The complex nature of depression after acute myocardial infarction: Evolution and consequences

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Chapter One

General introduction

I

Cardiovascular disease, and in particular acute myocardial infarction (MI), is one of the leading causes of morbidity and mortality in industrialized countries, including the Netherlands.[1-3] An acute MI is a life-threatening event that has a major impact on the lives of patients and their families. MI is not caused by dysfunction of the heart itself, but by a blockage in one or more of the coronary arteries, which perfuse the heart muscle with oxygen-enriched blood. Blockages in the coronary arteries are typically the result of atherosclerosis. A patient suffering from MI requires immediate treatment to prevent the loss of viable heart muscle. Several treatment options are available, including the use of thrombolytic agents, coronary artery bypass graft (CABG) surgery, and percutaneous coronary intervention (PCI). During PCI, a stent is often placed to prevent restenosis. All therapies are aimed at improving the blood flow to the heart muscle.

The last decades have witnessed continuous advances in the development of new treatment modalities and techniques with which to fight coronary artery disease (CAD), resulting in a decline in mortality rates.[4] Nevertheless, traditional risk factors can only explain a proportion of the variance of mortality in CAD patients. Hence, it seems timely to expand our focus to also include more non-conventional risk factors, such as psychological factors.[5]

There is growing evidence that psychological factors contribute to the pathogenesis and progression of CAD, besides biomedical and behavioral risk factors, such as diabetes mellitus, elevated blood pressure, unfavourable lipid profile, smoking, lack of physical exercise, etcetera.[6] Recently, the American College of Cardiology/American Heart Association and the European Society of Cardiology have recommended in their practice guidelines that the psychosocial status of patients should be evaluated, "including inquiries regarding symptoms of depression", and that "efforts to relieve stress should be emphasized whenever possible".[7,8]

THE IMPACT OF POST-MI DEPRESSION

In the year 2020, cardiovascular disease and major depression are predicted to be among the top contributors to the worldwide burden of disease.[9] In addition, depression is a common comorbid disorder with acute MI.[10,11] Both of them are associated with decreased quality of life and impose a significant economic burden on society.[12] Of all the psychosocial risks that have been studied in cardiovascular disorders, depression is the most prevalent and best supported by epidemiological studies.[13,14] Today, depression is increasingly recognized as a sequel following MI and an important determinant of recovery. Many studies have documented high rates of depression in patients recovering from MI[15], with prevalences ranging from 17-37%.[16,17] Since depression is common in cardiac patients, there has been a tendency to view

post-MI depression an a normal reaction to a life-threatening event. However, depression in patients with CAD has been found to be a more significant predictor of health status, symptom burden, and physical limitations than either left ventricular dysfunction or myocardial ischemia.[18] A recent study also showed that cardiac patients with persistent symptoms of depression after hospitalization were less likely to take their medications regularly, to attend cardiac rehabilitation, to exercise, and to quit smoking.[19] Moreover, in many well-designed studies, depression has been associated with a two- to four-fold increased risk of adverse clinical outcomes and impaired health status in post-MI patients.[20-29] Depression is a significant predictor of 6-[11], 12-[30], 18-month[22,31] and 5-year mortality[32] in hospitalized MI patients. The impact of depression on prognosis in these studies was about as large as, and independent of, other major prognostic factors like severity of coronary atherosclerosis[33], left ventricular dysfunction and history of previous MI[11]. A recent review reported relative risks for adverse outcome (mainly cardiac death) ranging from 2.5 to 5.7.[12] In addition to the mortality risk associated with post-MI depression, increased health care costs linked to both readmissions and out-patient contact in the first year after MI have been reported.[29]

However, a recent study indicated that depression had a negative impact on cardiac prognosis after MI, but that this influence was smaller than found in early studies.[34] Besides, some studies cannot confirm an impact of post-MI depression on cardiac prognosis.[35-38] Furthermore, a meta-analysis on the prognostic association of depression with adverse outcome post-MI indicated that of studies with significant results in bivariate analysis, only 55% conducted analyses adjusted for clinical variables.[39] This is particularly important in light of recent findings showing that the rate and severity of depressive symptoms was related to severity of left ventricular dysfunction, with recommendations that this should be taken into account when evaluating the effect of depression on cardiac prognosis.[40]

UNRESOLVED ISSUES REGARDING POST-MI DEPRESSION

Despite a growing body of literature, many questions about the nature, characteristics, evolution and predictive value of depression in post-MI patients remain unanswered. One issue pertains to whether the risk is restricted to individuals with depressive disorder or also extends to patients with less severe depression, including depressive symptoms.[41] A recent meta-analysis found no clear prognostic difference between studies that define depression through self-report and those that did so with a clinical interview.[42] In fact, some studies show that diagnosis of clinical depression does not add to the predictive power of relatively mild levels of depressive symptoms in cardiac patients.[22,43] In the latter study, there was even a tendency towards a higher recurrent cardiac event rate among patients with mild to moderate levels of depressive symptoms without a clinical diagnosis of depression as compared to

those with a diagnosis.[43] It has been suggested that minor depression might be particularly important in patients with comorbid medical illnesses.[22] Is it because most patients with milder forms of depression go on to develop major depression, or is there also a risk associated with milder or subthreshold depression? To answer this question, we need to know more about the specific aspects of depressive conditions that increase the risk for adverse clinical events.

Structured diagnostic interviews are the most rigorous and specific method for assessing depression. In clinical practice, the diagnosis of Major Depressive Disorder is based on the criteria listed in the DSM-IV and requires the presence of at least one core criterion (depressed mood or loss of interest) persisting for at least two weeks, accompanied by at least four of the following additional symptoms: Changes in appetite or weight, sleep difficulties, fatigue, psychomotor agitation or retardation, difficulty concentrating, feelings of guilt or worthlessness or thoughts of death or suicide. These symptoms must lead to significant functional impairments and represent a change from previous functioning.[44] However, self-report measures have been the standard method for assessing depressive symptoms in psychiatric epidemiology research for the past 20 years because of their ease of administration and scoring.[45] The term depression has been used interchangeably in post-MI depression research to indicate both major depression and depressive symptoms. As a result, the prevalence of post-MI depression highly depends on the definition of depression, with depressive symptoms usually generating higher prevalence rates than a clinical diagnosis. In this thesis, depression has been assessed with the Composite International Diagnostic Interview (CIDI)[46] and the self-report questionnaire Beck Depression Inventory (BDI)[47].

Furthermore, little is known about the characteristics and evolution of post-MI depression, and which elements of depression incur the most cardio-toxic effects in terms of predicting adverse health outcomes. Differential effects of somatic and cognitive symptoms of depression on medical comorbidity and prognosis in post-MI patients have been reported. Both somatic and cognitive symptoms of depression have been related to medical comorbidity, but the variance explained by the cognitive symptoms was less than 1%.[48] Other research showed that cognitive/affective symptoms of depression were not related to cardiovascular prognosis and only marginally related to health status, whereas somatic/affective symptoms were significantly related to health status and prognosis.[49] In contrast, it was found that negative affect but not somatic symptoms are predictive of mortality in CAD patients.[50] Recently, Doyle and colleagues recommended that studies concentrate on investigating different elements of depression, in order to determine whether it is somatic, affective, or cognitive symptoms or depression per se that is predictive of adverse outcomes in post-MI patients.[51]

Moreover, it remains unknown to what extent post-MI depression should be considered a transient distress reaction to a life-threatening event or a resurfacing of a pre-existing depressive vulnerability.[52] Depressive symptoms after MI may subside shortly after discharge, or they may persist for a longer time or develop only after discharge. Hence, it has been argued that transient depression after MI may not have prognostic importance.[15,31] In a study of CABG patients only persistent depression was related to mortality.[53] In contrast, pre-CABG depression has been shown to predict 6-month medical morbidity[54] and 2-year cardiac mortality[55]. Another study indicated that incident post-MI depression was related to impaired cardiovascular prognosis rather than post-MI depression per se.[56] However, recently it was shown that depressive symptoms after MI, irrespective of whether they persist, remit, or develop in the first month after hospitalization, were associated with adverse prognosis post-MI.[57] Spijkerman and co-workers found that in first-ever post-MI depression cases, depression might be triggered by the severity of the MI, whereas ongoing and recurrent depression was more related to personality.[52]

The optimal timing for the assessment of depression has also been the subject of much debate. Although it is convenient to screen cardiac patients undergoing coronary revascularization in hospital, these patients are best screened for depressive symptoms 1 month after the index procedure.[58] By contrast, in post-MI patients depression during hospitalization has been shown to be a significant predictor of mortality[32], emphasizing the importance of early identification of depression and in-hospital screening. Screening during hospitalization and 1 month after discharge has also been recommended by others.[57] However, several have advocated that hospitalization is not an optimal time point to assess psychological distress, as patients are not medically stable at that time.[59,60]

Taken together, there are several inconsistencies in the cardiac literature on depression, including the nature and course of depression post-MI and its determinants, and the optimal time of assessment. Knowledge on these issues in post-MI patients is needed in order to optimize risk stratification in clinical practice and to enhance secondary prevention.

IS DEPRESSION *THE* PSYCHOSOCIAL RISK FACTOR?

Researchers have tended to evaluate the effects of putative psychological risk factors for physical disease by analyzing or measuring only a single psychological construct at a time.[61] However, this single factor approach ignores the clustering of psychosocial risk factors for physical disease, which may act synergistically.[62] In addition, the increased risk of cardiac events may extend to patients with symptoms of negative affect other than depression, such as anxiety.[41,63,64] However, compared with the extensive literature on depression post-MI,

there is a paucity of studies that has investigated the effect of anxiety. Given the fact that depression and anxiety are highly comorbid disorders[65] and that symptoms of depression and anxiety frequently co-occur in post-MI patients[66], this is somewhat surprising. Some studies have reported symptoms of anxiety to be predictive of subsequent cardiac events and mortality post-MI, independent of established biomedical risk factors[27,67,68], while others found no association[36]. Since anxiety frequently co-exists with depression, some have argued that the higher mortality in anxious patients may be due to the presence of depression rather than anxiety per se.[69]

In contrast to a substantial body of literature linking negative emotional states to CAD, the effect of positive psychological factors has been less extensively investigated.[70,71] Several studies, indicating a protective effect of positive emotional states on cardiac outcomes[72], physiologic reactivity[73] and immune function[74], point to the importance of further exploring positive psychological factors and their effects on progression of CAD.

The clustering and overlap between affective dispositions may make specificity of emotion less critical for CAD risk.[61] That is, anxiety and depression may not exert distinctive, independent effects on prognosis, but may increase risk because they share a general disposition to experience chronic and intense negative emotions.[64] Personality may comprise such a general disposition that may act as a third variable promoting both emotional stress and CAD risk.[75] The type-D construct represents a personality profile characterized by both the tendency to experience negative emotions and the propensity to inhibit self-expression in social interaction.[76] Type-D personality has been associated with vulnerability to emotional distress[77] and an increased risk for adverse clinical events in CAD patients[63,78]. Type-D patients are also at increased risk for impaired quality of life[79], and seem to benefit less from medical and invasive treatment[80]. Consequently, in addition to assessing specific psychosocial factors, it is equally important to assess the effect of global traits and their interaction on prognosis in MI patients.

Without assessing multiple psychological constructs (e.g., depression, anxiety, positive affect, personality), it is difficult to know whether the essential features of distress in post-MI patients concern specific psychological concepts or one or more underlying dimensions, including negative affectivity. In the present thesis, both diagnostic interviews and self-report measures of psychological constructs were used. Identifying various forms of distress, even in their less severe forms, may provide an important avenue for early intervention. Effective treatment targeting psychosocial risk factors in CAD patients requires an accurate characterization of who is at risk for adverse outcomes, with a more detailed examination of CAD distress profiles likely enhancing the development of more effectively timed and more

specifically tailored behavioral interventions.

PATIENT-CENTERED OUTCOMES

Patient-centered care is that which helps clinicians to attend to patients' physical and emotional needs, and maintain or improve their quality of life. It also gives patients the opportunity to have a sense of locus of control in medical decision making.[81] Key components of patient-centered care include the assessment of patient-rated outcomes, like symptom burden, functional limitations, and health-related quality of life.[81] In a recent report of the National Heart, Lung, and Blood Institute Working Group on Outcomes Research in Cardiovascular Disease, the importance of studying health status and its determinants was emphasized as a means to enhance patient-centered care and to bridge the gap between research and clinical practice.[81]

The effects of post-MI depression are not limited to the previously described hard medical endpoints, but it also affects the patient's health status. Among CAD patients, depressive symptoms are strongly associated with patient-reported health status, including symptom burden, physical limitation, quality of life, and overall health.[82] Notably, the impaired health status observed among depressed CAD patients appears to be independent of left ventricular dysfunction and ischemic burden as detected through stress echocardiography.[82] In two recent prospective studies, post-MI depression had a strong effect on health status, irrespective of clinical risk factors including disease severity.[26,57] In the latter study, the association of depressive symptoms with patient health status was stronger and more consistent than traditional measures of disease severity.[57]

In addition to being an important outcome measure in its own right, impaired health status has been shown to predict subsequent mortality and morbidity in patients with cardiovascular disease.[83-86] Spertus and co-workers demonstrated that patient-reported health status was independently predictive of mortality and hospitalization in outpatients with CAD, even after adjustment for traditional clinical risk factors.[85] In another study, health status was strongly associated with subsequent 1-year cardiovascular mortality and hospitalization in patients with heart failure after an acute MI.[86] Consequently, patient-reported health status has incremental value in the identification of patients at elevated risk for adverse outcome.[87]

Current clinical trial strategies and regulatory policies consider the survival benefit of therapies in CAD patients as the gold standard for approval for use rather than their ability to improve health status. However, CAD patients may attach greater value to a reduction in symptoms rather than prolonged survival as the preferred therapeutic outcome, which

may be at odds with the preference of physicians with respect to end-of-life preferences.[88] The findings from the latter study underscore the need for incorporating patient-centered outcome measures in clinical practice and for clinicians to carefully explore and understand preferences for care expressed by their patients. Taken together, given discrepancies found between physician-rated and patient-rated functional status, health status may also serve as a valuable factor in risk stratification and guide clinical decision-management.

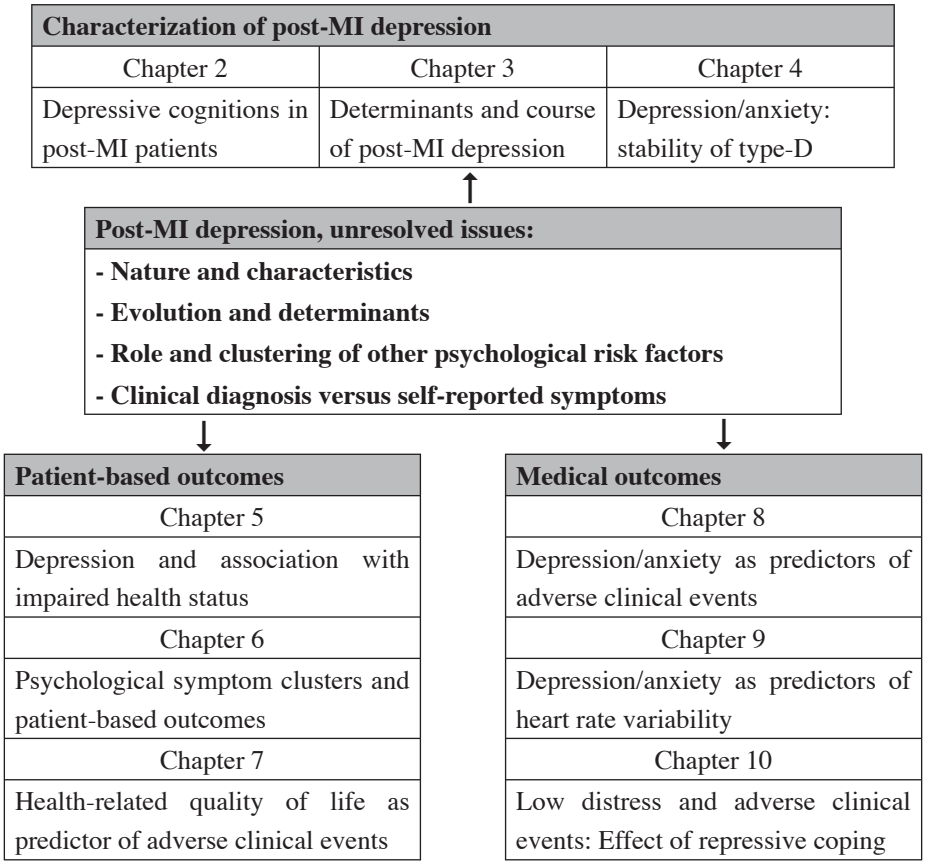
AIMS OF THIS THESIS

'To be sure that we are spiralling ahead in our understanding rather than circling towards dead ends, careful and constant evaluation of our concepts is crucial'.[89]

This thesis describes an ongoing longitudinal follow-up study in patients with acute MI. Patients were recruited during their hospitalization for acute MI at the inpatient clinic of the cardiology department from 4 teaching hospitals (Catharina Hospital, Eindhoven; St. Elisabeth Hospital, Tilburg; TweeSteden Hospital, Tilburg; and St. Anna Hospital, Geldrop) in The Netherlands. Patients were assessed on various psychological, demographic and medical variables during the initial hospitalization for MI, and 2-, 12-, and 18-months post-MI. The research protocol was approved by the medical ethics committees of the participating hospitals, and the study was conducted in accordance with the Helsinki Declaration. Written informed consent was obtained from every patient. The chapters described in the present thesis are based on data from this study, except for chapters 6 and 9. Chapter 6 is based on data from the randomized EXhaustion Intervention Trial (EXIT) that included consecutive exhausted PCI patients aged 35-68 from the university hospitals of Maastricht, Rotterdam, Nijmegen, and the Catharina Hospital in Eindhoven, The Netherlands. Chapter 9 rests on data involving 731 CAD patients recruited in 2 studies from the University Hospital of Antwerp, Belgium.

Although depression is often considered the most pathogenic factor in the link between psychology and CAD, and there has been a call for the recognition of depression as an established risk factor[17], some fundamental questions about depression in post-MI patients remain unanswered (Figure 1).

Figure 1. *Unresolved issues and organization of the thesis*



This thesis is divided into three parts, addressing the following unresolved issues:

PART A OF THIS THESIS FOCUSES ON THE CHARACTERIZATION OF POST-MI DEPRESSION.

- Despite a growing body of literature stressing the importance of depression in the pathogenesis of CAD, the nature of depression in MI patients remains unclear. In addition, the relative importance of the different components of post-MI depression has not been investigated systematically. Therefore, the aim of *Chapter 2* was to examine the extent to which negative cognitions, characteristic of depression in psychiatric patients, are present in depressed post-MI patients. Using a matched case-control design, depressed and non-depressed post-MI patients were compared with depressed psychiatric patients

on levels of depressive cognitions.

- There is a paucity of research on the evolution and determinants of depressive symptoms in the first year post-MI. Although evidence suggests that depression is highly prevalent and persistent, the question remains if patients exhibit divergent profiles of recovery, as reflected by different symptom levels and course trajectories post-MI. Moreover, it is important to determine which factors predict the course of depressive symptoms in post-MI patients. In *Chapter 3*, the course of depressive symptoms during the first year post-MI and the predictors of these symptom trajectories in 287 MI patients are studied.
- In addition to assessing mood states such as depression, it is also important to assess the impact of global traits and their interaction on prognosis in CAD. Personality may act as a third variable that promotes both emotional stress and CAD risk. *Chapter 4* focuses on the stability of type-D personality during the course of 18 months in 475 patients with acute MI and evaluates the influence of demographic and clinical risk factors and mood status on type-D over time.

PART B OF THIS THESIS FOCUSES ON PATIENT-BASED OUTCOMES.

- Since mortality rates after ACS have declined substantially due to interventions such as PCI, primary goals of therapy now include symptom control and maximizing health status including quality of life. However, little is known about the determinants of impaired health status. The objective of *Chapter 5* was to investigate whether history of depressive disorder was independently associated with impaired health status 2 months post-MI in 352 patients, and to evaluate the effect of current depressive disorder on this relationship.
- The association between psychological factors other than depression and patient-based outcomes is less well established. In addition, it is not known which symptoms are specific to post-MI distress, and whether there are reliably identifiable subgroups of patients with different psychological symptom profiles. In *Chapter 6*, we explore the degree to which psychological symptoms of distress in 324 post-MI patients represent one or more underlying dimensions and examine whether psychological symptom profiles based on these dimensions are differentially associated with depressive and anxiety disorder and impaired health status.
- Poor health status has been associated with increased risk of mortality in CAD patients. Nevertheless, little is known about the impact of health status following PCI on the risk for adverse clinical outcome. In *Chapter 7*, we examine the impact of health status at the time of the index PCI on both early and late adverse cardiac events at a median follow-up of 2 years in 667 exhausted CAD patients participating in the EXIT trial.

PART C OF THIS THESIS FOCUSES ON MEDICAL OUTCOMES.

- Although the impact of post-MI depression on prognosis has been studied extensively, the role that co-morbid anxiety plays in this relationship has been less well studied. In *Chapter 8*, we investigate the differential impact of 1) a clinical depressive and/or anxiety disorder; 2) depressive and/or anxiety symptoms on cardiac death and non-fatal MI 1.8 years post-MI in 434 patients.
- Reduced heart rate variability (HRV) is a prognostic factor for cardiac mortality. Given the relative paucity of knowledge about the potentially deleterious effects of depression and in particular anxiety on HRV, the aim of *Chapter 9* was to examine whether depression and anxiety differentially predict 24-hour time and frequency domain HRV indexes in 82 patients with recent MI.
- CAD patients who report low distress are considered to be at low psychological risk. However, patients who use a repressive coping style show clear physiological signs of distress but may fail to detect and report these signals of distress. In *Chapter 10*, the results of a 5-10 year prospective follow-up study of 731 CAD patients are presented. We tested the hypothesis whether repressive CAD patients are at increased risk for clinical events, despite low self-rated distress.

Finally, in the general discussion of this thesis, the main findings of the empirical studies are summarized, an evaluation of the role of depression in post-MI patients is given, and theoretical and clinical implications of the findings are discussed.

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Part A: Characterization of post-myocardial infarction depression

Chapter Two

Depressive cognitions in MI patients

II

Relative lack of depressive cognitions in post-myocardial infarction depression

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Abstract

Background: Depression has been associated with adverse clinical events in myocardial infarction (MI) patients, but many questions about the nature of post-MI depression remain unanswered. We examined whether depressive cognitions characteristic of depression in psychiatric patients are also present in post-MI patients with major depression (MD).

Methods: Non-depressed (n=40) and depressed (n=40) post-MI patients, and psychiatric outpatients (n=40) treated for clinical depression, matched on age and sex, were interviewed using a structured clinical interview to diagnose DSM-IV MD. All patients also completed the Beck Depression Inventory (BDI) and the Beck Cognition Checklist-Depression subscale (CCL-D).

Results: Mean levels of depressive cognitions were considerably higher in depressed psychiatric patients compared with depressed post-MI patients (34.9 versus 28.0; $p = .013$), and higher in depressed post-MI patients as compared to non-depressed post-MI patients (28.0 versus 17.8; $p < .0001$), adjusted for age, sex, educational level, and marital status. Younger age ($p = .024$), absence of a partner ($p = .016$) and depressed psychiatric status ($p = .016$) were independently associated with depressive cognitions. Psychiatric patients also had higher mean levels of depressive symptoms as compared to depressed post-MI patients (25.1 versus 17.8; $p = .001$).

Conclusions: The symptom presentation of MD in post-MI patients is both quantitatively and qualitatively different from that seen in psychiatric patients, suggesting that depressive symptoms in post-MI patients differ in content from those in psychiatric patients. These findings could have important consequences for the design and contents of therapeutic programs for treating depression in post-MI patients.

Introduction

Depression is an emerging risk factor for the development of coronary artery disease (CAD)[1,2], and about one in five patients is affected by major depression (MD) following myocardial infarction (MI)[3]. Both clinical depression and depressive symptoms have been associated with a two-fold increased risk of mortality, and increased morbidity and re-hospitalisation post-MI [4-8], although negative findings have been reported [9,10]. In turn, symptoms of depression moderate the benefits of cardiac rehabilitation, with depressed patients benefiting less from rehabilitation.[11] Despite a growing body of literature, many questions about the nature of depression in patients with CAD remain unanswered.[12] In addition, the relative importance of the different components of depression in post-MI patients has not been investigated systematically. According to Barefoot and collegues[13] it is necessary to move beyond demonstrations of these effects to a more detailed understanding of the phenomenon of depression in CAD patients. This would likely lead to more optimal risk stratification in clinical practice and enhance secondary prevention in these patients[14], in particular in light of the recent mixed findings of the ENRICHD[15] and SADHART[16] trials that targeted depression. A reduction in depressive symptoms in these trials did not lead to enhanced survival, although improvements in quality of life were seen in the SADHART trial.[17]

The clinical presentation of depression in medical patients may be less severe and symptoms more atypical compared with symptoms found in depressed psychiatric samples.[18] Typical symptoms of depression in psychiatric patients, such as low self-esteem, guilt and suicidal ideation, are generally uncommon in CAD patients, with less typical symptoms, such as anxiety and irritability, being more prevalent.[19] In addition, it is not known whether negative cognitions characteristic of depression in psychiatric patients are present in depressed post-MI patients. According to the cognitive theory of Beck[20], these depressive cognitions include negative views of the self, current experiences, and the future. Like all theories of depression, the cognitive theory was formulated and tested primarily in younger, psychiatric, and treatment-seeking people rather than in older, frequently subthreshold depressed, post-MI patients.[21] Furthermore, it is possible that the somatic manifestations of depression such as fatigue, weight loss and insomnia are interpreted as reflections of the medical condition and its treatment. According to Katon[22], too often patients' physical complaints are treated as symptomatic of CAD, with the underlying depression being left untreated.

The aim of the current study was to examine the extent to which depressive cognitions are characteristic of post-MI depression. In a matched case-control design, we compared depressed and non-depressed post-MI patients with depressed psychiatric patients on levels

of depressive cognitions.

Methods

Patient population and design

The study was conducted at the Maastricht University Hospital and three teaching hospitals (Catharina Hospital, Eindhoven; St. Elisabeth Hospital, Tilburg; and TweeSteden Hospital, Tilburg) in the Netherlands between December 2000 and June 2004. The study was approved by the medical ethics committees of the participating hospitals. The study was conducted in accordance with the Helsinki Declaration, and all patients provided written informed consent.

Non-depressed (n= 40) and depressed patients (n= 40) with acute MI admitted to the coronary care unit, and psychiatric outpatients (n= 40) treated for clinical depression in the psychiatry unit, were matched on age and sex. Inclusion criteria were age between 30-80 years, hospitalization due to MI (MI patients), or being treated for clinical depression (psychiatric patients). Exclusion criteria were significant cognitive impairments (e.g. dementia) and severe comorbidities (e.g. cancer for post-MI patients and psychosis for psychiatric patients).

For the diagnosis of MI, patients must have had troponin I levels more than twice the upper limit, with typical ischemic symptoms (e.g. chest pain) lasting for more than 10 min or ECG evidence of ST segment elevation or new pathological Q-waves. All MI patients were interviewed two months post-MI (Mean (SD)= 63 (16.3)). Psychiatric outpatients were interviewed in the psychiatry unit during treatment for clinical depression.

Patients were evaluated carefully by a trained psychologist using the Structured Clinical Interview for DSM-IV Axis I disorders (SCID)[23] or the Composite International Diagnostic Interview (CIDI) for DSM-IV[24]. Also obtained were demographic variables, and responses on two self-report depression measures.

Assessment

Diagnosis of depression

A diagnosis of DSM-IV[25] current major depressive disorder was assessed by a standardized structured interview. The SCID was used to diagnose the patients in the Maastricht University Hospital, while the CIDI was used in the three other hospitals. Although the CIDI may underdiagnose disorders compared with the SCID[26], it performs well as a research instrument to diagnose MD in medically ill patients[27]. In addition, both the SCID and CIDI are widely known instruments for assessing MD and have been used in studies

of MI patients.[28,29] According to the DSM-IV, a diagnosis of MD requires the presence of at least one core symptom (depressed mood or loss of interest), persisting for at least two weeks and accompanied by at least four of the following additional symptoms: changes in appetite or weight; sleep difficulties; fatigue; psychomotor agitation or retardation; difficulty concentrating; feelings of guilt or worthlessness or thoughts of death or suicide. In addition, these symptoms must lead to significant functional impairment and represent a change from previous functioning.

Symptoms of depression

The Beck Depression Inventory (BDI) is a 21-item self-report measure developed to assess the presence and severity of depressive symptoms. Each item is rated on a 0 to 3 scale. A total score is obtained by summing together all the items. The cognitive/affective subscale score was calculated by summing together items 1-13, while the remaining items were summed to obtain the somatic subscale.[30] The BDI is a reliable and well-validated measure of depressive symptomatology[31-33], and has been recommended for the assessment of psychosocial risk factors in CAD[34]. A BDI total score ≥ 10 is indicative of at least mild to moderate symptoms of depression and has been associated with poor prognosis in MI patients.[6,8,35,36]

Depressive cognitions

The 26-item Cognition Checklist (CCL) was developed by Beck and colleagues to assess the frequency of automatic thoughts or cognitions relevant to anxiety (12 items) and depression (14 items).[37] In the present study, we only assessed depressive cognitions (CCL-D). These items reflect negative thoughts about one's self, past experiences, and future expectations.[38] The following items illustrate the content of the CCL-D subscale: " I don't deserve to be loved", "I am a social failure", "I am worthless", "I am not worthy of people's attention or affection". The CCL-D items are rated on a 5-point scale, ranging from "never" (1) to "always" (5), with a score range of 14-70. A total score for the CCL-D is obtained by summing the ratings for the 14 items. Steer and colleagues have reported extensive validity and reliability data on the CCL, with Cronbach's alpha of .93.[38]

Definition of non-depressed versus depressed status

All patients were evaluated by means of a standardized structured interview. Post-MI patients were classified as non-depressed if they had a BDI score of <10 and no diagnosis of MD. Depressed status in post-MI and psychiatric patients was determined by a diagnosis of MD using the CIDI or the SCID.

Statistical Analysis

The χ^2 test and analysis of variance (ANOVA) were used to examine differences in baseline characteristics between the non-depressed and depressed post-MI patients and depressed psychiatric patients. The mean level of depressive cognitions was examined by ANOVA (GLM) with a post hoc Bonferroni test. Multiple linear regression analysis was used to examine to which extent depressive cognitions are present in depressed post-MI patients as compared to depressed psychiatric patients. In all analyses we adjusted for age, sex, marital status, and educational level. All statistical analyses were performed using SPSS 12.0.1 for Windows.

Results

Matching on gender and age was successful, as we found no differences between the three groups on gender and age (Table 1). However, non-depressed post-MI patients were more likely to have a partner than the depressed post-MI (p =.005) and psychiatric patients (p =.026). No other statistically significant differences were found between the groups on baseline characteristics.

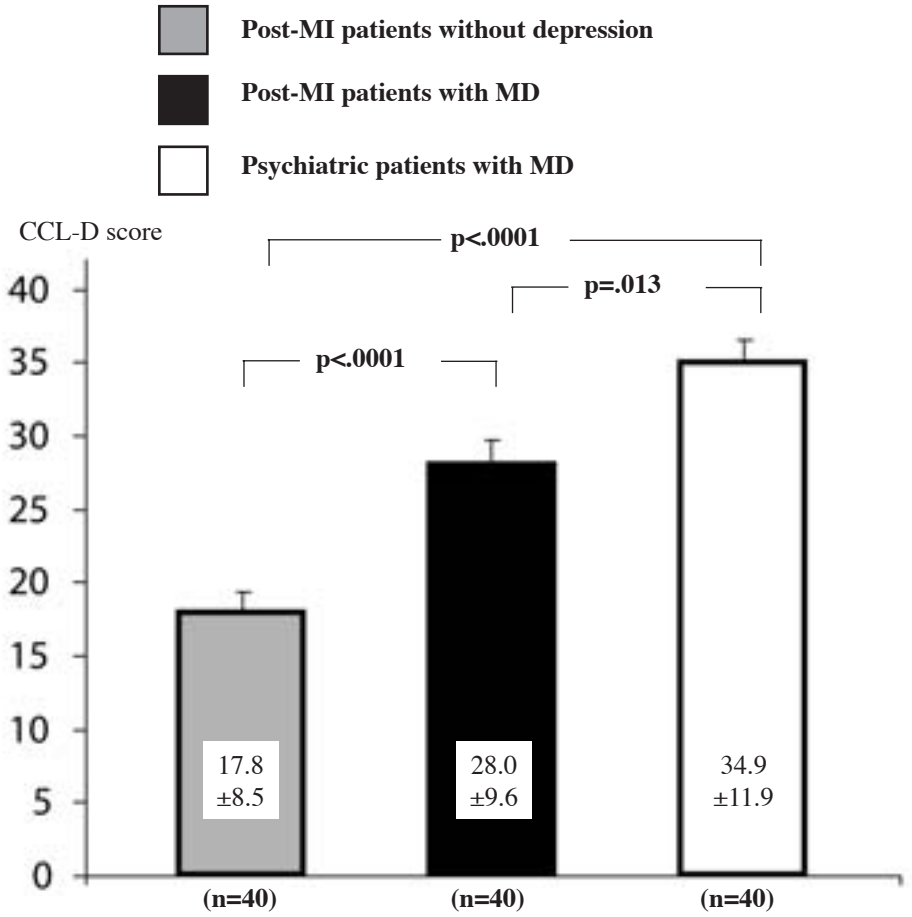
Table 1. *Demographic characteristics of post-MI patients and psychiatric patients*

	Post-MI patients without MD	Post-MI patients with MD	Psychiatric patients with MD	p-value
	(n=40)	(n=40)	(n=40)	
Age, mean ±SD	54.6 ±4.4	56.1 ±9.0	53.8 ±9.5	.406
Female sex, n (%)	15 (38)	12 (30)	18 (45)	.383
Marital status Partner, n (%)	36 (90)	24 (63)	28 (70)	.018
Educational level High, n (%)	21 (53)	15 (41)	24 (60)	.229

Depressive cognitions in post-MI versus psychiatric patients

Levels of depressive cognitions stratified by group are presented in Figure 1. Post-MI patients without depressive symptoms and post-MI patients with clinical depression differed significantly in mean CCL-D scores (17.8 versus 28.0; p <.0001). Importantly, depressed psychiatric patients reported significantly higher mean levels of depressive cognitions as compared to post-MI patients with clinical depression (34.9 versus 28.0; p =.013), adjusting for age, sex, educational level, and marital status.

Figure 1. *Depressive cognitions in post-MI patients and psychiatric patients, stratified by absence of depressive symptoms as indicated by BDI<10 and by diagnosis of major depression.*



Mean CCL-D score ± standard deviation are presented within each bar. Standard errors and p values are displayed.

CCL-D: 14 item self-report measure assessing cognitions characteristic of depression.

Depressive symptoms: decreased levels of depressive symptoms as indicated by BDI score < 10.

MD: diagnosis of Major Depression by means of a structured diagnostic clinical interview.

Independent predictors of depressive cognitions

A multiple linear regression analysis entering age, sex, marital status, educational level, and depressed disease status revealed that younger age, absence of a partner, and depressed psychiatric status were independently associated with depressive cognitions (Table 2). An adjusted R Square of .185 ($F_{5,71} = 4.445$, $p = .001$) indicated that 19% of the variance of the CCL-D scores was explained by the variables included in the tested model.

Table 2. *Predictors of depressive cognitions in depressed psychiatric patients as compared to depressed post-MI patients*

	Regression model	
	Beta	p-value
Age	-.255	.024
Sex	.074	.524
Marital status Partner vs. no partner	.260	.016
Educational level Higher vs. lower education	-.138	.218
Disease status MI* vs. psychiatric†	.272	.016

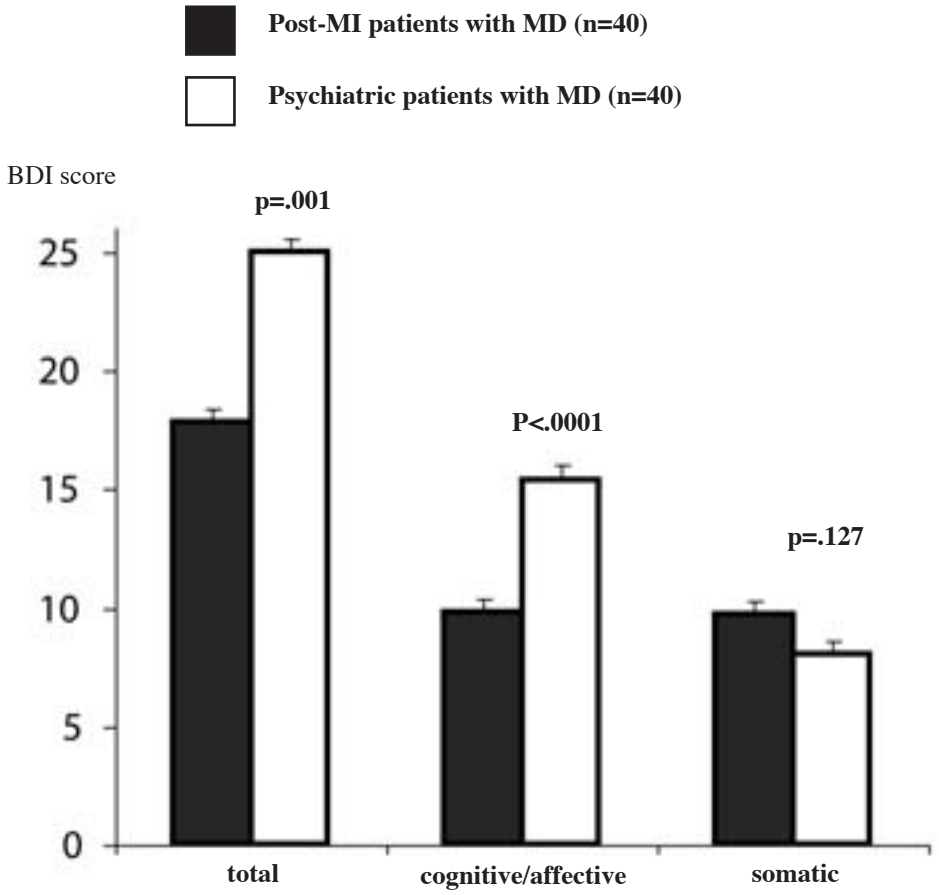
* Post-MI patients with a clinical diagnosis of major depression according to DSM-IV criteria.

† Psychiatric patients with a clinical diagnosis of major depression according to DSM-IV criteria.

Depressive symptoms in post-MI versus psychiatric patients

Examining the level of depressive symptoms in the two MD groups revealed that depressed psychiatric patients had higher mean levels of depressive symptoms as compared to depressed post-MI patients (25.1 versus 17.8; $p = .001$), indicating that psychiatric patients are more severely depressed (Figure 2).

Figure 2. *Depressive symptoms in post-MI patients and psychiatric patients with a diagnosis of major depression.*



BDI: 21 item self-report measure assessing depressive symptoms.

MD: diagnosis of Major Depression by means of a standardized structured interview.

In order to further investigate the nature of depressive symptoms in depressed post-MI patients compared with psychiatric patients, we divided the scores on the BDI into cognitive/affective symptoms and somatic symptoms. The cognitive/affective symptoms of depression were more prevalent in depressed psychiatric patients as compared to depressed post-MI patients (mean= 15.4 versus 9.8; p <.0001). However, there was no statistically significant difference in somatic symptoms between depressed post-MI and psychiatric patients (mean= 9.7 versus 8.0; p =.127).

Discussion

To our knowledge, this study is the first to investigate the presence of depressive cognitions in post-MI patients with a diagnosis of MD. A significant difference in depressive cognitions was found between post-MI and psychiatric patients, with depressive cognitions being less prevalent in post-MI patients with clinical depression as compared to depressed psychiatric patients. In addition, post-MI patients with MD had significantly more depressive cognitions as compared to post-MI patients without MD, confirming the validity of the CCL-D in cardiac patients. Psychiatric disease status was an independent predictor of depressive cognitions, adjusting for all baseline characteristics.

This finding is consistent with those of Clark and colleagues[18] who also found that psychiatric inpatients had more depressive cognitions than patients with somatic disease. Their study also used the CCL-D to assess depressive cognitions and compared depressed psychiatric inpatients and medical patients (including CAD patients) with a normal control group. Others have also reported a difference in the nature of depressive symptoms between depressed psychiatric and depressed CAD patients, with depressive symptoms in CAD patients being more atypical compared to symptoms seen in psychiatric patients.[19,39] Symptoms of depression typically seen in psychiatric patients, including low self-esteem, guilt and suicidal ideation, are often replaced by less typical symptoms such as anxiety and irritability in depressed CAD patients.[19] CAD patients tend to normalize their depression and attribute symptoms of depression to their heart disease. This makes it less likely for them to consider emotional causes for their complaints.[40]

Examining the level of depressive symptoms in depressed post-MI and psychiatric patients also revealed that psychiatric patients had higher levels of depressive symptoms, indicating that psychiatric patients are more severely depressed. Cognitive/affective symptoms of depression were more prevalent in the depressed psychiatric patients as compared to post-MI patients with MD. Conversely, depressed post-MI patients tended to report more current somatic symptoms of depression than depressed psychiatric patients, although this difference was not statistically significant. Overall, these findings indicate that the symptom presentation of MD in post-MI patients is both quantitatively and qualitatively different from that seen in psychiatric patients. In addition, these results confirm the notion that depressive symptoms reported by post-MI patients may differ in content from those reported by psychiatric patients, at least in terms of cognitive/affective symptoms.

Two recent studies, also using the BDI to asses depressive symptomatology, have shown

differential effects of somatic and cognitive symptoms of depression on medical comorbidity and prognosis in post-MI patients.[41,42] Watkins et al.[42] found that somatic and cognitive symptoms of depression were significantly related to medical comorbidity, but the variance explained by the cognitive symptoms was less than 1%. Other research showed that cognitive/affective symptoms of depression were not related to cardiovascular prognosis and only marginally related to health status, whereas somatic/affective symptoms were significantly related to health status and prognosis.[41] In comparison, Barefoot and colleagues[13] reported negative affect but not somatic symptoms to be predictive of mortality in CAD patients.

It has been suggested that the results of the ENRICHD trial, targeting depression in MI patients by means of cognitive-behavioral therapy (CBT), might have been influenced by the duration and timing of the intervention[15] and demographic characteristics of the participants[43]. The findings of the present study suggest that the results of the ENRICHD study may also have been influenced by the mode of treatment. Given the fact that depressive cognitions were less prevalent in post-MI patients, it is possible that CBT is not the treatment of choice for some depressed post-MI patients.

Taken together, these results show that it is important not only to identify the nature of depressive symptomatology in post-MI patients, but also those symptoms that are most toxic in terms of predicting morbidity and mortality in these patients.[44] Hence, knowledge of the characteristic features of depression in post-MI patients has both theoretical and clinical significance. It may help clarify the etiology of the disorder, guide the training of physicians in diagnosing the disorder in clinical practice, and help clinicians target their treatment procedures more precisely.[14] In addition, a better understanding of the syndrome of depression in post-MI patients is crucial to modify the depression mortality link by means of therapy, be it psychological, pharmacological, or a combination thereof.

Given the preliminary nature of this study, the findings need to be interpreted with some caution. First, the study was cross-sectional and does not allow for the determination of cause and effect. Second, the sample size was relatively small. Third, the use of two different standardized structured interviews may have influenced our results. Fourth, we had no information on severity of MI, length of treatment for depression in the psychiatric patients, and the difference between time since MI and psychological assessments.

Despite these limitations, the present study also has a number of strengths. We used a structured clinical interview to assess MD in post-MI and psychiatric patients, patients were matched on age and sex, and we used a standardized measure of depressive cognitions and

depressive symptoms. The BDI has been shown to predict adverse prognosis in post-MI patients.[6,8]

In conclusion, the results of this preliminary study show that the nature of depression in post-MI patients differs from depression seen in psychiatric patients, and that these differences are both quantitatively and qualitatively different. Further research into the nature of depression in post-MI patients is warranted together with the investigation of which depressive symptoms are most toxic in terms of predicting adverse health outcomes. These findings would have important consequences for the design and contents of therapeutic programs for treating depression in post-MI patients.

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Part A: Characterization of post-myocardial infarction depression

Chapter Three

Determinants and course of post-MI depression

III

Cardiac history, prior depression and personality predict course of depressive symptoms after myocardial infarction

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Abstract

Background: Although many studies have focused on post-myocardial infarction (MI) depression, there is limited information about the evolution and determinants of depressive symptoms in the first year post-MI. Therefore, we examined 1) the course of depressive symptoms during the first year post-MI and 2) the predictors of these symptom trajectories.

Methods: To assess depressive symptoms, 287 patients completed the BDI during hospitalization for MI, and 2-, and 12-months post-MI. Personality was assessed with the Type-D scale (DS14) during hospitalization. We used latent class analysis (SAS procedure TRAJ) to examine the evolution of depressive symptoms over a 1-year period and multinomial logit regression analyses to examine predictors of these symptom trajectories.

Results: The course of depressive symptoms was stable during the first year post-MI. Four groups were identified and classified as non-depressed (40%;intercept (IC)=2.52), mildly depressed (42%;IC=6.91), moderately depressed (14%;IC=13.73) or severely depressed (4%;IC=24.54). In multivariate analysis, cardiac history ($logOR_{severe}$=2.93;p=.02, $logOR_{moderate}$=1.81;p=.02, $logOR_{mild}$=1.46;p=.01), history of depression ($logOR_{severe}$=4.40;p <.001, $logOR_{moderate}$=1.97;p=.03) and type-D personality ($logOR_{severe}$=4.22;p<.001, $logOR_{moderate}$=4.17;p<.001, $logOR_{mild}$=1.66;p=.02) were the most prominent risk factors for persistence of depressive symptoms during the first year post-MI.

Conclusions: Symptoms of depression tend to persist during the first year post-MI. Cardiac history, prior depression and type-D personality were identified as independent risk factors for persistence of depressive symptoms. The results of this study strongly argue for routine psychological screening during hospitalization for acute MI in order to identify patients who are at risk for chronicity of depressive symptoms and its deleterious effects on prognosis.

Introduction

Ischemic heart disease and depression are two of the most prevalent conditions and causes of disability and early death in industrialized countries.[1,2] Furthermore, depression is a common co-morbid disorder with acute myocardial infarction (MI).[3,4] In many well-designed studies, depression has been associated with a two- to four-fold increased risk of adverse clinical outcomes and impaired health status in post-MI patients.[5-11] Hence, the American College of Cardiology/American Heart Association and the European Society of Cardiology practice guidelines recommend that the psychosocial status of patients be evaluated, "including inquiries regarding symptoms of depression", and that "efforts to relieve stress should be emphasized whenever possible".[12,13]

Despite a growing body of literature stressing the importance of post-MI depression in the pathogenesis of coronary artery disease, there is a paucity of research on the evolution and persistence of depressive symptoms following MI.[3] Although evidence suggests that depression is highly prevalent and persistent during the first 12 months post-MI[14-17], most studies have used relatively short follow-up periods, dichotomous data, and looked at prevalence rates across time rather than symptom patterns. Accordingly, the question remains if patients exhibit divergent profiles of recovery, as reflected by different symptom levels and course trajectories post-MI.

In a recent report of the National Heart, Lung, and Blood Institute Working Group on Outcomes Research in Cardiovascular Disease, the importance of promoting patient-centered care and its determinants was emphasized; i.e., clinicians need to attend to patients' physical and emotional needs in order to maintain or improve their quality of life.[18] Since depression has a major impact on patients' physical and emotional needs[6,19] and quality of life[20], it is important to determine which factors predict the course of depressive symptoms in post-MI patients. Knowledge of these determinants may point to targets for psychosocial intervention and lead to the design of more successful intervention trials. The two recent randomized controlled trials, ENRICHD[21] and SADHART[22], showed that a reduction in depressive symptoms did not translate into beneficial effects on survival, although benefits were found in quality of life[23]. Hence, it remains unclear how to enhance secondary prevention in cardiac patients with depressive comorbidity. A detailed analysis of the course of post-MI depressive symptoms and its predictors could help in determining the optimal timing for assessment of depression and might guide treatment efforts for depression in post-MI patients.

The aim of the present study was to examine the course of depressive symptoms during the first year post-MI and predictors of these symptom trajectories, using a sound and sophisticated statistical approach and evaluating a wide array of demographic, medical, and psychological variables as possible predictors of those trajectories.

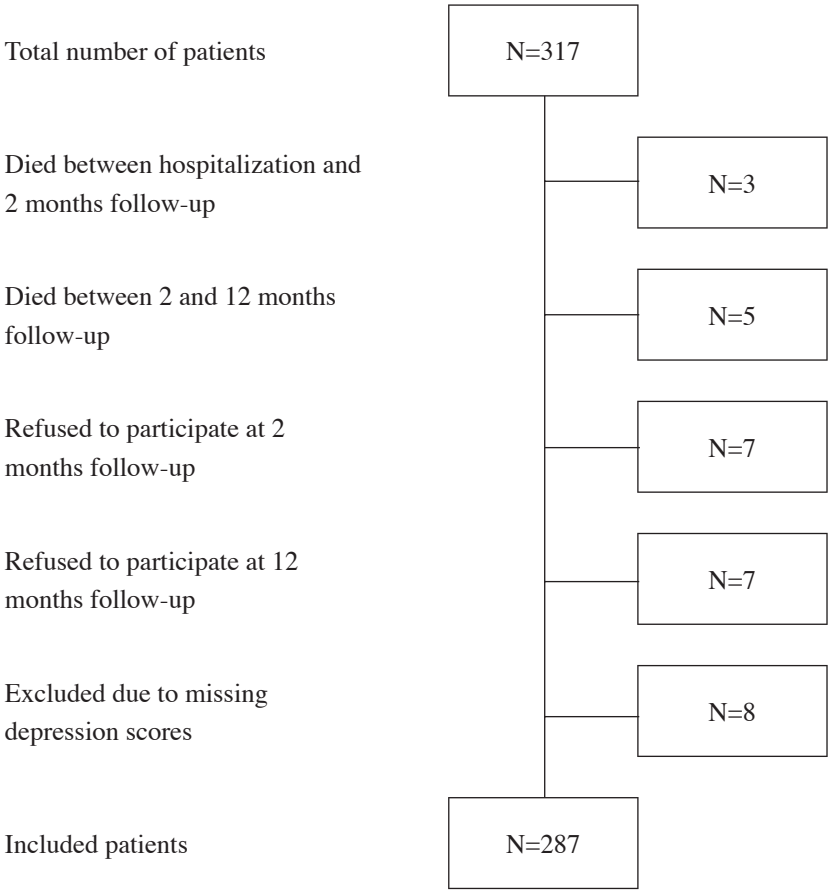
Methods

Study design and patient population

Between May 2003 and February 2005, 287 patients hospitalized for acute MI were included from four teaching hospitals (Catharina Hospital, Eindhoven; St. Elisabeth Hospital, Tilburg; TweeSteden Hospital, Tilburg; and St. Anna Hospital, Geldrop) in the Netherlands. MI was defined according to the following criteria: Troponin I levels more than twice the upper limit, with typical ischemic symptoms (e.g. chest pain) lasting for more than 10 minutes or ECG evidence of ST segment elevation or new pathological Q-waves. Patients with significant cognitive impairments (e.g. dementia) and severe comorbidities (e.g. cancer) were excluded. Patients were assessed during the initial hospitalization for MI, and 2- and 12 months post-MI in the cardiology department of the participating hospitals. The research protocol was approved by the medical ethics committees of the participating hospitals, and the study was conducted in accordance with the Helsinki Declaration. After complete description of the study to the patients, written informed consent was obtained.

Patients completed self-report measures of depressive symptoms during hospitalization, and at 2- and 12 months follow-up. In addition, they were assessed on type-D personality and lifetime diagnosis of major depressive disorder (MDD). Demographic and clinical variables were obtained from the medical records. Of the original 317 patients, 287 patients were included in the final analyses (Figure 1).

Figure 1. *Flowchart of patient selection*



Assessment

Demographic and clinical characteristics

Demographic variables included age, sex, marital status, educational level, and occupational status. Clinical variables included comorbidity (defined as arthritis, renal insufficiency or chronic obstructive pulmonary disease), cardiac history (defined as MI, angina, percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) surgery prior to the MI), multi-vessel disease, diabetes mellitus, PCI versus conservative treatment, anterior MI location, obesity (BMI ≥ 30), smoking status (self-report), participation in cardiac rehabilitation, cardiac medications (β-blockers, ACE-inhibitors, anti-coagulants, statins, diuretics, and aspirin) and psychotropics.

Depressive symptoms

The Beck Depression Inventory (BDI) is a 21-item self-report measure developed to assess the presence and severity of depressive symptoms.[24] Each item is rated on a 0-3 scale. A total score is obtained by adding up all item scores. The BDI is a reliable and well-validated measure of depressive symptomatology with a Cronbach's α of 0.81 in non-psychiatric samples[25,26], and is a widely used self-report measure of depression. BDI scores ≥10 are indicative of at least mild to moderate symptoms of depression and have been associated with poor prognosis in MI patients[7,8,27].

Clinical diagnoses of depression

The Composite International Diagnostic Interview (CIDI)[28] was used to assess lifetime diagnoses of MDD based on the diagnostic criteria listed in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)[29].

Type-D personality

The 14-item Type-D scale (DS14) was included to assess type-D personality.[30] Items are answered on a five-point Likert scale from 0 to 4. The scale consists of two 7 item sub-scales, negative affectivity (e.g. "I often feel unhappy") and social inhibition (e.g. "I am a closed person"). Patients were categorized as type-D using a standardized cut-off score ≥10 on the negative affectivity and social inhibition subscales.[30] The DS14 is a valid and reliable scale with Cronbach's α of 0.88/0.86 and a test-retest reliability over a 3-month period with r = 0.72/0.82 for the two subscales, respectively.[30] Type-D has been associated with a 4-8 fold increased risk of adverse clinical outcome[30-33] and comprises a risk factor for the onset of depressive symptoms 12 months post-PCI[34].

Statistical Analysis

Latent class analysis (SAS procedure TRAJ) was used to examine trajectories of depressive symptoms in post-MI patients over a 1-year period.[35] TRAJ fits a finite mixture model to identify groups of individuals following similar patterns of behavior over time. The time course of each trajectory is modeled using a polynomial with a maximum order of three. Subsequently, associations between group membership and covariates can be examined. To determine the optimal number of trajectories, the Bayesian Information Criterion (BIC) was used, with a higher BIC indicating a better fit. BIC is often used for comparing models, as it trades off model fit and model complexity. The optimal polynomial order of each trajectory was examined. Due to the number of measurement points, only constant, linear and quadratic parameters were used. The significance of all parameters (intercept, linear, quadratic) was investigated. If the quadratic parameter did not reach significance, it was dropped from the analysis and was tested for a linear trajectory. If the linear parameter did

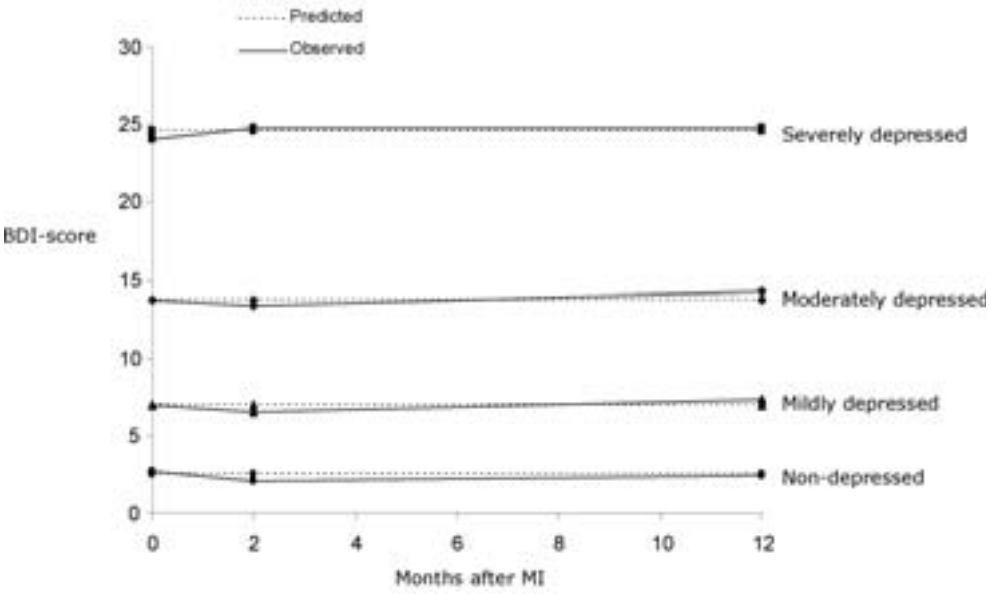
not reach significance, it was tested for a constant trajectory. Again, models were compared using the BIC. Multinomial logit regression was used to evaluate demographic, medical, and psychological variables as possible predictors of trajectories of depressive symptoms. Variables that were significant at $p<0.05$ in univariate analysis were evaluated in a final analysis by entering them simultaneously into a multivariate model.

Results

Prevalence and course of depressive symptoms

Based on the BIC criteria, a four-group model was found to be the best fitting model. This model was defined by intercept only. Quadratic and linear parameters were not significant. The level of depressive symptoms over time was stable in this sample of post-MI patients (Figure 2). The first group (40%) was classified as the non-depressed group with a predicted mean BDI score of 2.52 (95%CI: 1.69-3.35). The level of depressive symptoms in the second group (42%) was slightly higher than in the first group with a mean BDI score of 6.91 (95%CI: 5.72-8.11); hence, this group was classified as mildly depressed. According to the standardized BDI cut-off ≥10, groups three and four displayed significant depressive symptomatology. Group three (14%) had a predicted mean BDI score of 13.73 (95%CI: 12.46-14.99) and was therefore classified as moderately depressed. The fourth group (4%) was described as severely depressed, with a mean BDI score of 24.54 (95%CI: 22.88-26.20). Accordingly, based on the standardized BDI cut-off ≥10, the prevalence rate of depressive symptoms during the first year post-MI was 18%.

Figure 2. *Trajectories of depressive symptoms in post-MI patients*



The derived mixture model suggests a stable course of depressive symptoms in post-MI patients. In order to validate this result, change in depression scores was examined at 2 and 12 months using the baseline depression score as a reference. A clinically significant decrease at follow-up was defined as having a BDI score < 10 and a 50% decrease in the BDI score. A clinically significant increase at follow-up was defined as having a BDI score ≥ 10 and a 50% increase in BDI score. Only a minority of patients improved (severe group: n=0, moderate group: n=6) or deteriorated (mild group: n=29, non-depressed group: n=1) respectively. This suggests that even though there were clinically significant changes at the individual level, at group level the course of depressive symptoms was indeed stable.

Predictors of depressive symptom persistence

Univariate predictors of depressive symptom persistence are presented in Table 1. The estimates reported in Table 1 are log odds ratio's, using the non-depressed group as the reference category. Cardiac history was the most prominent clinical risk factor for depressive symptom persistence over the course of 1-year post-MI, with log odds varying from 1.44 to 2.70. In addition, history of MDD and type-D personality had the highest associated risk, with log odds varying from 1.52 to 3.71. Other predictors varying according to the level of depressive symptoms comprised gender, age, marital status, occupational status, diabetes, comorbidity, diuretics, aspirin and psychotropics.

Table 1. *Univariate predictors of depressive symptom persistence*[1]

	Mildly depressed			Moderately depressed			Severely depressed		
Covariate	Log OR	S.E.	p	Log OR	S.E.	p	Log OR	S.E.	p
Cardiac history[2]	**1.44**	**.51**	**.005**	**1.78**	**.56**	**.002**	**2.70**	**.80**	**.001**
Depression history	ns	ns	ns	**1.52**	**.55**	**.006**	**3.71**	**.90**	**<.001**
Type-D personality	**1.52**	**.65**	**.02**	**3.20**	**.66**	**<.001**	**3.10**	**.84**	**<.001**
Female sex	ns	ns	ns	**1.52**	**.48**	**.002**	**1.51**	**.70**	**.03**
Age > 60yrs	ns	ns	ns	**.97**	**.43**	**.03**	ns	ns	ns
Single	ns	ns	ns	**1.04**	**.47**	**.03**	**1.52**	**.69**	**.03**
High educational level	ns	ns	ns	ns	ns	ns	ns	ns	ns
Working	ns	ns	ns	**-1.35**	**.51**	**.009**	ns	ns	ns
Smoking[3]	ns	ns	ns	ns	ns	ns	ns	ns	ns
Obesity[4]	ns	ns	ns	ns	ns	ns	ns	ns	ns
Cardiac rehabilitation	ns	ns	ns	ns	ns	ns	ns	ns	ns
Anterior MI location	ns	ns	ns	ns	ns	ns	ns	ns	ns
Multi-vessel disease	ns	ns	ns	ns	ns	ns	ns	ns	ns
PCI[5]	ns	ns	ns	ns	ns	ns	ns	ns	ns
Diabetes	**1.19**	**.53**	**.03**	ns	ns	ns	ns	ns	ns
Comorbidity[6]	ns	ns	ns	ns	ns	ns	**1.96**	**.68**	**.004**
β-blockers	ns	ns	ns	ns	ns	ns	ns	ns	ns
Ace-inhibitors	ns	ns	ns	ns	ns	ns	ns	ns	ns
Anti-coagulants	ns	ns	ns	ns	ns	ns	ns	ns	ns
Statins	ns	ns	ns	ns	ns	ns	ns	ns	ns
Diuretics	ns	ns	ns	**1.92**	**.49**	**<.001**	ns	ns	ns
Aspirin	**-1.53**	**.67**	**.02**	**-1.64**	**.67**	**.01**	ns	ns	ns
Psychotropics	ns	ns	ns	**1.57**	**.54**	**.004**	**2.31**	**.65**	**<.001**

[1] Non-depressed group was used as reference category

[2] MI, angina, PCI or CABG prior to the MI

[3] Self-report

[4] BMI ≥ 30

[5] Reference group: conservatively treated

[6] Arthritis, renal insufficiency, chronic obstructive pulmonary disease

Variables that were significantly associated with one of the symptom trajectories were entered into a multivariate model. As displayed in Table 2, patients with a cardiac history and type-D personality were more likely to be in the mildly, moderately and severely depressed groups as compared to the non-depressed group. Furthermore, patients with a history of MDD and patients taking diuretics were more likely to be in the moderately depressed group, whereas patients with a history of MDD and comorbidities were more likely to be in the severely depressed group.

Table 2. *Multivariate predictors of depressive symptom persistence*[1]

	Mildly depressed			Moderately depressed			Severely depressed		
Covariate	Log OR	S.E.	p	Log OR	S.E.	p	Log OR	S.E.	p
Cardiac history[2]	**1.46**	**.58**	**.01**	**1.81**	**.77**	**.02**	**2.93**	**1.21**	**.02**
Depression history	ns	ns	ns	**1.97**	**.89**	**.03**	**4.40**	**1.26**	**<.001**
Type-D personality	**1.66**	**.68**	**.02**	**4.17**	**.85**	**<.001**	**4.22**	**1.13**	**.<.001**
Female sex	ns	ns	ns	ns	ns	ns	ns	ns	ns
Age > 60yrs	ns	ns	ns	ns	ns	ns	-2.12	1.09	0.05
Single	ns	ns	ns	ns	ns	ns	ns	ns	ns
Working	ns	ns	ns	ns	ns	ns	ns	ns	ns
Diabetes	ns	ns	ns	ns	ns	ns	ns	ns	ns
Comorbidity[3]	ns	ns	ns	ns	ns	ns	**2.78**	**1.21**	**0.02**
Diuretics	ns	ns	ns	**1.88**	**.80**	**.02**	ns	ns	ns
Aspirin	ns	ns	ns	ns	ns	ns	ns	ns	ns
Psychotropics	ns	ns	ns	ns	ns	ns	2.02	1.01	.05

[1] The non-depressed group was used as the reference category

[2] MI, angina, PCI or CABG prior to the MI

[3] Arthritis, renal insufficiency, chronic obstructive pulmonary disease

In post-hoc analyses, the risk of being in the mildly, moderately or severely depressed group was stratified by the most prominent risk factors cardiac history, history of MDD and type-D personality. There was a continuous relationship between the severity of depression group and number of risk factors, with the largest risk incurred in patients with all three risk factors.

Discussion

The aim of the current study was to examine the course of depressive symptoms and its predictors during the first year post-MI. Depressive symptoms were highly prevalent and the course of depressive symptoms stable. Four trajectories were observed, namely non-depressed, mildly depressed, moderately depressed and severely depressed. Cardiac history, history of MDD and type-D personality comprised the most prominent risk factors for experiencing depressive symptoms across the trajectories, with patients with all three risk factors being at highest risk for the moderately and severely depressive symptom trajectories.

The present results indicate that symptoms of depression following MI are not a transient phenomenon, with levels of depressive symptomatology persisting during the course of the first year post-MI. Although a minority of patients improved respectively deteriorated significantly at follow-up, at group level the course of depressive symptoms was stable. These results are in line with a recent review on the prevalence of depression in post-MI patients, showing that the majority of MI patients with depression during initial hospitalization remain depressed 1 to 12 months later.[19] In addition, in a prospective study of 288 MI patients, depressive symptoms were found to be prevalent and persistent, with only 6.7% of patients depressed in hospital experiencing no further symptoms of depression during the first year post-MI.[17] Although our results are consistent with previous studies, the majority of these studies had a relatively short follow-up period, used dichotomous data and did not assess symptom patterns but rather looked at prevalence rates across time.

One recent study, however, used the same methodology as applied in the current study to examine the course of depressive symptoms during the first year post-MI.[36] They identified five distinct courses in 475 post-MI patients. In line with our results, the course of depressive symptoms was relatively stable with 18% of patients experiencing elevated depressive symptom levels during the first year post-MI. Patients with persisting symptoms, which were of at least moderate intensity during all follow-up assessments, had the highest rate of new cardiovascular events, indicating the importance of examining the course of depressive symptoms. As in the present study, history of MDD and several psychological measures (e.g. neuroticism) played an important role in predicting significantly greater risk for severe/persistent symptom trajectories.[36] Furthermore, our findings are compatible with the study by Spijkerman and colleagues[37] reporting that personality was strongly related with ongoing and recurrent depression in 468 post-MI patients. Cardiac history, however, was not found to be a significant predictor of depression following MI, although some trends were observed.[37,38] In another recent study, prior MI was associated with depressive symptoms post-MI,

irrespective of whether they persisted, subsided, or newly developed in the first month after hospitalization.[39] In addition, history of MDD has been found to be a strong independent predictor of the development of post-MI depressive symptoms.[39,40]

Insight in the course of depressive symptoms after MI and its predictors is important for clinical practice. First of all, the chronicity of post-MI depressive symptoms found in the present study strongly argues for routine psychological screening during hospitalization for acute MI. Hospitalization is not only the most convenient moment to screen patients for depression, but early identification and treatment of depression may also prevent symptoms from becoming chronic and improve patients' quality of life. Since depressed cardiac patients have a higher risk of morbidity, mortality and impaired health status after MI[4-7,9,14,39,41], it is important to identify patients with elevated levels of depressive symptoms as early as possible. Those patients should be considered for treatment, be it pharmacological or psychological or a combination thereof. Furthermore, knowledge about the predictors of depressive symptom trajectories may point to targets for psychosocial intervention and lead to the design of more successful intervention trials. The management of depression in MI patients is both a clinical and interdisciplinary challenge, with the development of collaborative and integrative approaches combining the medical and psychological expertise being imperative. However, an important first step in the management of post-MI depression comprises the unravelling of the determinants of depression, which likely consist of a combination of clinical, psychosocial, and biological factors. Studying the biological determinants in future studies may be of particular value, as treatment options for post-MI depression should also have a positive effect on cardiovascular biology.[42]

The results of the current study should be interpreted with some caution. First, we had no information on left ventricular ejection fraction. However, we included multi-vessel disease to adjust for disease severity. Second, only 4% of patients were in the severely depressed group, which may have led to unreliable results due to the relatively small number of patients within this particular group. Nevertheless, the most prominent risk factors were consistent across trajectories. Third, prior to setting up a multivariate model to predict depressive symptom trajectories, we evaluated a large number of predictors in univariate analysis. Although most of the variables have been associated with depressive symptoms in previous studies, this procedure may have let to overfitting of our regression model. Finally, cardiac history was defined as MI, angina, PCI, or CABG surgery prior to the MI. Since negative affectivity has been associated with thoracic pain unrelated to cardiac ischemia, it is possible that a higher level of negative affectivity has contributed to misdiagnosed angina in this study. Yet, all clinical variables were obtained from the patients' medical records.

Depressive symptoms following MI are not a transient phenomenon, with levels of depressive symptoms persisting throughout the first year post-MI. Cardiac history, history of MDD and type-D personality were the most prominent risk factors for depressive symptom trajectories. These findings support the importance of including both clinical and psychological variables in cardiovascular research. Since this is one of the first studies to look at trajectories of depressive symptoms in the year following MI and its determinants, further research is warranted to replicate these findings using this new methodology to describe courses of post-MI depressive symptoms. However, the results of this study strongly argue for routine psychological screening during hospitalization for acute MI in order to identify patients who are at risk for chronicity of depressive symptoms and its deleterious effects on prognosis.

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Chapter Four

Stability of type-D

IV

Depression and anxiety: Influence on the stability of type-D personality in post-MI patients over an 18-month period

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Submitted

Abstract

Background: Type-D personality comprises a risk factor for adverse prognosis in patients with cardiovascular disease (CVD). However, concerns have been voiced that type-D may not be a stable personality taxonomy and that the progression of CVD may contribute to the manifestation of type-D personality. To address this concern, the present study aimed to examine the stability of type-D during the course of 18 months in patients with an acute myocardial infarction (MI), and evaluated the influence of demographic and clinical risk factors and mood status on the stability of type-D.

Meth**ods:** Patients hospitalized for acute MI (n=475) were assessed at three time points on demographic and clinical variables, type-D personality, depression and anxiety using both self-report measures and diagnostic interviews. Longitudinal, hierarchical latent class regression models were used to examine the stability of type-D and the influence of other predictors.

Results: Type-D personality was a stable construct. Multivariate analysis showed that demographic and clinical characteristics, time (p=.11), and intraindividual variability in depressive (p=.19) and anxiety symptoms (p=.18) over time did not affect type-D status. The mean levels of depressive (p=.05) and anxiety (p<.0001) symptoms within a subject over time were significantly related to type-D status.

Conclusions: Type-D personality is a stable taxonomy over an 18-month period in post-MI patients. Type-D classification was not confounded by variability in mood status and by disease severity. These findings support the importance of including personality variables in cardiovascular research and the need for intervention trials targeting this personality taxonomy in order to enhance secondary prevention in CVD patients.

INTRODUCTION

Accumulating evidence indicates that the distressed (type-D) personality comprises a risk factor for adverse prognosis[1-4], impaired health status[5-7], and increased emotional distress in patients with cardiovascular disease (CVD)[8-10]. Type-D was originally developed in patients with ischemic heart disease, but recent studies have shown that the construct is of value across CVD patient groups, including patients with chronic heart failure[7], peripheral arterial disease[5], patients having received an implantable cardioverter defibrillator[9], and patients treated with revascularization procedures and with drug-eluting stents[4,6]. See Pedersen and Denollet for a more extensive review.[11,12]

Type-D is defined by a high score on both negative affectivity and social inhibition.[13] Individuals with this personality taxonomy tend to worry, feel sad, and become easily irritated (negative affectivity). Simultaneously, they tend to be closed, avoid social interactions, and not share these negative emotions with others (social inhibition). Only individuals with a high score on both traits, as determined by a standardized cut-off, qualify for type-D caseness.[13]

It is important to emphasize that type-D is different from depression and negative affect in general, given that how individuals manage these high levels of distress is embedded within the construct through the inclusion of the social inhibition component. A recent study of patients treated with percutaneous coronary intervention (PCI) in the drug-eluting stent era confirmed that it is the presence of both components that incurs an increased risk, with social inhibition moderating the effect of negative affectivity on cardiac prognosis.[14] Moreover, type-D remained an independent risk factor for adverse clinical outcome, adjusting for levels of anxiety and depressive symptoms in addition to demographic and clinical baseline characteristics.[14] In the same cohort of patients, type-D was associated with a 3-fold increased risk of onset of depressive symptoms at 12 months post-PCI in patients free of depressive symptoms at 6 months.[8] These findings are in line with earlier studies on type-D, showing that type-D is different from general negative affect.[1,2]

Type-D can be assessed with the Type-D Scale (DS14), a brief 14-item measure. The DS14 is a valid and internally consistent instrument, that has good test-retest reliability over a 3-month period.[13] However, a recent prospective study of PCI patients showed that type-D personality did not exert a stable effect on health status over time, although the interaction effect type-D by time was only just significant.[15] This raises the concern whether type-D is a stable personality taxonomy. In addition, concerns have been voiced that the progression of CVD may contribute to the manifestation of type-D personality.

Hence, the objectives of the current study were to: (1) Examine the stability of type-D personality during the course of 18 months in patients with an acute myocardial infarction (MI), with type-D being assessed at three time points; (2) Evaluate the influence of demographic and clinical risk factors and mood status on the stability of type-D during a period of 18 months.

METHODS

Patient population

Patients hospitalized for acute MI (n=475) were included between May 2003 and June 2006 from four teaching hospitals (Catharina Hospital, Eindhoven; St. Elisabeth Hospital, Tilburg; TweeSteden Hospital, Tilburg; and St. Anna Hospital, Geldrop) in The Netherlands. Inclusion criteria were age >30 and hospitalization due to acute MI. Exclusion criteria were significant cognitive impairments (e.g. dementia) and severe comorbidities (e.g. cancer) in addition to their cardiac condition. For the diagnosis of MI, patients must have had troponin I levels more than twice the upper limit, with typical ischemic symptoms (e.g. chest pain) lasting for more than 10 minutes or ECG evidence of ST segment elevation or new pathological Q-waves.

The study was approved by the medical ethics committees of the participating hospitals. The study was conducted in accordance with the Helsinki Declaration, and all patients provided written informed consent.

Assessment

Demographic and clinical characteristics

Demographic variables included sex and age. Clinical variables were obtained from the patients' medical records and included comorbidity (defined as arthritis, renal insufficiency, and chronic obstructive pulmonary disease), cardiac history (defined as MI, angina, PCI or coronary artery bypass graft (CABG) surgery prior to the MI), multi-vessel disease, diabetes mellitus, PCI versus conservative treatment, anterior MI location, participation in cardiac rehabilitation, smoking status (self-report), body mass index (BMI), hypertension, hypercholesterolemia, HDL and LDL cholesterol levels, LDL/HDL ratio, and medications (beta-blockers, ACE-inhibitors, Ca-antagonists, anti-coagulants, statins, diuretics, A2-antagonists, vasodilators, aspirin, and psychotropics).

Type-D personality

The 14-item Type-D Scale (DS14) was included to assess type-D personality.[13] Items are answered on a five-point Likert scale from 0 to 4. The scale consists of two 7-item sub-scales, negative affectivity (e.g. "I often feel unhappy") and social inhibition (e.g. "I am a closed person"). Only patients scoring high on both subscales according to a standardized cut-off ≥10 are categorized as type-D.[13] The DS14 is a valid and reliable scale with Cronbach's α of 0.88/0.86 and a test-retest reliability over a 3-month period of r = 0.72/0.82 for the negative affectivity and social inhibition subscales, respectively.[13] The DS14 was administered during hospitalization, and 12- and 18 months post-MI.

Clinical diagnosis of depression and anxiety disorder

The CIDI[16] was used to assess lifetime diagnoses of (major) depressive disorder and anxiety disorder (consisting of panic disorder, social phobia, and/or generalized anxiety disorder) on the basis of the criteria listed in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)[17]. A trained psychologist conducted the interview 2 months post-MI.

Self reported symptoms of depression and anxiety

Symptoms of depression and anxiety were assessed using two self-report questionnaires: The Beck Depression Inventory (BDI) and the State Trait Anxiety Inventory (STAI). The BDI is a 21-item self-report measure developed to assess the presence and severity of depressive symptoms.[18] The BDI is a reliable and well-validated measure of depressive symptomatology[19], and is a widely used self-report measure of depression. The STAI is a self-report measure consisting of two 20-item scales developed to measure the level of general state and trait anxiety.[20] The STAI has been demonstrated to have adequate validity and reliability.[21] In the current study, we included the state scale of the STAI only.

Elevated scores on both the BDI and STAI have been associated with poor prognosis in MI patients.[22-25] The BDI and STAI were administered during hospitalization, and 12- and 18 months post-MI.

Statistical Analysis

A number of longitudinal, hierarchical latent class regression models (LatentGOLD)[26] were fit to examine whether type-D personality is stable during a period of 18 months and to determine whether latent classes could be identified within the present group of post-MI patients. LatentGOLD allows for inclusion of all patients at all measurement occasions irrespective of loss to follow-up. Furthermore, we examined the role of confounding variables on the stability of type-D personality.

A 1-class regression model was fit first. Type-D personality was considered a binomial count variable. Subsequently, we tested whether a 2-class solution would provide a better fit. Because of the dichotomous nature of the type-D personality construct, it was impossible to fit a solution with more than two latent classes. In the best fitting model at this stage, it was tested whether the intercept was significantly different for the classes in the model, and whether time affected the classes differently.

To test significance ($p<.01$) of potential biomedical, psychological, and behavioral confounders, t-tests and cross-tabulations (SPSS 14.0) were employed. When significant, confounders were included into a binary logistic regression model for all three measurement occasions to remove redundant covariates (if any). Significant ($p<.05$) confounders were then added as predictors to the latent class regression models for type-D. Given that we were interested in examining the temporal stability of type-D within patients (rather than between patients), we opted to preprocess the time-varying BDI and STAI scores by centering them across measurement occasions per subject and per variable. This procedure provides two variables: one representing the average level of BDI or STAI scores within a patient over time, the second representing intraindividual variability in depressive or anxiety symptoms over time, in which the interindividual differences in general levels are eliminated.

In the latent class analysis, the effects of the confounding variables were examined. In a final step, it was tested whether the effects of the confounding variables were similar for both classes. By comparing values of the Bayesian Information Criterion (BIC)[27] of each model, it was decided which model should be preferred (the lower the BIC, the better). In addition, likelihood ratio tests determined whether a model was a significant improvement compared to the former one that contained fewer classes or fewer restrictions. For all tests described above, the Wald statistic was used to evaluate the statistical significance of the individual independent variables.

Results

Patient characteristics

Table 1 shows demographic and clinical characteristics of the 475 MI patients. Seventy patients (17%) had a diagnosis of lifetime depressive disorder and 29 patients (7%) lifetime anxiety disorder. Table 2 describes the prevalence of type-D personality over the 18-month period.

Table 1. *Baseline characteristics of post-MI patients*[1]

Demographic variables	All patients (n=475)	Type-D (n=87) *	Non type-D (n=374) *	p-value
Age, mean (SD)	60 (11.6)	58 (10.9)	60 (11.7)	NS
Female sex	104 (22)	21 (24)	76 (20)	NS
Medical variables				
Current smoker	181 (38)	45 (52)	131 (35)	**.004**
BMI, kg/m^2, mean (SD)	27 (4.0)	27 (4.0)	27 (4.1)	NS
Comorbidity[2]	99 (21)	20 (23)	77 (21)	NS
Diabetes mellitus	69 (15)	7 (8)	59 (16)	.062
Cardiac history[3]	89 (17)	14 (16)	61 (17)	NS
Hypertension	130 (30)	19 (23)	106 (31)	NS
Hypercholesterolemia	56 (13)	10 (12)	44 (13)	NS
Laboratory results, mean (SD)				
HDL cholesterol level, mmol/l	1.2 (0.6)	1.2 (0.5)	1.2 (0.6)	NS
LDL cholesterol level, mmol/l	3.1 (1.0)	3.1 (1.0)	3.1 (1.0)	NS
LDL/HDL ratio, mmol/l	4.6 (1.2)	4.6 (1.1)	4.6 (1.2)	NS
Cardiac function				
Systolic BP, mean (SD)	140 (29)	136 (24.6)	141 (29.3)	NS
Diastolic BP, mean (SD)	82 (17)	80 (13.8)	83 (17.1)	NS
Disease severity				
Multi-vessel disease	157 (40)	25 (34)	128 (41)	NS
PCI	284 (61)	51 (59)	225 (62)	NS
Anterior MI location	171 (40)	29 (37)	136 (41)	NS
Cardiac rehabilitation	281 (67)	54 (68)	223 (68)	NS
Medication use				
Beta-blockers	398 (86)	77 (90)	311 (85)	NS
ACE-inhibitors	174 (38)	31 (36)	137 (38)	NS
Ca-antagonists	83 (18)	15 (17)	63 (17)	NS
Anti-coagulants	384 (83)	74 (86)	302 (83)	NS
Statins	421 (91)	81 (94)	330 (90)	NS
Diuretics	89 (19)	17 (20)	68 (19)	NS
A2-antagonists	44 (10)	7 (8)	36 (10)	NS
Vasodilators	148 (32)	31 (36)	116 (32)	NS
Aspirin	379 (82)	70 (81)	300 (82)	NS
Antiarrhythmica	33 (7)	5 (6)	28 (8)	NS
Psychotropics[4]	61 (13)	20 (24)	36 (10)	**<.0001**

ACE= angiotensin-converting enzyme BMI= Body mass Index BP= blood pressure
MI= myocardial infarction PCI= percutaneous coronary intervention

* Given that 14 patients did not have complete data on the baseline assessment of the DS14, baseline characteristics stratified by type-D are only shown for 461 patients; nevertheless, due to the nature of the statistical analyses used to model the stability of type-D, it is possible to include all 475 patients since they had a DS14 assessment at follow-up.

[1] Values are expressed as number (percentage) of patients unless otherwise indicated. Only p-values <0.10 are reported.

[2] Arthritis, renal insufficiency, chronic obstructive pulmonary disease

[3] Myocardial infarction, percutaneous coronary intervention, or coronary artery bypass graft surgery prior to the index myocardial infarction

[4] Selective serotonin reuptake inhibitors, benzodiazepines

Table 2. *Prevalence of type-D personality over time*

Assessment	N*	Prevalence of type-D
Baseline	461	18.3%
12 months	284	22.2%
18 months	224	23.2%

* Missing values were at random

Confounders

Depressive and anxiety symptoms at the three measurement occasions and CIDI-based lifetime diagnoses of depressive disorder and anxiety disorder were significant confounders for type-D status. Further significant univariate relations were found for smoking and psychotropic medication. However, only depressive and anxiety symptoms remained significant in multivariate analyses at a $p < .05$ level. None of the demographic and disease related characteristics were significantly related to type-D status in multivariate analyses.

Type-D personality

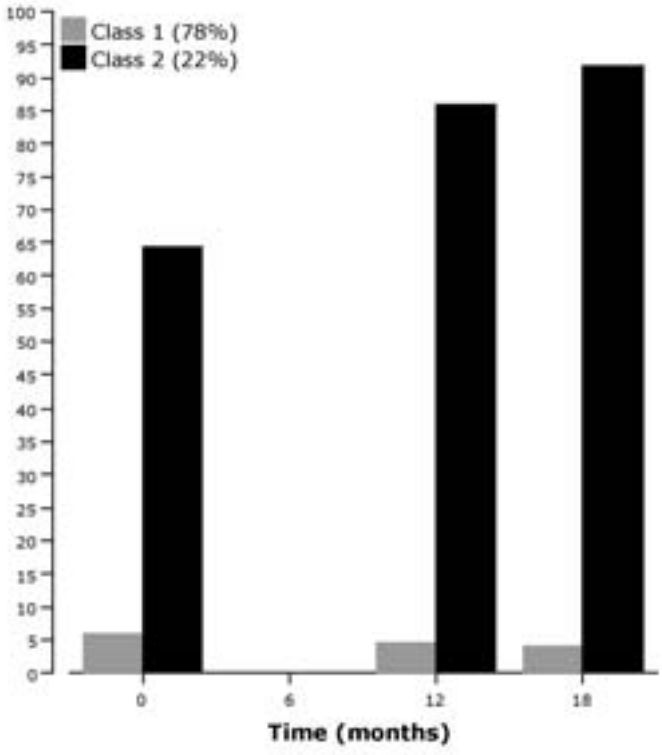
Latent class analysis (LCA) showed that a 2-class solution provided a better fit to the data than a 1-class solution (Table 3). In this 2-class model, classification error was small (7%), and the model explained 67% of the variance. Class 1 was most common, and included a large group of patients (78%) for which the odds of having a type-D personality was very small, i.e. less than 6% on all measurement occasions. Class 2 comprised 22% of the patients, who had a high probability of being type-D (between 64% and 91% for the three measurement occasions). Figure 1 shows the probability of being type-D in these two classes over the 18-month period.

Table 3. *Fit statistics for type-D personality*

No	Model	LL	BIC	NPar
1	1 class	-494.96	1002.24	2
2	2 classes	-412.65	855.20	5
3	Model 2 + class independent intercepts	-450.89	926.36	4
4	Model 2 + class independent time effect	-415.36	855.30	4
5	Model 2 + BDI and STAI	-221.53	509.88	12
6	*Model 5 + class independent BDI and STAI effects*	*-223.16*	*490.87*	*8*

BIC = Bayesian Information Criterion, based on LL (log likelihood). NPar = number of parameters estimated. Row printed in italics represents the best fitting model.

Figure 1. *Probability of having a type-d personality over the course of 18 months in post-MI patients.*



In this univariate, 2-class model, the class intercepts were significantly different, and time affected the classes differently (Table 3). When we added depressive and anxiety symptoms as additional predictors in the 2-class model, the fit of the model improved significantly. Mean depression and anxiety scores within a subject over time significantly predicted type-D status (with more chance of being type-D when mean depression or anxiety scores were higher), whereas intraindividual variability in depressive and anxiety symptoms over time had no effect on type-D status. In the final model, time was also not a significant predictor. Table 4 summarizes the estimates and significances for all relevant predictors per dependent variable in the best fitting model (italic in Table 3). The present results indicate that while the mean levels of depressive and anxiety symptoms are significantly related to type-D personality, mood fluctuations are not, rendering type-D personality stable over time.

Table 4. *Parameters estimates of the best fitting model*

Predictor	Estimate	S.E.	Wald statistic	p-value
Time	.38	.25	2.61	.11
BDI mean	.08	.04	3.84	.05
BDI variability	.07	.05	1.72	.19
STAI mean	.17	.03	33.07	<.000
STAI variability	.03	.02	1.81	.18

BDI mean (or STAI mean) represents the within-subject mean on BDI (or STAI) over the three measurement occasions

BDI variability (or STAI variability) represents the intraindividual variability in BDI (or STAI) score over time

S.E. = standard error. Significance is based on the Wald statistic.

DISCUSSION

This is the first study to look at the stability of type-D personality and whether type-D caseness is confounded by mood status and disease severity during a period of 18 months post-MI. The findings showed that type-D personality was a stable taxonomy, with time and intraindividual variability in depressive and anxiety symptoms over time not affecting type-D status. The mean level of depressive and anxiety symptoms within a patient were significantly related to type-D status, with more chance of being type-D when mean depression or anxiety scores were higher. This is not surprising since type-D patients are more inclined to experience emotional and interpersonal difficulties such as depression and anxiety.[11,28] More importantly, the fact that type-D classification was not significantly affected by changes in mood status corroborates the notion that type-D personality is a stable taxonomy.

Furthermore, demographic and clinical characteristics did not influence type-D caseness over the 3 assessment points in multivariate analyses, indicating that type-D caseness was not confounded by demographic and disease characteristics. This is in line with previous studies on type-D personality, indicating that type-D is a predictor of morbidity and mortality in CVD patients independent of established biomedical risk factors.[1-3]

The type-D personality construct was designed to reflect a chronic psychological condition, as opposed to more acute emotional states such as depression and anxiety. Personality refers to a complex organization of traits that reflect consistencies in the general affective level and behavior of individuals over time.[29] A sound personality construct needs to have high predictive value, good construct validity, and needs to be stable over time.[30] Type-D patients are at increased risk for a wide range of adverse health outcomes[5-10], including morbidity and mortality[1-4]. Moreover, the psychometric properties of the type-D scale are good with Cronbach's α of 0.88/0.86 and a test-retest reliability over a 3-month period with r = 0.72/0.82 for the two subscales, respectively.[13] In addition, type-D has been shown to be a stable construct over a 3-month period, and to be mood-state independent. In concordance with these previous results, the current study provides further evidence for type-D being conceptualized as a personality construct rather than an epiphenomenon of underlying cardiac disease or a reflection of mood status.

An advantage of a personality approach is that personality measures may be used as screening tools in clinical practice in order to identify patients at risk of adverse cardiac events and distress at an early stage, with personality factors likely having greater explanatory power than mood given its chronicity.[11] Thus, the type-D construct may be helpful in the process of identifying high-risk CVD patients. Findings from several prospective follow-up studies have provided empirical evidence to support this notion.[1,3] It is important to emphasize, however, that both personality and specific mood states should be examined in the context of CVD. Clinical diagnoses of affective disorder, self-report measures of negative emotions and personality test scores may all be independent predictors of adverse cardiac events[2], and the most powerful prediction scheme is likely to be one that incorporates both biomedical and psychological factors, including specific emotional states and global personality traits. Rather than ignoring specific negative emotions, use of the DS14 as a screening tool aims at the early detection of patients who are at increased risk of experiencing one of these forms of disease-promoting stress.[31]

Since type-D personality is an important determinant of patient-centered and clinical outcome and comprises a risk factor on par with left ventricular ejection fraction[12], it is important to develop intervention trials targeting this personality taxonomy in order to enhance secondary

prevention in CVD patients. Despite the common misconception that personality types and traits cannot be changed, there is evidence that counters this belief.[31,32] However, before appropriately designed intervention trials can be developed, studies are needed to determine which strategies are successful in moderating personality traits, and which processes mediate the relationship between personality and CVD, so that the intervention will actually affect prognosis.

The results of the current study should be interpreted with some caution. First, since not all patients had had an echocardiography we could only adjust for multi-vessel disease and not left ventricular ejection fraction as a measure of disease severity. Second, we did not assess type-D personality at 6 months post-MI. Since the main difference in the probability of being type-D was found between hospitalization and 12 months post-MI, and not between 12 and 18 months, it would be interesting to include a 6-month assessment in future studies.

The present study also has a number of strengths, including the use of reliable and well-validated measures like the DS14, BDI and STAI, and multiple assessments of depressive and anxiety symptoms. Second, we evaluated a broad spectrum of variables as possible predictors of type-D personality, including demographic, clinical, and psychological. Third, we used a structured diagnostic interview to assess lifetime diagnosis of depressive and anxiety disorder and state of the art statistical analysis by using hierarchical latent class regression models (LatentGOLD). The use of LatentGOLD allowed us to look at the stability of type-D within patients over time rather than at point prevalence rates during 18 months follow-up. Furthermore, it allowed for the inclusion of all patients at all measurement occasions irrespective of loss to follow-up.

In conclusion, type-D personality was a stable taxonomy over an 18-month period in post-MI patients, with type-D patients exhibiting the stable tendency to experience negative emotions and to be socially inhibited across time. Type-D classification was not affected by changes in mood status. These findings support the importance of including personality variables in cardiovascular research and the need for intervention trials targeting this personality taxonomy in order to enhance secondary prevention in this subset of CVD patients. Since this is the first study to look at the stability of type-D in post-MI patients, further research is warranted to replicate these findings in other CVD populations, including patients with chronic heart failure, peripheral arterial disease, arrhythmias and hypertension.

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Part B: Patient-based outcomes

Chapter Five

Depression and health status

V

Current depression but not history of depression is associated with impaired health status after myocardial infarction

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Submitted

Abstract

Background: Little is known about the determinants of impaired health status in cardiac patients. The objective of this study was to investigate whether history of major depressive disorder (MDD) was independently associated with impaired health status 2 months after myocardial infarction (MI).

Methods: A clinical diagnostic interview (Composite International Diagnostic Interview) was administered to 352 MI patients to evaluate the prevalence of DSM-IV lifetime and current MDD. The Seattle Angina Questionnaire (SAQ) was used to assess disease-specific health status. Endpoints were the physical limitation, angina frequency, angina stability, treatment satisfaction, and quality of life (QoL) scores of the SAQ.

Results: A total of 61 post-MI patients (17%) had a history of MDD. History of MDD significantly predicted more physical limitations (odds ratio [OR] 2.11, 95% CI 1.33-3.36) and worse QoL (OR 1.73, 95% CI 1.14-2.64) at 2 months post-MI adjusting for demographic and clinical factors. However, after additional adjustment for current MDD this relationship fell short of significance. Further analyses revealed that only patients with history of MDD and current MDD had significantly more physical limitation (OR 3.29, 95% CI 1.66-6.55) and worse QoL (OR 4.09, 95%CI 2.12-7.89) adjusting for demographic and clinical factors. Multiple linear regression with SAQ scores as continuous outcome variables showed similar results.

Conclusions: History of MDD was associated with significantly more physical limitation and worse QoL 2 months post-MI. However, further exploration revealed that this effect could be attributed to the influence of current MDD. These findings support the importance of depression as a risk marker for adverse health status post-MI.

Introduction

Since mortality rates after acute coronary syndromes (ACS) have declined substantially due to interventions such as percutanuous coronary intervention (PCI), primary goals of therapy now include symptom control and maximizing health status including quality of life (QoL).[1] In a recent report of the National Heart, Lung, and Blood Institute Working Group on Outcomes Research in Cardiovascular Disease, health status was defined as patients' perceptions of how their disease affects their function, their symptoms, and their QoL.[2] The importance of studying health status and its determinants was also emphasized in this report, as a means to enhance patient-centered care and bridge the gap between research and clinical practice. In addition to being an important outcome measure in its own right, impaired health status has been shown to predict subsequent mortality and morbidity in patients with cardiovascular disease.[3-5]

Depression is an emerging risk factor for the development of myocardial infarction (MI)[6,7], and about one in five patients is affected by major depressive disorder (MDD) following myocardial infarction (MI)[8]. Both clinical depression and depressive symptoms have been associated with a two-fold increased risk of mortality, and increased morbidity and re-hospitalisation post-MI[9-13], although negative findings have been reported[14-16]. Several studies have shown that depression is associated with worse health status in cardiac patients[17,18] and that depressive symptoms are a strong predictor of decline in health status in heart failure patients[19]. Recent studies have also associated history of depression with worse health status.[20,21] Rumsfeld and colleagues found a strong association between history of depression and both heavier angina burden and worse health status in 1957 patients with ACS.[21] In patients undergoing cardiac surgery, preoperative depressive symptoms and postoperative increases in depressive symptoms were associated with poorer QoL 6 months after surgery.[20] However, neither of these studies controlled for the effect of current depression. It is well documented that a history of depression is related to future depressive episodes in cardiac patients.[22,23] It is possible that the effect of history of depression on health status can be attributed to the influence of current depression.

The present study evaluated the association between history of MDD and health status two months post-MI. We examined whether history of MDD predicted worse health status two months post-MI independently of demographic and clinical factors, and whether this impact remained after adjusting for current MDD.

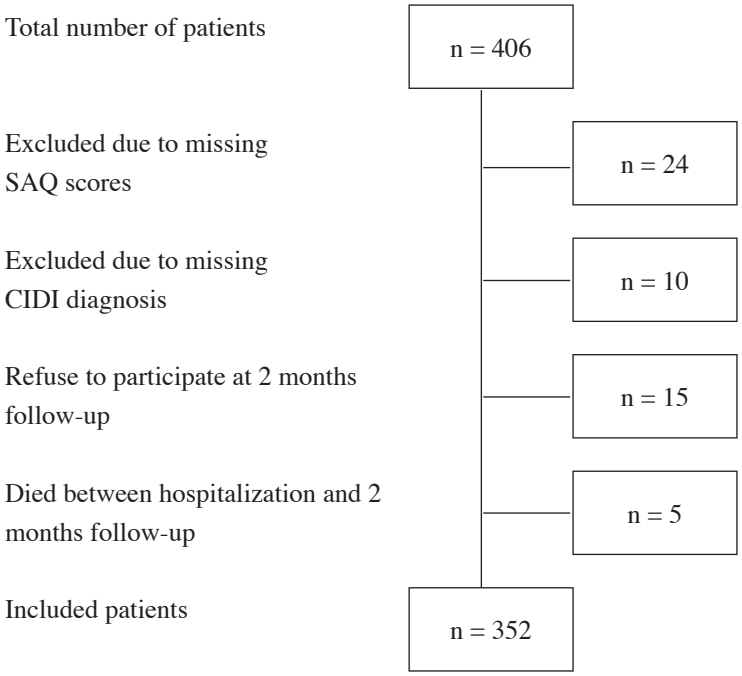
Methods

Patient population and design

Between May 2003 and September 2005, 406 patients hospitalized for acute MI were recruited from four teaching hospitals (Catharina Hospital, Eindhoven; St. Elisabeth Hospital, Tilburg; TweeSteden Hospital, Tilburg; and St. Anna Hospital, Geldrop) in the Netherlands. Two months post-MI, patients were evaluated carefully by a trained psychologist using the Composite International Diagnostic Interview (CIDI).[24] Also obtained were demographic and clinical variables, and responses on a disease-specific health status questionnaire. Inclusion criteria were age > 30 and hospitalization due to acute MI. Exclusion criteria were significant cognitive impairments (e.g. dementia) and severe comorbidities (e.g. cancer) in addition to their cardiac condition. For the diagnosis of MI, patients must have had troponin I levels more than twice the upper limit, with typical ischemic symptoms (e.g. chest pain) lasting for more than 10 minutes or ECG evidence of ST segment elevation or new pathological Q-waves. The study was approved by the medical ethics committees of the participating hospitals. The study was conducted in accordance with the Helsinki Declaration, and all patients provided written informed consent.

Analyses were based on patients who were alive 2 months after discharge from the index hospitalization for MI, who were assessed with the CIDI and had completed the health status questionnaire 2 months post-MI. Of the 406 patients, 15 patients refused to participate at 2 months follow-up, 5 patients died prior to the 2-months assessment, 24 patients were excluded due to missing health status scores, and 10 patients were excluded due to missing CIDI diagnosis. Hence, the final population for this study was comprised of 352 patients (87%) (Figure 1).

Figure 1. *Flowchart of patient selection*



CIDI = Composite International Diagnostic Interview

SAQ = Seattle Angina Questionnaire

Assessment

Demographic and clinical characteristics

Demographic variables included sex and age. Clinical variables were obtained from the patients' medical records and included comorbidity (defined as arthritis, renal insufficiency, and chronic obstructive pulmonary disease), cardiac history (defined as MI, angina, PCI or coronary artery bypass graft (CABG) surgery prior to the MI), multi-vessel disease, diabetes mellitus, PCI versus conservative treatment, anterior MI location, participation in cardiac rehabilitation, smoking status (by means of self-report), and cardiac medication (beta-blockers, ACE-inhibitors, anti-coagulants, statins, aspirin).

Clinical diagnosis of depression

The CIDI[24] was used to assess current and lifetime diagnoses of MDD on the basis of the criteria listed in the Diagnostic and Statistical Manual (DSM)-IV[25]. According to the DSM-

IV, a diagnosis of MDD requires the presence of at least one core criterion (depressed mood or loss of interest) persisting for at least two weeks, accompanied by at least four of the following additional symptoms: Changes in appetite or weight, sleep difficulties, fatigue, psychomotor agitation or retardation, difficulty concentrating, feelings of guilt or worthlessness or thoughts of death or suicide. These symptoms must lead to significant functional impairments and represent a change from previous functioning. The CIDI was conducted 2 months post-MI.

Health Status

Health status was measured with the Seattle Angina Questionnaire (SAQ).[26] The SAQ is a 19-item disease-specific self-report measure for patients with coronary artery disease (CAD) and has been used to assess patient outcomes in ACS.[27] It has been demonstrated to be a valid and reproducible measure, and to be sensitive to clinical change.[17,26] In addition, it has been shown to be predictive of 1-year mortality.[5] The SAQ is comprised of five scales: Physical limitations caused by CAD, angina frequency, angina stability over the preceding month, treatment satisfaction, and patients' perceptions of how their disease limits their QoL. Scores range from 0 to 100. Higher scores indicate higher functional levels in the preceding 4 weeks, e.g. less physical limitations and better QoL. The domains of the SAQ can be categorized to enhance clinical interpretability.[5,21] The physical limitation and angina frequency scores were classified as severe (scores 0-24), moderate (25-49), mild (50-74), and minimal (75-100). Angina stability scores were classified as much worse (0-24), slightly worse (25-49), unchanged (50), slightly better (51-75), and much better (76-100). The SAQ treatment satisfaction and QoL scores were classified as poor (0-24), fair (25-49), good (50-74), and excellent (75-100). The SAQ was administered two months post-MI.

Statistical Analysis

To examine whether characteristics of post-MI patients with and without a history of MDD differed on baseline characteristics, we used the χ^2 for nominal variables and Student's t-test for continuous variables. The bivariate association between history of MDD and the subscales of the SAQ was examined using the χ^2 test. Multivariable ordinal regression analyses were used to examine the impact of a history of MDD on health status. The validity of the proportional odds assumption was examined by fitting separate models for the higher-risk versus lower-risk categories within each outcome and confirming similar odds ratio's across the models. In multivariable analyses, we adjusted for sex and age, comorbidity, cardiac history, multi-vessel disease, anterior MI location, anti-coagulants, statins, and smoking status. We adjusted for covariates with a p-value <0.10, indicating significant differences between patients with and without a history of MDD (Table 1). Sex and age were adjusted for, since they are standardly included in psychosomatic research and have been associated with depression;

cardiac history, multi-vessel disease, anterior MI location were included to adjust for disease severity, ruling out the possibility that that impaired health status could be due to more severe cardiac disease; comorbidity may have a detrimental influence on QoL. In a subsequent step, we added current MDD as a covariate in order to explore whether the impact of history of MDD on health status remained when adjusting for current MDD. To assess the robustness of the results of our multivariable models, we conducted secondary analyses with the SAQ scores as continuous outcome variables using linear regression analysis. A p-value <0.05 was considered to be statistically significant. Odds ratios (OR) with 95% confidence intervals are reported. All statistical analyses were performed using SPSS 12.0.1 for Windows.

Results

Patient characteristics

A total of 61(17%) post-MI patients had a history of MDD, and 22 (36%) of these patients also had current MDD at 2 months post-MI. Patient characteristics stratified by history of MDD are shown in Table 1. Patients with a history of MDD were more likely to be female, to have had an anterior MI, to use anti-coagulant medication, and to be smokers. No other significant differences were found between post-MI patients with and without history of MDD on baseline characteristics.

Table 1. *Baseline characteristics stratified by history of major depressive disorder (MDD)*[1]

	Total sample	History of MDD	No history of MDD	
	(n=352)	**(n=61)**	**(n=291)**	**p-value**
Demographics				
Female sex	70 (20)	18 (30)	52 (18)	**0.04***
Age, mean (SD)	60.2 (11.3)	58.5 (10.9)	60.5 (11.4)	0.22
Clinical factors				
Comorbidity[2]	65 (19)	12 (20)	53 (19)	0.86
Cardiac history[3]	92 (26)	21 (34)	71 (25)	0.13
Multi-vessel disease	110 (31)	16 (33)	94 (39)	0.44
Diabetes mellitus	48 (14)	10 (16)	38 (13)	0.53
PCI[4]	209 (59)	34 (56)	175 (62)	0.41
Anterior MI location	131 (37)	16 (29)	115 (44)	**0.03***
Cardiac rehabilitation	203 (58)	33 (58)	170 (65)	0.32
Beta-blockers	292 (83)	52 (85)	240 (85)	0.89
ACE-inhibitors	133 (38)	21 (34)	112 (40)	0.45
Anti-coagulants	284 (81)	45 (74)	239 (84)	0.05
Statins	314 (89)	52 (85)	262 (92)	0.08
Aspirin	286 (81)	54 (89)	232 (82)	0.22
Smoking	135 (38)	31 (52)	104 (36)	**0.02***

[1] Values are expressed as number (percentage) of patients unless otherwise indicated. All numbers do not add up to 100% due to rounding

[2] Arthritis, renal insufficiency, chronic obstructive pulmonary disease

[3] MI, angina, PCI or CABG prior to the MI

[4] Reference group: conservatively treated

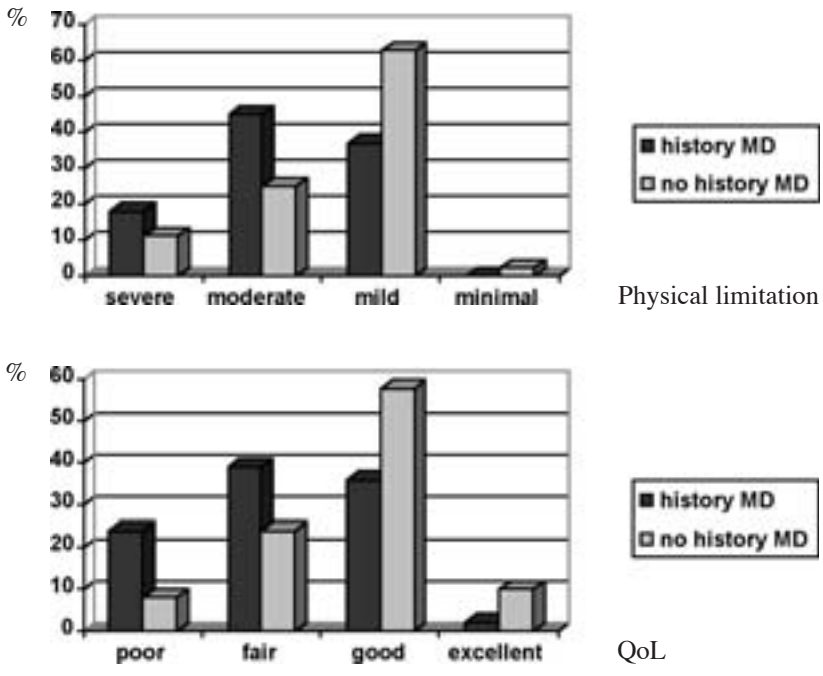
* $p < .05$

Unadjusted analyses

There was a significant relationship between history of MDD and more physical limitations ($p=.001$), worse QoL ($p\leq.0001$), and less angina stability ($p=.042$) 2 months post-MI. However, the most outspoken differences were found on physical limitations and QoL (Figure 2). For example, of patients reporting severe physical limitations, 18% had a history of MDD, whereas 11% of patients had no history of MDD.

Twenty-four percent of patients reporting poor QoL had a history of MDD, whereas 8% of patients had no history of MDD.

Figure 2. *Bivariate relationship between a history of depression and physical limitation and QoL as measured with the SAQ*



QoL = quality of life
SAQ = Seattle Angina Questionnaire

Adjusted analyses

In multivariable analyses, history of MDD was significantly associated with physical limitations and QoL. History of MDD predicted more physical limitations (OR 2.11, 95% CI 1.33-3.36, p=.001) and worse QoL (OR 1.73, 95% CI 1.14-2.64, p=.01) 2 months post-MI, adjusting for sex, age, comorbidity, cardiac history, multi-vessel disease, anterior MI location, anti-coagulants, statins, and smoking status.

However, after additional adjustment for current MDD this relationship fell short of significance. History of MDD did not predict more physical limitations (p=.07) and worse QoL (p=.37) after adjustment for sex, age, comorbidity, cardiac history, multi-vessel disease, anterior MI location, anti-coagulants, statins, smoking status, and current MDD. Further analyses revealed that only patients with a history of MDD and current MDD had significantly

more physical limitations (OR 3.29, 95% CI 1.66-6.55, p=.001) and worse QoL (OR 4.09, 95% CI 2.12-7.89, p<.0001). This suggests that current comorbid MDD mainly drives the relationship between history of MDD and worse health status. Similar results were found when analysing the SAQ subscales as continuous scores using linear regression analysis.

Discussion

History of MDD was independently associated with more physical limitations and worse QoL 2 months post-MI, after adjustment for demographic and clinical factors. However, after additional adjustment for current MDD the relationship between MDD history and more physical limitations and worse QoL fell short of significance. Further analyses revealed that only patients with a history of MDD *and* current MDD had significantly more severe physical limitations and worse QoL, indicating that this effect could be attributed to the influence of current depression.

The prevalence of history of MDD found in this study was 17% and is relatively low as compared to previous studies that reported prevalence rates of 23% to 26%.[20,21,28] However, it should be noted that these prevalences were based on self-report and not on a diagnostic interview as in the current study. In addition, a history of depression was assessed in many different ways (e.g. Beck Depression Inventory, documentation in medical record, one-item question). It is possible that a history of depression is overestimated when using self-report, perhaps because the definition of previous history may be unclear.

Burton and colleagues[29] found that patients undergoing angioplasty with a history of depression had a worse QoL and health status than those without prior history. Rumsfeld and colleagues[21] also found a strong association between history of depression and both heavier angina burden and worse health status in patients with ACS. However, neither studies examined the potential influence of current depressive symptoms. A recent study of post-MI patients focusing on both current and history of depression showed that post-MI depression had a far more profound effect on health status than pre-MI depression, independent of disease severity.[30] These findings are in line with the results of our study.

The results of this study indicate that is important to screen post-MI patients with a history of MDD for active depression, since only patients with a history of MDD and active depression had impaired health status. In addition, patients with a history of depression have a higher prevalence of current MDD.[31] Current MDD has been associated with worse health status[17] and adverse cardiac outcomes in CAD patients[22]. Moreover, it has been shown that

impaired health status is predictive of subsequent mortality and morbidity in patients with cardiovascular disease.[3-5]

Currently, there is no data indicating that treating post- MI depression will reduce mortality. However, according to the European Society of Cardiology[1], primary goals of therapy include symptom control and maximizing health status. It has been shown that treating depression with sertraline in the context of ACS does improve QoL and functional capacity[32] and that psychosocial interventions after MI improve depressive symptoms[33,34] and general health status[34]. The results of the current study suggest that it may be important to recognize and treat depression in post-MI patients to diminish physical limitations and improve QoL.

The results should be interpreted with some caution. First, we assessed health status only once, precluding the evaluation of serial changes in health status. Second, we had no information on left ventricular ejection fraction, which could influence health status. However, we did adjust for other measures of disease severity (e.g. multi-vessel disease). Third, the study was cross-sectional and does not allow for the determination of cause and effect. The present study also has a number of strengths, including the use of a structured diagnostic interview to assess history of MDD and current MDD. Second, health status was assessed with a disease-specific measure that may be more sensitive to capture symptoms in this patient group than a generic measure.

According to a recent editorial by Haas[35], it may be premature to assume that simply treating depression will improve health status, and the importance of including health status indicators as outcomes of interest was emphasized. Further research is needed to identify pathways by which depression influences health status and to determine optimal timing for the assessment of depression.[20] Understanding the impact of depression on health status may help to guide development of interventions to enhance health status following MI.

In conclusion, history of MDD was associated with significantly more physical limitations and worse QoL 2 months post-MI. However, further exploration revealed that this effect could be attributed to the influence of current depression. These findings support the importance of comorbid depression as a risk marker for adverse health status outcomes in patients recovering from an acute MI.

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Part B: Patient-based outcomes

Chapter Six

Symptom clusters and comorbidity post-MI

VI

PSYCHOLOGICAL SYMPTOM CLUSTERS, PSYCHIATRIC COMORBIDITY AND POOR SELF-REPORTED HEALTH STATUS FOLLOWING MYOCARDIAL INFARCTION

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Annals of Behavioral Medicine, in press

ABSTRACT

Background: Depression is a risk factor for adverse outcomes following myocardial infarction (MI). However, the importance of various other psychological factors is less well established. We wanted to 1) explore the degree to which self-reported psychological symptoms in post-MI patients represent one or more underlying dimensions and, 2) examine whether psychological symptom profiles based on these dimensions are differentially associated with major depressive disorder (MDD) and anxiety disorder (AD), and impaired health status.

Methods: Two months post-MI, the BDI, STAI, and Global Mood Scale were used to measure symptoms of depression, anxiety and mood status in 324 patients. The Composite International Diagnostic Interview was administered to diagnose DSM-IV MDD and AD. Health status was assessed by the Seattle Angina Questionnaire.

Results: Principal component analysis revealed 4 essential features of post-MI distress: depressed affect, anxious apprehension, positive affect, and emotional exhaustion. Cluster analysis using these components identified 3 subgroups with different symptom profiles: A No Distress subgroup (high positive affect, low on the remaining components), a first Increased Distress subgroup (ID1; elevated anxious apprehension/emotional exhaustion scores and decreased positive affect, $p<.001$, but absence of depressed affect, $p=.56$), and a second Increased Distress subgroup (ID2; decreased positive affect and elevated scores on the other components, all $p<.001$). Both Increased Distress subgroups were more likely to have psychiatric disorder (ID1: OR=5.4, 95%CI 1.3-22.1, $p=.018$; ID2: OR=27.1, 95%CI 6.4-114.7, $p<.0001$) and worse health status (ID1: $-.38<\beta<-.12$; all $p<.05$; ID2: $-.48<\beta<-.20$; all $p<.05$).

Conclusions: In addition to standard depressive symptoms, other affective components are important in understanding emotional adjustment in post-MI patients. These components are closely related to psychiatric comorbidity and poor health status post-MI.

INTRODUCTION

About one in five patients is affected by major depressive disorder (MDD) following myocardial infarction (MI).[1] In turn, both MDD and depressive symptoms have been associated with a two-fold increased risk of mortality, and increased morbidity and re-hospitalisation post-MI.[2-6] Although several literature reviews have concluded that there is evidence that various other psychological factors are related to prognosis in established coronary artery disease (CAD)[7-9], the importance of these factors is less well established. In addition, it is not known which symptoms are specific to post-MI distress, and whether there are reliably identifiable subgroups of post-MI patients with different psychological symptom profiles.

According to Frasure-Smith and Lespérance[10], most studies on psychosocial risk factors in CAD patients only used one psychological or social variable, making it impossible to examine the degree to which the variables represent one or more common dimensions. Without using multiple measures, it is difficult to know whether the essential features of distress in post-MI patients concern specific psychological concepts or one or more underlying dimensions, including negative affectivity. In addition, little is known about the psychological symptom profiles based on these dimensions and their relationship with adverse outcomes post-MI. Identification of CAD risk profiles across the spectrum of symptoms and syndromes characterizing psychological discomfort, including subsyndromal conditions, might increase the sensitivity of our epidemiologic prediction models and clarify the pathophysiological pathways linking negative psychological states to CAD.[11]

The objectives of the present study were 1) to explore the degree to which psychological variables of distress in post-MI patients represent one or more underlying dimensions, and 2) to examine whether psychological symptom profiles based on these dimensions are differentially associated with DSM-IV MDD and anxiety disorder (AD) and impaired self-reported health status.

METHODS

Patient population and design

Between May 2003 and August 2005, 402 patients hospitalized for acute MI were recruited from four teaching hospitals (Catharina Hospital, Eindhoven; St. Elisabeth Hospital, Tilburg; TweeSteden Hospital, Tilburg; and St. Anna Hospital, Geldrop) in the Netherlands. Two months post-MI, during an appointment specifically for this study, patients were evaluated by a trained psychologist using the Composite International Diagnostic Interview (CIDI)[12]

and completed self-report measures of depression, anxiety, emotional distress and disease-specific health status in the cardiology department of the participating hospitals. Inclusion criteria were age > 30 and hospitalization due to acute MI. Exclusion criteria were significant cognitive impairments (e.g. dementia), severe comorbidities (e.g. cancer) in addition to their cardiac condition, and psychiatric comorbidities other than MDD and AD (e.g. psychosis). Criteria for the diagnosis of MI included troponin I levels more than twice the upper limit, with typical ischemic symptoms (e.g. chest pain) lasting for more than 10 minutes or ECG evidence of ST segment elevation or new pathological Q-waves. The study was approved by the medical ethics committees of the participating hospitals. The study was conducted in accordance with the Helsinki Declaration, and all patients provided written informed consent.

Analyses were based on patients who were alive 2 months after discharge from the index hospitalization for MI, who were assessed with the CIDI and had completed the self-report questionnaires 2 months post-MI. Of the original 402 patients, 10 patients refused to participate at 2 months follow-up, 5 patients died prior to the 2-months assessment, and 63 patients were excluded due to missing CIDI diagnosis or missing self-report measures. Hence, the final population for this study was comprised of 324 patients.

Assessment

Symptoms of depression, anxiety, and mood status

The Beck Depression Inventory (BDI) is a 21-item self-report measure developed to assess the presence and severity of depressive symptoms during the past week.[13] Each item is rated on a 0 to 3 scale. The BDI is a reliable and well-validated measure of depressive symptomatology[14,15], and is the most widely used self-report measure of depression. BDI scores ≥ 10 are indicative of at least mild to moderate symptoms of depression and have been associated with poor prognosis in MI patients.[4,6,16,17]

The State Trait Anxiety Inventory (STAI) is a self-report measure consisting of two 20-item scales developed to measure the level of general state and trait anxiety.[18] In the current study we included the state scale of the STAI, which assesses the current level of general anxiety. Each item is rated on a four-point Likert scale. Elevated scores on the STAI have been associated with poor prognosis in MI patients.[19] The STAI has been demonstrated to have adequate validity and reliability.[20]

The Global Mood Scale (GMS) is a self-report measure assessing both positive (energy and sociability) and negative (fatigue and malaise) mood states in patients with heart disease.[21] It consists of 10 positive and 10 negative mood terms answered on a 5-point Likert scale. The

respondent is asked to rate the extent to which he/she has experienced each mood state lately. The GMS has been shown to be a valid and reliable measure of affective mood states[21,22], and is very responsive to treatment-related changes in mood status[23].

Clinical diagnoses of depression and anxiety disorder

The CIDI was used to assess current diagnoses of MDD and AD (consisting of panic disorder, social phobia, and/or generalized anxiety disorder) based on the diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV).[24] The CIDI was administered 2 months post-MI (1.8±0.6 months).

Health Status

Health status was measured with the Seattle Angina Questionnaire (SAQ).[25] The SAQ is a 19-item disease-specific self-report measure for patients with CAD and has been used to assess patient outcomes in acute coronary syndromes.[26] It has been demonstrated to be a valid and reproducible measure, and to be sensitive to clinical change.[25,27] In addition, it has been shown to be predictive of 1-year mortality.[28] The SAQ is comprised of five scales: Physical limitations caused by CAD, angina frequency, angina stability over the preceding month, treatment satisfaction, and patients' perceptions of how their disease limits their quality of life (QoL). Scores range from 0 to 100. Higher scores indicate higher functional levels in the preceding 4 weeks, e.g. less physical limitations and better QoL.

Demographic and clinical characteristics

Demographic variables included gender, age, educational level, and marital status. Clinical variables were obtained from the patients' medical records and included comorbidity (arthritis, renal insufficiency, and chronic obstructive pulmonary disease), cardiac history (MI, angina, percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) surgery prior to the MI), multi-vessel disease, diabetes mellitus, PCI versus conservative treatment, current smoking (self-report), and cardiac medication at discharge (β-blockers, ACE-inhibitors, Ca-antagonists, anti-coagulants, statins, diuretics, A2-antagonists, vasodilators, aspirin).

Statistical Analysis

Principal component analysis (PCA) with oblimin rotation was used to determine the underlying structure of the psychological distress measures (BDI, STAI, GMS). A Scree-plot was adopted to identify the number of components, and subsequent KMO and Bartlett's test of sphericity were applied as fit indices. The resulting components were used to construct homogeneous subscales of psychological distress. For each subscale, those six items with the highest component loadings and cross loading differences <.20 were selected. Subscale

homogeneity was examined by Cronbach's alpha. Identification of groups was obtained through cluster analysis. We used a two-stage clustering procedure as recommended by Hair & Black.[29] First, hierarchical clustering analysis (wards method; squared Euclidean distance) with standardized subscale measures (M=50; SD=10) derived the number of clusters through inspection of the agglomeration schedule. Second, the cluster centers obtained from hierarchical cluster analysis were used as initial seed points in non-hierarchical cluster analysis (i.e. K-means clustering) to fine-tune the solution. The combination of hierarchical and non-hierarchical methods results in a more valid cluster solution. For comparison between groups we used the chi-square test for discrete variables and ANOVA for continuous variables. Multivariate ANOVA was employed to examine differences on subscale measures between groups identified by cluster analysis. The Student-Neuman-Keuls test was used for post-hoc analysis. Logistic regression (method=enter) was used to assess the relationship between group membership and current psychiatric comorbidity (i.e. MDD and/or AD). Relevant assumptions were checked and met using the criteria recommended by Ottenbacher et al..[30] Multiple regression analysis (method = enter) was used to assess the relationship between group membership and health status while controlling for potential confounders. The following assumptions for multiple linear regression were checked and met[31]: multicollinearity (VIF: range 1.04-1.23), independent observations (Durbin-Watson: range 1.85-2.10), homoscedasticity (plot of standardized predicted dependent variable vs. standardized residuals; random patterns were found), normally distributed error (histogram of residuals). Linearity was not checked since all independent variables were dichotomous. Data were analyzed using SPSS 12.0.1 for Windows.

RESULTS

Components of psychological distress

PCA revealed a 4-component solution in the underlying structure of the psychological symptom measures (Table 1). KMO (0.95) and Bartlett's test of sphericity (χ^2 (1830) = 15217, p <.001) indicated that PCA was adequate for this data. The 6-item subscales that were constructed from the PCA reflected, respectively, "Depressed Affect" (component #3; Cronbach's α = .82; BDI items 1,3,5,6,7,8), "Anxious Apprehension" (component #1; α = .90; STAI items 1,3,4,5,12,13), "Positive Affect" (component #2; α = .91; GMS items 2,4,5,7,9,13), and "Emotional Exhaustion" (component #4; α = .92; GMS items 3,8,12,18,19; BDI item 17). The labeling of the components was based on previous literature.[21,22] For example, the items included in the Emotional Exhaustion subscale were drawn from the negative affect subscale of the GMS. The range of component loadings for items not reported in Table 1 was .30-.63 for component 1, .46-.69 for component 2, .30-.41 for component 3, and .38-.69 for component 4.

Table 1. *Four-component rotated solution for psychological distress measures*[1]

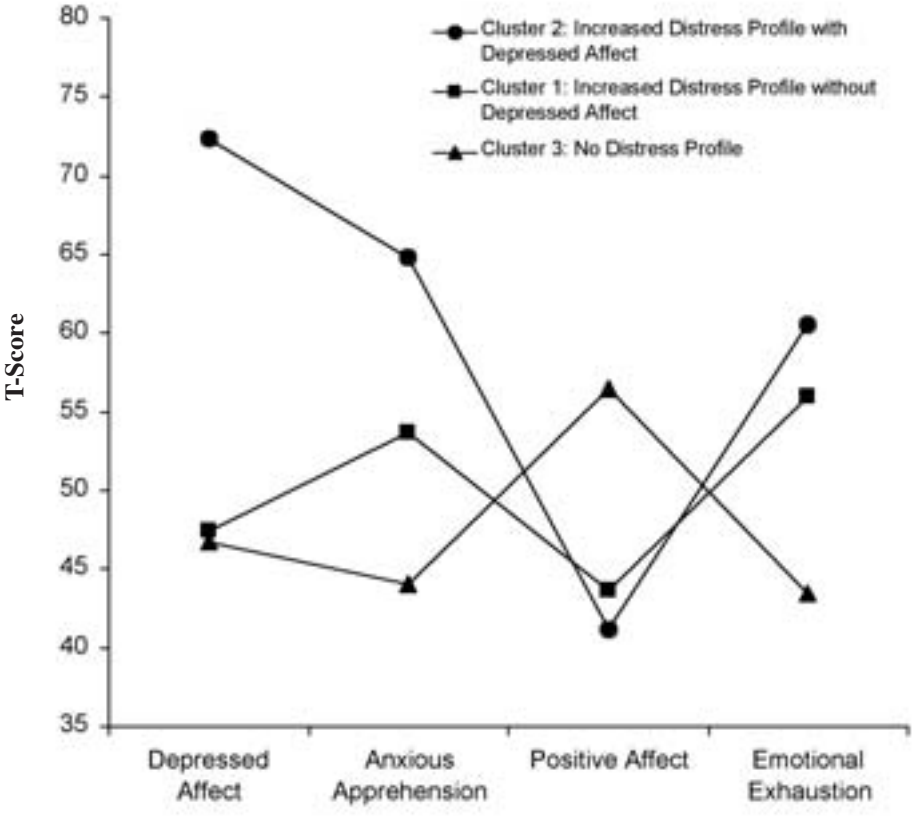
Items	Scale (#)	Comp-1	Comp-2	Comp-3	Comp-4
Depressed Affect					
Guilty feelings	BDI (5)			-.87	
Self-dislike	BDI (7)			-.84	
Self-criticism	BDI (8)			-.79	
Sense of failure	BDI (3)			-.79	
Punishment feelings	BDI (6)			-.61	
Feelings of sadness	BDI (1)			-.45	
Anxious Apprehension					
Being jittery	STAI (13)	.75			
Feeling restless	STAI (4)	.75			
Feeling calm	STAI (1)	-.73			
Feeling nervous	STAI (12)	.72			
Feeling at ease	STAI (5)	-.68			
Being tense	STAI (3)	.66			
Positive Affect					
Hard working	GMS (7)		.79		
Lively	GMS (9)		.79		
Enterprising	GMS (13)		.78		
Dynamic	GMS (4)		.76		
Active	GMS (2)		.74		
Bright	GMS (5)		.73		
Emotional Exhaustion					
Feeling tired	GMS (12)				.81
Feeling fatigued	GMS (18)				.80
Feeling tired	BDI (17)				.77
Feeling weakened	GMS (19)				.77
Feeling worn out	GMS (3)				.72
Feeling feeble	GMS (8)				.70

[1] No cross-loadings ≥.30 were found in the 6-item subscales. Only the 6 items with the highest component loadings are shown. 'comp'= component.

Psychological distress profiles

The agglomeration schedule obtained by hierarchical cluster analysis suggested a three-cluster solution. There was a sharp increase in within-cluster sum of squares between two and three clusters. Subsequently, K-means cluster analysis resulted in a final solution with 168 (52%) patients in the first cluster, 118 (36%) in the second cluster, and 38 (12%) in the third cluster. Figure 1 visualizes the three psychological distress profiles. Cluster 1 can be characterized by a relative absence of psychological distress and presence of positive affect, and is therefore labeled the No Distress group. Clusters 2 and 3 can both be labeled as Increased Distress groups. Cluster 2 is characterized by low positive affect and increased anxious apprehension/emotional exhaustion, but also by the absence of depressed affect. Cluster 3 is characterized by the presence of psychological distress, including depressed affect, and a relative absence of positive affect.

Figure 1. *Psychological symptom clusters*



Cluster characteristics are shown in Table 2. Patients in cluster 1 were more likely to be male and to have a high educational level, and less likely to have comorbidities and a cardiac history. Cluster 2 is characterized by more females, more patients with a low educational level, and more comorbidities than would be expected from the independence hypothesis. Finally, cluster 3 contains relatively more females, more patients without a partner, and more current smokers.

Table 2. *Demographic and medical*[1] *characteristics stratified by cluster membership*[2]

	No Distress (n=168)	Increased Distress without Depressed Affect (n=118)	Increased Distress with Depressed Affect (n=38)	p-value
Age, mean (SD)	60.1 (11.0)	60.0 (11.5)	56.7(11.5)	.22
Male sex	89 (149)	73 (86)	68 (26)	.001
Low educational level[3]	72 (120)	84 (99)	84 (32)	.03
Having no partner	13 (21)	14 (17)	34 (13)	.004
Being a smoker	37 (61)	35 (41)	66 (25)	.002
Cardiac history[4]	19 (31)	32 (36)	34 (13)	.03
Multi-vessel disease[5]	42 (67)	46 (51)	40 (15)	.75
Comorbidity[6]	13 (20)	29 (32)	29 (11)	.002
Diabetes	12 (19)	14 (16)	11 (4)	.77
PCI7	63 (100)	60 (67)	63 (24)	.89
β-blockers	87 (139)	85 (94)	84 (32)	.84
ACE-inhibitors	40 (64)	43 (47)	32 (12)	.48
Ca-antagonists	15 (24)	25 (27)	13 (5)	.09
Anti-coagulants	83 (133)	85 (94)	76 (29)	.49
Statins	94 (145)	94 (104)	87 (33)	.40
Diuretics	18 (28)	21 (23)	29 (11)	.28
A2-antagonists	8 (13)	10 (11)	8 (3)	.84
Vasodilators	24 (39)	33 (37)	26 (10)	.26
Aspirin	88 (141)	77 (85)	82 (31)	.06

1 In 4% of the cases medical data was unknown
2 Values are expressed as percentage (number) of patients unless otherwise indicated
3 No education completed, first level (primary school), or secondary level (first phase)
4 MI, angina, PCI or CABG prior to the MI
5 Reference group: one-vessel disease
6 Arthritis, renal insufficiency, chronic obstructive pulmonary disease
7 Reference group: non-invasive treatment

Multivariate ANOVA revealed that there was an overall significant main effect for cluster membership on psychological distress (Wilks lambda=0.32; F(8,450)=42.7, p<.0001) adjusting for sex, marital status, educational level, smoking, cardiac history, and comorbidity. This indicates that differences between clusters on psychological distress variables cannot be explained by the included covariates. Therefore, the clusters provide unique information on the identification of subgroups in CAD patients.

Psychological distress profiles and psychiatric comorbidity

Because of the relative low prevalence of MDD and AD in our sample, we created a single dichotomous variable: psychiatric comorbidity. Value one was assigned to those patients with current MDD and/or AD. The prevalence of psychiatric comorbidity was 2% (n=3/168; MDD, n=2; AD, n=2) in cluster 1, 9% (n=11/118; MDD, n=10, AD, n=2) in cluster 2, and 37% (n=14/38; MDD, n=12, AD, n=8) in cluster 3. Cluster membership was recoded into two dummy variables with the No Distress group as reference category. Subsequently, multivariate logistic regression analysis revealed that both the Increased Distress group with depressed affect (Cluster 3; OR=27.1; 95%CI 6.4-114.7, p <.0001) as well as the Increased Distress group without depressed affect (Cluster 2; OR=5.4; 95%CI 1.3-22.1, p =.018) were associated with psychiatric comorbidity (Nagelkerke $R^2 = 0.25$; Hosmer and Lemeshow test: p = 1). Hence, a subgroup of CAD patients was more likely to have psychiatric comorbidity despite their low levels of self-reported depressed affect. These patients were characterized, however, by increased levels of self-reported anxious apprehension and emotional exhaustion, and the relative absence of positive affect. The exact strength of the associations should be interpreted with some caution given the large confidence intervals and the small cell sizes, especially in cluster 1 (the reference category).

Psychological distress profiles and health status

Mean levels of health status were lowest among patients in cluster 3, while patients in cluster 2 reported lower levels of health status compared to cluster 1 patients (Table 3).In multivariate analyses, all health status subscales were associated with cluster membership. Patients in the Increased Distress group with depressed affect (Cluster 3; $-.48<\beta<-.20$; all p <.05) and the Increased Distress group without depressed affect (Cluster 2; $-.38<\beta<-.12$; all p <.05) experienced decreased health status compared with the No Distress subgroup. In addition, age, current smoking, aspirin usage, multi-vessel disease, cardiac history and comorbidity were also associated with decreased self-reported health status.

Table 3. *Mean levels of health status, as assessed by the Seattle Angina Questionnaire, stratified by cluster membership*[1]

	No distress	Increased distress without Depressed Affect	Increased distress with Depressed Affect	p-value
	M (SD)	M (SD)	M (SD)	
Physical limitation	39.7 (7.4)	33.1 (9.8)	29.9 (9.9)	<.0001
Angina stability	5.6 (0.9)	4.8 (1.5)	4.3 (1.6)	<.0001
Angina frequency	11.5 (1.3)	10.6 (2.0)	9.8 (2.5)	<.0001
Treatment satisfaction	17.5 (2.3)	16.4 (3.3)	15.5 (3.5)	<.0001
Quality of life	12.4 (2.1)	9.8 (2.8)	7.9 (3.0)	<.0001

[1] Results of pairwise comparisons were all significant (p<.05) Higher scores indicate better health status, e.g. less angina frequency and better quality of life.

DISCUSSION

The aim of the current study was to examine dimensions of psychological distress in post-MI patients and the associations of psychological symptom profiles with psychiatric comorbidity and health status. The underlying structure of self-reported psychological symptoms post-MI consisted of four components: depressed affect, anxious apprehension, positive affect, and emotional exhaustion. Cluster analysis based on these components revealed three psychological symptom clusters: A No Distress subgroup, characterized by a relative absence of psychological distress and presence of positive affect, and two Increased Distress subgroups characterized by absence of positive affect and presence of anxious apprehension and emotional exhaustion. Remarkably, one Increased Distress subgroup was characterized by a relative absence of depressed affect as well. Patients in the two Increased Distress subgroups were more likely to have MDD/AD and decreased health status as compared with the No Distress subgroup. This suggests that some post-MI patients may be more likely to have MDD/AD and impaired health status despite their low levels of self-reported depressed affect. Moreover, these results imply that the spectrum of psychological factors associated with CAD is larger than previously considered.

An increasing body of literature has demonstrated a relationship between depressive symptoms and the likelihood of subsequent adverse cardiac events[32], although negative findings have been reported[33-35]. Interestingly, in the current study one Increased Distress subgroup without

elevated scores on depressed affect, but characterized by the absence of positive affect and presence of anxious apprehension and emotional exhaustion, was associated with psychiatric comorbidity and decreased health status. This 'sub clinical' group can be an interesting study target, since it seems that these patients are more likely to have psychiatric comorbidity and decreased health status without having increased depressed affect. It is possible that the absence of positive affect is important is this subgroup.

In contrast to the data linking negative emotional states to CAD, the potential protective effect of positive psychological factors has been less extensively investigated[36], and data linking positive affect and health is not definitive[37]. In the largest study to date, subjects were assessed for optimistic versus pessimistic explanatory style and followed for 10 years. Results revealed a gradient relationship between levels of optimism and cardiac outcomes, with optimism halving the risk for cardiac events.[38] In addition, several studies have shown that positive psychological factors can dampen the physiologic reactivity to negative emotional stimuli[39] and can enhance immune function[40]. These findings point to the importance of further exploring positive emotional states and their potential protective effects against disease.

In addition, our findings show that anxious apprehension could be a potentially harmful negative emotion. Several large studies have noted a relationship between phobic anxiety and sudden cardiac death.[41,42] In addition, Grace et al.[17] reported nonphobic anxiety to have a negative effect on self-reported recurrent cardiac events following an ischemic coronary event. However, data linking the various forms of anxiety to CAD are relatively rare and more work is needed.

According to Suls and Bunde[43], there needs to be more appreciation that the clustering and overlap of negative affective dispositions may make specificity of emotion less critical for CAD risk, that is anxiety and depression may not have distinctive, independent effects. They may all increase risk because they share a general disposition to experience chronic and intense negative emotions. Kubzansky and colleagues[11] have also argued for the need to study various potential psychosocial risk factors and their relationship with CAD and CAD recurrence. Identifying various forms of distress, even in their less severe states, may provide an important avenue for early intervention. Effective treatment targeting psychosocial risk factors in CAD patients requires an accurate characterization of who is at risk for adverse outcomes. A more detailed examination of the CAD distress profiles may better inform the development of more effectively timed and more specifically tailored behavioral interventions. However, more research is needed to replicate these results and to study potential treatment implications.

Results of this study show that the Increased Distress profiles were associated with MDD/AD and impaired health status. According to the European Society of Cardiology[44], primary goals of therapy include symptom control and maximizing health status. In addition, health status has been shown to be predictive of 1-year mortality.[28] Understanding the association of negative and positive mood states with health status may help to guide development of interventions to enhance health status and outcome following MI.

The results of the current study should be interpreted with some caution. Since the study was cross-sectional, we were not able to assess the predictive value of the psychological symptom clusters. It would be interesting to evaluate the effect of the symptom clusters on cardiac morbidity and mortality. Ultimately these profiles will need to be examined prospectively against hard medical outcomes. Furthermore, we had no information on left ventricular ejection fraction, which could influence psychological symptoms post-MI. However, we did adjust for other measures of disease severity (e.g. cardiac history). We did not take into account the potential influence of history of psychiatric disorder. The present study also has a number of strengths, including the use of valid and reliable measures of multiple concepts, making it possible to identify various underlying dimensions of psychological symptoms post-MI. We also used a structured diagnostic interview to assess psychiatric comorbidity. In addition, health status was assessed with a disease-specific measure that may be more sensitive to capture symptoms in this patient group than a generic measure.

In conclusion, the underlying structure of self-reported psychological symptoms post-MI can be characterized by depressed affect, anxious apprehension, positive affect, and emotional exhaustion. Symptom profiles based on these features revealed a No Distress subgroup and two Increased Distress subgroups. Both Increased Distress subgroups were associated with psychiatric comorbidity and decreased health status, despite the relative absence of depressed affect in one of these subgroups. This study needs to be replicated in a similar sample using confirmatory factor analysis, measures of objective health status, and longitudinal data. The distress profiles based on the underlying structure reported here provide a basis for profile analysis of psychological symptom change in outcome studies with post-MI patients and are potentially valuable for both research and clinical practice.

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Part B: Patient-based outcomes

Chapter Seven

Poor quality of life, MACE and PCI

VII

Poor health-related quality of life is a predictor of early but not late cardiac events post PCI

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Abstract

Poor health-related quality of life (HRQL) is associated with mortality in cardiac patients. Patients (n=667) 2 years post percutaneous coronary intervention with poor HRQL had a higher incidence of early MACE compared with patients with good HRQL (p=0.008), whereas there was no difference in late MACE (p=0.80). Poor HRQL remained an independent predictor of early (HR:2.20;95%CI:1.34-3.61) but not late MACE (HR:0.81;95%CI:0.50-1.32), adjusting for other risk factors. The same pattern was found for early (HR:2.65;95%CI:1.08-6.52) and late death/non-fatal MI (HR:0.65;95%CI:0.30-1.44). Prior to recommending the use of HRQL measures as screening tools in clinical practice, further research is warranted.

Introduction

Health-related quality of life (HRQL), defined as the impact of disease on the patient's functioning as perceived and reported by the patient, is gaining increasing recognition as an important endpoint. A recent report from the National Heart, Lung, and Blood Institute working group on outcomes research in cardiovascular disease emphasized the importance of focusing on patient-centered outcomes, such as HRQL, in order to bridge the gap between research and clinical practice.[1] The various self-report measures used to assess HRQL are designed to evaluate how daily activities and physical, emotional, and social functioning are affected by the cardiac condition and its treatment. HRQL may also serve as a valuable factor in risk stratification in research and clinical practice and guide clinical decision-management given discrepancies found between physician-rated and patient-rated functional status.[2] However, despite studies showing that impaired HRQL comprises a risk factor for mortality and hospitalization in patients with established coronary artery disease (CAD)[3, 4] and heart failure[5-8] independent of traditional biomedical risk factors, it is not yet standard to assess HRQL in research and clinical practice[9]. In addition, the effect of HRQL on adverse clinical outcome has not yet been evaluated in a pure sample of patients treated with percutaneous coronary intervention (PCI).

Post PCI patients often experience new coronary events within the first 6 months after PCI.[10] These early events are mainly caused by factors related to the procedure itself, such as recoil of the vessel wall and neointimal hyperplasia. Late events, that is, events occurring after 6 months, are usually related to new lesions elsewhere in the coronary system. Hence, new coronary events after PCI can be divided into early events and late events.[11]

Since identifying high-risk patients is a cornerstone of current cardiovascular care, one potential use of formal HRQL assessment could be the identification of patients at risk for adverse clinical outcomes.[3] By describing the association between measures that quantify HRQL with prognosis, it is possible to create a better appreciation of how to interpret scores on these measures and support their broader use in clinical practice.[6]

In the current study, we examined the impact of HRQL on clinical outcome in exhausted patients following PCI. Specifically, we investigated whether poor HRQL at the time of the index PCI was associated with major adverse cardiac events (MACE) and a composite of death and non-fatal myocardial infarction (MI) at follow-up, adjusting for demographic and clinical risk variables. Since early (≤6 months) and late (>6 months) events post PCI may have a different pathological basis, we explored the effect of HRQL on early and late events separately.

Methods

Patient population and study design

Consecutive patients (n=667) post PCI aged 35-68 from the university hospitals of Maastricht, Rotterdam, Nijmegen, and the Catharina Hospital in Eindhoven, the Netherlands, who were included in the randomized EXhaustion Intervention Trial (EXIT), participated in the current study. Details of the study design have been published elsewhere.[10] In brief, EXIT was designed to evaluate the effect of a behavioral intervention targeting symptoms of exhaustion on new cardiac events occurring during a mean follow-up period of 2 years post PCI. Hence, patients who were included in the EXIT trial were all exhausted at baseline.

Exhaustion is defined as unusual fatigue, increased irritability, and demoralization, and is associated with a 2-3 fold increased risk of adverse clinical outcome in patients with established heart disease independent of disease severity.[12,13] Evidence from studies examining the physiological correlates of exhaustion indicates that exhaustion is not merely a somatoform disorder. Exhaustion has been related to increased inflammation[14,15], impaired fibrinolysis[16], and low vagal tone[17], all of which have been associated with the pathogenesis of CAD. In addition, a recent study showed that exhaustion but not depression was related to increased inflammation in women with CAD.[18]

In the EXIT trial, exhaustion caseness was determined on the basis of a two-step procedure. In the first step, at 2 weeks post-PCI patients were asked to complete the Maastricht Questionnaire (MQ), which is a self-report measure to denote those who are vitally exhausted using a standardized cut-off ≥14 (i.e. 7 or more complaints).[19] In the second step, patients who were exhausted based on the MQ were subjected to the Maastricht Interview for Vital Exhaustion (MIVE), using a cut-off ≥7 to determine exhaustion caseness.[10] MIVE comprises 23 questions and has been shown to be a more powerful predictor of adverse clinical events than the MQ.[20]

Of 1,254 patients interviewed, 527 patients were excluded prior to the intervention and 17 patients post-intervention (e.g. due to missing informed consent, not fulfilling the inclusion criteria, etc.)[10]. Of the 710 patients included in the EXIT study, 667 (94%) patients completed a questionnaire to assess HRQL at baseline. Non-responders were more likely to be female, smoking, and to have diabetes, but less likely to be prescribed beta-blockers and nitrates (all $p < 0.05$). No other statistically significant differences were found between responders and non-responders on baseline characteristics.

The EXIT study was approved by the medical ethics committees of the participating hospitals and the study was conducted in accordance with the Helsinki Declaration. All patients provided written informed consent.

Assessment

Demographic and clinical variables

Demographic variables included sex and age. Clinical variables (indication for PCI, previous MI, previous PCI, previous coronary artery bypass surgery (CABG), heart failure, multi-vessel disease, diabetes, smoking, cardiac and anti-depressant medication) were obtained from the patients' medical records. Comorbidity was assessed by asking the patients if they had seen a medical specialist in the year prior to PCI.

Health-related quality of life

HRQL was measured with the Dutch version of the MacNew Heart Disease Health-Related Quality of Life questionnaire.[21,22] Items are answered according to a 7-point Likert scale with '1' indicating poor HRQL and '7' good HRQL. The internal consistency of the Dutch version of the scale is good with Cronbach's alpha ranging from 0.79 to 0.91 for the subscales Emotional, Physical, and Social Functioning, and 0.92 for the total scale.[21] For the purpose of the current study, we only used the total scale score. The scale was administered at baseline.

Clinical Endpoints

The primary endpoint was MACE (a composite of death, non-fatal MI, CABG, and PCI), and the secondary endpoint was a composite of death or non-fatal MI. Endpoints were separated into early (≤6 months) versus late events (>6 months). The median follow-up was 2 years, and follow-up data was complete for all patients (100%).

Statistical Analysis

Prior to statistical analyses, scores on the MacNew were dichotomized with the lowest tertile indicating poor HRQL. Others have also advocated the use of dichotomization in order to enhance clinical interpretability.[9] Discrete variables were compared with the Chi-square test (Fisher's Exact test when appropriate) and continuous variables with Student's t-test for independent samples. Univariable and multivariable Cox proportional hazards regression analyses were performed to investigate the impact of poor HRQL on the occurrence of a new cardiac event at follow-up. In multivariable analysis, we entered HRQL, sex, age, comorbidity, CAD history (defined as MI, PCI or CABG prior to the index event), multi-vessel disease, smoking, participation in a behavioral intervention, and the use of anti-depressant medication. We chose to enter the covariates sex[23,24], age[25], comorbidity[24], previous cardiac history[25], and smoking[26] in the multivariable analyses, as they have all been associated with impaired HRQL

following revascularization or in patients with heart failure. Multi-vessel disease was added to control for disease severity, and participation in a behavioral intervention and the use of anti-depressants since there were significant differences on these variables between the two HRQL groups at baseline. All statistical tests were two-tailed. $P < 0.05$ was used for all tests to indicate statistical significance. Hazard ratios (HR) with 95% confidence intervals (CI) are reported. All statistical analyses were performed using SPPS version 12.0.1.

Results

Baseline characteristics

Patient baseline characteristics stratified by HRQL are presented in Table 1. Patients with poor HRQL were more likely to have participated in a behavioral intervention (60% versus 49%; $p = 0.01$), to have a previous cardiac history (48% versus 39%; $p = 0.02$), and to be treated with anti-depressants (10% versus 4%; $p = 0.01$) than patients with good HRQL. There were no other statistically significant differences between groups on baseline characteristics.

Table 1. *Baseline characteristics stratified by health-related quality of life*[1]

	Good HRQL (n = 446)	Poor HRQL (n = 221)	p-value
Demographics			
Female sex	91 (20)	54 (24)	0.24
Age, mean (SD)	53 (7)	53 (7)	0.63
Intervention			
Behavioral intervention	218 (49)	132 (60)	0.01
Clinical risk factors			
Comorbidity	42 (9)	30 (14)	0.10
Indication for PCI:			
Stable angina	63 (14)	20 (9)	
Unstable angina	248 (56)	134 (61)	
MI	88 (20)	34 (15)	
Post-MI angina	39 (9)	29 (13)	
Other	8 (2)	4 (2)	0.09
Cardiac history[2]	173 (39)	106 (48)	0.02
Heart failure	9 (2)	2 (1)	0.29
Multi-vessel disease	87 (20)	37 (17)	0.39
Diabetes mellitus	50 (11)	29 (13)	0.47
Smoking	81 (18)	53 (24)	0.08
Medication			
Beta-blocker	337 (76)	155 (70)	0.13
Calcium antagonists	159 (36)	94 (43)	0.09
ACE-inhibitors	93 (21)	54 (24)	0.29
Nitrates	246 (55)	133 (60)	0.22
Diuretics	51 (11)	30 (14)	0.43
Lipid lowering	335 (75)	165 (75)	0.90
Anti-depressants	18 (4)	21 (10)	0.01

MI = myocardial infarction; PCI = percutaneous coronary intervention

[1] Values are expressed as number (percentage) of patients unless otherwise indicated.

[2] MI, PCI or CABG prior to the index PCI

Predictors of major adverse cardiac events

There were 66 early (≤6 months) MACE, with 20 (33%) events attributed to death or non-fatal MI. Late (>6 months) MACE comprised 83 events, with death and non-fatal MI accounting for 33 (40%) of the events.

The incidence of early MACE was higher in patients with poor HRQL than in patients with good HRQL (32/221=15% versus 34/446=8%; p = 0.008). By contrast, there was no difference in the incidence of late MACE for patients with poor versus good HRQL (26/221=12% versus 57/446=13%; p = 0.80).

In multivariable analyses, poor HRQL remained an independent predictor of early MACE and was associated with a 2-fold increased risk (HR: 2.20; 95% CI: 1.34-3.61) adjusting for sex, age, comorbidity, CAD history, multi-vessel disease, smoking, participation in a behavioral intervention, and the use of anti-depressant medication (Table 2). By contrast, poor HRQL was not a predictor of late MACE (HR: 0.81; 95% CI: 0.50-1.32) (Table 2). Multi-vessel disease was also an independent predictor of early MACE, whereas comorbidity and cardiac history were associated with late MACE (Table 2).

Table 2. *Predictors of early (≤6 months) and late (>6 months) major adverse cardiac events (adjusted analyses)*[1]

	early MACE			**late MACE**		
Predictor variables	HR	[95% CI]	p-value	HR	[95% CI]	p-value
Poor HRQL	**2.20**	[1.34-3.61]	**0.002**	0.81	[0.50-1.32]	0.40
Female sex	0.93	[0.51-1.70]	0.82	1.13	[0.66-1.93]	0.66
Age	1.00	[0.97-1.04]	0.95	1.02	[0.98-1.05]	0.35
Behavioral intervention	1.55	[0.94-2.58]	0.09	0.82	[0.53-1.27]	0.37
Comorbidity	0.47	[0.17-1.31]	0.15	**3.33**	[1.95-5.70]	**<0.001**
Cardiac history[2]	0.69	[0.41-1.17]	0.16	**2.12**	[1.33-3.36]	**0.002**
Multi-vessel disease	**2.08**	[1.19-3.64]	**0.01**	1.11	[0.64-1.92]	0.72
Smoking	0.53	[0.25-1.12]	0.10	1.50	[0.91-2.47]	0.12
Anti-depressants	0.72	[0.22-2.32]	0.58	1.29	[0.59-2.84]	0.52

[1] Enter procedure

[2] MI, PCI or CABG prior to the index PCI

Predictors of death and non-fatal MI

The majority of MACE in the current study comprised revascularization procedures, which are largely symptom-driven. Since patient symptoms (e.g. the patient's perception of HRQL) may influence the rate of re-interventions, we performed secondary analyses to investigate whether poor HRQL was related to 'hard' events, defined as a composite of death and non-fatal MI. In multivariable analyses, poor HRQL (HR: 2.65; 95%CI: 1.08-6.52) was also a predictor of early death/non-fatal MI, adjusting for sex, age, comorbidity, CAD history, multi-vessel disease, smoking, participation in a behavioral intervention, and the use of anti-depressant medication (Table 3). As with late MACE, poor HRQL (HR: 0.65; 95% CI: 0.30-1.44) was not a predictor of late death/non-fatal MI (Table 3). Age, cardiac history, and multi-vessel disease were also independent predictors of early death/MI, whereas comorbidity and cardiac history were associated with late death/MI (Table 3).

Table 3. *Predictors of early (≤6 months) and late (>6 months) death or non-fatal MI (adjusted analyses)*[1]

	early death/MI			**late death/MI**		
Predictor variables	HR	[95% CI]	p-value	HR	[95% CI]	p-value
Poor HRQL	**2.65**	[1.08-6.52]	**0.03**	0.65	[0.30-1.44]	0.29
Female sex	0.68	[0.25-1.81]	0.44	1.01	[0.43-2.35]	0.98
Age	**1.07**	[1.00-1.15]	**0.04**	1.00	[0.93-1.03]	0.41
Behavioral intervention	1.56	[0.61-3.96]	0.35	1.51	[0.74-3.09]	0.26
Comorbidity	0.36	[0.05-2.76]	0.33	**3.86**	[1.61-9.25]	**0.002**
Cardiac history[2]	**0.28**	[0.09-0.83]	**0.02**	**2.49**	[1.19-5.21]	**0.02**
Multi-vessel disease	**3.55**	[1.33-9.48]	**0.01**	1.27	[0.53-3.03]	0.60
Smoking	0.87	[0.25-3.04]	0.83	1.87	[0.88-3.97]	0.10
Anti-depressants	0.00	[0.00-0.00]	0.98	1.47	[0.44-4.93]	0.53

[1] Enter procedure

[2] MI, PCI or CABG prior to the index PCI

Discussion

To our knowledge, this is the first study to examine the impact of poor HRQL on early versus late cardiac events in a pure sample of post PCI patients. Patients with poor HRQL at the time of the index PCI were at a 2-fold increased risk of early MACE, adjusting for demographic and clinical risk factors. However, poor HRQL did not predict events occurring beyond 6 months following revascularization. Since it is widely recognized that the decision to perform a re-intervention is to a large part influenced by symptom reporting, we conducted secondary analyses using 'hard' events, i.e. a composite of death and non-fatal MI, as an endpoint. A similar pattern was found, with poor HRQL predicting early but not late deaths/non-fatal MIs. This suggests that the impact of poor HRQL on MACE was not purely driven by revascularization procedures.

The results of the current study showed that poor HRQL, as assessed by the disease-specific MacNew Heart Disease Health-Related Quality of Life questionnaire, was a short- but not long-term predictor of adverse clinical outcome in PCI patients. This is in contrast to several other studies of patients with acute coronary syndrome or heart failure that found poor HRQL to be a predictor of poor prognosis and hospitalization[3-8]; although it should be noted that Rumsfeld and colleagues found that the Physical Component Summary but not the Mental Component Summary of the Short-Form Health Survey 36 was associated with increased risk of mortality[4]. The follow-up in these studies ranged from 6[4,8] to 36 months[7], but all studies evaluated the respective endpoints at one time point and not at two time points as in the current study. However, in PCI patients it may be important to separate events into early versus late events, given that PCI patients often experience new cardiac events within the first 6 months that are usually related to the procedure itself.[10,11] Hence, given the current findings, assessment of HRQL at the time of PCI may not be a good predictor of later clinical outcome, as it may comprise a proxy for disease severity and impending complications.

An alternative explanation for the different results in the current study compared with previous studies may be attributed to PCI patients generally being more healthy than MI, CABG and heart failure patients. In addition, the patients in the current study were relatively younger, in particular compared to studies focusing on heart failure that included patients up to 80 years of age.[5-7] In the studies by Soto and colleagues[6] and Heidenreich and colleagues[5], age was related to mortality and rehospitalization, although in the latter study age was not associated with impaired HRQL[5]. It should also be noted that the PCI patients included in the current study were all exhausted. Given that there is a conceptual overlap between exhaustion and HRQL, it may be that there is little additional room for HRQL to predict poor clinical outcome; exhaustion has been shown to predict morbidity and mortality post PCI.[13]

The results of the current study have some bearing on research and clinical practice. HRQL is an important patient-centered outcome, with heart failure patients emphasizing HRQL over prolonged survival.[27] In addition, the study of HRQL and its determinants have been advocated as a means by which to close the gap between research and clinical practice.[1] Nevertheless, we still know little about the mechanisms responsible for the relationship between impaired HRQL and prognosis. For poor HRQL to be conceptualized as a risk factor on par with established, traditional, biomedical risk factors, there must be one or more plausible mechanisms (e.g. physiological or behavioral) that may be responsible for the link between poor HRQL and adverse prognosis. In addition, studies need to demonstrate that HRQL is modifiable and that its modification will lead to improved clinical outcome. Although a sub study of the Sertraline Antidepressant Heart Attack Randomized Trial (SADHART) clinical trial showed that treatment with sertraline had a beneficial effect on HRQL scores both in the total group and in patients with recurrent depression[28], to our knowledge no studies have investigated whether improvement in HRQL leads to a concomitant increase in survival. Research is also warranted to investigate the short- and long-term prognostic value of the multitude of HRQL measures available, with a focus on both disease-specific and generic instruments. These measures need not only be valid and reliable, but also brief and the results directly applicable to clinical practice.[9] Finally, results on HRQL and prognosis should be replicable in multiple settings and across cardiovascular disease patient groups.[29]

The current study has several limitations. First, the results may not be generalizable to the total sample, given that responders and non-responders on the HRQL measure differed on some baseline characteristics. Second, given the relatively few number of 'hard' events, we had to adopt MACE as a primary endpoint. However, MACE is a relevant outcome measure to both patients and clinicians, and the same results were found for early MACE and early death/non-fatal MI versus late MACE and late death/non-fatal MI. Third, there may also be a potential selection bias both in relation to the patient selection for the original EXIT trial and for the current study since 43 patients (6%) had to be excluded due to lack of a HRQL score. The latter patients may have had a poorer HRQL than responders, although this would lead to an underestimation of the impact of HRQL on clinical events rather than an overestimation. In addition, in multivariable analyses we did not adjust for measures of distress, such as anxiety and depression. It is possible that poor HRQL may be confounded by emotional distress. Finally, the results may not be applicable to all post PCI patients, as the current study only focused on those who were exhausted.

The current study also has several strengths. HRQL was assessed with a disease-specific instrument, which may be more sensitive to capture the symptoms of cardiac patients compared with a generic measure. In addition, the response rate on the HRQL questionnaire at baseline was high with 94%.

In conclusion, this study demonstrated that poor HRQL was an independent predictor of cardiac events occurring 0-6 months post PCI but not events occurring beyond 6 months. These findings support the use of the MacNew questionnaire to identify patients at risk of early events post PCI in research and clinical practice in order to optimize risk stratification in this subgroup of patients. However, prior to a sound recommendation for the use of HRQL measures as screening tools in clinical practice, further research across cardiovascular disease patient groups is warranted to identify mechanisms responsible for the relationship between poor HRQL and prognosis, whether improvement in HRQL leads to increased survival, to compare the short- and long-term prognostic value of the multitude of HRQL measures available, and to adopt multiple assessments of HRQL in order to be able to evaluate the impact of changes in HRQL on prognosis. Multiple assessments of HRQL may also be a better risk indicator for adverse clinical outcome than a single 'snapshot' assessment.[9]

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Part C: Medical outcomes

Chapter Eight

Anxiety, depression and post-MI prognosis

VIII

Anxiety and depression predict adverse clinical events after myocardial infarction

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Submitted

Abstract

Background: Although the impact of post-myocardial infarction (MI) depression on prognosis has been studied extensively, the role that comorbid anxiety plays in this relationship has been less well studied. The aim of the present study was to examine the differential impact of 1) a clinical depressive and/or anxiety disorder; 2) depressive and/or anxiety symptoms on adverse clinical events in post-MI patients.

Methods: Two months post-MI, patients (n=434) completed the CIDI, BDI and STAI, in order to determine the presence or absence of an anxiety or depressive disorder, and the level of depressive and anxiety symptoms. Patients were followed-up for clinical adverse events at 1.8 years.

Results: There were 26 cardiac deaths and non-fatal MIs at follow-up. Symptoms of depression (HR:2.48; 95%CI:1.10-5.59) and anxiety (HR:2.32; 95%CI:1.03-5.22), but not clinical diagnosis, significantly increased the incidence of cardiac events, independent of biomedical and demographic risk factors. A multivariate analysis including both depressive and anxiety symptoms indicated that only patients with co-occurring symptoms (HR:2.82; 95%CI:1.12-7.09) had a substantially increased risk of adverse clinical events. Cardiac history and use of statins were also independent predictors of death/MI, with statin use showing a considerable protective effect.

Conclusions: Symptoms of depression and anxiety, and in particular co-occurring symptoms were independent predictors of cardiac death and non-fatal MI. In addition to depressive and anxiety symptoms alone, the co-occurrence needs to be considered to optimize risk stratification and treatment in post-MI patients.

Introduction

Self-reported symptoms of depression and anxiety in patients following myocardial infarction (MI) are highly prevalent, with prevalence rates for depression ranging from 17-37% and for anxiety from 24-31%.[1-6] Depression is considered the most pathogenic factor, and there has been a call for the recognition of depression as an established risk factor.[7] In many well-designed studies, depression has been associated with a two- to four-fold increased risk of adverse clinical outcomes, including mortality, in post-MI patients.[8-12] Yet, some fundamental questions about depression as a cardiac risk factor remain unanswered, including the issue whether this risk is restricted to individuals with depressive disorder or extends to patients with less severe depression, including depressive symptoms.[13] A recent meta-analysis found no clear prognostic difference between self-reported depression and clinical diagnosis of depression, as assessed by a diagnostic interview.[14] Other studies show that the diagnosis of clinical depression does not add to the predictive power of relatively mild levels of depressive symptoms in cardiac patients.[3,15]

In addition, the increased risk of cardiac events may extend to patients with symptoms of negative affect other than depression, such as anxiety.[13,16] However, compared with the extensive literature on depression post-MI, there is a paucity of studies that has investigated the effect of anxiety. Given the fact that depression and anxiety are highly comorbid disorders[17] and that symptoms of depression and anxiety frequently co-occur in post-MI patients[18], this is somewhat surprising. Some studies have reported symptoms of anxiety to be predictive of subsequent cardiac events and mortality post-MI, independent of established biomedical risk factors[4,19], while others found no association[5]. Furthermore, the impact of co-occurring symptoms of anxiety and depression has received far less attention in cardiac patients, with previous studies usually examining their separate impact on prognosis. Interestingly, one study reported that symptoms of anxiety independently predicted cardiac events, with anxiety accounting for the relationship between depressive symptoms and prognosis.[20] However, it is still unknown whether co-occurring anxiety and depression, or anxiety and depression alone, increase the risk for adverse clinical events post-MI, and whether the risk is restricted to individuals with anxiety or depressive disorder or also extends to patients with increased symptom levels.

Therefore, the aim of the present study was to examine the differential impact of 1) a clinical depressive and/or anxiety disorder; 2) depressive and/or anxiety symptoms on cardiac death and non-fatal MI 1.8 years after MI.

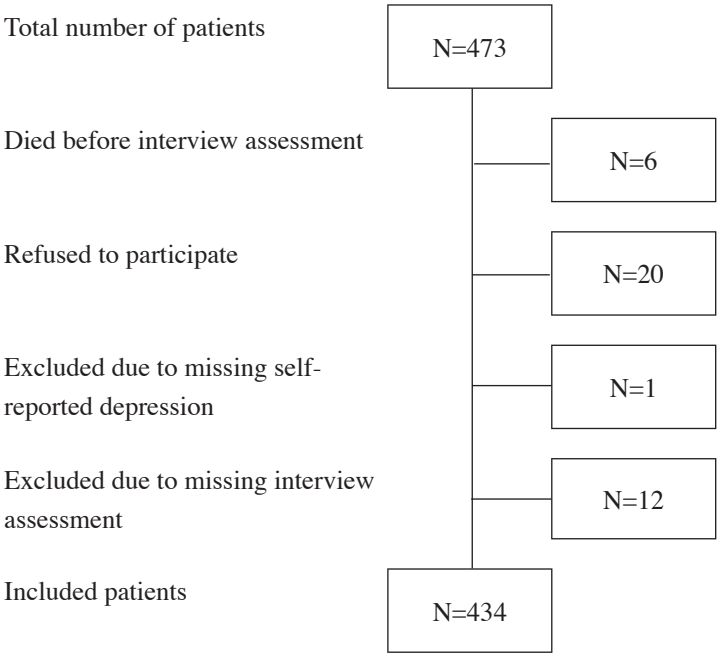
Methods

Study design and patient population

Patients hospitalized for acute MI (n=473) were recruited between May 2003 and May 2006 from four teaching hospitals (Catharina Hospital, Eindhoven; St. Elisabeth Hospital, Tilburg; TweeSteden Hospital, Tilburg; and St. Anna Hospital, Geldrop) in The Netherlands. Inclusion criteria were age >30 and hospitalization due to acute MI. Exclusion criteria were significant cognitive impairments (e.g. dementia) and severe comorbidities (e.g. cancer) in addition to their cardiac condition. 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 10 minutes or ECG evidence of ST segment elevation or new pathological Q-waves.

Patients were assessed during the initial hospitalization for MI, and 2- and 18 months post-MI in the cardiology department of the participating hospitals. Of the original 473 patients, 434 patients were included in the final analyses (Figure 1).

Figure 1. *Flowchart of patient selection*



The research protocol was approved by the medical ethics committees of the participating hospitals, and the study was conducted in accordance with the Helsinki Declaration. Written informed consent was obtained from every patient.

Assessment

Demographic and clinical characteristics

Demographic variables included age, sex, marital status, and educational level. Clinical variables were obtained from the patients' medical records and included cardiac history (defined as MI, percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) surgery prior to the MI), left ventricular ejection fraction (LVEF), multi-vessel disease, anterior MI location, diabetes mellitus, renal insufficiency, chronic obstructive pulmonary disease, arthritis, invasive versus conservative treatment, cardiac rehabilitation, medication use (beta-blockers, ACE-inhibitors, anti-coagulants, statins, aspirin, and selective serotonin reuptake inhibitors (SSRIs)), smoking status (self-report), body mass index (BMI), hypertension (SB>140, DB>90), hypercholesterolemia (total cholesterol >6.50 mmol/l), systolic and diastolic blood pressure.

Clinical diagnoses of depression and anxiety disorder

The WHO Composite International Diagnostic Interview (CIDI)[21] was used to assess lifetime diagnoses of (major) depressive disorder and anxiety disorder (consisting of panic disorder, social phobia, and/or generalized anxiety disorder), based on the diagnostic criteria listed in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)[22]. All patients were assessed by the first author (EJM), trained in the administering of the CIDI by the official World Health Organization CIDI Training Center.

Depression and anxiety symptoms

Self-reported symptoms of anxiety and depression were assessed using two standard questionnaires: The State Trait Anxiety Inventory (STAI) and the Beck Depression Inventory (BDI). The Beck Depression Inventory (BDI) is a 21-item self-report measure developed to assess the presence and severity of depressive symptoms.[23] The BDI is a widely used, valid and reliable measure of depressive symptomatology, with a Cronbach's α of 0.81 in non-psychiatric samples.[24-26] We used the standardized cut-off score $\geq$10, indicative of at least mild to moderate symptoms of depression.[3,27] The STAI is a self-report measure consisting of two 20-item scales developed to measure the level of general state and trait anxiety.[28] In the current study, we used the state scale of the STAI only. A cut-off $\geq$ 44 was used to indicate clinical levels of anxiety.[29] The STAI has been demonstrated to have adequate validity and reliability, with a Cronbach's α of 0.92.[30] Elevated scores on both the BDI and STAI have been associated with poor prognosis in MI patients.[4,27,31]

All psychological assessments, both self-report and interviews, were performed 2 months post-MI. All 434 patients included in final analyses completed both the clinical interview and the self-report questionnaires.

Clinical Endpoint

The endpoint was a composite of cardiac death and non-fatal MI. The median follow-up period was 1.8 years (SD = 0.7 years), and follow-up data was complete for all patients (100%). Given that all psychological factors were assessed two months post-MI, non-fatal MIs (n=12) occurring between hospitalization and 2 months follow-up were excluded from analyses.

Statistical Analysis

Discrete variables were compared with the Chi-square test and are presented as numbers and percentages. Continuous variables were compared with the Student's t-test and are presented as means ± standard deviations. Univariate and multivariate Cox proportional hazard regression analyses (enter procedure) were performed to investigate the impact of depression and anxiety on the occurrence of cardiac death and non-fatal MI at follow-up. Univariate analyses were used to test for the potentially confounding effect of biomedical and demographic factors on outcome. If significant at $p < 0.05$, the variables were included into a regression model to remove redundant covariates (if any). Subsequently, the significant confounders were added as covariates to the multivariate analyses for death/MI. Furthermore, multivariate stepwise (entry criteria= 0.05, removal criteria= 0.10) Cox proportional hazard regression analyses were used to test the effect of symptoms of depression and anxiety and their interaction effect on outcome. Patients were divided into 3 groups: no depression and anxiety, depression or anxiety, and co-occurring symptoms of depression and anxiety. The cumulative incidence of death/MI in these 3 patient groups was estimated according to the Kaplan-Meier method, comparing differences between groups with the log-rank test. The zero time point indicates the time of hospitalization. Multivariate Cox proportional hazard regression analysis was used to test the differential effect of the 3 patient groups on outcome. A p-value < 0.05 was used for all tests to indicate statistical significance. Hazard ratios (HR) with 95% confidence intervals (CI) are reported. All statistical analyses were performed using SPPS version 14.0.

Results

There were 26 events attributable to cardiac death (n=14) or non-fatal MI (n=15), with 3 patients experiencing both.

Patient characteristics

Patient baseline characteristics stratified by death/MI are presented in Table 1 (colums 1-3). Patients experiencing a clinical event were older (65 versus 59; $p = 0.022$), more likely to have a previous cardiac history (44% versus 14%; $p < 0.0001$), and to be treated with SSRIs (26% versus 11%; $p = 0.030$), but less likely to have had invasive treatment during hospitalization for the index MI (48% versus 67%; $p = 0.028$), to be treated with statins (74% versus 93%; $p = 0.002$) and aspirin (67% versus 84%; $p = 0.011$) than event-free patients. There were no other statistically significant differences between groups on baseline characteristics.

Table 1. *Demographic and clinical baseline predictors of death/MI (univariate analyses)*[1]

	All patients (n=434)	Death/MI (n=26)	Event-free (n=408)	Death/MI		
				HR	95% C.I.	p
Demographic characteristics						
Age, mean (SD)	**59.4 (11)**	**64.6 (14)**	**59.0 (11)**	**1.04**	**1.00-1.08**	**0.022**
Female sex	86 (20)	4 (15)	82 (20)	0.68	0.24-1.97	NS
Partner	357 (82)	19 (73)	338 (83)	0.50	0.23-1.31	NS
Educational level: high	240 (55)	12 (46)	228 (56)	0.73	0.34-1.58	NS
Clinical characteristics						
Disease severity						
Cardiac history[2]	**67 (15)**	**12 (44)**	**55 (14)**	**4.72**	**2.21-10.08**	**<.0001**
LVEF ≤40%[3]	74 (21)	7 (32)	67 (20)	1.86	0.76-4.56	NS
Multi-vessel disease	143 (39)	9 (45)	134 (38)	1.38	0.57-3.32	NS
Anterior MI location	161 (41)	10 (44)	151 (41)	0.79	0.49-2.56	NS
Comorbidity						
Diabetes mellitus	61 (14)	6 (22)	55 (14)	1.73	0.70-4.30	NS
Renal insufficiency	19 (4)	2 (7)	17 (4)	2.00	0.47-8.46	NS
COPD	43 (10)	4 (15)	39 (10)	1.58	0.55-4.58	NS
Arthritis	34 (8)	3 (11)	31 (8)	1.68	0.51-5.61	NS
Invasive treatment[4]	**293 (67)**	**13 (48)**	**280 (67)**	**0.43**	**0.20-0.91**	**0.028**
Cardiac rehabilitation	272 (68)	14 (52)	258 (69)	0.62	0.29-1.33	NS
Medication use						
Beta-blockers	373 (86)	23 (85)	350 (86)	0.95	0.33-2.76	NS
ACE-inhibitors	159 (37)	7 (26)	152 (38)	0.56	0.24-1.32	NS
Anti-coagulants	363 (84)	26 (96)	337 (83)	5.52	0.75-40.69	NS
Statins	**397 (92)**	**20 (74)**	**377 (93)**	**0.25**	**0.11-0.60**	**0.002**
Aspirin	**358 (83)**	**18 (67)**	**340 (84)**	**0.35**	**0.16-0.79**	**0.011**
SSRIs	**50 (12)**	**7 (26)**	**43 (11)**	**2.59**	**1.09-6.13**	**0.030**
Smoking	169 (39)	13 (48)	156 (38)	1.43	0.67-3.05	NS
BMI, kg/m^2, mean (SD)	26.9 (4)	26.1 (5)	26.9 (4)	0.94	0.84-1.04	NS
Hypertension	128 (31)	7 (26)	121 (31)	0.75	0.32-1.77	NS
Hypercholesterolemia	50 (12)	0 (0)	50 (13)	0.04	0.00-8.51	NS
Cardiac function						
Systolic BP, mean (SD)	141 (28)	133 (24)	142 (29)	0.99	0.97-1.00	NS
Diastolic BP, mean (SD)	83 (17)	78 (16)	83 (17)	0.98	0.95-1.00	NS

ACE= angiotensin-converting enzyme; BMI= Body mass Index; BP= blood pressure; CABG= coronary artery bypass graft surgery; COPD= Chronic obstructive pulmonary disease; LVEF= left ventricular ejection fraction; MI= myocardial infarction; SSRI= selective serotonin reuptake inhibitor

[1] Values are expressed as number (percentage) of patients unless otherwise indicated. NS= non significant (p-value >0.10)

[2] Myocardial infarction, percutaneous coronary intervention, or coronary artery bypass graft surgery prior to the index myocardial infarction

[3] Information on LVEF was only available for 350 patients (80.5%), in whom an echocardiography was performed

[4] Invasive treatment: percutaneous coronary intervention or coronary artery bypass graft surgery

Seventy patients (16%) had a diagnosis of lifetime depressive disorder and 29 patients (7%) lifetime anxiety disorder. Depressive symptoms were present in 107 patients (25%) and anxiety symptoms in 113 patients (26%) (Table 2).

Table 2. *Clinical diagnosis versus self-reported symptoms of anxiety and depression as predictors of death/MI (multivariate analyses)*[1]

	All patients (n=434)	**Death/MI (n=26)**	**Event-free (n=408)**	**Death/MI**		
				HR	**95% C.I.**	**p**
Clinical diagnosis[2]						
Anxiety disorder	29 (6.7)	4 (15)	25 (6)	1.42	0.47-4.28	0.073
Cardiac history				4.47	2.08-9.62	<.0001
SSRIs				2.41	1.00-5.83	0.051
Statins				0.29	0.12-0.71	0.006
Depressive disorder	70 (16.1)	7 (26)	63 (15)	1.11	0.44-2.76	NS
Cardiac history				**4.55**	**2.12-9.87**	**<.0001**
SSRIs				2.46	0.99-6.12	0.052
Statins				**0.29**	**0.12-0.70**	**0.006**
Self-reported symptoms[3]						
Self-reported anxiety	**113 (26)**	**13 (50)**	**100 (25)**	**2.32**	**1.03-5.22**	**0.041**
Cardiac history				**4.39**	**2.05-9.43**	**<.0001**
SSRIs				1.84	0.74-4.61	NS
Statins				**0.25**	**0.11-0.61**	**0.002**
Self-reported depression	**107 (25)**	**13 (50)**	**94 (23)**	**2.48**	**1.10-5.59**	**0.029**
Cardiac history				**4.68**	**2.15-10.18**	**<.0001**
SSRIs				1.94	0.78-4.84	NS
Statins				**0.25**	**0.11-0.60**	**0.002**

[1]Values are expressed as number (percentage) of patients unless otherwise indicated. NS= non significant (p-value >0.10)

[2]Per the WHO Composite International Diagnostic Interview (CIDI)

[3]Per the Beck Depression Inventory ≥10, and the State Trait Anxiety Inventory ≥44

Confounders

Age, cardiac history, invasive treatment, statins, aspirin, and SSRIs were significant confounders for death/MI in univariate analyses (Table 1, colums 4-6). When entering all significant confounders in a multivariate analysis, only cardiac history, statins, and SSRIs remained significant. Hence, we adjusted for these covariates in all subsequent multivariate analyses.

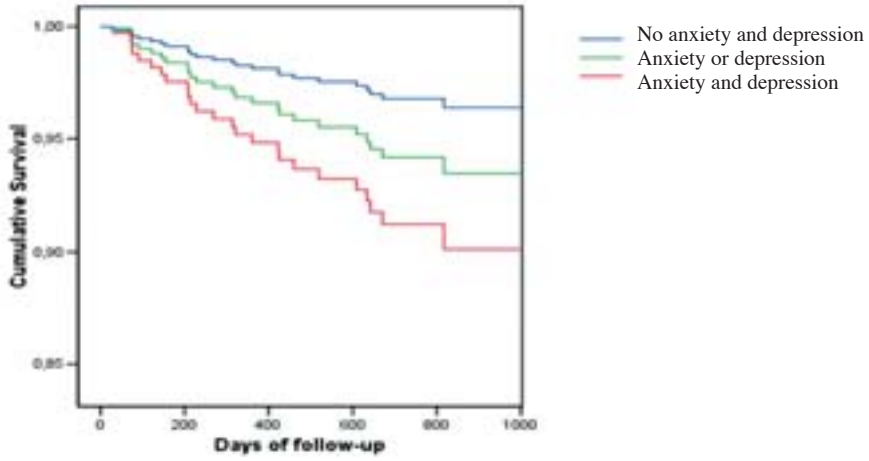
Clinical diagnosis and symptoms of depression and anxiety as predictors of death/MI

No difference was found in the incidence of death/MI for patients with versus without depressive disorder and anxiety disorder ($p = 0.073$). By contrast, the incidence of death/MI was higher in patients with depressive symptoms (50% versus 23%) and anxiety symptoms (50% versus 25%) compared with patients with no symptomatology (Table 2). Furthermore, the mean level of symptoms of depression (11.4 ±10.6 versus 6.1 ±5.8; $p < 0.0001$) and anxiety (44.9 ±17.1 versus 36.0 ±11.7; $p < 0.001$) was higher in patients with an event versus event-free patients. In multivariate analyses, neither depressive disorder nor anxiety disorder were predictive of death/MI (Table 2). However, self-reported symptoms of depression (HR: 2.48) and anxiety (HR: 2.32) remained independent predictors of death/MI and were associated with a 2-fold increased risk, adjusting for cardiac history, SSRIs, and statins (Table 2). In addition, mean levels of depressive (HR: 1.06; 95% CI: 1.02-1.11) and anxiety symptoms (HR: 1.05; 95% CI: 1.02-1.08) independently predicted adverse outcome.

Co-occurring symptoms of depression and anxiety as predictors of death/MI

In a model containing depressive symptoms, anxiety symptoms and their interaction effect, only the interaction effect (HR: 3.29; 95% CI: 1.50-7.26) was significantly related to death/MI. Therefore, patients were divided into 3 groups stratified by depressive and anxiety symptoms (no depression and anxiety, depression or anxiety, and co-occurring depression and anxiety). Patients with co-occurring symptoms were at cumulative increased risk of death/MI at 1.8 years compared with patients without symptoms of depression and anxiety, or depressive symptoms or anxiety symptoms alone (Figure 2). In multivariate analysis, only patients with co-occurring depressive and anxiety symptoms were at increased risk for death/MI (HR: 2.82) (Table 3). Cardiac history and use of statins were also independent predictors of death/MI (Table 3), with statins showing a substantial protective effect in the order of 70-75%.

Figure 2. *Cumulative survival stratified by depressive and anxiety symptoms (n=434)*



Numbers at risk						
No anxiety *and* depression	287	284	281	279	277	276
Anxiety *or* depression	75	73	71	71	70	70
Anxiety *and* depression	72	69	66	64	63	62

Table 3. *Symptoms of anxiety and depression versus co-occurring symptoms as predictors of death/MI (multivariate analysis)*[1]

	Death/MI (n=26)		
Variable	**HR**	**95% C.I.**	**p**
Cardiac history	**4.66**	**2.14-10.13**	**<.0001**
Statins	**0.24**	**0.10-0.59**	**0.002**
SSRIs	1.83	0.72-4.65	0.203
Anxiety *or* depression[2]	1.84	0.62-5.48	0.274
Anxiety *and* depression[3]	**2.82**	**1.12-7.10**	**0.027**

[1] Per the State Trait Anxiety Inventory ≥44, and the Beck Depression Inventory ≥10

[2] Anxiety but no depressive symptoms, or no anxiety but depressive symptoms (n=75)

[3] Comorbid anxiety and depressive symptoms (n=72)

Discussion

In the current study, self-reported symptoms of both anxiety and depression, but not a clinical diagnosis, significantly increased the incidence of cardiac death and non-fatal MI in post-MI patients at 1.8 years follow-up, independent of established biomedical and demographic risk factors. A multivariate analysis including both anxiety and depressive symptoms indicated that only patients with co-occurring anxiety and depressive symptoms had a substantially increased risk of adverse clinical events at follow-up. Anxiety or depressive symptoms alone did not influence outcome. Cardiac history and use of statins were also independent predictors of death/MI, with statin use showing a considerable protective effect.

Given the success of state of the art interventional cardiology in reducing mortality in acute coronary syndromes, it seems timely to shift focus towards the identification of subgroups of patients at increased risk of mortality. This may warrant expanding our focus to include more non-conventional risk factors, such as psychological factors.[32] The findings of the current study support the notion that psychological factors are related to poor prognosis after MI[20,33,34], and that symptoms of anxiety and depression need to be considered in the risk stratification and treatment of post-MI patients. Although most previous studies focused on either depression[8-11] or anxiety[19,35] as a single risk indicator, we examined the influence of these negative emotions simultaneously. We found that only co-occurring symptoms of anxiety and depression were associated with an increased risk of death/MI, with the risk being two-fold. The few studies in post-MI patients that have investigated the effect of both anxiety and depressive symptoms usually examined their separate impact on prognosis and have yielded inconsistent results.[4,5,6,20,36,37] Strik et al.[20] found that anxiety was a predictor of cardiac events and accounted for the relationship between depressive symptoms and prognosis, whereas Frasure-Smith et al.[4] showed that both depression and anxiety independently predicted cardiac events post-MI. Several other studies examining the impact of depression and anxiety symptoms on post-MI prognosis did not find an association.[5,6,36,37] Given that these studies have varied in location, patient population, sample size, follow-up period, and the manner in which they assessed depression and anxiety, some variation in results is perhaps hardly surprising.

However, it is still unclear whether the risk for adverse cardiac events is restricted to individuals with anxiety or depressive disorder or also extends to patients with relatively mild levels of anxiety and depressive symptoms. Some studies have shown that the diagnosis of clinical depression does not add to the predictive power of relatively mild levels of depressive symptoms in cardiac patients.[3,15] In the latter study, there was a tendency towards higher

cardiac event rates among patients with mild to moderate levels of depressive symptoms and no clinical diagnosis of depressive disorder compared to those with a diagnosis.[15] However, Frasure-Smith et al.[4] found that both depressive disorder and symptoms of depression and anxiety predicted cardiac events 12 months post-MI. The results of the current study are consistent with these studies but also extend previous findings, since both anxiety and depressive disorder and symptomatology were assessed. The risk for adverse cardiac events was not restricted to individuals with anxiety or depressive disorder; in fact, only patients with increased symptoms of anxiety and depression were at increased risk. Since anxiety frequently co-exists with depression, some have argued that the higher mortality rate in anxious patients may be due to the presence of depression rather than anxiety per se.[38] Furthermore, at the present time, we do not know which elements of depression incur the most cardio-toxic effects.[39] However, our study suggests that in addition to assessing depressive symptoms it may be equally important to assess anxiety in post-MI patients. According to Suls and Bunde[40], there needs to be more appreciation for the notion that clustering and overlap between negative affective dispositions may make specificity of emotion less critical for coronary artery disease (CAD) risk. That is, anxiety and depression may not exert distinctive, independent effects on prognosis, but may increase risk because they share a general disposition to experience chronic and intense negative emotions. Kubzansky and colleagues[41] have also argued for the need to study various potential psychosocial risk factors and their relationship with CAD and CAD recurrence.

In the current study, we also found that statins had a protective effect for adverse clinical events in the order of 70-75%. Statins have been described as the principal and most effective agents for reducing serum cholesterol levels.[42] In addition, clinical evidence has demonstrated that statin therapy markedly reduces the risk of new or recurrent cardiovascular events and improves survival of patients with a history of CAD.[43-45] Emerging evidence supports the existence of other mechanisms than lipid modulation concerning the clinical benefits of statins, including modification of endothelial function, thrombus formation, plaque stability and inflammatory pathways.[46] Our results give support to statin use as an effective therapy for improving cardiac prognosis in post-MI patients.

Our results have some implications for research and clinical practice. Identifying various forms of distress, even in their less severe forms, may provide an important avenue for early intervention. Effective treatment targeting psychosocial risk factors in CAD patients requires an accurate characterization of who is at risk for adverse outcomes, with a more detailed examination of CAD distress profiles likely enhancing the development of more effectively timed and more specifically tailored behavioral interventions. In addition, anxiety and depression should be studied in concert, as we found that patients with co-occurring symptoms

were at increased risk of cardiac death and non-fatal MI as compared to patients with anxiety or depressive symptoms alone. A recent study of PCI patients using health-related quality of life as outcome measure similarly found that anxiety enhanced the detrimental effect of depressive symptoms on health-related quality of life.[47] Taken together, these findings may help explain why interventions specifically designed to treat depression yielded mixed results concerning the improvement of prognosis in post-MI patients.[48,49] A more comprehensive approach to treatment, including individualized treatment of a wide variety of psychological factors may be more successful in terms of improving prognosis.[50]

This study had some limitations, including the relatively small number of cardiac events. Second, patients who died between hospitalization and 2 months post-MI did not have the opportunity to complete the psychological assessments, which may have biased our results as the sickest patients were excluded. However, several have advocated that hospitalization is not an optimal time point to assess psychological distress and its potential influence on post-MI prognosis, as patients are not medically stable at that time.[51,52] Nevertheless, a strength of the study is that anxiety and depression were studied in concert, using both self-reported symptomatology and standardized clinical diagnoses. Second, we evaluated a broad spectrum of variables as possible predictors of adverse prognosis, including demographic, clinical, and psychological.

In the current study, we could not confirm that a clinical diagnosis of anxiety and depressive disorder was associated with prognosis. However, self-reported symptoms of anxiety and depression, and in particular co-occurring symptoms, were independent predictors of cardiac death and non-fatal MI during a period of 1.8 years post-MI. These findings support the notion that symptoms of emotional distress are related to cardiac prognosis after MI. Apart from anxiety and depressive symptoms alone, the co-occurrence must be considered to optimize risk stratification and treatment of post-MI patients. Future studies are warranted that replicate our findings on the impact of co-occurring symptoms on prognosis.

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Part C: Medical outcomes

Chapter Nine

Depression, anxiety and HRV

IX

Depression and anxiety as predictors of heart rate variability four months after myocardial infarction

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Submitted

Abstract

Background: Reduced heart rate variability is a prognostic factor for cardiac mortality. Both depression and anxiety have been associated with increased risk for mortality in patients with coronary artery disease. Low heart rate variability may act as an intermediary in this association. The present study aims to examine to what extent depression and anxiety differently predict 24-hour heart rate variability indices recorded four months post-myocardial infarction (MI).

Methods: Ninety-three patients were recruited during hospitalization for MI and assessed on self-reported symptoms of depression and anxiety. In addition, they were assessed on clinical diagnoses of lifetime depressive and anxiety disorder 2 months post-MI. Adequate 24-hour ambulatory electrocardiography data were obtained from 82 patients four months post-MI.

Results: In unadjusted analyses, depressive disorder was a significant predictor of both lower SDANN (ß=-.25,P=.023) and SDNN (ß=-.26,P=.022), and anxiety disorder of lower RMSSD (ß=-.23,P=.039). Self reported symptoms of depression and anxiety did not significantly predict heart rate variability indices. After adjustment for age, sex, cardiac history, and multi-vessel disease, depressive disorder was no longer significantly predictive of heart rate variability indices. Anxiety disorder significantly predicted reduced HF power (ß=-.22,P=.039) and RMSSD (ß=-.25,P=.019), even after additional adjustment of anxiety symptoms.

Conclusions: Clinical anxiety but not depression negatively influenced parasympathetic modulation of heart rate in post-MI patients. These findings elucidate the physiologic mechanisms underlying anxiety as a risk factor for adverse outcomes, but also raise questions about the potential role of heart rate variability as an intermediary between depression and post-MI prognosis.

Introduction

Heart rate variability (HRV) analysis is a widely used method for studying cardiac autonomic modulation.[1] Impaired autonomic nervous system control of heart rate is a strong independent predictor of long-term mortality in post-myocardial infarction (MI) patients.[2-6] In turn, depression has been associated with a two-fold increased risk of mortality, and increased morbidity and re-hospitalisation post-MI.[7-10] Some studies have also reported symptoms of anxiety to be predictive of subsequent cardiac events and mortality post-MI, independent of established biomedical risk factors.[11-13]

Alterations in cardiac autonomic tone, reflected by increased sympathetic or decreased parasympathetic nervous system activity, predisposes cardiac patients to ventricular fibrillation and tachycardia, and sudden cardiac death[14,15], and can be a mechanism linking depression and anxiety to increased mortality in cardiac patients[16,17]. Several studies have demonstrated an association between depression and low 24-hour HRV in post-MI patients.[18-20] A review on HRV in depressive and anxiety disorders indicated that patients with anxiety disorders exhibit chronically reduced HRV[21], with panic disorder patients having reduced parasympathetic innervation to the heart compared with normal adults[22,23]. Consequently, low HRV may act as an intermediary between depression and anxiety and adverse outcomes in cardiac patients. However, negative findings have also been reported. In one study, depression but not anxiety was found to negatively influence autonomic control of heart rate in post-MI patients[20], whereas another study found that anxiety but not depression was independently associated with reduced HRV post-MI[24]. A recent cross-sectional study on 873 outpatients with stable coronary artery disease (CAD) found no association between depression and HRV raising questions about the potential intermediate role of HRV.[25]

Given the relative paucity in knowledge about the potentially deleterious effects on HRV of depression and in particular anxiety, the present study aims to examine to what extent depression and anxiety differently predict 24-hour time and frequency domain HRV indexes four months post-MI.

Methods

Study design and patient population

Ninety-three patients hospitalized for acute MI were recruted from the St. Elisabeth Hospital, Tilburg, in the Netherlands between September 2003 and November 2005. MI was defined according to the following criteria: Troponin I levels >1.0, with typical ischemic symptoms

(e.g. chest pain) lasting for more than 10 minutes or ECG evidence of ST segment elevation or new pathological Q-waves. Inclusion criteria were age > 30 and hospitalization due to acute MI. Exclusion criteria were significant cognitive impairments (e.g. dementia), severe comorbidities (e.g. cancer), and insufficient command of the Dutch language.

Symptoms of depression and anxiety were assessed at the time of MI, using two self-report measures, and demographic and medical characteristics were obtained. Two months post-MI, patients were evaluated carefully in the cardiology department by a trained psychologist using the Composite International Diagnostic Interview (CIDI)[26] for diagnoses of depression and anxiety. At this visit, patients were asked to participate in an additional study, concerning digital 24-hour electrocardiogram (ECG) recordings (Holter). This Holter recording took place four months post-MI due to logistic reasons. The research protocol was approved by the medical ethics committee of the participating hospital, and the study was conducted in accordance with the Helsinki Declaration. Written informed consent was obtained from every patient before entering the study.

Assessment

Demographic and clinical characteristics

Age, sex, and smoking status were determined by questionnaire. Medical variables obtained from the medical records included comorbidity (defined as arthritis, renal insufficiency or chronic obstructive pulmonary disease), cardiac history (defined as MI, angina, percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) surgery prior to the MI), multi-vessel disease, anterior MI location, blood pressure, HDL and LDL cholesterol levels, LDL/HDL ratio, cardiac rehabilitation, medications (beta-blockers, ACE-inhibitors, statins, vasodilators, aspirin, and psychotropics), diabetes mellitus, and obesity (BMI ≥ 30).

Clinical diagnoses of depression and anxiety disorder

The World Health Organization-authorized Dutch version of the CIDI[26,27] was used to assess lifetime diagnoses of major depressive disorder and anxiety disorder (consisting of panic disorder, social phobia, and/or generalized anxiety disorder) based on the diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)[28]. The CIDI has acceptable interrater and test-retest reliability for most nonpsychotic diagnosis, including major depressive disorder.[29,30]

Self reported symptoms of depression and anxiety

Symptoms of depression and anxiety were assessed using two self-report questionnaires: The Beck Depression Inventory (BDI) and the State Trait Anxiety Inventory (STAI). The BDI is a 21-item self-report measure developed to assess the presence and severity of depressive

symptoms[31] The BDI is a reliable and well-validated measure of depressive symptomatology[32], and a widely used self-report measure of depression. BDI scores ≥ 10 are indicative of at least mild to moderate symptoms of depression and have been associated with poor prognosis in MI patients.[8,9,33]

The STAI is a self-report measure consisting of two 20-item scales developed to measure the level of general state and trait anxiety.[34] In the current study, we included the state scale of the STAI. Elevated scores on the STAI have been associated with poor prognosis in MI patients.[35] The STAI has been demonstrated to have adequate validity and reliability.[36] Both the BDI and STAI have been used in previous studies regarding HRV in post-MI patients.[18,24]

Heart rate variability

All patients received a digital, 24-hour electrocardiogram (ECG) Holter recording from a 3-lead configuration. ECG data were digitized at a sampling rate of 125 Hz. Computer software (Mars 6.5; General Electrics Medical Systems Information Technologies, Freiburg, Germany) was used to detect and label each QRS complex. A qualified Holter analyst, who was not otherwise involved in the study, processed all ECG recordings. If preventricular contractions (PVCs) reached >100/hour, the recording was excluded from analysis (n=8). On average, 0.56% PVCs were found in the 24-hour recordings, and were discarded automatically by the computer program, together with the 2 consecutive beats before and after the PVC.

The following time domain measures of HRV were assessed: the standard deviation of all normal-to-normal (NN) intervals (SDNN) as a measure of total variance in heart rate, the standard deviation of all 5-minute mean NN intervals (SDANN), reflecting long-term or irregular modulation of HRV, and the root mean square of successive differences (RMSSD), reflecting parasympathetic modulation of heart rate. Frequency domain measures were also extracted from the ECG data using standardized fast Fourier transformation, and included the very low frequency spectral power (VLF; 0.003-0.04 Hz), reflecting long-term trends in HRV, the low frequency spectral power (LF; 0.04-0.15 Hz) as a measure of sympathetic modulation of heart rate, and the high frequency spectral power (HF; 0.15-0.40 Hz) reflecting parasympathetic modulation of heart rate. Furthermore, LF/HF ratio was computed as a measure of autonomic balance.[1]

Statistical Analysis

The HRV distributions were tested for outliers. If HRV values were more than 3 SD distant from the mean, values were excluded from analyses. After correction for outliers HRV distributions were near normal (skewness<1.4). Therefore, it was not necessary to normalize the data. Pearson correlations were used to determine whether the demographic and medical

variables that have been associated with HRV in previous studies[37], were significantly associated with HRV in this study. Variables that emerged from these analyses as potential confounders were then entered into separate multiple regression analyses to remove redundant covariates (if any). All retained variables where then used as covariates in the adjusted models. The bivariate relation between depression/anxiety and HRV was examined using regression analysis. Separate multiple linear regression analyses were used to examine the independent impact of depression/anxiety on HRV indices. In a subsequent step, we adjusted for depressive and anxiety symptoms, respectively, in order to examine the impact of depression/anxiety above and beyond the impact of symptoms on HRV. A p-value of <.05 was considered significant in all tests. P values <.10 were reported in the results tables. All statistical analyses were performed using SPSS 12.0.1 for Windows.

Results

Patient characteristics

Of the 93 post-MI patients, 82 patients were included in the final analyses (Figure 1). Nineteen (23%) patients had lifetime diagnoses of depressive disorder and seven (9%) of anxiety disorder. Only three (4%) patients had diagnoses of both depressive disorder and anxiety disorder. Table 1 shows demographic and clinical characteristics of the 82 study participants. The valid ambulatory recording time was on average 23:47 hours (SD = 0.51 minutes). Table 2A presents the means and standard deviations for all HRV indices, stratified by diagnoses.

Figure 1. *Flowchart of patients included in the study*

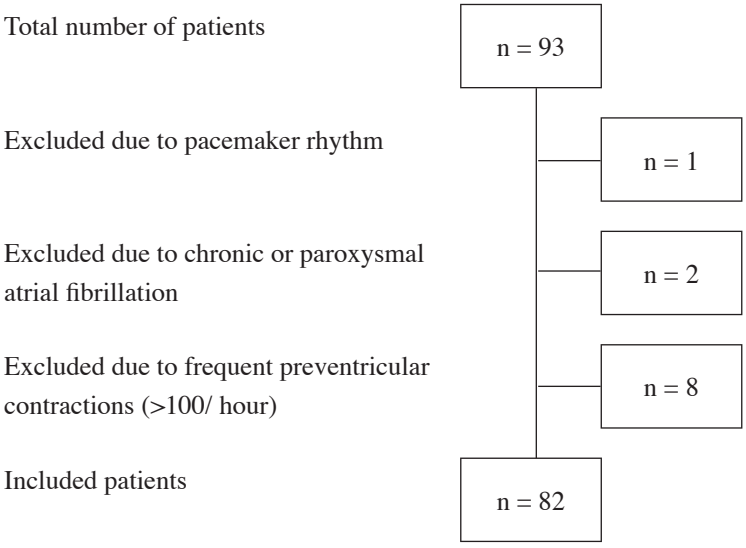

Table 1. *Characteristics of 82 patients with acute MI*[1]

Age, mean (SD)	56 (10)	Disease severity	
Female sex	15 (18)	Multi-vessel disease	26 (35)
Current smoker	36 (44)	PCI[4]	52 (63)
Body mass Index, kg/m^2, mean (SD)	27 (3.6)	Anterior MI location	28 (36)
Comorbidity[2]	17 (21)	Cardiac rehabilitation	55 (75)
Diabetes mellitus	11 (13)	Medication use	
Hypertension	30 (40)	Beta-blockers	74 (90)
Hypercholesterolemia	30 (38)	ACE-inhibitors	22 (27)
Cardiac history[3]	16 (20)	Ca-antagonists	13 (16)
Laboratory test results, mean (SD)		Anti-coagulants	69 (84)
HDL cholesterol level, mmol/l	1.2 (0.3)	Statins	74 (90)
LDL cholesterol level, mmol/l	3.2 (0.9)	Diuretics	16 (20)
LDL/HDL ratio, mmol/l	4.6 (1.1)	A2-antagonists	12 (15)
Cardiac function		Vasodilators	40 (49)
Systolic blood pressure, mean (SD)	138 (27)	Aspirin	67 (82)
Diastolic blood pressure, mean (SD)	81 (19)	Psychotropics[5]	8 (10)
		Depressive disorder[6]	19 (23)
		Anxiety disorder[6]	7 (9)
		Depression score (BDI), mean (SD)	6.7 (6.6)

1Values are expressed as number (percentage) of patients unless otherwise indicated
2Arthritis, renal insufficiency, chronic obstructive pulmonary disease
3MI, angina, PCI or CABG prior to the MI
4Reference group: conservatively treated
5SSRI, benzodiazepines
6Per the Composite International Diagnostic Interview (CIDI)

Unadjusted analyses

In unadjusted analyses, depressive disorder was a significant predictor of both lower SDANN and SDNN 4 months post-MI. Anxiety disorder was found to be predictive of lower RMSSD and a trend was observed for reduced HF power. Depressive and anxiety symptoms were not significantly predictive of HRV indices, although trends were observed for depressive symptoms and reduced VLF power, LF power, and SDNN, and for anxiety symptoms and reduced LF/HF ratio (Table 3A).

Table 2. *Twenty-four-hour averages of heart rate variability measures and the influence of age, sex, cardiac history, and multi-vessel disease*

A. Twenty-four-hour averages of heart rate variability measures[1]				B. Covariates								
HRV Index	Total sample	Patients without depressive or anxiety disorder	Depressive disorder	Anxiety disorder	Age		Female sex		Cardiac history		Multi-vessel disease	
(n=82)	(n=59)	(n=19)	(n=7)	ß	p	ß	p	ß	p	ß	p	p
VLF (ms^2)	28.3 (9.2)	29.1 (9.3)	25.4 (8.9)	24.2 (8.2)	**-.35**	**.010**	.04	.779	**-.30**	**.027**	.19	.150
LF (ms^2)	18.2 (7.1)	18.5 (7.4)	17.4 (6.4)	15.5 (6.3)	**-.38**	**.003**	-.07	.582	**-.36**	**.005**	**.25**	**.047**
HF (ms^2)	10.2 (4.3)	10.4 (4.8)	9.8 (3.0)	7.4 (2.4)	**-.47**	**<.0001**	**.26**	**.039**	-.16	.209	.24	.056
LF/HF (ms^2)	1.9 (0.5)	1.9 (0.5)	1.8 (0.5)	2.1 (0.4)	-.15	.242	**-.48**	**<.0001**	-.18	.175	-.04	.767
SDANN (ms)	105.8 (29.3)	111.7 (30.2)	92.6 (26.0)	89.0 (24.1)	-.02	.871	.08	.569	-.29	.052	.11	.449
SDNN (ms)	122.4 (32.3)	128.6 (33.5)	107.6 (27.0)	103.7 (27.2)	-.07	.622	.10	.478	**-.32**	**.029**	.13	.352
RMSSD (ms)	25.6 (9.2)	25.9 (10.1)	24.9 (7.4)	18.7 (5.2)	**-.38**	**.004**	**.29**	**.021**	-.21	.107	**.32**	**.013**

[1]Values are expressed as mean (SD).

Three patients had comorbid depression and anxiety and were included in both the depression and anxiety columns.

Adjusted analyses

Consistent with findings from previous studies, age, sex, beta-blockers, aspirin, cardiac history, and disease severity (anterior MI location and multi-vessel disease) were related to one or more HRV indices. Age, sex, cardiac history, and multi-vessel disease were retained in the multiple regression analyses and therefore entered as covariates into the adjusted models (Table 2B). After adjustment for these covariates, depressive disorder was no longer predictive of HRV indices. Anxiety disorder significantly predicted reduced HF power and RMSSD, and trends were observed for lower VLF power, LF power, SDANN, and SDNN. Depressive and anxiety symptoms were not predictive of HRV indices and no trends were observed (Table 3B).

Table 3.

A. Unadjusted HRV in post-MI patients with depression and anxiety

	Depressive disorder		**Anxiety disorder**		**Depressive symptoms**		**Anxiety symptoms**	
	ß	p	ß	p	ß	p	ß	p
VLF	-.17	ns	-.14	ns	-.20	.082	-.12	ns
LF	-.06	ns	-.12	ns	-.19	.086	-.16	ns
HF	-.06	ns	-.20	.072	-.04	ns	.01	ns
LF/HF	-.04	ns	.12	ns	-.17	ns	-.19	.090
SDANN	**-.25**	**.023**	-.18	ns	-.18	ns	-.06	ns
SDNN	**-.26**	**.022**	-.18	ns	-.20	.078	-.09	ns
RMSSD	-.04	ns	**-.23**	**.039**	-.05	ns	-.02	ns

B. Adjusted HRV in post-MI patients with depression and anxiety[1]

	Depressive disorder		**Anxiety disorder**		**Depressive symptoms**		**Anxiety symptoms**	
	ß	p	ß	p	ß	p	ß	p
VLF	-.15	ns	-.19	.085	-.14	ns	-.09	ns
LF	-.06	ns	-.17	.090	-.10	ns	-.08	ns
HF	-.11	ns	**-.22**	**.039**	-.01	ns	-.02	ns
LF/HF	.04	ns	.08	ns	-.09	ns	-.06	ns
SDANN	-.18	ns	-.21	.075	-.14	ns	.09	ns
SDNN	-.20	ns	-.22	.063	-.16	ns	.05	ns
RMSSD	-.09	ns	**-.25**	**.019**	-.01	ns	-.03	ns

[1]Age, sex, cardiac history, and multi-vessel disease were entered into the adjusted models

After additional adjustment for depressive symptoms, depressive disorder remained non-predictive of all HRV indices. However, when adjusting for anxiety symptoms, anxiety disorder remained predictive of reduced HF power and RMSSD, and strong trends were observed for reduced SDANN and SDNN with p-values of .050 and .051 respectively (Table 4).

Table 4. *Major depressive disorder and anxiety disorder as multivariate predictors of HRV*[1]

	Depressive disorder2		**Anxiety disorder3**	
	ß	p	ß	p
VLF	-.15	ns	-.18	ns
LF	-.06	ns	-.17	ns
HF	-.12	ns	**-.22**	**.043**
LF/HF	.04	ns	.10	ns
SDANN	-.16	ns	-.23	.050
SDNN	-.18	ns	-.23	.051
RMSSD	-.13	ns	**-.25**	**.022**

[1]Age, sex, cardiac history, and multi-vessel disease were entered into both multivariate models.

[2]Depression score (BDI) was entered into the multivariable model.

[3]Anxiety score (STAI) was entered into the multivariate model.

Discussion

The present study estimated the predictive power of lifetime depressive disorder, anxiety disorder, and self reported symptoms of depression and anxiety on 24-hour HRV, assessed in both the time and frequency domain, four months post-MI. After adjustment for significant demographic and clinical confounders, depressive disorder was no longer predictive of HRV indices, while anxiety disorder predicted reduced HF power and RMSSD. Further analyses revealed that after additional adjustment for current anxiety symptoms, lifetime anxiety disorder remained predictive of reduced HF power and RMSSD, suggesting a chronically reduced activity of the parasympathetic nervous system.[1] In addition, strong trends were observed for reduced SDANN and SDNN, indicating a potentially altered function of more long-term influences on HRV, which might reflect a smaller range of physical activity engaged in by these patients.[38]

To date, only few studies have examined the predictive value of anxiety on HRV measures

in patients with CAD, and these have shown mixed results. In the present study, we found no relation between self-reported current depressive and anxiety symptoms and HRV. Watkins et al. reported that levels of anxiety symptoms, but not depression, were associated with reduced vagal control in both patients with recent MI[24] and in non-cardiac patients with depressive disorder[17]. However, other studies have shown that depressive but not anxiety symptoms negatively influence autonomic control of heart rate in hospitalized MI patients[20] and CABG patients[39].

Regarding the clinical diagnosis of anxiety, our study provides evidence that anxiety disorder is an independent predictor of reduced vagal control of the heart in post-MI patients. This is consistent with the conclusion of a recent review incorporating over 20 studies indicating that anxiety disorder is associated with autonomic nervous system dysregulation, and that patients with heart disease and anxiety are at increased risk for morbidity and mortality.[40] One exception is a study in CAD patients with panic disorder that showed unchanged parasympathetic activity, while sympathetic modulation of HRV was reduced as compared to CAD patients without panic disorder.[41]

In adjusted analyses we found no association between depressive disorder or depressive symptoms and indices of HRV. Some studies have reported reduced HRV in relation to depressive disorder and depressive symptoms in CAD patients[18-20], but others have found only a small or no relationship[25,42,43]. In line with our results, the Heart and Soul Study[25] reported no association between depressive disorder and both time and frequency domain indices of HRV in 873 CAD patients. As a reaction to this study Birkhofer et al.[44] very recently proposed that the age difference between depressed and non-depressed patients could be an alternative explanation for the absence of differences in HRV. In their reply, Gehi et al.[45] showed that this was not the case, like in our study. In two studies of CAD patients by Carney et al., depressive disorder was only associated with SDANN and not with SDNN index, RMSSD, and pNN50[42], and no relation was found between depressive disorder and a HRV measure equivalent to SDNN[43]. Conversely, these authors also reported in some other studies that depressive disorder was associated with reduced HRV in both the frequency and time domain[18,46,47], and with decreased survival[47]. The effect of depression on survival in this latter study was only partially mediated by low HRV. Another recent study indicated that patients with post-MI depressive disorder showed lower SDNN but that this autonomic dysfunction was not a mediator of increased mortality observed in these patients during a 5-year follow-up.[48] Hence, it is still unclear whether autonomic nervous system dysfunction is a plausible mechanism linking depression to adverse outcomes in post-MI patients.

There are several possible explanations for the inconsistent findings and differences

between our results and those of prior studies. Variation in assessment of the physiological and psychological measures, patient population, time of assessment, and study design may account for the inconsistent findings. In addition, the use of self-report measures or clinical diagnosis of depression and anxiety yields different results regarding HRV. Studies are very heterogeneous in nature, which makes it hard to compare our results with the literature. The only fairly consistent finding in the literature, which is in line with our results, is that anxiety disorder is associated with impaired HRV.[21] However, it should be noted that these studies have been conducted in non-cardiac patients. In unadjusted analyses, our results regarding depression are similar to the adjusted results of Carney et al.[18]. The fact that depression was not predictive of HRV in our adjusted analyses may be explained by the relatively small sample size. To get a comprehensible and inclusive image of the relation between depression and anxiety and HRV, it is important for future studies to assess both diagnosis and symptoms of depression and anxiety, and to assess a variety of HRV indices in both the time and frequency domain in post-MI patients.

The results of this study have implications for research and clinical practice. Screening for symptoms of depression and anxiety may not be sufficient since our results indicate that we need clinical diagnosis to detect post-MI patients that are at risk for reduced HRV. The predictive value of anxiety disorder with reference to low values of parameters reflecting parasympathetic cardiac modulation of heart rate may help identify patients at high risk of cardiac events. A recent study in post-MI patients indicated that anxious patients were at increased risk of 8-year cardiac mortality and that reduced HF power increased this risk.[49] However, since to date only a few studies have been performed on the mechanisms underlying the link between anxiety and prognosis, the findings of the current study need to be replicated, preferably in a larger sample, with anxiety disorder, HRV and mortality assessed prospectively. This is in line with a recent call for further studies including patients with co-existing anxiety disorders and heart disease, incorporating assessment of indices of HRV.[40]

A limitation of this study may be the fact that we used lifetime diagnosis instead of current diagnosis of depressive and anxiety disorder, as a result of the limited amount of current diagnoses in this sample. Yet, the use of lifetime diagnosis would rather lead to a conservative estimation of the effect on HRV. Moreover, the inclusion of a lifetime diagnosis may indicate more long-term influences on HRV. Recently, several studies have shown depression and CAD to have genetic communalities.[50] Similarly, since lifetime diagnosis seems to have a chronic influence on HRV, this might be caused by a shared, underlying genetic predisposition.[50,51] Shared genes may underlie both depressive and anxiety disorder[52], and HRV in cardiac patients. A further limitation was the relatively small sample size. Third, we had no information on

left ventricular ejection fraction as a measure of disease severity. Instead, we adjusted for multi-vessel disease. Fourth, we had no data on physical activity levels during the day, which can be an important confounding variable. Despite these limitations, the present study also has several strengths. We included both the clinical diagnosis and symptoms of depression and anxiety, all assessed by standardized validated measures. Furthermore, the design of our study was prospective in nature, resulting in the opportunity to draw conclusions beyond the correlational level.

In conclusion, anxiety disorder but not depressive disorder was an independent predictor of reduced parasympathetic cardiac modulation in post-MI patients. These findings indicate the potentially important role of anxiety in determining individual differences in HRV and cardiac risk in post-MI patients. Whether these anxiety-related alterations in HRV actually explain increased morbidity and mortality in post-MI patients is subject for further study.

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Part C: Medical outcomes

Chapter Ten

Clinical events in repressive CAD patients

X

Clinical events in coronary patients who report low distress: Adverse effect of repressive coping

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Submitted

Abstract

Background: Coronary artery disease (CAD) patients who report low distress are considered to be at low psychological risk. However, patients with a repressive coping style may fail to detect and report these signals of distress. We hypothesized that repressive CAD patients are at risk for clinical events, despite low self-rated distress.

Methods: At baseline, 731 CAD patients filled out Trait-Anxiety (distress) and Marlowe-Crowne (defensiveness) scales; 159 patients (22%) were classified as 'repressive' (low anxiety but high defensiveness) and 360 as 'non-repressive'. In addition, type-D personality was present in 212 patients. Endpoints were composite of total mortality/myocardial infarction (MI) and cardiac mortality/MI after 5-10 years of follow-up (M=6.6).

Results: After 5-10 years of follow-up (M=6.6), 91 patients experienced a clinical event (death or MI) and 67 patients a cardiac event (35 cardiac deaths and 32 MIs). Repressive patients were at increased risk for death/MI (13%) as compared to non-repressive patients (6%); OR=2.33, 95%CI 1.23-4.41, p=.009. Poor systolic function, poor exercise tolerance, 3-vessel disease, index MI and type-D personality also predicted clinical events. After controlling for these variables, repressive patients still had a 2-fold increased risk of death/MI (OR=2.17, 95%CI 1.10-4.08, p=.025). These findings were replicated for cardiac mortality/MI.

Conclusions: CAD patients who use a repressive coping style are at increased risk for clinical events, despite their claims of low distress. This phenomenon may cause an underestimation of the effect of stress on the heart.

Introduction

Depression is a frequent comorbidity in medical patients[1], and emotional distress associated with depression and anxiety has been related to coronary artery disease (CAD)[2-5]. As a consequence, CAD patients who report little distress are considered to be at low risk for clinical events. However, individuals greatly differ in their threshold for responding to negative stimuli with self-reports of emotional distress[6] and in their ability to recognize emotional stimuli[7]. Individuals with a repressive coping style typically report low levels of emotional distress.[7-16]

Repressive coping is the tendency to avoid/repress negative emotions.[16] It protects against psychiatric disorder[8], but is also associated with less accurate detection of sadness/fear[7], less eye movements towards threatening stimuli[9], increased blood pressure[10], decreased heart rate variability[11,12], and cortisol dysregulation[13]. Hence, repressive individuals may show overt behavioral and physiological signs of distress despite their claims of low distress.

We previously hypothesized that repressive patients' tendency to minimize distress causes underdiagnosis of high-risk CAD patients with low levels of distress.[14] Hence, research may underestimate the effect of stress on the heart; patients reporting little distress typically have been assigned a low-risk status whereas, in fact, the low-risk reference group in these studies may include a subgroup of 'false negative' patients who use a repressive coping style. The aim of the present 5-10 year prospective follow-up study was to test this a priori hypothesis. We predicted that, given their tendency to be unaware of internal signals of distress, repressive CAD patients would be at risk for clinical events.

Methods

Patients

This study involves 731 CAD patients (656 men/75 women; m=56.0±8.0 years) from the University Hospital of Antwerp. They were recruited in 2 studies that were designed to examine the effect of emotional distress and repressive coping on cardiac prognosis. The design of both studies was similar; methodological details have been described previously.[17,18] In the first study, 303 CAD patients[17] were screened for decreased left ventricular ejection fraction (LVEF) with ventricular angiography; the present study included an additional 106 patients[19] with echocardiographic screening of LVEF. In the second study, a new sample of 322 CAD patients[18] was examined. The pooled data from these studies included 392 patients (54%) with a myocardial infarction (MI) and 535 (73%) who had coronary artery bypass graft surgery (CABG) or percutaneous coronary intervention (PCI), with 196 patients experiencing both a MI and invasive intervention. Patients with other life-threatening diseases were excluded. At

baseline, all patients had an exercise stress test and provided informed consent. The study was approved by the local hospital ethics committee.

Assessment

Repressive Coping

The Marlowe-Crowne Social Desirability (MCSD) scale[20] has been shown to be a valid defensiveness scale in a number of experimental and clinical studies[7-15]. Weinberger et al.[21] provided construct validity for distinctions among low-anxious, high-anxious, and repressive styles as three general patterns of coping with threatening situations.

The State Trait Anxiety Inventory (STAI) is a self-report measure consisting of two scales developed to measure the level of general state and trait anxiety.[22] In the current study we included the trait scale of the STAI. The STAI has been demonstrated to have adequate validity and reliability.[23]

Patients who avoid/repress negative emotions typically score low on the STAI[22] but high on the MCSD[20] scale. Both measures were used in this study to define repressive coping. According to previously published cut-off scores[14], 159 CAD patients (22%) were classified as repressive (STAI≤42 and MCSD≥22).

End Points

According to prior research on the effect of emotional distress and its treatment in CAD[24], the primary endpoint was a composite of total mortality or nonfatal MI. The secondary endpoint was cardiac mortality or nonfatal MI. As described previously[17,18], mortality/MI data were derived from hospital records and the patient's attending physician was involved in the classification of cause of death. The follow-up interval varied between 5 and 10 years (m= 6.6±1.7y).

Risk Factors

LVEF, exercise tolerance and extent of CAD are indices of disease severity that are powerful predictors of clinical events in this sample of CAD patients.[17,18] Overtly impaired (≤44%) but also borderline decreased (45-54%) LVEF has been associated with poor prognosis[25]; decreased systolic function was defined as LVEF≤54%. Poor exercise tolerance is associated with progression of atherosclerosis[26], and was defined by a median split for peak workload on a symptom-limited exercise test (i.e., ≤140 and ≤120 Watt for younger and older men; ≤100 and ≤80 Watt for younger and older women, respectively). A great extent of CAD was defined as 3 vessels with ≥70% reduction in internal diameter. We also controlled for age, sex, type-D personality and clinical indices of cardiac risk. Clinical indices included an index MI, anterior MI, CABG or PCI, beta-blocker and ACE-inhibitor therapy, hypertension, hyperlipidemia, and smoking.

Distressed Personality (type-D)

We previously showed that type-D patients from the current sample are at increased risk for clinical events.[17,18] According to the cut-off scores on the STAI[22] and Heart Patients Psychological Questionnaire (HPPQ) Social Inhibition[27] scales used in these studies, 212 patients (29%) in the current study were classified as type-D (STAI≥43 and HPPQ≥12). In contrast to repressive patients, type-D patients are well aware of their level of emotional distress as indicated by high scores on distress measures. Therefore, repressive coping would have to predict clinical events above and beyond the effect of type-D personality.[17,18]

Reference Group

Patients with a non-repressive coping style were used as a reference group, and included both (a) patients with low scores on trait-anxiety and defensiveness (STAI≤42 and MCSD≤21), and (b) patients with a high score on trait-anxiety but a low score on social inhibition (STAI≥43 and HPPQ≤11). These patients were conceptualized as non-repressive because their strategy for regulating emotions is in accordance with their levels of distress based on their self-reports.

Statistical Analyses

T-test, chi-square test and logistic regression were used to analyze differences in baseline characteristics as a function of repressive coping. Multivariate logistic regression analysis was used to examine the effect of disease severity on 5-10 year prognosis. Logistic regression models were also constructed to investigate the prognostic value of repressive coping in addition to disease severity and type-D personality. All variables were entered simultaneously in these final regression models. Analyses were performed using SPPS for Windows version 12.0.

Results

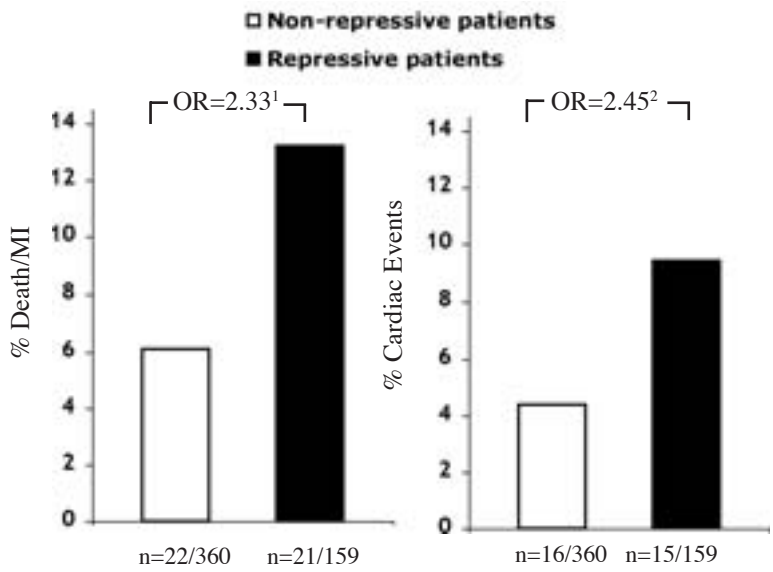
No patients were lost to follow-up; 91 patients (12%) had a clinical event (death or MI) and 67 had a cardiac event (35 cardiac death and 32 MI). All deaths were attributable to natural causes. The rate of clinical events in patients who score low on both trait-anxiety/defensiveness (15/206=7%) and those who score high on trait-anxiety but low on social inhibition (7/154=5%) was not significantly different (p=.28). Hence, merging of these subgroups into one reference group (n=360; 49% of total sample) of non-repressive patients was warranted.

At baseline, repressive patients were less likely to have suffered a MI compared to non-repressive patients (50% vs 61%, p=.014);. In addition, they were somewhat older (57.5±7.8 vs 55.6±8.0 year, p=.007) and more likely to have been treated invasively (81% vs 71% p=.011) because of 3-vessel disease. They did not differ from non-repressive patients in terms

of gender, LVEF, exercise tolerance, anterior MI, use of β-blockers and ACE-inhibitors, hypertension, hyperlipidemia or smoking.

Repressive patients had more than 2 times the risk for death/MI as compared to non-repressive patients (Figure 1, left). This adverse effect of repressive coping was not accounted for by demographic differences (p=.009, after adjustment for age and gender). These findings were replicated when using cardiac events as an endpoint (Figure 1, right); i.e., repressive patients had an increased risk of cardiac death/MI, adjusting for age and gender (p=.018).

Figure 1. *Percentage of repressive patients versus non-repressive patients who had a clinical event*



The association between repressive coping and clinical events after 5-10 year follow-up was analyzed for all cause mortality/MI (left) and for cardiac death/MI as cardiac events (right), respectively.

[1]95%CI [1.23-4.41], p=.009; adjusted for age and gender

[2]95%CI [1.17-5.15], p=.018; adjusted for age and gender

Patients who died or had a nonfatal MI also differed from patients with an event-free survival on several medical characteristics at baseline. They were more likely to perform worse on markers of disease severity, and less likely to have been treated invasively with CABG/PCI (Table 1). Multivariate logistic regression analysis yielded decreased LVEF, poor exercise tolerance, three-vessel disease and index MI as independent predictors of death/MI (Table 1, bottom). These same indicators of disease severity also independently predicted cardiac events.

Table 1. *Demographic/clinical characteristics according to death/MI at follow-up*

Baseline Characteristics	**Event-free** (N=640)	**Death/MI** (N=91)	OR	[95% CI]	p-value
Demographic			**Univariate Analyses**		
Age (mean±SD)	56.0±8.0 y	55.8±7.9 y	**0.99**	[0.97-1.02]	.781
Gender (male)	90% (574)	90% (82)	**1.05**	[0.50-2.18]	.901
Disease Severity					
Decreased LVEF[1]	27% (174)	47% (43)	2.40	[1.54-3.75]	**.0001**
Poor exercise tolerance[2]	35% (225)	63% (57)	3.09	[1.96-4.87]	**.0001**
Three-vessel disease	33% (214)	52% (47)	2.13	[1.37-3.31]	**.001**
Index MI at baseline	57% (367)	69% (63)	1.67	[1.04-2.68]	**.032**
Anterior MI	24% (152)	33% (30)	1.58	[0.98-2.54]	.059
Clinical variables					
CABG/PCI	74% (477)	64% (58)	0.60	[0.38-0.95]	**.031**
Beta-blockers	52% (331)	53% (48)	1.04	[0.67-1.62]	.854
ACE-inhibitors	6% (36)	6% (5)	0.98	[0.37-2.55]	.961
Hypertension	27% (173)	25% (23)	1.04	[0.72-1.50]	.832
Hyperlipidemia	33% (213)	31% (28)	0.89	[0.55-1.43]	.634
Smoking	20% (126)	23% (21)	1.22	[0.72-2.07]	.451
Predictors of Death/MI (n=91)			**Multivariate Analysis**		
Decreased LVEF			**1.95**	[1.19-3.17]	.008
Poor exercise tolerance			**2.84**	[1.76-4.58]	.0001
Three-vessel disease			**2.19**	[1.35-3.55]	.001
Index MI at baseline			**1.94**	[1.13-3.34]	.016
Predictors of Cardiac Events (n=67)					
Decreased LVEF			**2.38**	[1.37-4.13]	.002
Poor exercise tolerance			**2.73**	[1.59-4.71]	.0001
Three-vessel disease			**1.96**	[1.13-3.41]	.017
Index MI at baseline			**2.26**	[1.19-4.32]	.013

Number of subjects appears in parentheses. CABG= coronary artery bypass surgery;

MI= myocardial infarction; OR= Odds ratio; PCI= percutaneous coronary intervention

[1]Left ventricular ejection fraction ≤54%[25]

[2]≤140/≤120 Watt for younger/older men; ≤100/≤80 Watt for younger/older women

As reported previously[17,18], type-D patients had a high risk of clinical events (48/212=23%) as compared to non-type-Ds (43/519=8%; p<.0001). To determine whether repressive coping was an independent psychological predictor of death/MI, repressive coping, type-D and disease severity were all entered simultaneously in a regression model. Repressive coping was associated with a 2-fold increased risk of death/MI after adjustment for disease severity, and predicted clinical events above and beyond the effect of type-D personality (Table 2). Repressive coping also independently predicted cardiac death/MI (Table 2, bottom). Decreased LVEF, poor exercise tolerance, three-vessel disease and index MI remained independent predictors of death/MI and cardiac events in these final analyses.

Table 2. *Repressive coping as independent predictor of 5-10 year prognosis*

Clinical Endpoint		OR	[95% CI]	p-value
Death/MI (n=91)	**Repressive coping**	**2.17**	[1.10-4.08]	**.025**
	Gender (male)	1.21	[0.55-2.66]	.639
	Age	0.98	[0.95-1.01]	.269
	Type-D personality	3.80	[2.17-6.64]	**.0001**
	Decreased LVEF[1]	1.81	[1.10-3.00]	**.021**
	Poor exercise tolerance[2]	2.63	[1.61-4.31]	**.0001**
	Three-vessel disease	2.22	[1.33-3.68]	**.002**
	Index MI at baseline	1.89	[1.09-3.28]	**.024**
Cardiac Events (n=67)	**Repressive coping**	**2.16**	[1.01-4.65]	**.047**
	Gender (male)	2.17	[0.72-6.54]	.168
	Age	0.97	[0.94-1.00]	.074
	Type-D personality	3.96	[2.08-7.53]	**.0001**
	Decreased LVEF[1]	2.23	[1.27-3.94]	**.006**
	Poor exercise tolerance[2]	2.56	[1.46-4.49]	**.001**
	Three-vessel disease	2.01	[1.12-3.61]	**.020**
	Index MI at baseline	2.14	[1.11-4.13]	**.023**

MI= myocardial infarction; OR= Odds ratio

[1]Left ventricular ejection fraction ≤54%25

[2]≤140/≤120 Watt for younger/older men; ≤100/≤80 Watt for younger/older women

Discussion

The findings of this study clearly showed that repressive CAD patients were at a two-fold increased risk of long-term mortality or MI, despite their claim to experience low levels of distress. These findings were confirmed after adjustment for the severity of cardiac disease, and were replicated when looking at cardiac events as a secondary endpoint.

Accumulating evidence indicates that individuals who experience feelings of distress are at risk for clinical events, including MI and cardiac death.[2-5] As a consequence, there is an implicit assumption that patients scoring low on distress measures can be regarded as low-risk individuals in terms of stress-related CAD. However, our findings suggest that this assumption may not apply to a subgroup of CAD patients who use a repressive coping style. Although repressive patients reported very low levels of distress, they had an increased risk of 5- to 10-year clinical events.

The present findings should be interpreted with some caution. There were significant differences on several baseline characteristics between repressive and other patients but we did control for these differences in multivariable analyses. The present findings may not generalize to women, as female patients only comprised a minority of the sample. Finally, defensiveness was assessed by the MCSD scale that has been shown to detect susceptibility to unconscious forms of distress in experimental research[8-12]; the use of other measurement tools (physiological measurement, brain imaging, behavioral assessment) is needed to further examine the role of unconscious emotions in the clinical course of CAD. However, the present findings confirm our a priori hypothesis[14] that repressive coping would predict clinical events in patients who report low levels of distress but score high on the tendency to minimize this distress.

Our findings may have important implications for clinical research and practice. Considering the impact for clinical research, these findings suggest that the adverse effect of stress and negative emotions may have been underestimated in previous research. Individuals reporting little distress typically have been assigned a low-risk status whereas, in fact, the low-risk reference group in these studies includes a subgroup of 'false negative' individuals who are characterized by repressive coping. The tendency of repressive patients to report low levels of distress may go some way towards explaining the lack of an association between self-reported distress and cardiac events in some studies.[28]

A number of physiological pathways may explain the worse clinical outcome in repressive patients. For example, repressive individuals have been found to exhibit a less favorable cardiovascular function than non-repressors, putatively being the consequence of a hyperresponsiveness of the sympathetic nervous system to stressful events. They have shown elevated heart rate and blood pressure responses to laboratory stressors[10,15], enhanced reductions of heart rate variability[11], and cortisol dysregulation[13]. Repressive coping is also associated with elevated ambulatory blood pressure[29] and has been shown to predict the incidence of hypertension[30].

In terms of clinical intervention, CAD is a life-threatening disease causing much patient burden. An important objective of self-management interventions for CAD patients is to help them cope with their chronic condition. However, there is some evidence suggesting that we need to consider the timing and nature of behavioral intervention strategies carefully in repressive patients. Some of these interventions have been associated with unfavorable medical outcomes in repressive CAD patients[31,32], possibly due to the fact that the intervention may have interfered with these patients' normal coping strategy to minimize distress.

Recently, we have argued that we need to learn more about factors that may modulate the impact of negative emotions on cardiac prognosis.[33] The active inhibition of consciously experienced negative emotions, for example, may be a source of chronic stress that increases susceptibility to clinical events in CAD.[34] The present findings suggest that repressive coping may modify the risk associated with patients' self-reports of low distress. We found clinical evidence that repressive CAD patients are at risk for death/MI. This phenomenon may cause an underestimation of the effect of stress on the heart, and possibly undertreatment of some high-risk patients. Inclusion of repressive coping as a modulating factor may lead to a better understanding of the relationship between emotional distress and prognosis in patients with CAD.

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Chapter Eleven

General summary and discussion

XI

The present thesis described an ongoing longitudinal follow-up study in a large sample of acute myocardial infarction (MI) patients. During hospitalization for MI, and 2-, 12-, and 18-months post-MI, patients were assessed on a wide variety of demographic, clinical and psychological variables. Several aspects of the complex relationship between depression and coronary artery disease (CAD) were broached. In this part of the thesis, the main findings of the present research and their implications for research and clinical practice are discussed.

CHARACTERIZATION OF DEPRESSION IN POST-MI PATIENTS

The first part of this thesis gave more insight into the characteristics of post-MI depression, examining the nature, evolution and determinants of post-MI depression and the role of stable traits.

Chapter 2 investigated whether depressive cognitions characteristic of depression in psychiatric patients were also present in post-MI patients with depressive disorder. Non-depressed (n=40) and depressed (n=40) post-MI patients, and psychiatric outpatients (n=40) treated for clinical depression, matched on age and sex, were interviewed using a structured clinical interview to diagnose DSM-IV depressive disorder. All patients also completed the Beck Depression Inventory (BDI) and the Beck Cognition Checklist-Depression subscale. Results showed a significant difference in depressive cognitions between post-MI and psychiatric patients, with depressive cognitions being less prevalent in post-MI patients with clinical depression as compared to depressed psychiatric patients. Psychiatric disease status was an independent predictor of depressive cognitions, adjusting for all baseline characteristics. Psychiatric patients also had higher levels of depressive symptoms, indicating that they are more severely depressed than MI patients. Overall, the findings showed that symptom presentation of depressive disorder in post-MI patients is both quantitatively and qualitatively different from that seen in psychiatric patients.

Since there is a paucity of research on the evolution and determinants of depressive symptoms, *Chapter 3* reported on the course of depressive symptoms during the first year post-MI and the predictors of these symptom trajectories. 287 patients completed the BDI during hospitalization for MI, and 2- and 12 months post-MI. Personality was assessed with the type-D scale (DS14) during hospitalization. The Composite International Diagnostic Interview (CIDI) was used to assess the prevalence of DSM-IV lifetime diagnosis of depressive disorder. Results showed that symptoms of depression tend to persist during the first year post-MI. Cardiac history, prior depression and type-D personality were identified as independent risk factors for persistence of depressive symptoms over time. The results of this study strongly argue for routine psychological screening during hospitalization for acute

MI in order to identify patients who are at risk for chronicity of depressive symptoms and to prevent its deleterious effects on prognosis.

Personality refers to a complex organization of traits that reflect consistencies in the general affective level and behavior of individuals over time. The type-D personality construct was designed to reflect a chronic psychological condition, as opposed to more acute emotional states such as depression. A sound personality construct needs to have high predictive value, good construct validity, and to be stable over time. However, concerns have been voiced that type-D may not be a stable personality taxonomy and that the progression of CAD may contribute to the manifestation of type-D personality. Therefore, in *Chapter 4* we examined the stability of type-D during the course of 18 months in patients with an acute MI, and evaluated the influence of demographic and clinical risk factors and mood status on the stability of type-D over time. Patients (n=475) were assessed during hospitalization for acute MI, and 12- and 18 months post-MI on type-D personality (DS14), and depression and anxiety using both self-report measures (BDI, State Trait Anxiety Index; STAI) and a diagnostic interview (CIDI). Type-D personality was a stable taxonomy over an 18-month period, and was not confounded by variability in mood status and disease severity. These findings support the importance of including personality variables in cardiovascular research and the need for intervention trials targeting this personality taxonomy in order to enhance secondary prevention in CAD patients.

Overall, the results from these studies showed that the nature of post-MI depression may be both quantitatively and qualitatively different from that seen in psychiatric patients and that symptoms of depression tend to persist during the first year post-MI, with cardiac history, prior depression and type-D personality being important determinants of chronicity of depressive symptoms. Furthermore, type-D patients exhibited the stable tendency to experience negative emotions and to be socially inhibited across time, without being confounded by variability in mood status and by disease severity.

Patient-based outcomes

The second part of this thesis centered on patient-based outcomes. The relationship between depression and health status (including quality of life) and the impact on adverse cardiac events was examined.

Since little is known about the determinants of impaired health status, *Chapter 5* focused on the impact of history of depressive disorder on health status 2 months post-MI in 352 patients. The CIDI was administered to evaluate the presence of lifetime and current depressive disorder.

The Seattle Angina Questionnaire (SAQ) was used to assess disease-specific health status. Results indicated that history of depressive disorder was associated with significantly more physical limitations and worse quality of life 2 months post-MI adjusting for demographic and clinical factors. However, further exploration revealed that this effect could be attributed to the influence of current depression. These findings support the importance of depression as a risk marker for adverse outcomes post-MI.

The importance of other psychological factors than depression is less well established in post-MI patients. Moreover, it is not known which symptoms are specific to post-MI distress, and whether there are reliably identifiable subgroups of patients with different psychological symptom profiles. In *Chapter 6*, we explored the degree to which psychological symptoms of distress post-MI represent one or more underlying dimensions and examined whether psychological symptom profiles based on these dimensions are differentially associated with patient-based outcomes. Two months post-MI, the BDI, STAI, and Global Mood Scale were used to measure symptoms of depression, anxiety and mood status in 324 patients. The CIDI was administered to diagnose DSM-IV depressive and anxiety disorder. Health status was assessed by the SAQ. Results showed that the underlying structure of self-reported psychological symptoms post-MI could be characterized by depressed affect, anxious apprehension, positive affect, and emotional exhaustion. Symptom profiles based on these features revealed a No Distress subgroup and two Increased Distress subgroups. Both Increased Distress subgroups were associated with psychiatric comorbidity and decreased health status, despite the relative absence of depressed affect in one of these subgroups.
This suggests that some post-MI patients may be more likely to have adverse outcomes despite their low levels of self-reported depressed affect. Moreover, these results imply that, apart from standard depressive symptoms, other affective components are important in understanding emotional adjustment in post-MI patients.

In addition to being an important outcome measure in its own right, impaired health status has been shown to predict subsequent mortality and morbidity in patients with CAD. However, the effect of health status on adverse clinical outcome has not yet been evaluated in a pure sample of patients treated with percutaneous coronary intervention (PCI). In *Chapter 7*, we examined the impact of health status (as measured with the Dutch version of the MacNew Heart Disease Health-Related Quality of Life questionnaire) at the time of the index PCI on both early and late adverse cardiac events at a median follow-up of 2 years in 667 exhausted CAD patients participating in the randomized EXhaustion Intervention Trial (EXIT). Results demonstrated that poor health status was an independent predictor of cardiac events occurring 0-6 months post PCI but not events occurring beyond 6 months. These findings support the use of health status to identify patients at risk of early events post PCI in research and clinical

practice in order to optimize risk stratification in this subgroup of patients. However, prior to a sound recommendation for the use of health status measures as screening tools for adverse events in clinical practice, further research is warranted.

Taken together, the results from these three studies showed that both depression and other affective components are important risk markers for patient-based outcomes post-MI. Moreover, health status was identified as an independent predictor of early but not late cardiac events in post-PCI patients.

Medical outcomes

The last part of this thesis concentrated on medical outcomes. The impact of post-MI depression on adverse cardiac events and heart rate variability (HRV) was examined. Moreover, we examined whether repressive CAD patients were at increased risk for adverse clinical events, despite low self-rated distress.

Although the impact of post-MI depression on prognosis has been studied extensively, the role that comorbid anxiety plays in this relationship has been less well studied. In *Chapter 8*, we investigated the differential impact of 1) a clinical depressive and/or anxiety disorder; 2) depressive and/or anxiety symptoms on cardiac death and non-fatal MI 1.8 years post-MI. Two months post-MI, 434 patients completed self-reported measures of anxiety (STAI) and depressive (BDI) symptoms, and were assessed on lifetime depressive and anxiety disorder, using the CIDI. Results indicated that self-reported symptoms of both anxiety and depression, but not a clinical diagnosis, significantly increased the incidence of cardiac death and non-fatal MI, independent of established biomedical and demographic risk factors. A multivariate analysis, including both anxiety and depressive symptoms, indicated that only patients with co-occurring symptoms were at increased risk of adverse clinical events at follow-up, with the risk being almost three-fold. Cardiac history and use of statins were also independent predictors of death/MI, with statin use showing a considerable protective effect. In addition to depressive and anxiety symptoms alone, the co-occurrence needs to be considered to optimize risk stratification and treatment in post-MI patients.

Given the relative paucity of studies on the potentially deleterious effects of depression and in particular anxiety on HRV, *Chapter 9* examined to what extent depression and anxiety predict 24-hour time and frequency domain HRV indexes in patients with recent MI. Ninety-three patients were assessed on symptoms of depression (BDI) and anxiety (STAI) before discharge and clinical diagnoses of lifetime depressive and anxiety disorder were made 2 months post-MI using the CIDI. After adjustment for significant demographic and

clinical confounders, depressive disorder was no longer predictive of HRV indices, while anxiety disorder predicted reduced HF power and RMSSD 4 months post-MI, even after additional adjustment for anxiety symptoms. This suggests a chronically reduced activity of the parasympathetic nervous system in anxious patients. These findings elucidate the physiologic mechanisms underlying anxiety as a risk factor for adverse outcomes, but also raise questions about the potential role of HRV as an intermediary between depression and post-MI prognosis.

CAD patients who report low distress are considered to be at low psychological risk. However, patients with a repressive coping style show clear physiological signs of distress but may fail to detect and report these signals. *Chapter 10* reports on the results of a 5-10 year prospective follow-up study of 731 CAD patients, examining whether repressive patients were at increased risk for clinical events, despite low self-rated distress. Patients completed the Marlowe-Crowne Social Desirability scale and the STAI to assess repressive coping. Repressive patients were at a two-fold increased risk of long-term mortality or MI, despite their claim of experiencing low levels of distress. These findings remained after adjustment for the severity of cardiac disease, and were replicated when looking at cardiac events as a secondary endpoint. Repressive coping may lead to an underestimation of the effect of stress on the heart, and possibly undertreatment of a subgroup of high-risk patients. Inclusion of repressive coping as a modulating factor may lead to a better understanding of the relationship between emotional distress and prognosis in CAD patients.

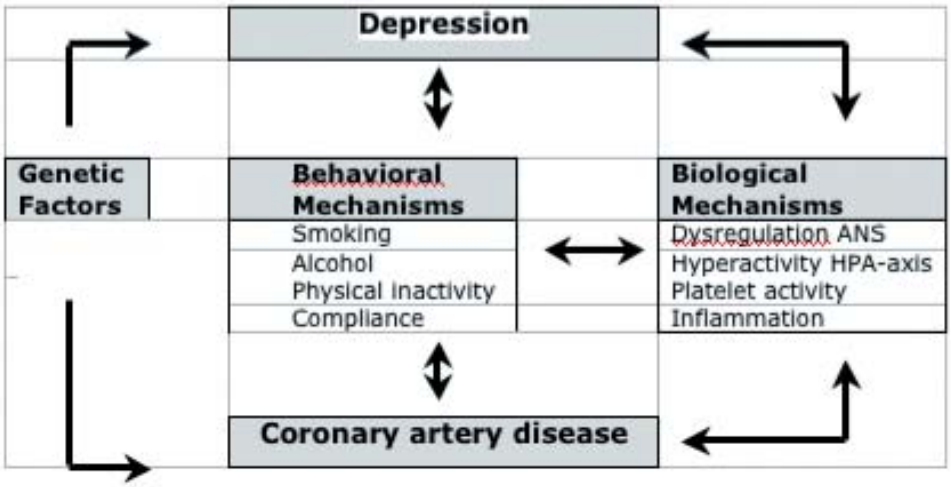
Overall, the results from the latter studies indicate that both depression and anxiety are important mood states in relation to medical outcomes post-MI. However, the relative influence of self-reported symptoms versus a clinical diagnosis of depressive and anxiety disorder remains unclear. In addition, repressive CAD patients are at increased risk for adverse medical outcomes despite low levels of distress, leading to an underestimation of the effect of stress on the heart.

Potential mechanisms linking depression and CAD

In the present thesis, the importance of depression in relation to both patient-based and medical outcomes in CAD was demonstrated. However, the potential mechanisms underlying the depression-CAD relationship are still poorly understood, although these mechanisms are the focus of current research interest.[1] Generally, the mechanisms can be divided into behavioral and biological. Behavioral mechanisms comprise unhealthy lifestyle behaviors, such as smoking[2,3] and alcohol consumption[4], physical inactivity[5] and poor patient compliance[6,7]. Plausible biological candidates include dysregulation of the autonomic nervous system

and the hypothalamic-pituitary-adrenocortical axis (HPA-axis), increased platelet activity, and alterations in immune functioning and inflammation. HRV may act as an intermediary between psychological distress and post-MI prognosis[8,9], with decreased HRV reflecting a dysregulation of the autonomic nervous system. Although depression was not associated with altered HRV in our study, anxiety was. Still, several other potential biological pathways must be considered in this context, including increased platelet activity, which may point to an increased tendency to thrombus formation.[10] The adverse effects of depression on CAD may also be mediated via the HPA-axis. A dysregulation of the HPA-axis has been found in subjects with depressive disorder.[11] Recently, evidence has emerged to suggest that alterations in immune functioning and inflammation may also be involved in the link between depression and cardiac prognosis.[12,13] Possibly, there are several interactions between the potential mechanisms associating depression with CAD; e.g., if exposure to stress is long-lasting, the activity of the HPA-axis may decrease, leading to an increased activation of immune-mediated inflammation.[14,15]

Because we do not yet fully understand the link between depression and CAD at a pathophysiologic level, further research is needed to identify biological pathways by which depression influences adverse outcomes in CAD patients. Furthermore, since both depression and CAD have genetic underpinnings, future work should concentrate on identifying pleiotropic genetic factors that increase risk for both depression and CAD. As an indication, a twin study recently provided evidence for a genetic risk factor common to both depression and heart disease.[16]



Model for the relationship between depression and coronary artery disease

Implications for research and clinical practice

To date there are four main randomized controlled trials that aimed at reducing negative affect in CAD patients, two of them pharmacological and two behavioral. The SADHART (Sertraline AntiDepressant Heart Attack Trial) investigation demonstrated that sertraline is a safe treatment for depressive disorder in patients with recent MI or unstable angina.[17] A reduction in depressive symptoms was hypothesized to decrease mortality, although the study was not powered to investigate this objective. Unfortunately, sertraline was not a highly efficacious treatment for depression, with virtually no difference in depression change scores between the sertraline and placebo groups. In MIND-IT (Myocardial INfarction and Depression-Intervention Trial), patients with a post-MI depressive disorder were randomized to receive antidepressants or usual care.[18] No difference was observed in depression outcome between the 2 randomization arms. Moreover, antidepressant medication treatment did not improve cardiac prognosis at 18 months post-MI.[19]
The primary aim of ENRICHD (ENhancing Recovery In Coronary Heart Disease) was to determine whether behavioral treatment of depression and low perceived social support increased event-free survival after acute MI.[20] The study showed that cognitive-behavioral therapy had modest effects on depression and social support but no effect on cardiovascular mortality or morbidity. The EXIT (randomized EXhaustion Intervention Trial), another behavioral intervention trial, aimed at reducing feelings of exhaustion in PCI patients by improving coping with stressors leading to exhaustion and promoting rest and making rest more efficient.[21] Beneficial effects on feelings of exhaustion were found, but a reduction in exhaustion did not lead to a concomitant increase in survival within two years.
Although the findings of these important trials indicated that intervention did not improve cardiac prognosis, positive effects on health outcomes were reported in subgroup analyses[4,22]; e.g., the EXIT did reduce the risk of a cardiac event by 55% in patients without a previous history of CAD and comorbidity[21], and post-hoc analyses in ENRICHD suggested that white men may have benefited from the intervention[23].

Demonstrating that a relationship exists between treatment of negative affect and subsequent improvement in morbidity and mortality has not yet been convincingly accomplished. There is a paucity of knowledge regarding the optimal anti-depressive treatment strategy in patients with CAD.[24] A better understanding of the syndrome of depression in post-MI patients, together with the investigation of which depressive symptoms are most toxic in terms of predicting adverse health outcomes, is crucial to modify the depression mortality link by means of therapy, be it psychological, pharmacological, or a combination thereof. Furthermore, knowledge of the characteristic features of depression in post-MI patients

may help clarify the etiology of the disorder, guide the training of physicians in diagnosing the disorder in clinical practice, and help clinicians target their treatment procedures more precisely.[25] According to de Jonge et al., future studies should focus on a reconceptualization of depression in CAD along with the identification of relevant subtypes of post-MI depression and the development of treatments tailored to these specific subtypes.[26]

Moreover, identifying various forms of distress, even in their less severe states, may provide an important avenue for early intervention. In addition to standard depressive symptoms, other affective components and the co-occurrence of various affective states are important in understanding emotional adjustment in post-MI patients.[27] We found that patients with co-occurring symptoms of depression and anxiety were at increased risk of cardiac death and non-fatal MI as compared to patients with depressive or anxiety symptoms alone. The degree of conceptual and empirical overlap among negative emotions and the possible interrelationships make this issue especially complex. Further exploration of positive emotional states and their potential protective effects against disease may also be important in this context.[28] The findings of the present thesis may help explain why interventions specifically designed to treat depression yielded mixed results concerning a survival benefit.[17,19,20] A more comprehensive approach to treatment, including individualized treatment of a wide variety of psychological factors may be more successful in improving prognosis.[29] These psychosocial factors should include depression, anxiety, positive affect, and personality, among others. A more nuanced picture of the mental state of CAD patients may help in the development of more effectively timed and more specifically tailored interventions to reduce adverse outcomes following MI.

According to Suls and Bunde, there needs to be more appreciation of the clustering and overlap of negative affective dispositions.[30] This implies that, in addition to assessing specific emotional factors, it is important to assess broad and stable dimensions of distress in post-MI patients. In this context, the type-D construct may be helpful in the process of identifying high-risk post-MI patients, in particular since it is a stable taxonomy that is not confounded by variability in mood status and disease severity. In addition, type-D has been shown to be an important determinant of patient-centered and clinical outcome[31]. Hence, future intervention trials are warranted that target this personality taxonomy in order to enhance secondary prevention in CAD patients.

Furthermore, our findings suggest that the adverse effect of stress and negative emotions may have been underestimated in previous research. Patients reporting little distress typically have been assigned a low-risk status, whereas, in fact, the low-risk reference group in these studies includes a subgroup of 'false negative' patients who use a repressive coping style. The tendency

of repressive patients to ignore signals of distress may go some way towards explaining the lack of association between self-reported distress and cardiac events in some studies.[32] Inclusion of repressive coping as a modulating factor may lead to a better understanding of the relationship between emotional distress and prognosis in patients with CAD.

The present thesis provides no definite answer as to the relative importance of self-reported symptoms versus a clinical diagnosis of depressive and anxiety disorder on health outcomes post-MI. Results show that self-reported symptoms of both anxiety and depression, but not a clinical diagnosis, significantly increase the incidence of cardiac death and non-fatal MI, independent of established biomedical and demographic risk factors. By contrast, it was found that screening for symptoms of depression and anxiety might not be sufficient since we need the clinical diagnosis to detect post-MI patients that are at risk for reduced HRV. Additional research is needed to learn more about the active ingredients of the relationships observed in those studies and their implications for treatment.

The extent to which post-MI depression should be considered a transient distress reaction to a life-threatening event or a resurfacing of a pre-existing depressive vulnerability has been subject of debate.[33,34] The present results indicate that depressive symptoms following MI are not a transient phenomenon, with levels of depressive symptoms persisting throughout the first year post-MI. Cardiac history, prior depression and type-D personality were the most prominent risk factors for persistence over time. Although there is no agreement as to the best time for screening for depression in MI patients[34,35], these results strongly argue for routine psychological screening during hospitalization for acute MI in order to identify patients who are at risk for chronicity of depressive symptoms and its deleterious effects on prognosis.

According to the European Society of Cardiology, primary goals of therapy in CAD patients include symptom control and maximizing health status.[36] In addition, the study of health status and its determinants has been advocated as a means by which to close the gap between research and clinical practice.[37] Results of this thesis suggest that it may be important to recognize and treat depression in post-MI patients, in order to diminish physical limitations and improve quality of life. Understanding the impact of depression on health status and subsequent prognosis may help to guide development of interventions to enhance health status following MI.[38] Nevertheless, we still know little about the mechanisms responsible for the relationship between impaired health status and medical prognosis. For health status to be conceptualized as a risk factor on par with established, traditional, biomedical risk factors, there must be one or more plausible mechanisms (e.g. biological or behavioral) that are responsible for the link between poor health status and adverse prognosis. In addition, studies need to demonstrate that health status is modifiable and that its modification will

lead to improved clinical outcome. Research is also warranted to investigate the short- and long-term prognostic value of the multitude of health status measures available, with a focus on both disease-specific and generic instruments.[39] These measures should not only be valid and reliable, but also brief and the results directly applicable to clinical practice.[38] In addition to clinical factors, patients' evaluation about their health status should be taken into account in the process of clinical decision-making, since a discrepancy has been found between physician- and patient-rated symptomatology.[40]

The complexity of managing depression and CAD together can be quite demanding even for physicians with specific training and experience in this area.[41] The management of depression in CAD patients is both a clinical and interdisciplinary challenge, with the development of collaborative and integrative approaches combining the medical and psychological expertise being imperative. However, an important first step in the management of post-MI depression comprises the unravelling of the determinants of depression, which likely consist of a combination of clinical, psychosocial, and biological factors. Studying the biological determinants may be of particular value, as treatment options for post-MI depression should also have a positive effect on cardiovascular biology.[42]

Limitations and strengths of the present thesis

The results presented in this thesis should be interpreted with some caution. First, not all patients had had an echocardiography and cardiac angiography. Therefore, information on multi-vessel disease and left ventricular ejection fraction was only present for a subsample of patients. Second, we had no information on the overall response rate of the study. However, we were able to look into a subsample of patients (n=63). Of the 63 patients who met the inclusion criteria, 46 gave informed consent, leaving a response rate of 73%. In addition, the retention rate per chapter has been fully reported. Third, we had no assessment between 2 and 12 months post-MI, which is a relatively large time gap. It would be interesting to include a 6-month assessment in future studies, in particular in relation to the stability of type-D personality. Fourth, the mean follow-up period of 1.8 years in this study was relatively short, and it will be important to replicate the findings in relation to long-term clinical outcomes. Fifth, with increasing health-care costs, growing interest has arisen in studies that provide information about patterns of health-care utilization. Although data on health-care utilization were not provided in this thesis, this will be examined in the near future in this patient sample.

Despite these limitations, the present study also has several strengths, including the use of valid and reliable measures of several psychological constructs and multiple assessments. We also included both a diagnostic interview and self-reported measures of depression and anxiety, and evaluated a broad spectrum of demographic, clinical, and psychological variables. Furthermore, this was a multi-center study, making generalization of our results to Dutch CAD patients in general more justified.

Concluding remarks

The co-occurrence of depression and CAD represents a great challenge and opportunity for those interested in exploring the complex interactions between the brain and the heart. The present thesis demonstrates the importance of psychological factors in CAD and their deleterious effects on patient-based and medical outcomes. Clearly, depression is not the only psychological factor with prognostic significance in post-MI patients, as anxiety had incremental value to depression in predicting adverse outcomes post-MI. In addition, the symptom presentation of depression in post-MI patients is both quantitatively and qualitatively different from that seen in psychiatric patients. A reconceptualization of depression in post-MI patients and the identification of those psychological symptoms that are most toxic in terms of predicting adverse health outcomes could lead to effective treatment strategies to prevent future cardiac events. More information is needed to understand the exact role of depression and other psychological factors in CAD and their implications. It seems timely for research and clinical practice to address this issue and its potential consequences for patient-based and medical outcomes.

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Chapter Twelve

Nederlandse samenvatting en discussie (Dutch summary and discussion)

XII

Nederlandse samenvatting en discussie (Dutch summary and discussion)

Gebaseerd op:
Elisabeth J. Martens & Nina Kupper. Verband tussen depressie en hart-en vaatziekten. PatientCare, Neuropsychiatrie & Gedragsneurologie, Nederlandse editie. 2006;5:169-172.

"My life... sinks down to earth, oppress'd with melancholy" (Shakespeare, Sonnet 45).

Al eeuwenlang wordt ervan uit gegaan, dat er een relatie bestaat tussen lichaam en geest, en in het bijzonder tussen het hart en de geest. Deze aanname wordt echter pas sinds kort wetenschappelijk onderzocht. Volgens de Global Burden of Disease Study zijn depressie en hart- en vaatziekten (HVZ) de meest voorkomende ziektebeelden in de westerse wereld.[1] Tevens blijkt uit verschillende studies, dat depressieve mensen een vier keer hoger risico van vroegtijdig overlijden hebben dan niet-depressieve mensen.[2-4] Dit verschil wordt vooral verklaard door sterfte als gevolg van niet-natuurlijke oorzaken en HVZ. Depressie en HVZ zijn tevens vaak comorbide ziekten. Niet alleen zijn er aanwijzingen dat depressie bijdraagt aan het ontstaan van HVZ, maar ook dat depressie na een myocardinfarct (MI) een negatieve invloed heeft op de medische prognose.[5]

Depressie en incidentie van hart- en vaatziekten

Eén van de eerste publicaties over een mogelijk verband tussen depressie en HVZ, is een studie van Malzberg uit 1937.[6] In een cohort depressieve patiënten bleek de cardiovasculaire mortaliteit hoger te zijn dan op basis van gegevens uit de algemene bevolking verondersteld mocht worden. Meer recent volgde de Precursors Study 1.190 mannelijke geneeskundestudenten gedurende veertig jaar.[7] De cumulatieve incidentie van depressie was 12%. Mannen die een depressie ontwikkelden, bleken een meer dan tweemaal zo groot risico op HVZ te hebben dan mannen die depressievrij bleven. Dit risico van de ontwikkeling van een MI bleef zelfs tien jaar na aanvang van de eerste depressieve episode bestaan. In Denemarken werd van 1964 tot 1991 een cohort gevolgd van in 1914 geboren personen.[8] Mensen met depressieve klachten hadden een bijna tweemaal verhoogde kans op mortaliteit en het krijgen van een MI dan mensen zonder depressieve klachten Ook in Nederland wordt onderzoek gedaan naar de relatie tussen depressie en de ontwikkeling van HVZ. Penninx en collega's volgden 2.847 mannen en vrouwen tussen de 55 en 85 jaar oud.[9] Mensen zonder HVZ, maar met een depressie, hadden bijna vier keer meer kans op overlijden als gevolg van cardiale oorzaken dan mensen zonder depressie (zelfs na controle voor belangrijke risicofactoren als roken en hypertensie). Hoewel de meeste studies een verband aantonen tussen depressie en HVZ, is er ook een aantal dat negatieve resultaten heeft gevonden. Zo vond één studie alleen een verband tussen depressie en HVZ bij vrouwen[10], terwijl een andere studie alleen een verband bij mannen aantoonde.[11]

Depressie en prognose na een myocardinfarct

MI-patiënten ervaren vaak stemmingsklachten. Mede afhankelijk van de definiëring van depressie, wordt de prevalentie na een MI geschat op ongeveer twintig tot dertig procent.[12] Daarnaast zijn depressieve klachten bij MI-patiënten veelal langdurig van aard. Recent onderzoek laat zien, dat depressieve symptomen geen tijdelijk probleem vormen, maar persistent zijn gedurende het eerste jaar na het MI.[13] Omdat depressie zo frequent voorkomt bij MI-patiënten, wordt vaak gedacht, dat een zekere mate van depressie een normale reactie is op de cardiale gebeurtenis. Afgezien van het feit dat een depressie de kwaliteit van leven drastisch vermindert, heeft de depressie ook een negatieve invloed op het herstel en de prognose van de patiënt. Depressieve hartpatiënten hebben een grotere kans op het ontwikkelen van nieuwe cardiale gebeurtenissen dan MI-patiënten die geen depressie doormaken.[14,15]
De groep van Lespérance en Frasure-Smith uit Canada heeft veel onderzoek verricht naar dit onderwerp. Zo hebben zij aangetoond, dat depressie na een MI het risico van overlijden verzesvoudigd in het eerste jaar na ontslag uit het ziekenhuis, onafhankelijk van andere belangrijke prognostische factoren.[16] Ook lieten zij in twee andere studies zien, dat depressie bij gehospitaliseerde MI-patiënten een voorspeller was van sterfte zes en twaalf maanden later, en dat de invloed van depressie op de prognose net zo relevant was als die van verminderde linker ventrikel ejectiefractie (pompfunctie van het hart) en cardiale voorgeschiedenis.[17,18] Andere onderzoekers hebben studies gerapporteerd die deze bevindingen ondersteunen: depressie verhoogt de morbiditeit en mortaliteit in de eerste maand na het MI[19] en de kans op cardiale sterfte en ritmestoornissen[20]. Tevens bleken mensen met HVZ en depressieve klachten 69% meer kans te hebben op cardiale mortaliteit tijdens een periode van vijftien jaar.[21]

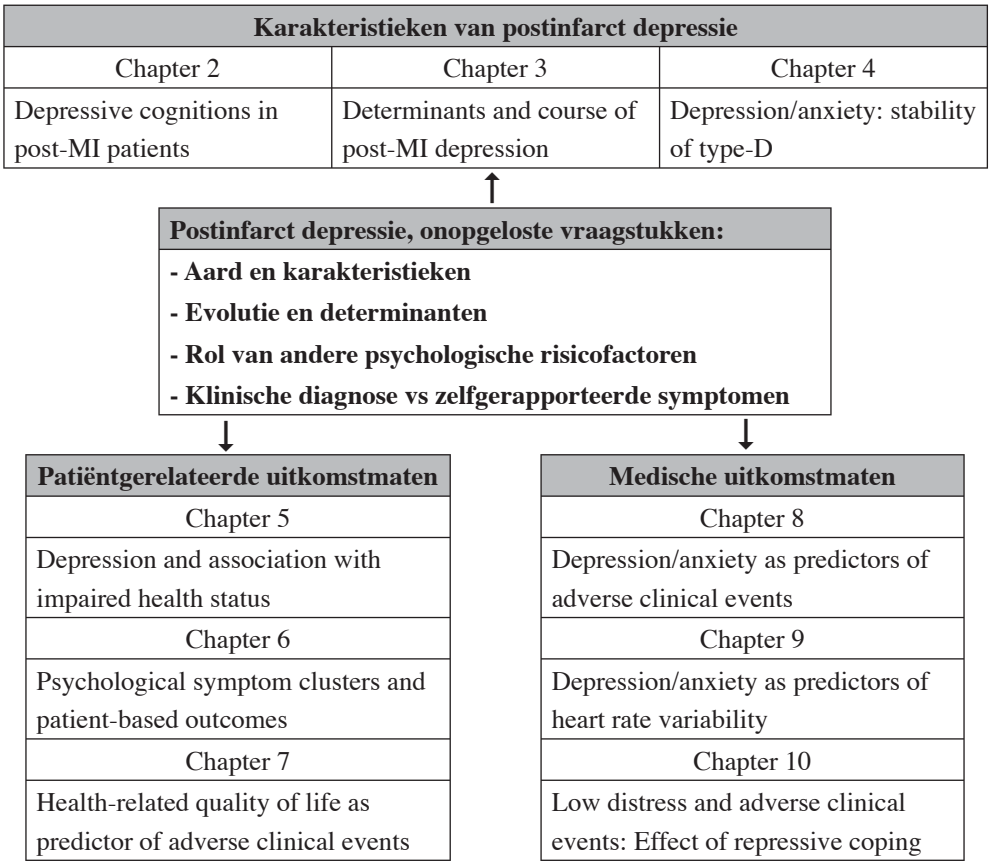
Doel van dit proefschrift

Dit proefschrift is gebaseerd op een longitudinale studie bij 475 patiënten die een acuut MI doormaakten in de periode mei 2003 tot juli 2006. Patiënten werd gevraagd om deel te nemen aan de studie tijdens hun ziekenhuisopname op de afdeling cardiologie van het Catharina Ziekenhuis Eindhoven, St. Elisabeth Ziekenhuis Tilburg, TweeSteden Ziekenhuis Tilburg, en het St. Annaziekenhuis te Geldrop. Patiënten werden onderzocht op verschillende medische, psychologische, en demografische factoren tijdens hun ziekenhuisopname en 2, 12 en 18 maanden na het MI. De verschillende hoofdstukken van dit proefschrift zijn gebaseerd op gegevens die zijn voortgekomen uit deze studie, met uitzondering van hoofdstuk 6 en 9. Hoofdstuk 6 is gebaseerd op data van de EXIT studie, waaraan vitaal uitgeputte dotterpatiënten van het Academisch Ziekenhuis Maastricht, Rotterdam, Nijmegen, en het Catharina Ziekenhuis Eindhoven deelnamen. Hoofdstuk 9 bevat data van 731 patiënten

met HVZ die in het kader van 2 studies verzameld werden in het Academisch Ziekenhuis Antwerpen, België.

Ondanks dat we de afgelopen jaren een duidelijke opmars hebben gezien van onderzoek naar het verband tussen depressie en HVZ, blijven verschillende fundamentele vragen over de aard, karakteristieken, evolutie en voorspellende waarde van depressie onbeantwoord. Figuur 1 geeft een schematische weergave van deze onopgeloste vraagstukken en de samenhang met de verschillende hoofdstukken van dit proefschrift.

Figuur 1. *Onopgeloste vraagstukken en organisatie van het proefschift*



Bevindingen van dit proefschrift

Karakteristieken van postinfarct depressie

Het eerste deel van dit proefschrift richt zich op de aard en karakteristieken van depressie na een MI. De resultaten van *hoofdstuk 2* laten zien dat de symptoompresentatie van depressie bij MI-patiënten zowel kwalitatief als kwantitatief verschillend is van depressie bij psychiatrie patiënten. Depressieve cognities (gedachten die kenmerkend zijn voor depressie, zoals: 'het leven is de moeite niet waard', 'ik ben waardeloos') zijn minder aanwezig in MI-patiënten met een depressieve stoornis, en tevens vertonen zij lagere niveaus van depressieve symptomen, wat aangeeft dat zij minder ernstig depressief zijn dan psychiatrie patiënten. Deze resultaten benadrukken dat meer inzicht in de aard en karakteristieken van depressie van belang is voor de ontwikkeling van effectieve depressietherapieën voor MI-patiënten.

Hoofdstuk 3 gaat dieper in op de evolutie en determinanten van depressie bij MI-patiënten. Het blijkt dat depressieve symptomen geen tijdelijk probleem vormen, maar persistent zijn gedurende het eerste jaar na het MI. Cardiale voorgeschiedenis, depressieverleden, en type-D persoonlijkheid zijn de belangrijkste risicofactoren voor dit persistente verloop. Hieruit volgt dat psychologische screening en behandeling in een vroeg stadium belangrijk zijn om te voorkomen dat de symptomen chronisch worden, en om de negatieve invloed daarvan op de kwaliteit van leven en medische prognose te verminderen.

Het is tevens interessant om, naast stemmingstoestanden zoals angst en depressie, te kijken naar meer globale persoonlijkheidstrekken. Uit onderzoek bij hartpatiënten is reeds gebleken dat het type-D ('Distressed') persoonlijkheidstype een grote rol speelt bij het ervaren van psychologische stress[22,23], en bovendien een negatieve invloed heeft op de kwaliteit van leven[24,25] en prognose[26,27]. Patiënten met een type-D persoonlijkheid ervaren frequent negatieve emoties, en voelen zich gelijktijdig geremd om in het bijzijn van anderen hun emoties te uiten.[28] Het type-D construct is ontwikkeld om een chronische psychologische conditie weer te geven, in tegenstelling tot de meer acute stemmingstoestanden.[29] Uit de resultaten van *hoofdstuk 4* blijkt dat type-D inderdaad een stabiel construct is gedurende een periode van 18 maanden na het MI. Type-D wordt niet beïnvloed door stemmingstoestand en ziekte-ernst, wat aangeeft dat type-D patiënten, ongeacht hun mentale en lichamelijke toestand, de stabiele neiging vertonen om negatieve emoties ervaren en sociaal geremd zijn. Gezien deze bevindingen is het raadzaam om persoonlijkheidsvariabelen te betrekken in onderzoek naar de relatie tussen psychologische factoren en HVZ.

Patiëntgerelateerde uitkomstmaten

In de afgelopen decennia is continu vooruitgang geboekt in de ontwikkeling van nieuwe medische interventies, zoals de dotterbehandeling. Daardoor zijn sterftecijfers als gevolg

van acute coronaire syndromen sterk gedaald.[30] Een belangrijke doestelling van therapie is momenteel het verbeteren van de gezondheidstoestand van patiënten, waaronder hun kwaliteit van leven.[31] Patiënten prefereren kwaliteit van leven vaak boven levensverlenging.[32] In het tweede deel van dit proefschrift wordt daarom gekeken naar patiëntgerelateerde uitkomstmaten, zoals gezondheidstoestand. Omdat er nog weinig bekend is over de determinanten van verminderde gezondheidstoestand, wordt in *hoofdstuk 5* onderzocht wat de invloed is van een depressieverleden op de gezondheidstoestand van MI-patiënten. Resultaten laten zien dat depressieverleden geassocieerd is met meer lichamelijke beperkingen en verminderde kwaliteit van leven 2 maanden na het MI, rekening houdend met demografische en klinische factoren. Echter, uit nader onderzoek blijkt dat dit effect toegeschreven kan worden aan de invloed van huidige depressie. Patiënten met een depressieverleden en actieve depressie hebben een meer dan driemaal zo groot risico op lichamelijke beperkingen, en zelfs 4 keer meer kans op een verminderde kwaliteit van leven dan patiënten zonder depressie. Deze bevindingen tonen aan dat depressie een belangrijke risicofactor is voor verminderde gezondheidstoestand na een MI.

De rol van psychologische factoren anders dan depressie, is minder uitgebreid onderzocht in MI-patiënten. Bovendien is het niet bekend welke symptomen van stress specifiek zijn na een MI, en of er subgroepen van patiënten bestaan met verschillende psychologische symptoomprofielen. Uit *hoofdstuk 6* blijkt dat symptomen van stress na een MI hoofdzakelijk bestaan uit depressieve gevoelens, angstgedachten, emotionele uitputting, en afwezigheid van positieve emoties. Symptoomprofielen gebaseerd op deze kenmerken, bestaan uit 2 Stressgroepen en een groep zonder stress. Beide Stressgroepen zijn geassocieerd met psychiatrische co-morbiditeit en verminderde gezondheidstoestand, ondanks de afwezigheid van depressieve gevoelens in een van deze Stressgroepen. Hieruit volgt dat sommige MI-patiënten meer kans hebben op negatieve uitkomsten, ondanks hun lage niveaus van depressieve gevoelens. Deze resultaten benadrukken het belang van andere affectieve componenten dan depressie in de relatie tussen psychologische stress en patiëntgerelateerde uitkomstmaten.

Gezondheidstoestand is, naast een belangrijke patiëntgerelateerde uitkomstmaat, tevens een voorspeller van mortaliteit en morbiditeit bij hartpatiënten.[33,34] Echter, het effect van gezondheidstoestand op de medische prognose is nog niet eerder onderzocht in dotterpatiënten. De resultaten van *hoofdstuk 7* laten zien dat dotterpatiënten met een slechte gezondheidstoestand 2 keer meer kans hebben op cardiovasculaire gebeurtenissen, zoals bijvoorbeeld MI, bypass operatie, en sterfte, in de eerste 6 maanden na de dotterprocedure. Gezondheidstoestand is geen voorspeller van cardiovasculaire gebeurtenissen die plaatsvinden 6 maanden tot 2 jaar na de dotteroperatie. Meer onderzoek is nodig om het belang van gezondheidstoestand aan te tonen in de identificatie van dotterpatiënten met een ongunstige medische prognose.

Medische uitkomstmaten

Het laatste deel van het proefschrift richt zich op medische uitkomstmaten. De invloed van depressie op de medische prognose van hartpatiënten is uitgebreid onderzocht, ofschoon de rol van angst in dit verband nog vrijwel onbekend is.[35,36] Uit *hoofdstuk 8* blijkt dat MI patiënten met symptomen van depressie en angst, en vooral met co-morbiditeit van depressie en angst, een bijna driemaal zo groot risico op cardiale sterfte en MI hebben dan patiënten zonder deze symptomen. Om de risicostratificatie en behandeling van MI-patiënten te optimaliseren, is het belangrijk om naast depressie- en angstsymptomen apart, te kijken naar de co-morbiditeit van deze symptomen.

Verminderde parasympathische en verhoogde sympathische activiteit zijn risicofactoren voor cardiovasculaire morbiditeit en mortaliteit.[37] Onderzoek naar veranderingen in het autonome zenuwstelsel van hartpatiënten heeft zich onder andere gericht op hartslag en hartslagvariabiliteit. De meeste studies die zich richten op hartslag en hartslagvariabiliteit laten zien, dat depressieve patiënten een hogere rusthartslag hebben dan niet-depressieve patiënten.[38] Dit is een risicofactor voor het krijgen van een hartstilstand en het bevordert aderverkalking.[38,39] Normaal gesproken laat de hartslag een periodieke variatie zien in het tijdsinterval tussen opeenvolgende hartslagen. Dit fenomeen wordt ook wel hartslagvariabiliteit genoemd en wordt gebruikt als maat voor parasympathische en sympathische sturing van het hart.[40] Een verlaagde hartslagvariabiliteit is een onafhankelijke voorspeller voor het ontstaan van HVZ en mortaliteit als gevolg van HVZ.[41] Er is relatief nog weinig bekend over het effect van depressie, en vooral van angst, op de hartslagvariabiliteit van MI-patienten. Daarom wordt in *hoofdstuk 9* gekeken naar de invloed van depressie en angst op hartslagvariabiliteit, gemeten door middel van een 24-uurs meting van het elektrocardiogram (ECG). Na rekening te hebben gehouden met demografische en klinische factoren, blijkt een angstdiagnose, maar niet depressie, een negatieve invloed te hebben op parasympatische modulatie van het hartritme van MI-patiënten. Deze bevindingen geven meer inzicht in de rol van autonome dysfunctie in de relatie tussen angst en HVZ, maar roepen ook vragen op over hartslagvariabiliteit als biologische mechanisme dat het verband tussen depressie en HVZ kan verklaren.

Aangezien psychologische stress geassocieerd is met HVZ[42,43], worden hartpatiënten die weinig stress rapporteren beschouwd als een laagrisico groep voor ongunstige medische prognose. Patiënten met een repressieve copingstijl hebben de neiging om negatieve emoties te vermijden en onderdrukken. Dit beschermt tegen de ontwikkeling van psychiatrische stoornissen[44], maar is ook gerelateerd aan onder andere een toename in de bloeddruk[45] en cortisol disregulatie[46]. Met andere woorden, patiënten met een repressieve copingstijl vertonen duidelijk fysiologische signalen van stress maar detecteren en rapporteren deze niet. De resultaten van *hoofdstuk 10* laten zien dat hartpatiënten met een repressieve copingstijl, ondanks hun lage niveaus van stress, een duidelijk verhoogde kans hebben op sterfte en MI gedurende een periode van 5 tot 10 jaar. Dit fenomeen veroorzaakt mogelijk onderbehandeling

van hoogrisicopatiënten en een onderschatting van het effect van stress op het hart.

Potentiële mechanismen

Hoewel veel studies een verband hebben gevonden tussen depressie en HVZ, is er relatief weinig bekend over de onderliggende mechanismen die dit verband kunnen verklaren. Zowel gedragsgerelateerde als biologische mechanismen komen in aanmerking als mogelijke verklaring.

Gedragsgerelateerde mechanismen

Recente studies hebben laten zien, dat bepaalde gedragsfactoren kunnen bijdragen aan een slechtere prognose van depressieve patiënten. Zowel MI-patiënten als gezonde mensen met een depressie roken en drinken significant meer en zijn fysiek minder actief dan mensen die niet depressief zijn. Deze gedragsfactoren zijn belangrijke risico-indicatoren voor het ziekteverloop na een MI.[47,48] Tevens houden depressieve MI-patiënten zich minder goed aan de voorgeschreven behandeling of therapie.[49] Verminderde therapietrouw verlaagt de overlevingskans van deze patiënten.[50]

Biologische mechanismen

Een aantal lichamelijke processen is kenmerkend voor zowel HVZ als depressie. Dit zijn bijvoorbeeld ontregeling van het autonome zenuwstelsel (AZS), hyperactiviteit van de hypothalamus-hypofyse-bijnier-as (HPA-as), verhoogde aanwezigheid van ontstekingsgerelateerde factoren en een verhoogde bloedplaatjesactiviteit. Door de aanwezigheid van deze risicofactoren in beide ziekten, kan mogelijk het verband tussen depressie en HVZ verklaard worden.

Zoals eerder vermeld zijn verminderde parasympathische en verhoogde sympathische activiteit risicofactoren voor cardiovasculaire morbiditeit en mortaliteit.[37] Onderzoek naar veranderingen in het autonome zenuwstelsel van hartpatiënten heeft zich gericht op enerzijds catecholamine-niveaus, met name norepinefrine, en anderzijds hartslag en hartslagvariabiliteit. Norepinefrine-niveaus zijn lastig te interpreteren, omdat verscheidene mechanismen verantwoordelijk kunnen zijn voor het overschot aan norepinefrine. Bovendien is het onduidelijk of de lokale sympathische activiteit in de arm, waar het bloed verzameld wordt, representatief is voor de gehele lichamelijke sympathische activiteit, waaronder het hart.[51]

Wat betreft hartslagvariabiliteit, zijn studies niet eenduidig in het beantwoorden van de vraag of depressie bij hartpatiënten zorgt voor een extra verlaging van de hartslagvariabiliteit. Zo staan bijvoorbeeld twee grote Amerikaanse studies lijnrecht tegenover elkaar. De

resultaten van de ene studie zijn gebaseerd op data die verzameld werden in het kader van een grote klinische trial (ENRICHD). In dit onderzoek werd bij 424 niet-depressieve en 380 depressieve MI-patiënten een 24-uurs meting van het ECG gedaan. Resultaten lieten zien dat verscheidene maten van hartslagvariabiliteit verlaagd waren in de depressieve patiëntengroep.[52] De tegenpool van deze studie maakt deel uit van de 'Heart & Soul study', die een vergelijking maakte van 195 depressieve en 678 niet-depressieve patiënten met stabiele coronaire hartziekte. Ook hier kregen alle deelnemers een 24-uursopname van het ECG. De resultaten met betrekking tot hartslagvariabiliteit verschilden echter niet voor depressieve en niet-depressieve patiënten.[53] De inconsistente resultaten op dit gebied zijn deels te verklaren door verschillen in patiëntenpopulaties, de variabelen waarvoor in de statistische analyse gecorrigeerd wordt en de vele methoden waarmee depressie gemeten wordt. Uitgebreide, goed gedocumenteerde studies zullen nodig zijn om een uiteindelijk oordeel te kunnen geven over de rol van autonome dysfunctie in de relatie tussen depressie en MI.

Schadelijke gevolgen

Cortisol is een steroïdhormoon dat wordt uitgescheiden door de bijnierschors en betrokken is bij allerlei lichaamsprocessen, zoals de regulatie van vaatvernauwing, het suikergehalte en het afweersysteem. Ook in stressreacties speelt cortisol een belangrijke rol. Cortisol is het eindproduct van een zeer nauwkeurig afgestelde hormonale cascade die begint in de hersenen en via de hypothalamus en de hypofyse eindigt in de bijnierschors, met terugkoppeling van cortisol op elk van deze tussenstations. Als gevolg van chronische of frequent herhaalde stressvolle gebeurtenissen kan cortisol chronisch verhoogd uitgescheiden worden, wat potentieel schadelijke gevolgen heeft. Voortdurende blootstelling aan verhoogde cortisolniveaus kan namelijk leiden tot hypertensie en coronaire hartziekte.[54,55] Verschillende onderzoeken rapporteren, dat depressie geassocieerd is met verhoogde cortisolniveaus gedurende de dag en een veranderde stressreactiviteit. Patiënten met een depressie laten over het algemeen wel een normale stressreactie zien, maar tijdens de herstelperiode blijven de cortisolwaarden veel hoger dan bij controleproefpersonen zonder depressie.[56] Het is dus mogelijk, dat het verband tussen depressie en HVZ onder invloed staat van chronisch verhoogde cortisolniveaus.

Chronisch ontstekingsproces

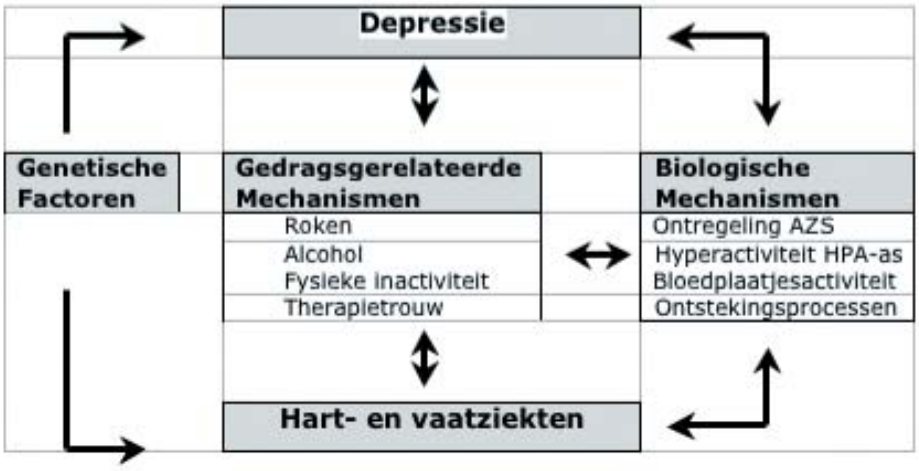
Bepaalde vormen van HVZ ontstaan door een chronisch ontstekingsproces dat in gang wordt gezet door schade aan de vaatwand. Immunologische factoren spelen een rol bij de afzetting van vet in de slagaders en in de proliferatie en migratie van gladde spierweefselcellen. Als gevolg van vasculaire schade treden er ontstekingsreacties op in het lichaam om de schade te herstellen. De continue aanwezigheid van ontstekingsfactoren kan de herstellende functie echter op negatieve wijze beïnvloeden en beschadigingen veroorzaken. Er bestaat een overlap

tussen de immunologische factoren die betrokken zijn bij depressie en degene die geassocieerd worden met HVZ. Verscheidene onderzoeken rapporteren verhoogde CRP-niveaus (een aspecifieke marker van systemische ontsteking) bij zowel hartpatiënten als depressieve patiënten. Ook ontstekingsfactoren als de pro-inflammatoire cytokines IL-6 en TNF-α zijn verhoogd in beide ziekten. Deze resultaten wijzen erop, dat het immuunsysteem een mogelijke link zou kunnen zijn tussen depressie en HVZ. Zowel het autonome zenuwstelsel als de HPA-as zijn belangrijke regulatoren van het immuunsysteem. Zoals eerder gezegd worden depressieve hartpatiënten gekenmerkt door een verlaagde parasympathische activiteit. Aangezien het parasympathische zenuwstelsel macrofaagactivering remt, is het mogelijk dat een verlaging in parasympathische activiteit kan bijdragen aan verhoogde aanwezigheid van ontstekingsparameters, zoals de bovengenoemde pro-inflammatoire cytokines.[57]

Patiënten met een depressie hebben een verminderde hoeveelheid serotonine transporters en een verhoogde hoeveelheid serotoninereceptoren. Deze bevinden zich niet alleen in de hersenen, maar ook op de bloedplaatjes. Bij depressieve patiënten zijn de bloedplaatjes hierdoor verhoogd reactief. Deze verhoogde activiteit kan leiden tot coronaire vaatvernauwing en schade aan de vaatwand als gevolg van de vorming van plaques. De voortgang van HVZ bij depressieve patiënten kan daarmee te maken hebben.[58]

Genetische basis

Recentelijk is onderzocht of depressie en HVZ (deels) hun grondslag hebben in dezelfde genetische factoren. Een tweelingonderzoek met 6.903 mannen liet zien, dat de relatie tussen depressie en HVZ volledig te verklaren is door genetische factoren.[59] Er is ook gekeken of er in het genoom locaties geïdentificeerd kunnen worden, die vaker voorkomen bij zowel mensen met een depressie, als mensen met HVZ. Dit onderzoeksveld staat nog in de kinderschoenen, maar voorlopige resultaten laten zien, dat genen die betrokken zijn bij de serotoninehuishouding en ontstekingsreacties bij beide patiëntengroepen naar voren komen als kandidaat-genen die de gedeelde genetische invloed kunnen verklaren.[60]



Model voor de relatie tussen depressie en hart-en vaatziekten

Concluderende opmerkingen

In dit proefschrift is de relevantie van depressie en andere psychologische factoren, in relatie tot patiëntgerelateerde en medische uitkomstmaten, aangetoond. Het is duidelijk dat depressie niet de enige psychologische factor is waarmee rekening gehouden moet worden, aangezien angst en persoonlijkheid ook een grote rol spelen bij MI patiënten. In de voorbije jaren hebben we een duidelijke opmars gezien van onderzoek naar het verband tussen depressie en HVZ. De resultaten van deze onderzoeken kunnen, gezien de prevalentie van depressie bij HVZ en de betekenis voor de cardiale prognose, grote gevolgen hebben voor de gehele nazorg van hartpatiënten. Het managen van depressie in hartpatiënten is zowel een klinische als een interdisciplinaire uitdaging, waarbij het combineren van de medische en psychologische expertise van cruciaal belang is. Adequate screening en behandeling door professionals is essentieel voor de prognose en kwaliteit van leven van deze grote groep patiënten.

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Chapter Thirteen

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XIII

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Everything means nothing, if I ain't got you with me…

NYC, 24 februari 2007

Chapter Fourteen

About the author

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About the author

Elisabeth Martens was born on October 2nd 1978, in Eindhoven, The Netherlands. She completed her pre-university education at the Bisschop Bekkers College Eindhoven in 1998, and started her graduate training in Psychology at Tilburg University. She specialized in medical psychology and during her master's research, she was introduced to the world of cardiovascular behavioral medicine. In December 2001, she started her Ph.D. research at Tilburg University, Department of Medical Psychology, regarding the nature, evolution, and consequences of depression in patients who have had a myocardial infarction. During her Ph.D. research, she obtained her M.Sc. degree, cum laude, in (clinical) Affective Neuroscience at an international, postgraduate trans-university program that was jointly awarded by the Universities of Maastricht and Florence (Italy). In December 2006, she accepted a position as a postdoctoral researcher at Tilburg University, Department of Medical Psychology. Recently, she visited Yale University School of Medicine, Section of Cardiovascular Medicine (USA), where she worked on neuroscience applications to cardiovascular behavioral medicine. Besides her scientific work, she is co-founder and executive of P&M Arbeidsreïntegratie, Eindhoven, were she works as a clinical psychologist.