Although the validity of the HDRS was shown for depression [Strik *et al.* 2001], the validity of the HARS has not been studied in MI patients yet.

Anxiety and depressive disorder

The presence of a current major depressive disorder (MDD) and anxiety disorder (consisting of panic disorder, social phobia, and generalized anxiety disorder) based on the diagnostic criteria listed in the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) [American Psychiatric Association 1994] was assessed by means of the Composite International Diagnostic Interview (CIDI) [World Health Organization 1990]. Two months after hospital admission for acute MI the patients were assessed by one of the authors (EJM), trained in the administration of the CIDI by the official WHO CIDI training centre.

Endpoint

The composite endpoint combining all-cause mortality and/or recurrent MI was verified by medical records. The same criteria as for inclusion in the study were used to assess MI at follow-up. The mean follow-up period was 3.8 years (SD=1.1 years), median=4.0 years (range 28-2003 days), and follow-up data were complete for all patients (100%).

Statistical analysis

Discrete and continuous variables were compared with the chi-square test and the independent-samples t-test. Sensitivity and specificity of the HARS (cutoff score ≥ 18) to detect anxiety disorder was established. Principal component analysis (PCA) with oblimin rotation was used to assess whether we could replicate the underlying structure of the HARS. The number of components was identified by a scree plot. The Kaiser-Meyer-Olkin (KMO) test and Bartlett's test of sphericity were applied as fit indices. The association between the identified components was investigated using the Pearson product-moment correlation coefficient. Linear regression analyses were used to evaluate the relationship between factor scores for the specific components using the regression method [Distefano *et al.* 2009] and LVEF. To investigate the impact of anxiety symptom components on mortality and recurrent MI at follow-up, first univariate Cox proportional hazard regression analyses were performed. In subsequent multivariate analyses we adjusted for potential predictors of mortality, namely age, gender, cardiac history, and LVEF. In addition, we tested whether other potential characteristics of cardiac disease severity that significantly differed between the event-free and the adverse outcome group were independent predictors of recurrent MI and mortality and subsequently adjusted for these variables in sensitivity analyses. The original HARS total score was transformed to z-scores to compare the association of anxiety symptom dimensions with adverse outcome with the association of the HARS total score with outcome.

In addition, a PCA was performed for the HARS and HDRS items combined to assess the overlap between symptom dimensions of anxiety and depression. A similar procedure as described above was followed to assess the associations between the identified components and mortality and recurrent MI.

Hazard ratios (HR) with 95% confidence intervals (CI) are reported. For all analyses, SPSS 18 for Windows was used and significance level was set at 0.05, two-tailed.

Results

Of the original 477 patients, 59 did not have a HARS assessment and 7 patients were missing one or two answers to HARS questions. The missing values were replaced by individual average item-scores, leaving 418 (88%) patients to be included in the final analyses. Patients who did not have a HARS assessment were more likely to be female ($p<0.01$), but there were no differences concerning age ($p=0.11$) and measures of cardiac disease severity including LVEF ($p=0.42$), and cardiac history ($p=0.15$).

The demographic and clinical characteristics of the current sample are shown in Table 1. Fifty (12%) patients died or had a recurrent MI during the follow-up period of which 24 events were attributable to recurrent MI and 26 to all-cause mortality.

Prevalence of anxiety symptoms

Forty (9.6%) patients had a HARS score of 18 or higher. The prevalence of individual symptoms of the HARS indicating moderate severity (score 2 or higher) was highest for insomnia (32.5%), respiratory symptoms (23.0%), somatic symptoms (muscular) (21.5%), and autonomic symptoms (20.6%). Prevalence of other somatic symptoms was below 20%. For the psychological symptoms the prevalence was highest for anxious mood (19.9%), cognitive changes (19.6%), and tension (17.2%). Prevalence of other psychological symptoms was below 15%.

Sensitivity and specificity of the HARS

Sixteen (3.9%) patients met criteria for diagnosis of a current anxiety disorder as measured with the CIDI. Mean HARS score for patients with an anxiety disorder was 21.8 (SD=9.1), compared with a mean HARS score of 6.9 (SD=6.7) for patients without an anxiety disorder. The

sensitivity (69%) and specificity (93%) of the HARS were adequate for the predetermined cutoff of 18.

Component structure of the HARS

The KMO test (0.85) and Bartlett's test of sphericity ($p < 0.01$) indicated that PCA was adequate for these data. Although 3 components had eigenvalues >1 the scree plot indicated a 2 component solution and therefore we determined the optimal number of factors to be 2 (Table 2). The total explained variance was 42%. There was a moderately positive correlation between the two components ($r=0.40$, $p<0.01$). The two components that were constructed from the PCA reflected somatic and psychological symptoms of anxiety. However, contrary to earlier research [Hamilton 1959], insomnia loaded on the somatic component and loadings for genitourinary symptoms were weak for both components. Factor loadings were negative for the psychological component. Therefore, regression factor scores were multiplied by -1 to ensure that high regression factor scores reflected high psychological anxiety.

Anxiety symptoms and LVEF

Somatic ($\beta = -0.05$, $t = -0.95$, $p = 0.34$) and psychological anxiety symptoms ($\beta = 0.04$, $t = 0.84$, $p = 0.40$) were both unrelated to LVEF as a marker of disease severity.

Demographic and clinical predictors of recurrent MI and mortality

The demographic and clinical characteristics of patients stratified by outcome are presented in table 1. Patients who died or experienced a recurrent MI were older ($p<0.01$), more likely to have a history of MI, PCI, or CABG prior to the index MI ($p<0.01$) and to have a lower mean LVEF ($p<0.01$) than patients free of events. Further, patients with an adverse outcome during follow-up were more likely to have comorbid diseases ($p=0.01$) and less likely to have hypercholesterolemia ($p=0.04$), and were more likely to be treated with diuretics ($p<0.01$) and

SSRIs (p=0.02) and less likely to be treated with statins (p<0.01) compared with event-free patients. Patients with an adverse outcome were also less likely to have had invasive treatment (p=0.03) and cardiac rehabilitation (p=0.04) and more likely to have a diagnosis of current MDD (p=0.04) and anxiety disorder (p=0.02) than patients free of events. When entering age, cardiac history, LVEF, comorbidity, invasive treatment, cardiac rehabilitation, hypercholesterolemia and use of diuretics and statins into a multivariate analysis, age (p=0.04), cardiac history (p<0.01) and the use of statins (p=0.02) remained independently related to recurrent MI and mortality while there was a trend for LVEF to predict adverse outcome (p=0.06).

Anxiety dimensions and recurrent MI and mortality

In univariate analyses, the somatic anxiety dimension (HR: 1.32; 95% CI: 1.05-1.64; p=0.02) was associated with recurrent MI and mortality, but the psychological anxiety dimension (HR: 1.14; 95% CI: 0.89-1.47; p=0.31) was not (Table 3, models 1a and 1b).

When controlling for age, gender, cardiac history and LVEF, the somatic anxiety dimension (HR: 1.32; 95% CI: 1.03-1.69; p=0.03) significantly predicted recurrent MI and mortality (Table 3, model 2a) and the psychological anxiety dimension (HR: 1.29; 0.99-1.67; p=0.06) showed a trend to predict adverse outcome (Table 3, model 2b). Because patients who had an event were less likely to be treated with statins and the use of statins was an independent predictor of adverse outcome, we adjusted for this variable in a sensitivity analysis. However, further adjustment for use of statins did not change the effect (somatic anxiety= HR: 1.33; 1.04-1.70; p=0.03; psychological anxiety= HR: 1.27; 95% CI: 0.98-1.65; p=0.07).

When including both anxiety dimensions in the same model, neither was significantly associated with the endpoint after adjustment for covariates (somatic anxiety= HR: 1.25; 95% CI: 0.96-1.63; p=0.10; psychological anxiety= HR: 1.19; 95% CI: 0.90-1.57; p=0.22).

Total anxiety score and prognosis

The total anxiety score of the HARS was a significant predictor of recurrent MI and mortality in both unadjusted (HR: 1.28; 95% CI: 1.02-1.61, p=0.04) and adjusted (HR: 1.38; 95% CI: 1.07-1.78; p=0.01) analyses. Survival curves for patients with clinically significant symptoms of anxiety (HARS score ≥ 18) versus other patients are presented in figure 1. There was a trend for patients with clinically significant anxiety to be at an increased risk of adverse outcome in unadjusted (HR: 1.93; 95% CI: 0.91-4.11; p=0.09) analyses and after adjustment for age, sex, cardiac history and LVEF (HR: 2.04; 95% CI: 0.94-4.39; p=0.07).

Overlap of anxiety and depressive symptoms and prognosis

The HARS and the HDRS were highly correlated (r=0.86; p<0.01). When combining the HARS and HDRS in a PCA the scree plot indicated a 4 component solution. When retaining 4 components the explained variance was 46% and correlations between the 4 components ranged from r=0.16 to r=0.30; p<0.01. The 4 component solution represented the following dimensions: 1. psychological distress, 2. sleeping problems, 3. cardiopulmonary/autonomic symptoms, 4. functional disability/fatigue. Psychological distress (HR: 1.29; 95% CI: 1.02-1.63; p=0.03) predicted recurrent MI and mortality after adjustment for age, gender, cardiac history and LVEF. Also cardiopulmonary/autonomic symptoms (cardiovascular, respiratory, gastrointestinal, autonomic, muscular and sensory symptoms from HARS, gastrointestinal and somatic anxiety symptoms from HDRS), independently predicted adverse outcome (HR: 1.36; 95% CI: 1.06-1.75; p=0.02). Sleep problems (HR: 1.03; 95% CI: 0.79-1.35; p=0.82) and functional disability/fatigue (HR: 1.17; 95% CI: 0.89-1.55; p=0.26) did not predict outcome in adjusted analyses.

Discussion

This study is the first to assess the association between anxiety dimensions and cardiac prognosis in a sample of patients who had experienced an acute MI. We replicated the existence of a somatic and psychological anxiety symptom dimension as measured with the HARS in this group of MI patients but, contrary to previous research in psychiatric samples [Hamilton 1959; Maier *et al.* 1988], insomnia loaded highly on the somatic component instead of the psychological component. This is consistent with studies focusing on dimensions of depression in which insomnia was also counted as a somatic symptom [De Jonge *et al.* 2006; Martens *et al.* 2010*b*; Roest *et al.* 2011]. Somatic or psychological symptoms of anxiety were not associated with LVEF at baseline. After adjustment for demographic and clinical variables, including measures of disease severity, the somatic anxiety symptom dimension predicted recurrent MI and mortality at follow-up while a trend was shown for an association between psychological anxiety and outcome. In addition, the total anxiety score of the HARS was the strongest predictor of recurrent MI and mortality. There was a large overlap between psychological symptoms of anxiety and depression and a dimension of psychological distress was independently related to adverse prognosis. When looking at the somatic symptoms of anxiety and depression, three dimensions were found of which only one (cardiopulmonary/autonomic symptoms) predicted recurrent MI and mortality.

To our knowledge one previous study assessed the association between symptom dimensions of anxiety and development of CHD. In this study in adults initially free from cardiovascular disease, anxiety, and particularly somatic anxiety, was related to an increased risk of CHD in women but not in men [Nabi *et al.* 2010]. When comparing our results with previous findings on the association of depression dimensions with cardiac disease severity and prognosis in patients with heart disease, our findings are somewhat different. In studies representing patients with different stages of cardiac disease, including women with suspected myocardial ischemia [Linke *et al.* 2009], patients with MI or ACS [De Jonge *et al.* 2006; Smolderen *et al.*

2009; Martens *et al.* 2010*b*; Roest *et al.* 2011], and chronic heart failure patients [Schiffer *et al.* 2009], an adverse association of somatic depressive symptoms, but not of cognitive/affective depressive symptoms, was found with medical prognosis. On the other hand, studies in CABG patients showed an adverse impact of cognitive/affective depressive symptoms and not of somatic depressive symptoms on cardiac morbidity and mortality [Connerney *et al.* 2010; Tully *et al.* 2011]. In addition, some studies highlighted specific cognitive/affective symptoms, like anhedonia [Davidson *et al.* 2010] and hopelessness [Denollet *et al.* 2013] as important predictors of cardiac outcomes, and these symptoms might be particularly important in relatively younger patients [Denollet *et al.* 2013].

More research is needed to understand why studies on the relationship between dimensions of distress and cardiac prognosis report conflicting findings [Carney and Freedland 2012]. A potential source of conflicting findings is the type of measurement used to assess depressive and anxiety symptoms. Previous research indicated that self-reported symptoms of anxiety and depression are closely related in MI patients [Denollet *et al.* 2006]. In the current study, standardized interview ratings of a psychological distress dimension that involves the co-occurrence of anxiety and depression symptoms, predicted recurrent MI and all-cause mortality. However, in a previous report of this study a cognitive/affective depression dimension measured with the Beck Depression Inventory version 1 (BDI-I) was not related to a combined endpoint of recurrent MI and cardiac mortality [Martens *et al.* 2010*b*]. This finding is similar to another study in which both somatic and cognitive/affective depressive symptoms were associated with adverse outcome following MI when measured with a structured diagnostic interview [Hoen *et al.* 2010*a*] while in the same sample a cognitive/affective dimension measured with the BDI was not associated with cardiac prognosis [de Jonge *et al.* 2006]. These findings suggest that the type of instrument used to measure depressive and anxiety symptoms could influence the estimates of the associations of symptom dimensions with cardiac prognosis.

Another difference between previous studies focusing solely on depression is that we found support for three somatic dimensions which represented cardiorespiratory/autonomic symptoms, sleep problems, and symptoms of functional disability/fatigue, while most studies included only one somatic dimension. However, similar clusters of somatic health complaints have been found previously in MI patients [Denollet 1994]. Future studies should assess whether these factors truly represent distinct dimensions of distress, since the use of other instruments than the HARS and HDRS might produce different underlying factors, and whether the different associations with outcome following MI can be replicated.

Anxiety is potentially related to various pathophysiological processes in patients with MI, including increased risk of ventricular arrhythmias [Watkins *et al.* 2006], reduced heart rate variability (HRV) [Martens *et al.* 2008], inflammatory processes [Pitsavos *et al.* 2006], increased platelet activity [Cameron *et al.* 1990] and HPA axis dysregulation [Vreeburg *et al.* 2010]. Unhealthy behavior, such as non-adherence to treatment, physical inactivity, an unhealthy diet and smoking might also explain part of the association. Anxiety is related to an unhealthy lifestyle in individuals at risk of CHD [Bonnet *et al.* 2005], and with lower adherence to various risk reducing recommendations in patients following an acute cardiac event [Benninghoven *et al.* 2006; Kuhl *et al.* 2009]. An avoidant coping strategy is a maladaptive way of downregulating anxiety that might lead to a decline in cardiac health behavior among anxious post-MI patients [Benninghoven *et al.* 2006]. More research is needed to identify the pathophysiological and behavioral pathways underlying the association of general and specific manifestations of anxiety and cardiac prognosis. This is especially relevant since a variety of these mechanisms failed to explain the increase in risk of future cardiovascular events associated with generalized anxiety disorder in a previous study of patients with stable CHD [Martens *et al.* 2010*a*].

Future research is also needed to assess whether demographic and clinical variables differentially predict somatic and psychological symptoms of distress. In post-hoc analyses we

found distinct associations between anxiety dimensions with variables included in the multivariate model in this study. Females were more likely to experience somatic symptoms of anxiety, while no association was found for psychological anxiety with gender. Further, cardiac history was positively related to somatic anxiety only. In addition, patients with more psychological anxiety symptoms tended to be younger (data not shown). Further research on this topic could give indications on factors related to the etiology of somatic and psychological distress. Also, future studies should evaluate whether there are differential associations between symptom dimensions of distress and mechanisms leading to adverse cardiac outcomes. Lower HRV has been shown to be associated with somatic but not with cognitive/affective depressive symptoms in patients with CHD [de Jonge *et al.* 2007]. In a study on persons with depression and/or anxiety, especially somatic symptoms of depression and anxiety were related to inflammatory markers [Duivis *et al.* 2013] although these associations might for a large part be the result of an unhealthy lifestyle associated with depression and anxiety [Duivis *et al.* 2013]. Overall these findings indicate that more research is warranted to assess whether specific relations between dimensions of distress and physiological, but also behavioral mechanisms, can be identified.

Notably, both the somatic and psychological dimensions of anxiety were not related to LVEF as a marker of disease severity in the current study. In contrast, previous studies in patients with MI or ACS indicated that somatic depressive symptoms measured with the BDI-I were related to LVEF or Killip class [De Jonge *et al.* 2006; Martens *et al.* 2010*b*; Roest *et al.* 2011]. Future studies could assess whether the association between depression and LVEF can be explained by specific somatic depressive symptoms. For example, a recent study showed that scores on the BDI-I may partly reflect symptoms of the medical condition in MI patients [Delisle *et al.* 2012], although this does not appear to be the case for the BDI-II [Thombs *et al.* 2010].

Previous studies also showed that risk estimates of anxiety predicting cardiac outcomes were only slightly or not attenuated after adjustment for disease severity [Roest *et al.* 2010; Roest *et al.* 2012]. In order to reduce possible confounding in the period immediately after the MI, anxiety was measured at 2 months post-MI, and we adjusted for various cardiac risk factors. However it is impossible to completely rule out the possibility of residual confounding and underlying pathophysiology might still explain part of the relationship between anxiety and cardiac prognosis in the current study.

Although the HARS is a widely used instrument to assess anxiety, there is a large overlap with depression features and one item specifically addresses depressed mood [Maier *et al.* 1988]. In addition, especially the somatic symptoms of the HARS could be indicative of higher levels of depression severity [Vaccarino *et al.* 2008]. Because of the high correlation between the HARS and the HDRS we could not assess whether the association of anxiety and its dimensions with cardiac prognosis is independent from depression which is an important limitation of this study. Nonetheless, the results of the current study suggest that anxiety and depression in MI patients might be better seen as two aspects of a general distress construct from which a psychological and one or more somatic dimensions can be deduced. However, this should be further investigated by studies using anxiety and depression measurements that are more distinctly different from each other. Another limitation is that, because of the relatively small sample size, we could not assess potential gender differences in the relationship between symptoms dimensions of anxiety and cardiac outcomes. In addition, females were less likely to have a HARS assessment and this may have led to a relatively low prevalence of patients with severe anxiety and depression. The prevalence of anxiety disorders and MDD was lower in the current study as compared to other studies in MI and stable CHD patients [Roest *et al.* 2012, Martens *et al.* 2010a]. Although, a study in patients with stable coronary artery disease showed that most of the risk associated with elevated depressive and anxiety symptoms was in patients with MDD or

GAD [Frasure-Smith and Lespérance 2008], several other studies showed a dose-response relationship between depressive and anxiety symptom scores and adverse outcomes in different patient groups [Zuidersma *et al.* 2013; Rosenbloom *et al.* 2009]. This indicates that mild symptoms of distress are also related to cardiac prognosis. Finally, we had no information on the overall response rate of the study. However, we previously reported that the response rate in a subsample of patients was 73% [Martens *et al.* 2010*b*]. Despite the aforementioned study limitations, a broad spectrum of possible confounding factors was evaluated in this study. Furthermore, this study was a multi-centre study, making generalization of our results to the population of acute MI patients more justified.

In summary, this study showed that anxiety was associated with adverse prognosis in MI patients with significant associations for somatic anxiety and total anxiety. There was a large overlap in anxiety and depressive symptoms and when combining anxiety and depression items, psychological distress and cardiopulmonary/autonomic symptoms predicted recurrent MI and mortality. Future research might better focus on dimensions of anxiety and depression simultaneously in MI patients. Also future studies should identify whether these symptom dimensions have different etiologies and whether mechanisms leading to adverse cardiac outcomes vary for dimensions of psychological and somatic distress.

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Table 1. Demographic and clinical characteristics

Characteristics	**All patients (n=418)**	**Mortality/MI (n=50)**	**Event-free (n=368)**	**p**
Demographic variables				
Age, years mean (SD)	59 (11.4)	65 (13.3)	58 (10.8)	<0.01
Female gender	79 (18.9)	8 (16.0)	71 (19.3)	0.58
Partner	345 (82.7)	39 (79.6)	306 (83.2)	0.54
Educational level: high	229 (54.9)	22 (44.9)	207 (56.2)	0.13
Clinical characteristics				
Cardiac history	65 (15.6)	20 (40.0)	45 (12.2)	<0.01
LVEF %, mean (SD)	50 (9.5)	45 (11.2)	50 (9.0)	<0.01
Multi-vessel disease	135 (37.8)	18 (45.0)	117 (36.9)	0.32
Anterior MI location	155 (40.8)	15 (34.9)	140 (41.5)	0.40
Comoborbidity	88 (21.2)	17 (34.0)	71 (19.4)	0.02
Invasive treatment	258 (61.7)	24 (48.0)	234 (63.6)	0.03
Cardiac rehabilitation	263 (67.1)	26 (54.2)	237 (68.9)	0.04
Medication use				
Beta-blockers	361 (86.6)	43 (86.0)	318 (86.6)	0.90
ACE-inhibitors	154 (37.0)	15 (30.0)	139 (38.0)	0.27
Anti-coagulants	351 (84.2)	44 (88.0)	307 (83.7)	0.43
Statins	382 (91.6)	40 (80.0)	342 (93.2)	<0.01
Aspirin	344 (82.5)	37 (74.0)	307 (83.7)	0.09
Diuretics	78 (18.8)	18 (36.0)	60 (16.4)	<0.01

SSRIs	50 (12.2)	11 (22.0)	39 (10.8)	0.02
Smoking	163 (39.1)	20 (40.0)	143 (39.0)	0.89
BMI, mean (SD)	27.0 (4.0)	26.7 (4.6)	27.0 (3.9)	0.62
Hypertension	88 (22.1)	7 (14.3)	81 (23.1)	0.16
Hypercholesterolemia	43 (10.7)	1 (2.1)	42 (11.9)	0.04
Cardiac function				
Systolic blood pressure, mean (SD)	141 (29)	138 (27.1)	141 (28.9)	0.38
Diastolic blood pressure, mean (SD)	83 (17)	79 (17.9)	83 (16.5)	0.13
Psychiatric morbidity				
HARS score ≥ 18	40 (9.6)	8 (16.0)	32 (8.7)	0.10
Current anxiety disorder	16 (3.9)	5 (10.0)	11 (3.1)	0.02
Current MDD	23 (5.6)	6 (12.0)	17 (4.7)	0.04

Values are expressed as n (%) of patients unless otherwise indicated

ACE= angiotensin-converting enzyme; BMI= Body mass Index; COPD= chronic obstructive pulmonary disease; HARS= Hamilton Anxiety Rating Scale; LVEF= left ventricular ejection fraction; MDD= major depressive disorder; MI= myocardial infarction; SSRIs= selective serotonin reuptake inhibitor.

Table 2. Pattern matrix of principal component analysis

HARS items	Somatic component	Psychological component
1. Anxious mood	0.11	-0.84
2. Tension	0.13	-0.81
3. Fears	-0.12	-0.29
4. Insomnia	0.47	-0.14
5. Intellectual	0.28	-0.30
6. Depressed mood	0.09	-0.77
7. Somatic (muscular)	0.62	-0.04
8. Somatic (sensory)	0.66	0.06
9. Cardiovascular symptoms	0.58	0.04
10. Respiratory symptoms	0.59	-0.08
11. Gastrointestinal symptoms	0.68	0.10
12. Genitourinary symptoms	0.17	-0.15
13. Autonomic symptoms	0.77	-0.02
14. Behavior at interview	0.27	-0.59

Table 3. Association between somatic and psychological anxiety with recurrent MI and mortality

Predictor variables	**HR**	**95% CI**	**p**
Model 1a			
Somatic component	1.32	1.05-1.64	0.02
Model 1b			
Psychological component	1.14	0.89-1.47	0.31
Model 2a			
Somatic component	1.32	1.03-1.69	0.03
Age	1.04	1.01-1.07	<0.01
Female gender	0.67	0.31-1.47	0.32
Cardiac history	2.36	1.26-4.41	<0.01
LVEF %	0.96	0.94-0.99	<0.01
Model 2b			
Psychological component	1.29	0.99-1.67	0.06
Age	1.04	1.02-1.07	<0.01
Female gender	0.75	0.35-1.62	0.47
Cardiac history	2.72	1.49-4.98	<0.01
LVEF %	0.96	0.94-0.99	<0.01

HR = hazard ratio; CI = confidence interval

Figure 1. HARS score ≥ 18 and association with recurrent MI and mortality