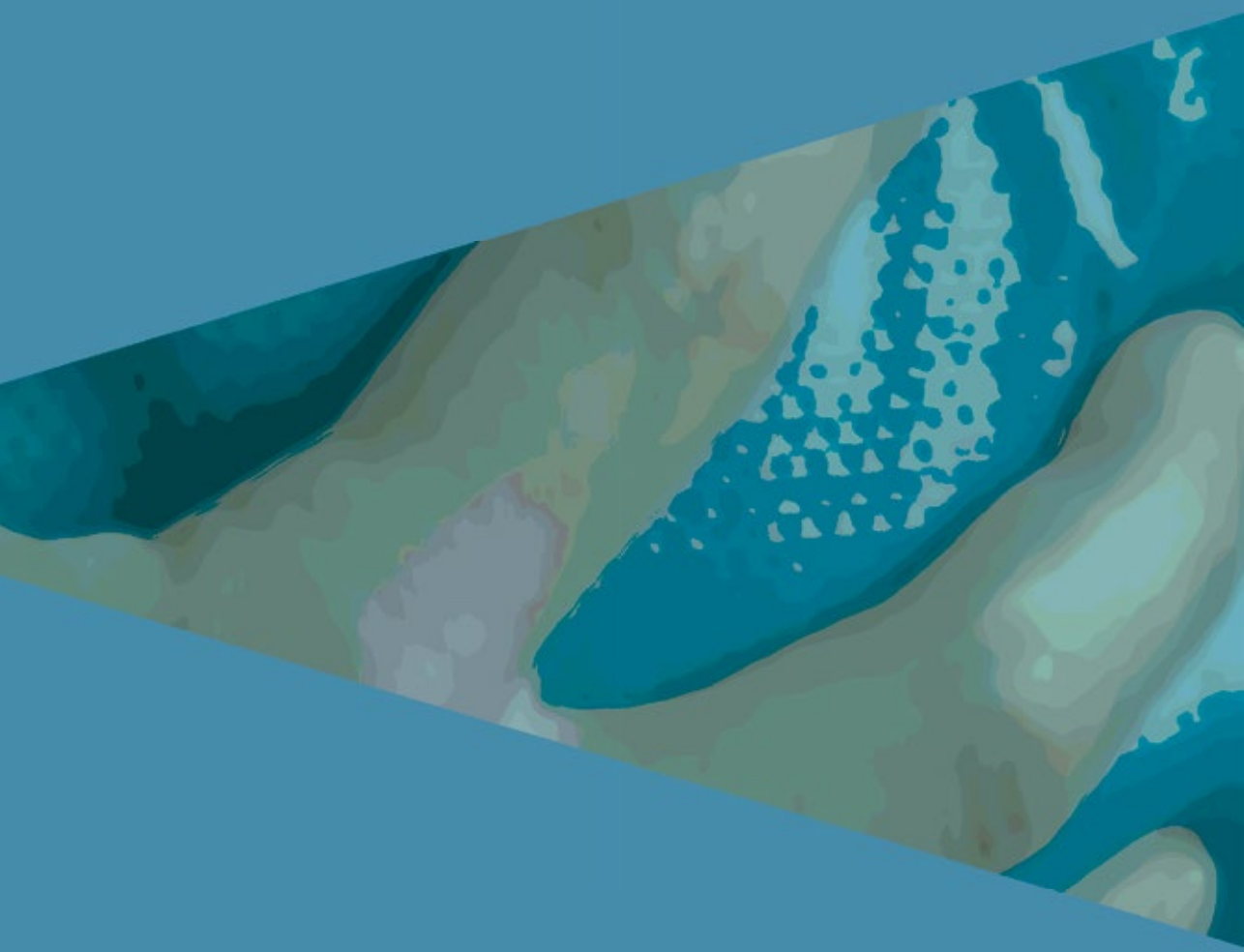
CARDIAC ANXIETY

when the heart is thought to be in danger



M.H.C.T. (Marleen) van Beek

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Maria Helena Catharina Theodora van Beek

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Prof. dr. A.E.M. Speckens
Prof. dr. A.J.L.M. van Balkom (VU medisch centrum)
Prof. dr. R.C. Oude Voshaar (Universitair Medisch Centrum Groningen)

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Prof. dr. A.H.E.M. Maas (voorzitter)
Prof. dr. P. de Jonge (Universitair Medisch Centrum Groningen)
Prof. dr. A. Honig (VUmedisch centrum)

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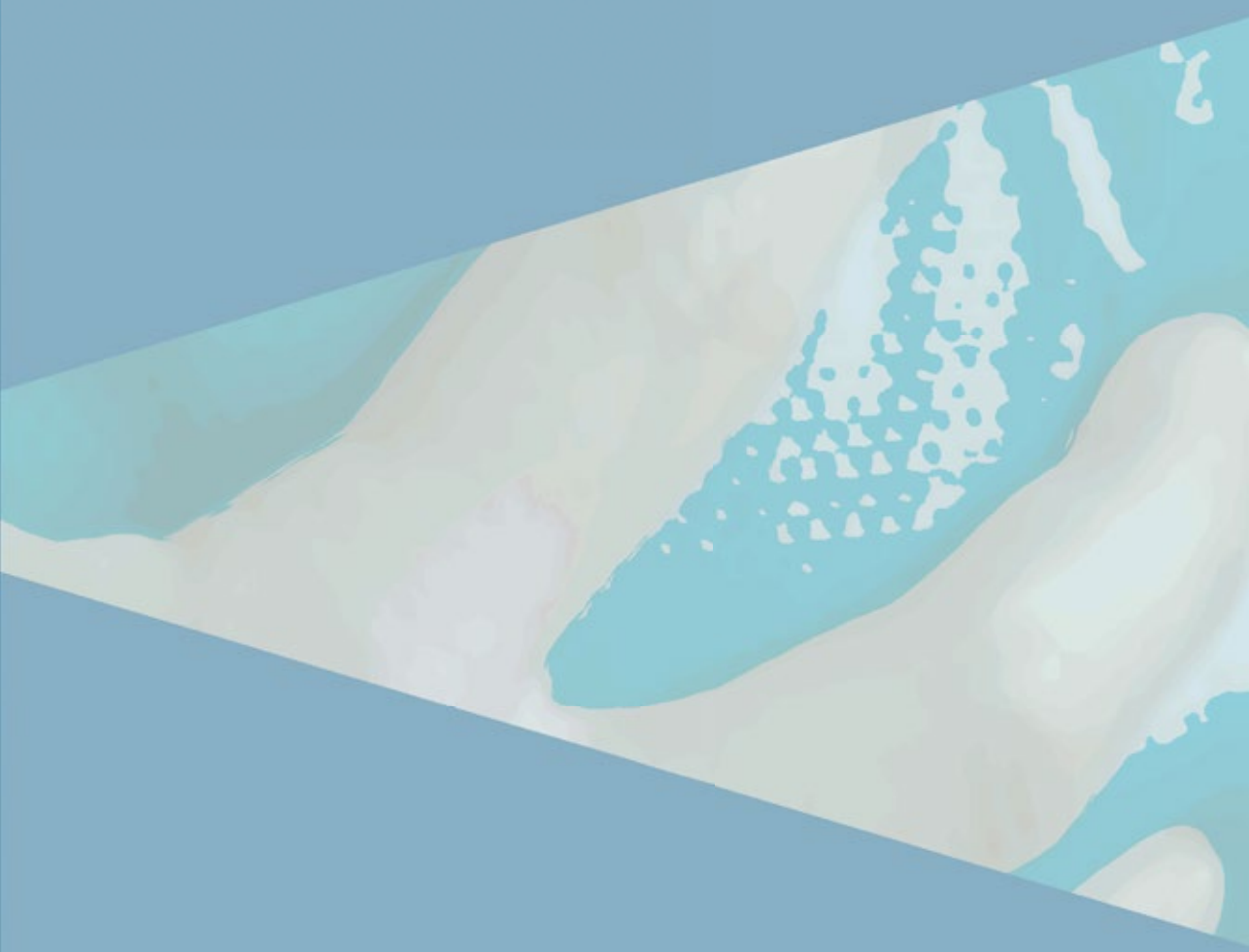
CHAPTER 1

General Introduction



General Introduction

Anxiety is a common emotion in reaction to a threatening stressor. Anxiety can range on a scale from normal to pathological. Normally, when a person detects danger, he or she responds by feeling anxious, which in turn activates the body and enables him or her to react physically to the perceived threat: either fight or flight. In this way, anxiety is adaptive. However, when anxiety is disproportionate, in type, extent and/or duration, and limits a person to function adequately in daily life, it becomes maladaptive or pathological.

At the pathological end of the anxiety spectrum are the anxiety disorders, which are among the most prevalent psychiatric disorders [1] and are defined by anxiety and distress, anxiety-related avoidance behavior and functional impairment. Almost one-third of all people experience an anxiety disorder during their life [2]. An example of an anxiety disorder is panic disorder, which is characterized by sudden and repeated attacks of intense fear. During these panic attacks, patients experience symptoms of physical arousal (like a racing heart or hyperventilation) and have fearful thoughts (e.g. being out of control or having a fear of dying). In between panic attacks patients fear new attacks.

Pathological anxiety often coincides with depression: a state of low mood and/or anhedonia (loss of interest in activities formerly found amusing) that influences wellbeing and interferes with daily life. In the majority of the patients with a diagnosed anxiety disorder a comorbid (current or lifetime) depression is present [3]. Additionally, in patients with a somatic disorder (pathological) anxiety is highly prevalent [4] and often concomitant with depression, and vice versa: e.g. in 90% of the depressed patients with a myocardial infarction mixed anxiety-depression is present one month post-MI [5].

Anxiety results from a perceived threat. This threat can be caused by internal triggers (like physical symptoms or worrying thoughts) or external triggers (like threatening behavior of other people or dangerous events), both real or imagined. An example of a serious threat is a heart disorder. When the heart is (thought to be) in danger, this can be (experienced as) life-threatening and as such provoke fear. The present thesis focuses on this subtype of anxiety related to the heart: cardiac anxiety.

This general introduction starts by putting cardiac anxiety in context by given background information about coronary artery disease (CAD), its associations with depression and anxiety and the hypothesized postulated mechanisms underlying these associations. Within this context, I will point to the importance of investigating

subtypes of anxiety and will introduce the concept of cardiac anxiety. Next, current research findings of cardiac anxiety in patients with a myocardial infarction (MI) are outlied, after which the focus is switched to non-cardiac chest pain (NCCP) patients. These patients experience symptoms of cardiac disease (chest pain) in the absence of a diagnosed cardiac origin. Research findings of (cardiac) anxiety in this population are discussed. Moreover, possible treatment options regarding cardiac anxiety are described. Finally, the aims and outline of the current thesis are presented.

Coronary Artery Disease and Myocardial infarction

Coronary artery disease (CAD), also called ischaemic heart disease, is the most common type of heart disease. It is a condition in which the coronary arteries which supply the heart of oxygen are completely or partially blocked, causing damage to the heart muscle. A wellknown type of CAD is a myocardial infarction (a heart attack).

As CAD is a potentially disabling and lethal disorder, it represents a major health problem with a large burden. CAD is the leading cause of death worldwide [6]. Although age-specific death rates for CAD are projected to decline, ageing of the population will result in significantly increasing total deaths over the coming years with global cardiovascular deaths expected to increase from 16.7 million in 2002 to 23.3 million in 2030 [7]. At present, approximately 3.8 million men and 3.4 million women worldwide die each year from CAD according to WHO data [8]. In the Netherlands, CAD is the second cause of death after cancer responsible for 9 720 deaths per year (CBS). A myocardial infarction (MI) was in 2012 responsible for 64% of the deaths caused by CAD, and for 35% of the hospital admissions caused by CAD in the Netherlands (CBS).

In addition to mortality rates, disease burden can be expressed by disability adjusted life years (DALYs), which are the total years of life lost due to premature mortality and years of health lost due to disability. The global burden of CAD increased by 29 million DALYs between 1990 and 2010, predominantly due to population growth and aging [9]. Although non-fatal CAD has increased more than the CAD deaths since 1990, CAD mortality remains the greatest contributor to disease burden [9]. Regarding DALYs, CAD is together with diabetes mellitus in the Netherlands third in the order of rank, after cancer and neuropsychiatric diseases.

As can be expected in review of the previous numbers, the economic impact of CAD is also high and even exceeds that of other diseases [10]. In the Netherlands, CAD is second in the order of rank regarding health care costs [11].

Pathophysiology and symptomatology

CAD is a late stage of atherosclerosis and characterized by the forming of atherosclerotic plaques in the coronary arteries. These plaques consist of substances found in the blood like fat, cholesterol, and calcium. Atherosclerosis narrows the arteries and impairs the blood flow. Plaque rupture may occur, exposing the underlying tissue, initiating platelet adherence, aggregation and further narrowing of the arteries (thrombosis), potentially leading to damage of the heart muscle. When the myocardium is injured, cardiac enzymes (e.g. troponin or creatinkinase) of dying heart cells are released in the blood, and as such may serve as a biological marker for heart damage. Depending on the severity of the impairment, CAD can be asymptomatic or symptomatic. Symptomatic CAD –also called Acute Coronary Syndrome- presents its-self as unstable angina (chest pain or discomfort in rest) or a myocardial infarction (a heart attack).

Diagnosis:

According to the World Health Organization [12] criteria a diagnosis of MI can be established when at least two out of the three following criteria are met: 1) chest pain for at least 20 minutes, 2) typical changes in electrocardiogram (ECG): the development of pathological Q-waves and/or new significant ST-segment-T-wave changes or a new left bundle branch block, 3) a typical rise and fall of cardiac enzyme levels creatin kinase MB fraction and troponin (T and I).

Treatment:

Treatment consists of reperfusion (restoring blood flow), which includes anti thrombotic treatment (pharmacological reperfusion), as well as coronary angiography followed by revascularisation if appropriate (mechanical reperfusion by percutaneous coronary intervention). The remaining heart function is determined by assessing the left ventricular ejection function (LVEF) by echo-cardiogram and patients are assigned for cardiac rehabilitation. Secondary prevention measures consist of management of cardiovascular risk factors (like hypertension, dyslipidemia, diabetes mellitus, tobacco use, and physical inactivity) with lifestyle changes and drug therapy as indicated.

In regard to cardiac rehabilitation, several aspects should be considered. In addition to setting physical aims (like optimizing the physical condition and coping with physical limitations), psychological aspects (like coping) as well as social aspects (like

social support) deserve attention. An illustration of this is the presence of anxiety and depressive symptoms, which may interfere with the physical recovery aims: patients can become physically inactive due to anxiety-related avoidance or due to energy loss and anhedonia in depression [13,14]. Overcoming fear of exercise, regaining emotional balance, and adequately coping with the heart disease could therefore be important psychological aims in cardiac rehabilitation. Regretfully, research findings suggest that depressive and anxiety symptoms are in fact associated with non-attendance to these cardiac rehabilitation programs [15].

Psychological impact

As a potential life-threatening event, a myocardial infarction (MI) also has psychological impact. During the event, patients may experience anxiety as a natural response to the pain and the circumstances surrounding a heart attack [16]. Afterwards, when the acute stress of the event itself and its treatment is expected to be settled down, patients have to deal with insecurities and with the feeling that the body is unreliable: they need to find a new balance in life [17]. Whereas some patients will manage to cope, the majority of the patients may experience significant symptoms of depression and/or (pathological) anxiety post-MI and a quarter to a third of the MI patients may continue to experience these symptoms one year after the MI [14,18-20].

In recent years, there has been increasing interest on the relationship between physical and mental health in CAD and MI, with the specific focus on depression and -more recently- anxiety. These concomitant affective symptoms are not only associated with a higher medical consumption [21] and a lower quality of life [22,23], but they also are associated negatively with cardiac prognosis (see below). If this prognostic association in fact turns out to be causal, it is clinically very relevant, especially since both depression and anxiety are potentially modifiable.

Depressive symptoms and cardiac prognosis in ischaemic heart disease/ after a myocardial infarction

For depression, a bidirectional association with CAD has been described. In community based populations, meta-analyses showed an association between depressive symptoms and incident CAD with higher depression levels leading to more incident CAD [24-26]. In MI patients, recent meta-analyses demonstrated that depressive symptoms increase the risk of new cardiac events [27] and mortality [27,28]. Unfortunately randomized controlled trials examining the efficacy of interventions for depressive symptoms (respectively Cognitive Behavioral Therapy (CBT), and antidepressants mirtazepine/citalopram, sertralin) did not find improving effects on

cardiac outcome [29-31]. These findings challenge the idea that these associations are causal. Some explanations can be put forward.

Firstly, one of these meta-analyses found that only eight of the 34 studies adjusted for left ventricular ejection function as marker for cardiac disease severity, which attenuated the estimated risk of depression with almost 50% from 2.18 to 1.53 [28]. This suggests that the prognostic effect of depression on cardiac outcome may be partly dependent on cardiac disease severity.

Secondly, most studies evaluating the prognostic effect of depression, assessed depressive symptoms with self-report questionnaires like the Beck Depression Inventory (BDI). This self-report questionnaire consists of a cognitive-affective dimension (assessing e.g. "sadness") and of a somatic-affective dimension (inquiring e.g. about "energy loss"). Previous studies reported a prognostic impact of the somatic-affective items with cardiac outcome, whereas no association was seen for the cognitive-affective items [32-35]. This suggests that the somatic-affective symptom dimension of the BDI picks up symptoms from the underlying medical condition. A recent study indeed found that at lower severity levels the BDI predominantly assessed somatic symptoms in MI patients [36].

Another explanation might be that measurements of depression and/or psychological stressors are not specific enough. As most psychological constructs related to mood- and anxiety disorders partly overlap, it may explain that different constructs are prospectively associated with cardiac prognosis, but also why some studies are negative. In this thesis, therefore, we specifically focus on cardiac anxiety (see below).

The impact of (general) anxiety on cardiac prognosis after a myocardial infarction

Like all diseases, a myocardial infarction by its very nature poses some level of threat [37]. Among patients with cardiac disease, anxiety can be functionally appropriate when it motivates them to immediately seek treatment for acute cardiac symptoms [14] or to adhere well to medical risk-reducing recommendations [38]. Some studies indeed found a protective effect of anxiety in patients with CAD on cardiac outcome [39-40]. However, anxiety may have negative consequences (including difficulty in making recommended lifestyle changes or in decreasing risky behaviors) when it is persistent or severe [14] and develops to pathological anxiety: a disproportionate and inappropriate reaction as to type, intensity or duration of the eliciting stimulus [41,12].

Findings of three recent meta-analyses of prospective community-based studies examining the prognostic association of anxiety on incident CAD [42-44] have demonstrated that anxiety is associated with an increased incidence of CAD. The first

meta-analysis [42] of 20 studies published up to 2009 showed a prognostic association for anxiety symptoms: these were associated with a 26% increased risk for CAD and a 48% increased risk of cardiac mortality, after adjustment for demographics, cardiac risk factors and health behaviors. The second meta-analysis [43] included 37 studies published up to 2013 of which 9 studies assessed anxiety disorders. This meta-analysis found that -after adjustment for publication-bias- the presence of anxiety increased the risk of CAD (combined with stroke and peripheral vascular disease) with 41%. These findings were consistent for studies examining anxiety disorders as well as for those evaluating anxiety symptoms. Results were also consistent between studies that took comorbid depression into account and those who did not. A third meta-analysis [44] focused on 12 studies reporting on panic disorder specifically and showed a 47% increased risk of CAD in the presence of a panic disorder.

The latter three meta-analyses of community based prospective studies were all in persons initially free of CAD. In addition to these findings, a meta-analysis in 1649 MI patients (i.e. in patients with established CAD) -including 12 studies published up to 2009 - showed in anxious versus non-anxious MI patients a pooled odds risk of 1.36 and 1.47 for adverse cardiac outcomes and all-cause mortality respectively [45]. Thus, although there are controversial findings, the presence of anxiety seems to be associated with the development of new CAD, both in patients originally free of CAD and in MI patients with established CAD.

Although in the meta-analysis in MI patients after multivariate analysis only three studies remained significant in showing an inverse association for anxiety with cardiac prognosis, effect estimates of the included positive studies [18,46-48] that did adjust for Left Ventricular Ejection Fraction were only slightly or not attenuated. Furthermore, in a prospective study generalized anxiety disorder was associated with a higher risk of cardiovascular events and mortality in MI patients, and this prognostic association was independent from cardiac disease severity parameters [49]. This suggests that the relationship between anxiety and cardiac prognosis post-MI might be less confounded by cardiac disease severity than that between depressive symptoms and cardiac prognosis.

As stated previously, recent research findings trying to disentangle the unique contribution of depression on cardiac prognosis, indicate the importance of looking into subtypes of depression. Likewise, as it remains unclear which specific aspects of anxiety are associated with cardiac prognosis, the need to examine the unique contribution of types of anxiety on cardiovascular risk has been recommended [42,50]. Recently, a community-based study indeed found that worry predicted non-fatal cardiac outcome over a three-year follow-up, whereas panic and phobia did

not [51]. Furthermore, a recent study in CAD patients undergoing coronary artery bypass graft surgery showed different associations of different types of anxiety with cardiac prognosis: no association of the fear and panic disorders and their symptom dimensions, but an adverse association with generalized anxiety disorder [52].

These findings suggest that different types of anxiety may be differently related with cardiac prognosis. With regard to cardiac prognosis, this thesis therefore specially focuses on a relatively unexplored subtype of anxiety: cardiac anxiety (see below).

Potential mechanisms

The association between anxiety and ischemic heart disease might be explained by both behavioral and biological mechanisms, which in turn may be associated with specific subtypes of anxiety. Anxiety appears to be associated with unhealthy behavior, which includes both more cardiac-risk-increasing behavior (like smoking) and less adherence to risk reducing advises (like medication, cardiac rehabilitation and physical activity). General anxiety (assessed with Hospital Anxiety and Depression Scale) in outpatients at risk of CAD is reported to be associated with poor diet (including higher cholesterol and alcohol intake) and more physical inactivity and smoking [53]. General anxiety symptoms (assessed with the State-Trait Anxiety Inventory (STAI) in MI patients are associated with non-attendance of cardiac rehabilitation programs, although this association lost significance in multivariate analysis [15]. Another study suggested less adherence of anxious MI patients (assessed with the Beck Anxiety Inventory) to risk reducing recommendations like reducing stress, cessation of smoking and increasing socialization, but better adherence to carrying medical supplies [54].

After a MI, patients have been demonstrated to develop symptoms of post-traumatic stress disorder (PTSD) [55,56]. PTSD is an anxiety like disorder provoked by a safety-threatening event (among which a MI) and includes arousal, re-experiences of the event (by e.g. intrusions and/or nightmares) and avoidance. PTSD symptoms secondary to MI are associated with lower levels of adherence to medical treatment among those MI patients diagnosed with PTSD compared to those without PTSD [57,58]. An explanation may be the avoidance symptoms of PTSD: the patient is unable to face the MI and avoids reminders of its traumatic nature [59]. In addition to the onset of PTSD symptoms, also the onset of panic attacks and agoraphobia have been described post-MI [60]. In respect to mechanisms of non-adherence and physical inactivity, catastrophic misinterpretation of cardiac symptoms is likely to be a factor in this anxiety subtype [59].

Also, various potential biological mechanisms explaining the negative prognostic

association between anxiety and CAD have been suggested. These mechanisms include rhythm disturbances due to increased sympathetic or decreased parasympathetic nervous activity as well as atherosclerosis promoting abnormalities like increased platelet activity or inflammation. A recent study showed anxiety disorder to be an independent predictor of reduced vagal control of the heart in post-MI patients, whereas no association was found between self-reported general anxiety (assessed with the State Trate Anxiety Inventory (STAI)) symptoms and heart rate variability [61]. In another study, general anxiety post MI (assessed with STAI) was significantly related to reduced baroflex control in multivariate analysis [62]. Furthermore, in patients without established CAD, anxiety appeared to be associated with increased platelet activity [63] or inflammation [64], arrhythmic mechanisms [65] and metabolic abnormalities as hypertension [66] and increased cholesterol levels [67].

Cardiac Anxiety in MI

Current anxiety questionnaires predominantly assess general anxiety, avoidance behavior, worrying and fear of bodily sensations. However, after a MI, cardiac-related stimuli and sensations may trigger specific anxiety symptoms, based upon their assumed negative consequences [68]. Heart-related fear is frequently associated with attention to and avoidance of cardiac-related stimuli and sensations [69,70]. When patients have more heart-focused attention, it is likely that they, regardless of their specific condition, will become concerned about cardiac-related sensations (e.g. chest-pain or heart palpitations). They may be afraid to experience a (new) heart attack especially during chest discomfort or changes in heart activity. Consequently, in order to diminish anxiety, patients may tend to anxiously check their pulse, avoid activities believed to induce symptoms, and may tend to time and again seek reassurance from health care practitioners and/or family members [68]. This specific fear and anxiety-related behavior can be conceptualized as cardiac anxiety.

Although some extent of cardiac anxiety may in fact be normal after a MI, at some point cardiac anxiety can shift toward the pathological side of the anxiety spectrum. In respect to this, not only the degree of cardiac anxiety but also its course should be considered. Unfortunately, only few studies have evaluated cardiac anxiety in cardiac patients (mainly heterogeneous populations of both CAD and non-CAD patients) and all but one [37] had a cross-sectional design [68,71,72]. The only longitudinal study showed that one fifth of cardiac patients (n=90) continued to experience clinically elevated levels of cardiac anxiety after elective bypass surgery for six months after the surgery, while levels of global anxiety and depression decreased [37]. However, due to lack of information on cardiac outcome, it is difficult to interpret the clinical relevance

of this increased and persistent cardiac anxiety. To date, no studies in a homogeneous sample of MI patients have focused on cardiac anxiety. Therefore, the present thesis studies cardiac anxiety in MI patients specifically, by evaluating both cross-sectional associations and the longitudinal course of cardiac anxiety after a MI.

Assessment of Cardiac Anxiety in MI patients

Eifert et al. has developed the Cardiac Anxiety Questionnaire (CAQ) within a heterogeneous population of both hospitalized and outpatients with and without CAD [68] . Eifert et al. evaluated the relevance of 63 items potentially assessing cardiac anxiety. These items originated from semi-structured interviews in cardiac outpatients and a literature review. Finally, 18 items were selected as potentially relevant (and unique and not overlapping) for a self-report questionnaire, assessing different aspects of cardiac anxiety by questions like "When I have chest discomfort, or when my heart is beating fast: I get frightened", "I avoid activities that make my heart beat faster" or "I pay attention to my heart beat". Each item was rated on a 5-point Likert scale ranging from 0 (never) tot 4 (always). An exploratory factor analysis was performed on these 18 items, yielding a factor structure of three factors, assessing fear, avoidance and attention. Internal consistency was checked showing a good internal consistency of the total and subscale scores.

Convergent and divergent validity of the CAQ was assessed in 30 post-angiography patients and 12 outpatients suffering from either panic disorder, generalized anxiety disorder or hypochondriasis. Correlation coefficients indicated high to moderate correlations between CAQ and convergent anxiety measures (the body sensations questionnaire, anxiety sensitivity index and illness attitude scales), and with one exception (fear scale of fear of negative evaluation scores), no association was found between CAQ and divergent validity measures (activities of daily living, brief fear of negative evaluation scale), indicating good divergent validity. The CAQ subscale fear was in general more related to convergent anxiety measures than the other two CAQ subscales. In short, the CAQ appeared to be suitable to measure cardiac anxiety, had good psychometric properties and successfully differentiated cardiac anxiety from general anxiety in psychiatric patients [68].

Good psychometric properties of the CAQ were confirmed in a cross-validation study in CAD outpatients [72]. However, in this study a fourth subscale assessing safety-seeking behavior was detected. The relevance of exploring different aspects of cardiac anxiety as assessed with the CAQ subscales is made clear in two studies. A cross-sectional study in post-angiography patients (of which one third had no or minimal CAD) demonstrated greater cardiac attention, but no greater avoidance nor fear of

cardiac sensations in patients with CAD who smoked compared those without CAD or those who were nonsmokers [71]. A longitudinal study in patients undergoing elective cardiac surgery [37] described a varying course of different aspects of cardiac anxiety after surgery: fear declined significantly 6 weeks after surgery and remained stable, whereas no change was found in heart-focused attention and in contrast, avoidance was stable 6 weeks after surgery, but then declined to a level that was lower than that before surgery. These findings show that different indicators of cardiac anxiety need to be considered separately. Due to the inconsistencies found in the number of CAQ subscales in the previously mentioned validation studies (revealing either a three or four factor structure), there is a need to validate the CAQ in an independent sample. Another reason for a cross-validation is that previous validation studies evaluated the CAQ in a heterogeneous population instead of in MI patients specifically. Therefore, the present thesis validates the CAQ in a population of MI patients.

Obviously, when aiming to explore cardiac anxiety, the preferred method is to assess it directly, e.g. with an instrument like the CAQ. However, as the research field of cardiac anxiety in cardiac patients is relatively unexplored, it would be interesting to see if cardiac anxiety can be addressed when it is not explicitly measured, as is the case in some existing datasets on MI patients like in the Depression after Myocardial Infarction (DepreMI) study [73,74]. In the previously mentioned longitudinal study in cardiac patients undergoing planned surgery [37], the CAQ scales were - as can be expected - generally more strongly associated with anxiety than with depression, but - more importantly - (negative) correlations of cardiac anxiety were stronger with physical quality of life than with psychological quality of life. Therefore, the present thesis explicitly assessed cardiac anxiety with the CAQ but also tried to capture cardiac anxiety by using self-reported physical health as measured in the DepreMI study.

Cardiac anxiety and Non-Cardiac Chest pain

Cardiac anxiety may not be limited to those with a myocardial infarction or ischaemic heart disease. Higher cardiac anxiety is also reported in patients at increased risk for arrhythmias and sudden cardiac death because of a personal or a family history of an inherited cardiac disorder [75]. Furthermore, a recent study evaluated the presence of cardiac anxiety in the general population showing higher cardiac anxiety to be associated with increasing age, a lower education level, unemployment, and not being in a stable relationship [76].

A subgroup particularly at risk for developing high cardiac anxiety are persons who experience cardiac sensations (like chest pain) in the absence of a diagnosed organic substrate, as happens in patients with non-cardiac chest pain (NCCP). These patients

report significantly higher levels of both general and cardiac anxiety compared to the general population [77] and similar to higher levels of cardiac anxiety compared to patients with established CAD [78]. This is in line with other studies showing a prevalence of up to 50% of psychiatric symptoms in patients with NCCP [78,79], reporting high levels of general anxiety, depression, catastrophic thinking, and physical disability [81,82]. Additionally, the prevalence of psychiatric diagnoses in NCCP is high, with reported percentages of 44% for a current psychiatric disorder, 41% for a current anxiety disorder and 13% for a mood disorder [83]. With respect to the diagnosis of panic disorder, some studies reported even higher percentages in NCCP patients of almost 40% [81,82]. Although cardiac anxiety and a diagnosis of panic disorder are essentially two different phenomena, which can co-occur independently, due to the experienced chest pain it is likely that the main anxiety theme of panic attacks in NCCP patients diagnosed with a panic disorder is characterized by cardiac anxiety.

When NCCP patients present themselves to a hospital with chest pain, common practice is to reassure them and refer them back to primary care. Unfortunately, the prognosis of NCCP is poor: despite reassurance by medical professionals, more than half of patients continue to report chest pain and remain concerned about having a serious heart disease [84,85]. In other words, they are assumed to experience high and persistent levels of cardiac anxiety. This is a pity, since psychiatric disorders like panic disorder and depressive disorder can be treated effectively, e.g. with cognitive behavioral therapy [86,87]. Therefore, the present thesis investigates the effect of a short CBT intervention in NCCP patients diagnosed with panic and/or depressive disorder.

Aim of the present thesis

In the present thesis three main questions concerning the concept of cardiac anxiety will be raised and addressed.

First of all, can cardiac anxiety be assessed validly and reliably with the Cardiac Anxiety Questionnaire (CAQ) in a (Dutch) population hospitalized for myocardial infarction, and if so, what is the prevalence and what are correlates of cardiac anxiety in patients hospitalized for MI?

Subsequently, what is the course of cardiac anxiety in the year after a MI and what is the impact of cardiac anxiety post MI on both quality of life and cardiac prognosis? Can a possible prognostic impact of cardiac anxiety be explored in independent populations of MI patients and by assessing cardiac anxiety on different ways: explicitly (with the CAQ) and indirectly (by using self-reported cardiac health complaints)?

Finally, can anxiety and depressive symptoms and disease severity be targeted with

cognitive behavioral therapy (CBT) in patients with non-cardiac-chest-pain who present themselves at the cardiac emergency unit and are diagnosed with a comorbid panic disorder and/or depressive disorder?

Outline of the present thesis:

This thesis focuses on aspects of cardiac anxiety in two cohorts of MI patients (chapters 2-5 and chapter 6 respectively) and in patients with NCCP (chapter 7). Validity (chapter 2), cross-sectional associations (chapter 3), longitudinal course (chapter 4) and prognostic impact of cardiac anxiety on cardiac prognosis are studied (chapters 5-6), and the effect of brief cognitive-behavioral therapy is compared with treatment as usual in a randomized controlled trial (chapter 7).

In chapter 2 we cross-validated the CAQ in a sample of 237 patients admitted for an acute coronary syndrome (ACS) and a control group of 49 patients admitted for an exacerbation of rheumatoid arthritis (RA). We evaluated the validity of cardiac anxiety as opposed to general anxiety measured with established questionnaires (Beck Anxiety Inventory, Spielberger State-Trait Anxiety Inventory and Agoraphobic Cognitions Questionnaire) and we compared the levels of cardiac anxiety in the ACS patients with the non-cardiac hospital inpatients, thereby controlling for general distress level (anxiety and depression) associated with acute hospitalization. Furthermore we tested the internal consistency and test-retest-reliability of the CAQ.

In chapter 3 we studied the cross-sectional associations between cardiac anxiety and several socio-demographic, psychological (depressive symptoms, agoraphobic cognitions and avoidance behavior respectively) and cardiac disease characteristics in for the same cohort of MI patients.

In chapter 4 we described the course of cardiac anxiety during the year after a MI in a subsample of 194 MI patients of the previously mentioned cohort. We assessed cardiac anxiety in the days after admission, and one, three, six and twelve months after discharge. Latent class growth analysis (LCGA) was performed to identify groups based on cardiac anxiety course. Between group differences were checked on several relevant socio-demographic, cardiac and psychiatric variables.

In chapter 5 we evaluated the prognostic association of cardiac anxiety on cardiac prognosis in a subsample of 193 MI patients of the previously mentioned cohort. Within one week of hospitalization and approximately three months after discharge the CAQ was administered. Study endpoint was a major adverse cardiac event (MACE) defined as a readmission for ischemic cardiac disease or all-cause mortality within 4.3 (2.0) years after the index-MI. The prognostic impact of CAQ on MACE

was evaluated with Cox regression analysis, adjusted for age, cardiac disease severity (i.e. Left Ventricular Ejection Fraction, cardiac history as defined by a history of a previous MI), and depressive symptoms (Beck Depression Inventory).

In chapter 6 we investigated the prognostic association of health complaints (as a proxy for cardiac anxiety although this was not explicitly assessed in this study) on MACE in another cohort of MI patients recruited consecutively from four hospitals in the north of the Netherlands: the DepreMI study. The somatic subscale of the self-report Health Complaints Scale (HCS) was administered to 424 MI-patients at 3 and 12 months post-MI. The prognostic impact of the HCS on MACE was evaluated with Cox regression analysis, adjusted for all socio-demographic, cardiac and psychiatric variables that were associated with MACE univariately ($p<0.10$), among which sex, age, education-level, left ventricular ejection fraction, history of MI, depressive symptoms (Beck Depression Inventory) and a diagnosis of a generalized anxiety disorder. In addition, the type of physical health complaints as well as their trajectories over time were explored.

In chapter 7 we diagnosed 103 patients visiting the cardiac emergency unit of a university medical center for non-cardiac chest pain with a comorbid depression and/or panic disorder and randomized them over a CBT intervention (n=60) or treatment as usual (n=53). After 24 weeks we evaluated the effects on disease severity as assessed by a blinded independent rater, and on several self-reported depressive and anxiety symptoms.

In chapter 8 we summarized the main results of chapter 2 to 7.

In chapter 9 we reflected in the discussion on the concept of cardiac anxiety and our research findings, on strengths and limitations of the studies described in the previous chapters, and on implications for clinical practice and future research.

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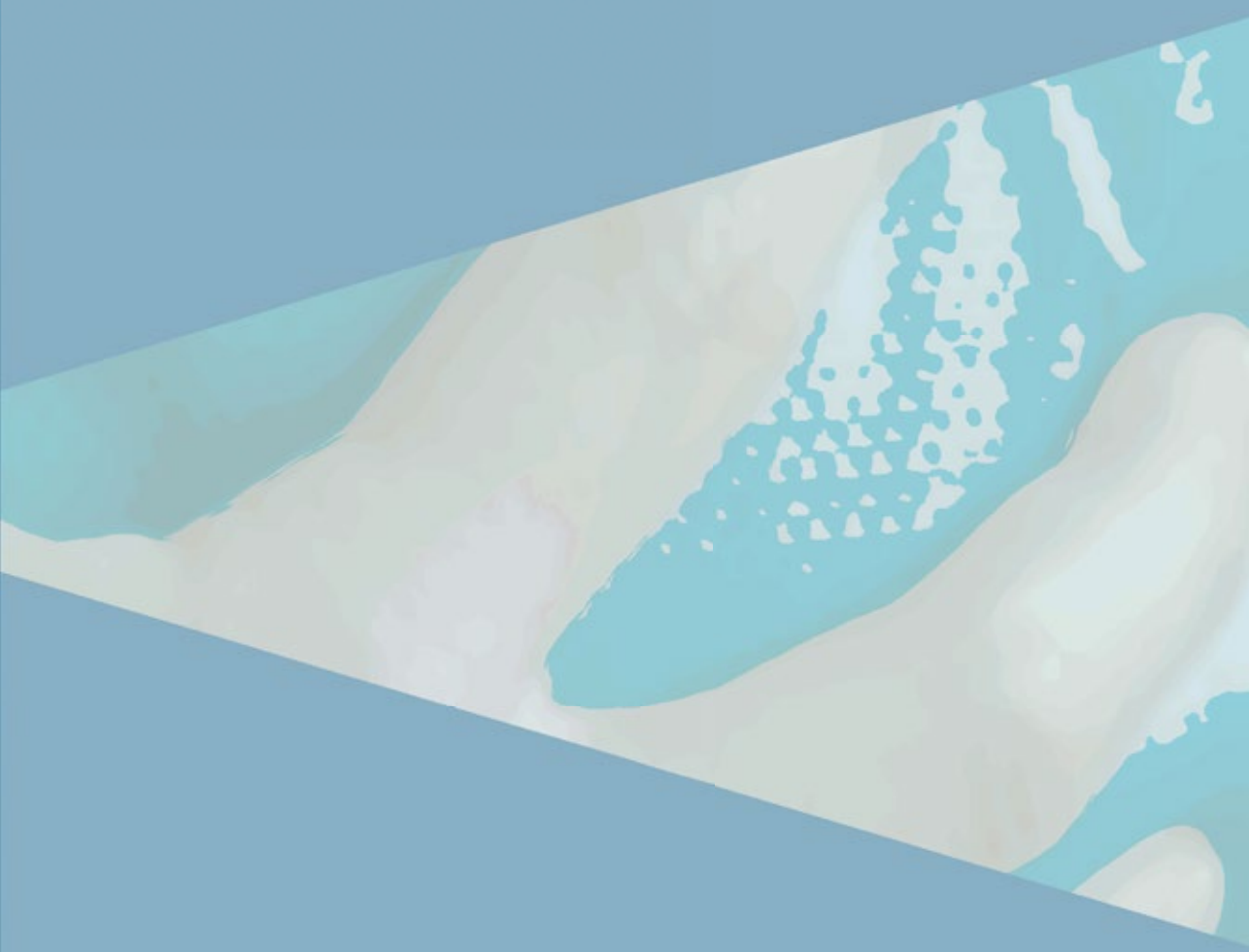
CHAPTER 2

The cardiac anxiety questionnaire: cross-validation among cardiac inpatients



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Abstract

Objective – General anxiety symptoms are common in patients with cardiac disease and considered to have an adverse effect on cardiac prognosis. The role of specific cardiac anxiety, however, is still unknown. The aim of this study is to examine the factor structure, reliability and validity of the Dutch version of the Cardiac Anxiety Questionnaire (CAQ), which was specifically designed to assess heart focused anxiety.

Methods – 237 patients admitted for an acute coronary syndrome (ACS) and a control group of 49 patients admitted for an exacerbation of rheumatoid arthritis (RA) completed the CAQ, the Agoraphobic Cognitions Questionnaire, Mobility Inventory, Beck Depression Inventory, Beck Anxiety Inventory and the State-Trait Anxiety Inventory.

Results – Although the original three-factor solution (fear, avoidance and attention) was acceptable (model fit parameters: CFI=0.89 and TLI=0.87), our data were best explained by a four factor model including safety seeking behaviors. Internal consistency and test-retest reliability were good. The CAQ had moderate correlations with the other anxiety and depression questionnaires. Recently admitted ACS patients had significantly higher scores than RA patients, even after controlling for general anxiety and depressive symptoms ($p<0.001$).

Conclusion – The CAQ is a reliable and valid instrument to assess cardiac anxiety in patients hospitalized with ACS. These results enable longitudinal studies to examine the relationship of heart-focused anxiety with cardiac prognosis and to evaluate interventions specifically targeted at anxiety in cardiac patients.

Keywords – anxiety, cardiac, heart, psychometrics, questionnaires.

Introduction

Coronary heart disease is the leading cause of death in the United States of America, with 1,200,000 cases of coronary events per year. Psychiatric co-morbidity in this population is common. Up to 50% of patients with myocardial infarction (MI) suffer from clinically relevant anxiety or depressive symptoms [1]. Numerous studies have shown [2,3] that depressive symptoms or general distress have a negative impact on duration of admission, prognosis and quality of life in cardiac patients [4,5].

Fewer studies, however, have focused on the role of anxiety in cardiac patients. Some studies suggest that anxiety may be an independent risk factor for MI in patients with and without a cardiac history [6,7]. A recent meta-analysis of 12 prospective studies with 5750 MI patients demonstrated that anxious patients had a 36% increased risk for mortality and cardiac events compared to non anxious patients [8]. Anxiety was assessed by self-report questionnaires like the State-Trait Anxiety Inventory (STAI) or Hospital Anxiety and Depression Scale (HADS). Since the STAI does not clearly differentiate anxiety from depression [9] and several emotional disturbances have been related to cardiac outcome [10], the authors state the need for new instruments to examine which particular aspects of anxiety are related to vascular events[8].

Current anxiety questionnaires predominantly assess general anxiety or fear of bodily sensations. However, as a life-threatening event, MI might evoke anxiety symptoms specific for cardiac related sensations and situations. Eifert and colleagues have developed the Cardiac Anxiety Questionnaire (CAQ) to specifically assess cardiac anxiety, heart-focused attention and related avoidance behaviors [11]. They demonstrated the CAQ to have adequate psychometric properties. It also successfully differentiated cardiac from general anxiety in psychiatric outpatients [11].

The aim of this study is to examine the factor structure, internal consistency, test-retest reliability, convergent and divergent validity of the Dutch version of the CAQ in patients hospitalized with an Acute Coronary Syndrome (ACS).

Methods

Setting and design

The study population consisted of patients admitted to the Department of Cardiology of the Radboud University Medical Center, the Netherlands, between November 2006 till March 2008. Patients were assessed for eligibility by a cardiologist within two days of admission. Patients with a diagnosis of ACS, both ST Elevated Myocardial Infarction (STEMI) and Non ST Elevated Myocardial Infarction (NSTEMI) were

eligible. The diagnosis was confirmed by the rise and fall of troponin I (> 0.20 μ/l) [12-14]. Exclusion criteria were: age above 85 years, discharge within two days of admission, and inability to fill in questionnaires.

Between day 2 and day 7 after admission, patients completed four questionnaires: the Cardiac Anxiety Questionnaire [11], Agoraphobic Cognitions Questionnaire [15], Mobility Inventory [16], and Beck Depression Inventory [17,18]. Socio-demographic data and information about cardiovascular risk factors, cardiac history and co-morbidity were extracted from the medical records. Furthermore, a subgroup, consisting of those patients admitted between December 2008 and March 2008 and who were still hospitalized, completed the CAQ again one week later to evaluate the test-retest reliability.

In December 2007, a comparison group of patients admitted to the Department of Rheumatology of the same hospital was recruited, using the same exclusion criteria. In this subsample, two more questionnaires were administered: the Beck Anxiety Inventory [19] and the STAI [20].

Measures

Cardiac Anxiety Questionnaire (CAQ) - The CAQ is an 18-item, self-report questionnaire, designed to measure heart-focused anxiety, rated on a 5-point Likert scale ranging from 0 (never) tot 4 (always). Heart- focused anxiety was defined as "the fear of cardiac-related stimuli and sensations because of their perceived negative consequences" [11]. It may be relevant to medical syndromes characterized by chest pain and psychological distress, among which cardiac and non-cardiac chest pain and panic disorder. The original factor analysis identified three subscales: heart-related fear (8 items); avoidance (5 items); and attention (5 items) [11]. The CAQ had good internal consistency of both total (Cronbach α =0.83) and subscale scores (Cronbach α of 0.83, 0.82 and 0.69 respectively).

Agoraphobic Cognitions Questionnaire (ACQ) - The ACQ is a 14-item scale assessing catastrophic thoughts while experiencing anxiety [15], rated on a 5-point Likert scale from (1) '*thought never occurs*' to (5) '*thought always occurs*'. It consists of two subscales: social-behavioral and physical concerns. It has high internal consistency (Cronbach α= 0.87), moderate test-retest reliability (r= 0.67 for 1 month) and sensitivity to changes due to treatment [15]. It also differentiates between persons with and without anxiety disorders [21].

Mobility Inventory (MI) - The MI is a self-report questionnaire assessing avoidance behavior. The level of avoidance is rated (from 0 "never avoid" through 4 "always

avoid") in 26 situations. The questionnaire has good internal consistency (Cronbach α= 0.94), convergent and divergent validity, and high test-retest reliability (r=0.90) [16].

Beck Depression Inventory (BDI) - The BDI is a 21-item self-report questionnaire measuring depressive symptoms on a 4 point scale. The total sum score (range 0-63) represents the severity of depressive symptoms, with a score of 10 or higher representing mild to severe symptoms [17,18]. It has good internal consistency (Cronbach α= 0.93) [17] and is an acceptable instrument of screening for depression in patients post-MI [22].

Beck Anxiety Inventory (BAI) - The BAI is a 21-item self-report questionnaire measuring symptoms of clinical anxiety, rated on a 4-point scale ranging from 0 (not at all) to 3 (severely). It has good internal consistency, with reported Cronbach alphas of 0.93 and 0.94 [23,24], and discriminates well between patients with and without anxiety disorder [25].

Spielberger State-Trait Anxiety Inventory (STAI) – The STAI is a self-report questionnaire with two subscales; one measuring state anxiety (STAI-S) and one measuring trait anxiety (STAI-T). Each consists of 20 items on a 4-point scale (0-3). The STAI-S measures the transitional emotional states evoked by a stressful situation, like a MI. The STAI-T reflects individual differences in anxiety proneness. Both scales have been found to be reliable (Cronbach α> 0.89) and valid [20].

Statistical analysis

First, a confirmatory factor analysis (CFA) for continuous data was conducted to test the model of Eifert et al. [11] in our ACS population (n=237). Model fit was evaluated by calculating the Tucker–Lewis Index (TLI) and the Comparative Fit Index (CFI) [26,27]. The TLI and CFI range from 0 (indicating no fit) to 1 (perfect fit) and apply a penalty function for estimating more parameters. Values of 0.90 or above indicate an acceptable fit.

As our CFA did not strictly confirm the original solution of Eifert et al. [11], we performed an exploratory factor analysis (EFA), using oblique (Oblimin) rotation, similar to Eifert et al. [11]. Since both analyses were conducted in the same sample, we controlled for possible optimism bias by checking our findings in multiple independent samples. Using bootstrapped samples, confidence intervals of the model results were calculated for both the 3- and 4-factor solution.

How the items of a questionnaire are related to each other is measured with the internal consistency. It is preferably high, but not too high, ensuring that each item

contributes some unique information. Internal consistency was determined for total and subscale scores. Test-retest reliability was measured by conducting the bivariate correlation test of Spearman.

Construct validity is the extent to which the questionnaire really measures the psychological construct of cardiac anxiety we assume it measures. Construct validity was determined by an EFA using Oblique rotation on the subscales of the used questionnaires.

Two further aspects of construct validity are convergent and divergent validity. Convergent validity is the extent to which the questionnaire is similar to other questionnaires assessing similar pathology. To measure convergent validity, a Pearson correlation coefficient was employed to assess the correlation between the different questionnaires. Divergent validity is the extent to which the questionnaire differentiates between populations. This was measured by comparing CAQ scores of ACS with RA patients. Differences in CAQ sum and subscale scores between both populations were tested by ANOVA controlling for possible confounders.

The CFA and bootstrapping procedures were conducted using Mplus [28], all other analyses using SPSS for Windows, version 15.0. All tests were two-tailed, with $P \leq 0.05$ considered statistically significant.

Results

Study population

Of the 254 eligible ACS patients, 237 patients (93.3%) gave informed consent and were included. The study sample consisted of 158 males (66.7%; mean age = 59.7, SD = 11.0) and 79 females (33.3%; mean age = 65.0, SD = 11.5). Further socio-demographic characteristics are presented in table 1. Of the patients, 128 (54%) suffered from STEMI and 109 (46%) from NSTEMI. Non-participants had a significantly higher prevalence of STEMI and higher troponin-level (81.2% vs. 54.4%, p=0.04 and mean difference 22.1 u/l, p=0.04, respectively) than participants.

Of the 54 eligible RA patients, 49 (90.7%) gave informed consent and formed the comparison group. In table 1, the RA patients are compared to the 56 patients with ACS recruited after December 2007. RA patients differed significantly from ACS patients regarding gender, marital status, work, cardiac risk factors (hypertension and hypercholesterolemia) and arthritis (see Table 1).

Table 1: Characteristics of the subjects

	Whole sample	**Sample needed for divergent validity**		**Statistics**
	ACS (n=237)*	ACS (n=56)	RA (n=49)	P value
Sociodemographics:				
Age (mean)	61.5 (SD 11.4)	58.9 (11.2)	57.7 (10.2)	.56
Male gender (%)	66.7	71.4	40.8	.002
Married (% yes)	82.3	91.1	71.4	.09**
Higher education (% yes)	25.3	21.4	20.4	.90
Working (% yes)	43.9	44.6	22.4	<.001**
Cardiac risk factors (%):				
Hypertension	44.7	41.1	8.2	<.001**
Diabetes Mellitus	17.3	16.1	8.2	.29
Hypercholesterolemia	27.4	25.0	4.1	.007**
Co-morbid somatic disorders (%):				
History of cardiac disease	32.1	28.6	18.4	.28
Peripheral Atherosclerosis	13.1	8.9	18.4	.25
Stroke	3.4	1.8	2.0	.65
Lung disease	16.0	12.5	18.4	.47
Cancer	10.5	5.4	2.0	.43
Arthritis	6.3	3.6	100.0	<.001**

* All patients including those recruited after December 2007

Factor structure

The CFA for the 3-factor-solution described by Eifert et al. [11] yielded a CFI of 0.89 and TLI of 0.87. As both parameters were (slightly) below 0.90, we subsequently conducted an exploratory factor analysis. According to both Kaiser's criterion (eigenvalues > 1) and scree plot analysis, this solution included five factors. However, two factors were difficult to interpret. Based on interpretability of the factor solution, a 4-factor-solution was subsequently extracted and appeared the most suitable for our data (explaining a total variance of 56.8%). The first three factors were identical to the original model [11], except for item 4 ("Chest pain/discomfort wakes me up at night.") loading on factor fear instead of attention, and items 11 ("I feel safe being around a hospital.") and 18 ("I tell my family and friends.") loading on factor attention instead of fear. The fourth

factor consisted of three items and could be labeled as "safety seeking behaviors" (see table 2). Using 1000 bootstrapped samples, confidence intervals of the model results were calculated for both the 3- and 4-factor solution. Within the 3-factor solution, a 95% confidence interval about the correct assignment of an item to a specific factor could not be found for 5 items (6, 11, 13, 17, and 18). For the 4-factor solution, such confidence could not be found for only 2 items (6 and 17). This indicates that the 4-factor solution is more robust, but that the items 6 ("I check my pulse") and 17 ("I like to be checked out by a doctor") remain difficult to fit for both models.

Internal consistency

Cronbach's alpha for the overall scale was 0.84, indicating a good internal consistency. In our 4-factor-model, good internal consistency was found for the subscales "fear" and "avoidance" ($\alpha = 0.77$, $\alpha = 0.90$, respectively). Moreover, the internal consistency was substantially higher for subscale "physical attention" ($\alpha = 0.60$) and for additional factor "safety seeking behavior"($\alpha = 0.57$) compared to the original subscale "attention".

Test-retest reliability

A subsample of 34 ACS patients were asked to complete the questionnaires one week later and all agreed. This subgroup did not differ from all ACS patients on any of the characteristics presented in table 1. Spearman rank correlations between CAQ at admission and after one week were high for the total score ($r=0.88$, $p<0.001$). The test-retest reliability for the four subscales was also high (fear, $r=0.88$; attention, $r=0.94$; avoidance, $r=0.80$; safety seeking behavior, $r=0.84$, all p-values < 0.001).

Similar results were found for the individual items. Test-retest reliability was moderate for item 11 ($r=0.63$), moderately high for items 5, 8, 9, 10, 13, 15 ($r=0.70$-0.79), and high for the majority of items ($r>0.80$).

Construct validity

Entering the subscales of the CAQ, BDI, ACQ and MI, the EFA identified three factors with eigenvalues greater than one. This solution had a cumulative variance of 65.4%. Factor 1 contained all CAQ subscales, indicating cardiac anxiety as separate construct distinct from depressive and general anxiety symptoms (see table 3).

Table 2: Factor loadings of factor analyses (n=237 patients)

Original subscales, item numbers and text	Model 1 (Eifert)			Model 2 (based on own PCA)			
	Fear	Avoid-ance	Atten-tion	Fear	Avoi-dance	Atten-tion	Safety
Subscale 1: Fear							
10. If tests come out normal, I still worry about my heart	**0.54**	0.29	0.05	**0.54**	0.30	0.08	0.04
11.I feel safe being around a hospital, physician or medical facility	0.20	0.18	0.61	0.03	0.12	0.21	**0.65**
13. I worry that doctors do not believe my chest pain is real	**0.56**	0.19	0.21	**0.63**	0.13	0.06	0.19
14. I worry that I may have a heart attack	**0.68**	0.05	0.09	**0.64**	0.06	0.01	0.17
15. I have difficulty concentrating on anything else	**0.68**	0.01	0.08	**0.68**	0.04	0.05	0.10
16. I get frightened	**0.76**	0.01	0.07	**0.83**	0.06	0.14	0.03
17. I like to be checked out by a doctor	**0.63**	0.01	0.33	0.38	0.07	0.13	**0.60**
18. I tell my family or friends	0.28	0.12	0.45	0.09	0.03	0.21	**0.82**
Subscale 2: Avoidance							
2. I avoid physical exertion	0.06	**0.87**	0.02	0.05	**0.85**	0.05	0.00
5. I take it easy as much as possible	0.08	**0.83**	0.05	0.07	**0.80**	0.08	0.17
7. I avoid exercise or other physical work	0.03	**0.88**	0.03	0.01	**0.87**	0.01	0.02
9. I avoid activities that make my heart beat faster	0.00	**0.86**	0.05	0.03	**0.84**	0.06	0.03
12. I avoid activities that make me sweat	0.03	**0.78**	0.11	0.08	**0.79**	0.11	0.03
Subscale 3: Attention							
1. I pay attention to my heart beat	0.24	0.30	0.38	0.06	0.20	**0.59**	0.26
3. My racing heart wakes me up at night	0.28	0.17	0.45	0.24	0.14	0.43	0.20
4.Chest pain/discomfortwakes me up at night	0.55	0.06	0.18	0.48	0.05	0.26	0.03
6. I check my pulse	0.07	0.10	**0.43**	0.22	0.05	**0.66**	0.01
8. I can feel my heart in my chest	0.42	0.09	0.47	0.23	0.01	**0.66**	0.01
Explained variance	11.7%	29.0%	8.4%	29.0%	11.7%	7.7%	8.4%

Bold factors: score > 0.50 and a difference with the other factors >0.20.

Table 3 Factor analysis of scale scores (n=237 patients)

	Factor loadings		
	1	**2**	**3**
Component 1: Cardiac anxiety			
CAQ attention	**0.82**		
CAQ avoidance	**0.72**		
CAQ fear	**0.71**		
Component 2: Avoidance			
MI avoidance activities when alone		**0.96**	
MI avoidance activities when together with others		**0.96**	
Component 3: General anxiety and mood			
ACQ social/behavioural			**0.71**
ACQ physical			**0.89**
BDI sum score			**0.64**

Bold factors: score > 0.50 and a difference with the other factors >0.20

Convergent validity

CAQ total score was moderately correlated to all anxiety questionnaires (ACQ, r=0.31; BAI, r=0.32; STAI-S, r=0.39, STAI-T, r=0.36) and weakly to the BDI (r=0.27) and Mobility Inventory (alone, r=0.21; together, r=0.22). A similar pattern for all CAQ subscales of the 3- and 4-factor-solutions was shown, except for the subscale "avoidance" that correlated less with all other questionnaires (range r=0.09 - 0.19, with exception of the STAI-T, r=0.37).

Divergent validity

Divergent validity was assessed by comparing CAQ scores of ACS and RA patients. Univariate ANOVA revealed a significantly higher mean (SD) CAQ score in ACS compared to RA patients (1.36 (0.64) versus 0.73 (0.49), p<0.001) and the four subscales: "fear" (2.09 (0.76) versus. 1.36 (0.59), F=29.3, p<0.001), "avoidance" (2.58 (1.05) versus 10.87 (0.74), F=15.6, p<0.001), "physical attention"(1.98 (0.59) versus. 1.56(0.70), F=11.5, p=0.001) and "safety seeking behaviors"(3.38(0.93) versus. 2.65(0.81), F=18.1, P<0.001). Correcting for gender, work status, marital status, level of depressive symptoms (BDI score) and general anxiety (BAI, STAI) using ANOVA did not change these results (mean (SE) corrected CAQ total score of 1.33 (0.08) versus 0.77 (0.08), F=19.4, 94, p<0.001).

Discussion

Cross-validation of the CAQ in patients hospitalized for an acute coronary syndrome (ACS) yielded good psychometric properties. Importantly, our study contributes to the validity of cardiac anxiety as opposed to general anxiety measured with established questionnaires (BAI, STAI, and ACQ). Its validity is further supported by a significantly higher level of cardiac anxiety in cardiac compared to non-cardiac hospital inpatients, even after controlling for general distress level (depression and anxiety) associated with acute hospitalization.

In contrast to the original study, our data were best explained by a 4-factor-model. This solution resembled the original 3-factor-model [11], with exception of an additional subscale of "safety seeking behaviors". Interestingly, this subscale was also identified in a study of 658 persons referred for screening on coronary heart disease [29]. In this study, the stability of the CAQ was further supported by the fact that the same 4-factor-solution applied to patients with and without coronary heart disease.

Our 4-factor-solution yielded a further differentiation between internal cues triggering anxiety (physical attention) and behaviors aimed at preventing possible catastrophes (safety seeking behaviors). This is in accordance with modern cognitive behavioral models of anxiety that increasingly differentiate between selective attention and safety seeking behaviors [30]. A minor difference was item 4 ("chest pain/discomfort wakes me up at night") which in our study did not load on factor attention but on the factor fear. A possible explanation is that our subjects were all inpatients, and sleeping disturbances in cardiac inpatients are linked with several factors including anxiety [31].

Reliability of the CAQ

Although the 4-factor-solution was most suitable to explain our data and appeared to be clinically meaningful, the original 3-factor-solution [11] was still satisfactory. In addition, we found good internal consistency for the total CAQ score and for subscales "fear" and |"avoidance" in both solutions. The internal consistency for subscale "attention" of the 3-factor-solution substantially improved by dividing it into two subscales, "physical attention" and "safety seeking behaviors". Finally, high test-retest reliabilities for both total score and subscales were found.

Validity of the concept of cardiac anxiety

The moderate correlations between CAQ and the other questionnaires confirm that cardiac anxiety is a different concept from panic attacks (ACQ), somatic anxiety (BAI), worry or generalized anxiety (STAI) and depression (BDI). This correlation is

consistent with previous research in ACS indicating an association between anxiety and depression [6,32,33]. High general anxiety has been identified as an independent predictor for cardiac events and increased health care consumption [34]. As our data support the presence of specific heart-focused anxiety in cardiac patients, one might hypothesize that this might have an even more specific (negative) effect on cardiac prognosis and might need more targeted interventions. This hypothesis is in accordance with research in patients after cardiac surgery showing that cardiac anxiety might remain high despite significantly decreased general anxiety [35].

Strengths and weaknesses of the study

This cross-validation shows good psychometric properties of the CAQ in cardiac inpatients and therefore justifies further prospective studies on the predictive validity. Some methodological issues, however, should be discussed.

First of all, a high number of eligible patients was willing to take part in the study. Nevertheless, non-participants had a significantly higher troponin level and were more often diagnosed with a STEMI. Therefore, we cannot exclude the possibility of a selection bias excluding the most severe cases who might have experienced more cardiac anxiety.

Secondly, we used only self-report questionnaires. The use of continuous scales has the advantage of measuring a broader continuum of symptoms. This is relevant since previous research has demonstrated a linear association between depressive symptoms and coronary artery diseases [36,37]. Moreover cardiac anxiety, as a concept, is not included in the DSM-IV-classification system. It might be interesting for future research though, to assess the relationship of cardiac anxiety with formal psychiatric diagnoses such as anxiety disorders or major depression.

Finally, it might be important to consider the nature of the comparison group. The choice of RA patients was made for several reasons. First of all, both groups were admitted for an acute event: exacerbation of RA and ACS, respectively. Secondly, both diseases share overlapping pathophysiological processes with regard to inflammation [38]. Thirdly, the prevalence of general anxiety and depressive symptoms in RA and cardiac patients is similar [39,40]. In our study, however, RA patients reported significantly less general anxiety. This might be explained by a longer duration of the underlying illness and a less urgent nature of the admission. However, even after controlling for general anxiety, the level of cardiac anxiety remained significantly higher in ACS patients. This is in line with the findings of Hoyer et al. [35], in patients undergoing cardiac surgery who found that 6 months after surgery, scores on all CAQ

subscales had declined compared to pre-surgery, but were still elevated compared to a comparison group of orthopedic inpatients without known cardiac disease.

Conclusion

We conclude that the CAQ is a valid and reliable instrument to assess cardiac anxiety in patients hospitalized for ACS. The high anxiety level in cardiac patients, its negative effect on the cardiac prognosis [41] and the availability of suitable treatment options for both general [42] and cardiac anxiety [29], make a convincing case for further research [6]. In addition to further prospective cohort studies of cardiac patients examining prognostic significance of cardiac anxiety, general anxiety and depressive symptoms, randomized controlled trials are necessary to evaluate the effectiveness of targeted interventions to reduce cardiac anxiety.

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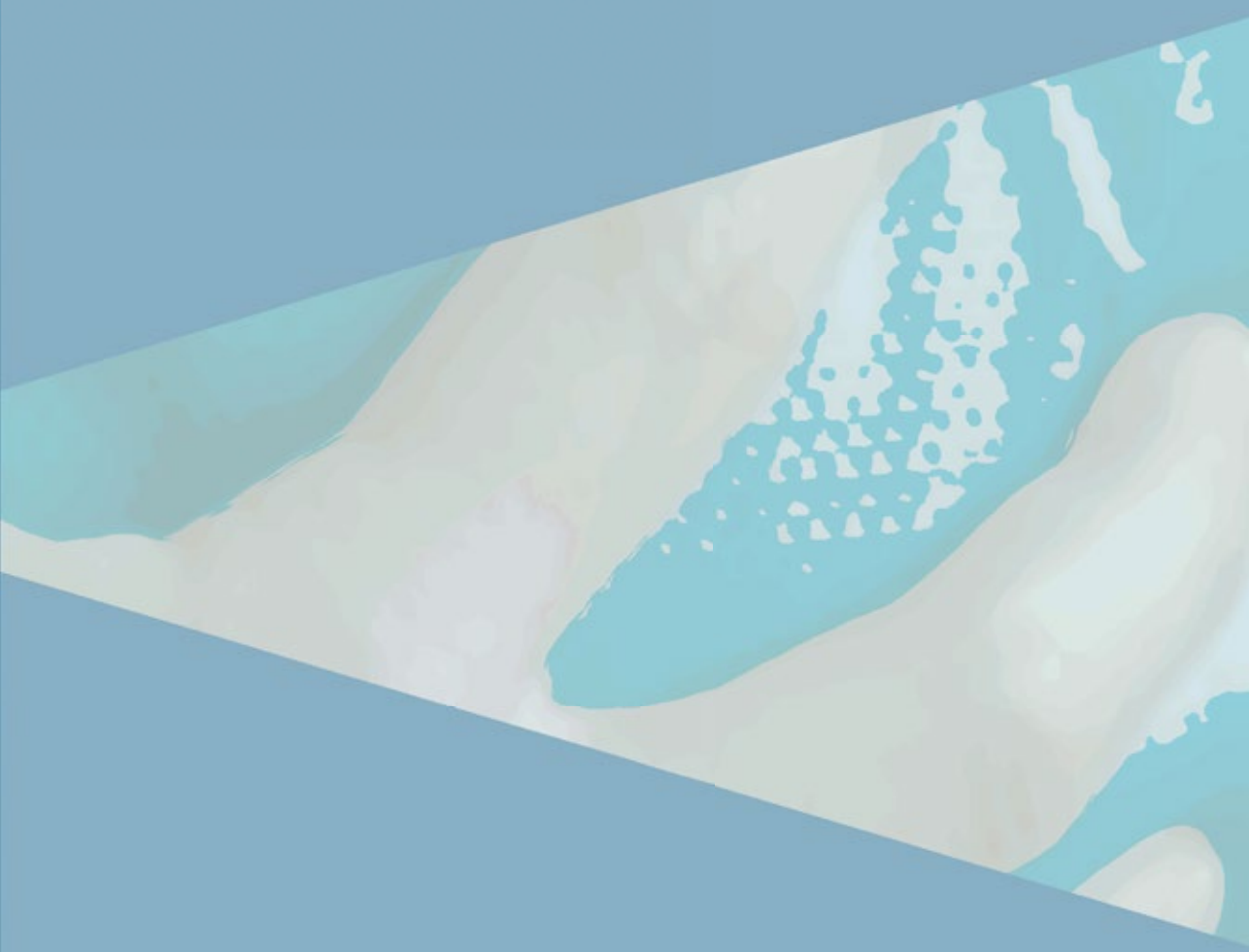
CHAPTER 3

Inverse correlation between cardiac injury and cardiac anxiety: a potential role for communication



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Abstract

Objective – General anxiety in cardiac patients is associated with worsened cardiac course. An Acute Coronary Syndrome (ACS) might evoke specific cardiac anxiety. We explored characteristics associated with cardiac anxiety in ACS patients.

Methods – In 237 patients admitted with ACS we assessed cardiac anxiety using the Cardiac Anxiety Questionnaire and gathered information on socio-demographic, psychological and cardiac disease characteristics. Univariate, multivariate logistic and linear regression analyses were used to determine which characteristics were associated with cardiac anxiety.

Results – Cardiac anxiety was not associated with socio-demographic variables. More severe cardiac injury - as indicated by ST-Elevated Myocardial Infarction (STEMI) and troponin level - was associated with less cardiac anxiety. Psychological variables (depressive symptoms, agoraphobic cognitions, avoidance behavior) were associated with more cardiac anxiety.

Discussion – Cardiac anxiety in ACS patients is associated with more psychological distress, but lower severity of cardiac injury as indicated by STEMI and troponin level. Two explanations seem likely for this latter finding. Anxious persons might seek help earlier, thus being diagnosed more often with minor cardiac pathology. Secondly, cardiac anxiety might partly be caused by diagnostic uncertainty. Future research should focus on communication strategies to reassure patients more efficiently.

Keywords – anxiety, myocardial infarction, cardiac injury, heart, questionnaires.

Introduction

General anxiety and depression symptoms are common after an acute coronary syndrome [1-3]. Most research has been conducted on depression, whereas in recent years more attention has been paid to anxiety. These more recent studies show that about 30-40% of hospitalized patients experience significant anxiety after a myocardial infarction [1-3]. As the co-occurrence of cardiac disease and significant anxiety levels are higher than can be expected by chance, a causal relationship between cardiac disease and anxiety has been postulated. To date, several studies examined the bidirectional relationship between psychiatric disease and cardiovascular disease. Interestingly, meta-analyses of these studies have found that anxiety disorders are independent risk factors for myocardial infarction in otherwise healthy people [4], and that high anxiety after a myocardial infarction significantly worsens the prognosis of the cardiac disease [5]. A recent meta-analysis which included 12 studies in patients with a myocardial infarction (MI) showed that higher anxiety levels increase the risk of adverse cardiac outcomes after a MI with 36%, with reported hazard ratios (HR) of 1.23 (95% CI 1.03-1.47) for cardiac death, 1.47 (95% CI 1.02-2.13), for overall death and 1.71 (95% CI 1.31-2.23) for cardiac events [4]. In patients with a MI, generalized anxiety disorder is associated with an almost twofold increased risk of adverse outcomes in ten years follow-up independent of demographic and clinical variables and depression [6].

Although the potential mechanisms linking anxiety and depression with impaired cardiovascular prognosis are still poorly understood, there are some theories concerning effects on the HPA-axis, inflammation (e.g. C-reactive protein), platelet aggregation as well as several behavioral mechanisms [7-11].

The studies described above, however, include general measures of anxiety, whereas it is likely that an Acute Coronary Syndrome (ACS) evokes anxiety specifically related to cardiac disease such as fear of recurrence. Such specific cardiac fears may be different than general anxiety in associations with other variables, for example in being more strongly associated with avoidance behaviors than general fears, thus having a greater and more negative impact on the prognosis [5]. To assess cardiac anxiety, the Cardiac Anxiety Questionnaire has been developed [12], with good psychometric properties in a recent cross-validation in the Netherlands [13]. To guide future studies on the value of cardiac anxiety with respect to cardiac prognosis as well as to guide the development of (nursing) interventions to lower cardiac anxiety, more knowledge is needed on the determinants of cardiac anxiety. The objective of the present study was to explore characteristics associated with cardiac anxiety. The hypothesis was that a higher severity of cardiac anxiety is associated with both psychological characteristics (increased levels of depressive symptoms and general anxiety symptoms), as well as a

higher extent of cardiac injury.

Methods

Participants

Eligible patients received oral and written information about the study and were asked informed consent. Included were patients admitted to the department of cardiology of a university medical center who were diagnosed with an acute coronary syndrome (ACS) confirmed by the presence of a rise and fall of troponin I (Troponin I > 0.20 μ/l) [14-16]. Patients with both ST Elevated Myocardial Infarction (STEMI) and Non ST Elevated Myocardial Infarction (Non-STEMI) were included. Exclusion criteria were: age above 85 years, discharge out of hospital within two days of admission, and inability to fill in questionnaires (due to insufficient knowledge of the Dutch language, cognitive impairments or being too ill to participate). The study protocol was approved by the local Medical Ethics Committee.

Psychosocial assessment

Within one week of admission, all participants completed a set of four self-report questionnaires. The primary outcome parameter was cardiac anxiety as measured with the Cardiac Anxiety Questionnaire (CAQ). This self-report questionnaire consists of 18 items rated on a 5-point Likert scale ranging from 0 (never) tot 4 (always) and is designed to measure heart-focused anxiety. The questionnaire assesses heart-related fear (e.g. "I worry that I may have an heart attack"), avoidance (e.g. "I take it easy as much as possible"), attention (e.g. "I can feel my heart in my chest") and safety seeking behavior (e.g. "I like to be checked out by a doctor". It is well-validated in both psychiatric and cardiac populations [12,13]. A recent cross validation in the Netherlands [13] reported good internal consistency of both total (Cronbach α 0.84) and subscale scores (Cronbach α between 0.6-0.9) and a high test-retest-reliability (0.88, p<.001). In another independent cross validation study in 658 persons referred for screening for coronary artery disease comparable results were shown [17].

Furthermore, three well-validated self-report questionnaires were administered, being the Agoraphobic Cognitions Questionnaire (ACQ) [18], the Mobility Inventory [19], and the Beck Depression Inventory (BDI) [20,21].

The ACQ is a self-report-questionnaire which is designed to assess the frequency of catastrophic thoughts during the experience of fear. It contains 14 items which are rated on a 5-point Likert scale from (1) '*thought never occurs*' to (5) '*thought always*

occurs'. The ACQ consists of two subscales, i.e. 1) social or behavioral concerns (e.g. act foolish), and 2) physical concerns (e.g. heart attack). The ACQ has high internal consistency (Cronbach α=0.87) and moderate test-retest reliability (r=0.67 for 1 month), as well as sensitivity to changes due to treatment [18].

The Mobility Inventory is a self-report questionnaire, which scores the level of avoidance behavior (from 0 "never avoid" through 4 "always avoid") in 26 situations (e.g. being home alone). Avoiding these situations is assessed in two conditions; when accompanied and when alone. The MI has good internal consistency (Cronbach α=0.94), high test-retest reliability (r=0.90), and good convergent and discriminant validity [19,22].

The BDI is a widely used well-validated 21-item-self-report-questionnaire assessing depressive symptoms. The total sum score ranges from 0 to 63, a score of 10 or higher is indicative of mild to severe depressive symptomatology [20,21]. It is proven to be an acceptable screening instrument (Cronbach α=0.81) in somatic populations [23] including patients with MI [24].

Cardiovascular assessment

In addition, socio-demographic data and information about cardiovascular risk factors, cardiac history and co-morbidity and in-hospital clinical course were extracted from the medical records. All cardiovascular variables were collected by a cardiologist in training and independently checked by a consultant cardiologist. This double check did not reveal any disagreement between the two.

Cardiovascular variables – The diagnosis of a MI was based on clinical history and a rise and fall of troponin I (>0.20 μ/l). Creatinin Kinase (CK) was determined with an enzymatic assay (ArchitectC16000 analyzer Abbott Diagnostics Hoofddorp (Netherlands). Based on the electro cardiogram (ECG), patients were classified as having a ST-Elevated MI (STEMI: ≥0.2 mV in men or ≥ 0.15 mV in women in leads V2–V3 and/or ≥0.1 mV in other leads) or Non ST-Elevated MI (NSTEMI). C-reactive Protein level (CRP) on the first day of hospitalization was extracted from the medical records (available for only 74.7% (n=177) of our patients). In routine clinical care CRP is assessed with turbidimetric assay (CRP antigen plus antiCRP antibody-> antigenantibodycomplex, type reaction; end-up).

Statistical analyses

The association of the CAQ with four categories of potential determinants was explored, namely socio-demographic variables, cardiovascular risk factors, psychosocial

variables, and finally, the severity of the ACS as defined by electrocardiography (STEMI versus Non-STEMI) and by the blood levels of troponin and maximum Creatinin Kinase (CK). First univariate associations were explored (using Pearsons correlation or Spearman rank correlation based upon the distribution of the variables), and subsequently a block-wise, linear regression analysis with a stepwise procedure per block in order to examine possible independent determinants of cardiac anxiety.

Finally, post-hoc analyses were conducted to examine whether the hypothesized explanation between cardiac injury and psychosocial variables were mediated by CRP levels, as there is evidence for an association between CRP level and affective pathology in cardiac patients [10,11].

Results

A total of 237 patients were included (mean age of 61.5 (SD=11.4), 66.7% (n=158) males). The mean CAQ item score was 1.33 (SD=0.65). Table 1 presents the correlation coefficients with all variables of interest.

In contrast to the hypotheses, more severe ACS as indicated by three severity markers of the ACS (STEMI/Non-STEMI, troponin level, maximum CK) appeared to be associated with a lower level of cardiac anxiety (see table 1); the association with STEMI/Non-STEMI was significant ($p<0.05$), whereas the negative correlation with maximum CK and troponin was not ($p=0.055$ for both).

The block-wise, linear regression analysis yielded five independent determinants of a higher level of cardiac anxiety, i.e. having no cardiac history ($\beta=0.12$, $p=.045$), a higher level of depressive symptoms ($\beta=0.21$, $p=.003$), a higher degree of avoidance behavior ($\beta=0.19$, $p=.003$), more agoraphobic cognitions ($\beta=0.17$, $p=.011$) and having had a Non-STEMI injury ($\beta=0.16$, $p=.008$) (model statistics: $F=14.2$, 5,213, $p<.001$).

Table 1 Socio-demographic, cardiovascular and psychosocial variables and their correlation scores with cardiac anxiety

Determinants	Mean (SD) / n (%)	Correlation-with CAQ	p-value
Socio-demographic			
Age	61.5 (SD=11.4)	0.08	0.23
Sex (% male) (0=female, 1=male)	158 (66.7%)	0.55	0.40
Marital status, n (%) stable relationship	195 (82.3%)	-0.04	0.66
Higher education, n (%) (0=no, 1=yes)	60 (25.3%)	0.04	0.50
Employed, n (%) (0=no, 1=yes)	104 (43.9%)	<.001	1.00
Cardiovascular risk factors			
Hypertension, n (%)(0=no, 1=yes)	106 (44.7%)	0.00	0.96
Hypercholesterolemia, n (%) (0=no, 1=yes)	65 (27.4%)	0.03	0.71
Diabetes mellitus, n (%)(0=no, 1=yes)	41 (17.3%)	0.05	0.45
History of ACS, n (%)(0=no, 1=yes)	76 (32.1%)	0.21	0.002*
PTCA/CABG intervention, n (%) (0=no, 1=yes)	182 (76.8%)	-0.13	0.043*
Psychosocial			
Depressive symptoms (BDI)	7.2 (SD=5.8)	0.34	<0.001*
Agoraphobic cognitions (ACQ)	1.3 (SD=0.3)/236	0.32 (S)	<0.001*
Avoidance behavior			
(MI together)	0.32 (SD=0.46)	0.23 (S)	<0.001*
(MI alone)	0.39 (SD=0.54)	0.25 (S)	<0.001*
Severity of Myocardial Infarction			
STEMI, n (%)(0=no, 1=yes)	128 (54.0%)	-0.18	0.004*
Troponin (ng/L), mean (SD)	42.1 (40.1)	-0.13 (S)	0.055
CK max (U/L), mean (SD)	1179 (1571)	-0.13 (S)	0.055

* significant correlation of p<0.05 of variable with total CAQ score in Pearson (P)/Spearman ranking (S) test
Abbreviations: CAQ, Cardiac Anxiety Questionnaire, total score; BDI, Beck Depression inventory; ACQ Agoraphobic cognitions questionnaire; MI, Mobility Inventory; ACS, acute coronary syndrome; STEMI ST-elevated Myocardial Infarction; CK max, maximum Creatinin Kinase level; PTCA, Percutaneous transluminal coronary angioplasty; CABG, Coronary artery bypass grafting.

Interestingly, no collinearity was found between the three different psychological variables, each independently contributing in explaining the variance in the level of cardiac anxiety. However, as collinearity with a STEMI/Non-STEMI injury might have caused non-significance for the troponin-level and the CKmax level, both markers were tested using linear regression with again cardiac anxiety as the dependent variable and corrected for all independent determinants as found previously, but not including a STEMI/Non-STEMI injury. This analysis revealed that having a troponin level at the lowest quartile was also associated with a higher level of cardiac anxiety (β=-0.13, p=.042), whereas having higher CKmax levels did not reach significance (β=-0.06, p=.31).

CRP levels were known for only 74.7% (n=177) of our patients. However, as CRP is known to be associated with affective psychopathology [15,16], all regression models were repeated with additional adjustment for the CRP level. The additional analyses showed that CRP was not a determinant of cardiac anxiety, whereas the association between cardiac anxiety and the previously identified determinants did not change substantially (data not shown).

Discussion

Our results show that in patients hospitalized for a troponin-positive acute coronary syndrome both, the severity of the cardiac injury as well as general measures of psychopathology are determinants of the level of cardiac anxiety. As expected, cardiac anxiety was positively associated with other measures of psychological distress like depressive symptoms, agoraphobic cognitions and avoidance behavior. In contrast to the hypothesis, patients with a more severe myocardial infarction, as defined by the level of cardiac injury (STEMI versus Non-STEMI and troponin level), had lower severity of cardiac anxiety. This association was independent of their cardiac history, treatment received and inflammatory markers known to be associated with affective psychopathology [10,11].

The direction of the association between cardiac anxiety and severity of cardiac injury was puzzling at first instance, as a meta-analysis (12 studies, 5750 patients) on the effect of anxiety on cardiac prognosis showed that high anxiety levels predict cardiac events (4). Nevertheless, only one study [25] corrected for cardiac injury (as measured by left ventricular ejection fraction LVEF<30%) alone. They reported an increase of the odds ratio for general anxiety levels when corrected for severity of cardiac injury. This is consistent with the direction of the association we found. In the other studies [26-28], the independent effect of severity of cardiac injury on anxiety was difficult to

assess since correction was done for numerous confounders simultaneously.

Two, not mutually exclusive explanations may account for the present findings. A first explanation could be that in case of less severe cardiac injury, patients are confronted with more uncertainty. In case the ECG does not show an ST elevation (non-ST elevated ACS), patients have to wait for the confirmation of the blood tests and thus the definitive diagnosis. In this particular group, patients themselves experience that something is wrong (as they experience the signs for which they visited the emergency department), whereas the first message they receive is "nothing is wrong, but we have to wait for the blood results". Such uncertainties may account for higher levels of cardiac anxiety, as these patients feel bodily distressed, but remain unsure as to whether this distress is based on a medical condition; they experience a lack of control. This uncertainty may lead to increased awareness for cardiac symptoms, resulting in cardiac anxiety. In line with this hypothesis are the findings of a cross sectional study in 184 patients with acute coronary syndrome that showed that if persons attributed their symptoms to a heart attack this was related to experienced fear of dying [29].

A second explanation could be selection bias as the chance to visit (by themselves) or the chance to be referred by their general practitioner to the emergency department may be affected by the patients' anxiety level. One may argue that persons who experience higher cardiac anxiety levels are more likely to seek medical help for their symptoms, with more chance to be diagnosed with "minor" cardiac pathology, as opposed to non-anxious patients who may not seek help for mild symptoms. Selection bias may occur especially in the group of patients with only mild cardiac injury. In this subgroup, the diagnosis of an acute coronary syndrome is not always easy to made. This contrasts with patients with an ST elevation. These patients directly know that they have heart problems (and thus that nurses and physicians will take good care of them).

The clinical implications of our results lie in the high prevalence of anxiety in cardiac patients and the negative effect of anxiety on the cardiac prognosis [4-6]. A first step in improving health care, is thus the detection of anxiety. As nurses are closest to providing care to cardiac patients, they have a good chance of signaling and targeting anxiety. A first step in reducing anxiety levels after detection, is taking anxiety symptoms as seriously as somatic signs and symptoms as well as providing appropriate information and reassurance. This requires specialized communication skills. A recent study showed that a patient's comprehension about what is going on with them on an emergency ward, is closely related to level of comprehension of the nurses [30]. Therefore efficient communication between doctors and nurses is

important as well as highly trained nurses with sufficient knowledge of cardiology and psychiatry. Furthermore, several studies point to the importance of communication skills of nurses and possibility of training for nurses [31-34]. Although most of these studies are conducted in cancer patients (assumed to have a higher stress level), two recent studies suggest that communication skills may be equally important in cardiac patients with high anxiety levels [33,34]. Firstly, a randomized controlled trial showed that a nursing intervention targeted at communication skills significantly increased enrollment in cardiac rehabilitation programs [33]. Secondly, a randomized controlled pilot study suggested that nurse-initiated preoperational education and counseling is associated with a reduced level of anxiety following coronary artery bypass graft [34]. Therefore specialized communication strategies to reassure patients efficiently should be developed as these might be relevant for both, the subgroup of patients placed in a situation of uncertainty due to minor cardiac injury (see above, explanation 1) as well as the subgroup of patients with higher levels of cardiac anxiety in general (see above, explanation 2).

Although the results are strengthened by a large sample size, well-validated measure of cardiac anxiety and well-defined study population, it has to be acknowledged that the size of the correlations seems rather small. This may partly be due to the relatively low CAQ mean item score of 1.33 (SD 0.65) in our population. Although the CAQ has not yet an established cut-off score to identify cases with clinically relevant cardiac anxiety, data of a recent study, consisting of one-year-follow up data of the majority of the here described ACS patients, suggest that a clinically relevant cut-off lies somewhere in between 1.45 and 1.90 [35].

As the study has been conducted in the Netherlands, one should be careful to generalize these results to other (Western) countries. Nevertheless, guidelines for diagnosing ACS at the emergency department are comparable between countries [36,37].

Future research should be conducted on the clinical relevance of our findings as well as the possibility to reduce cardiac anxiety by specific communication strategies applied directly by nurses at the emergency department.

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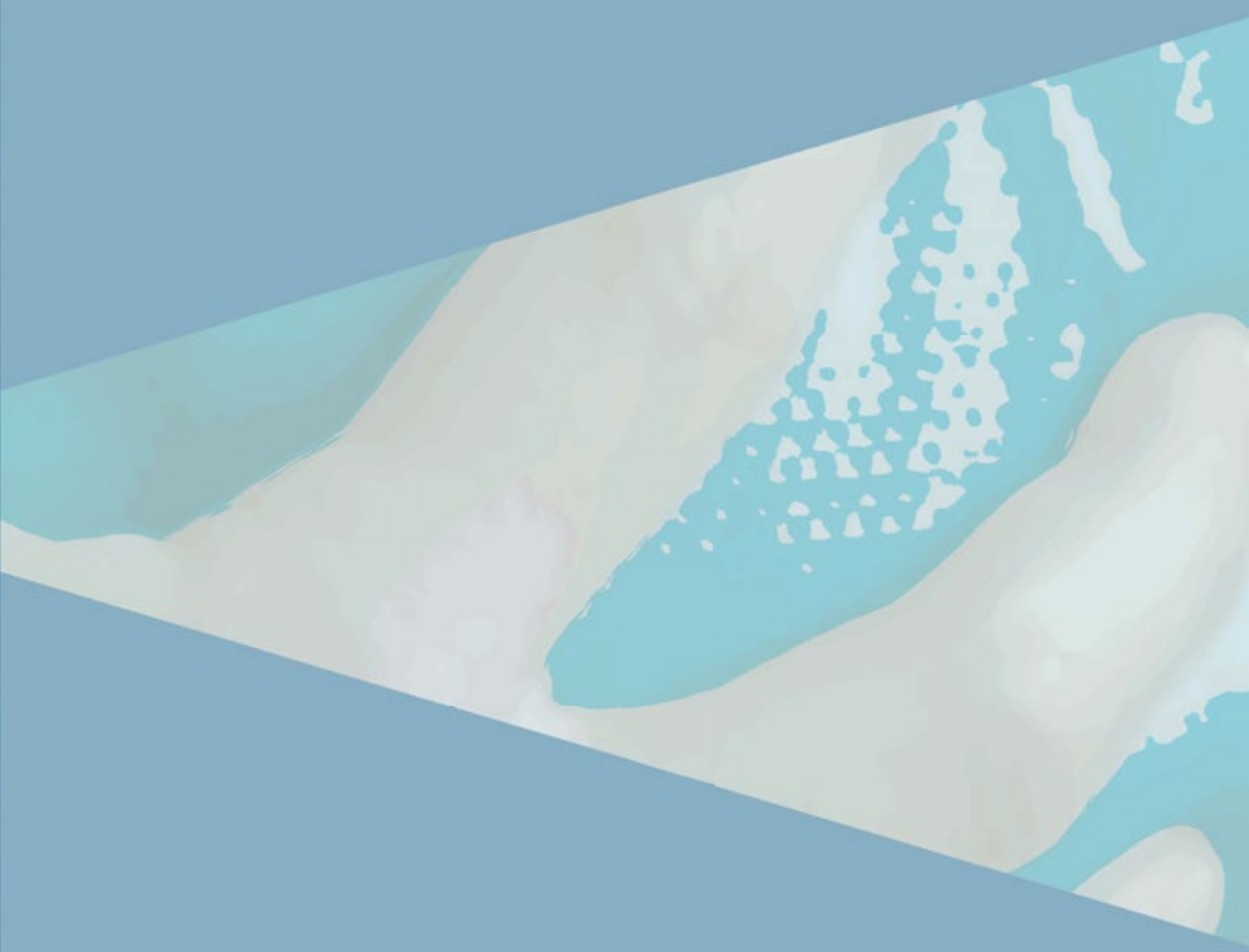
CHAPTER 4

One-year follow up of cardiac anxiety after a myocardial infarction: a latent class analysis



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Abstract

Introduction – Longitudinal elevated depressive symptom scores are associated with a less favorable cardiac outcome. Although anxiety has received less attention, meta-analysis suggests that high baseline levels of general anxiety might worsen cardiac outcome. The objective of this study was to explore the longitudinal course of cardiac anxiety after a myocardial infarction (MI).

Methods – The Cardiac Anxiety Questionnaire (CAQ) was administered to 194 patients hospitalized for MI after admission, and one, three, six and twelve months after discharge. Latent class growth analysis (LCGA) was performed to identify groups based on cardiac anxiety course. Between group differences were checked on relevant socio-demographic, cardiac and psychiatric variables.

Results – LCGA identified three groups with stable CAQ levels over time, indicative of high (7.7%), intermediate (45.4%) and low (30.4%) levels of cardiac anxiety, respectively. A fourth group (16.5%) reported high levels of cardiac anxiety that decreased over time. Between group differences were of particular interest for the two subgroups that started high in cardiac anxiety, since these may differentiate patients with spontaneous remission from those who might be in need of treatment. Patients in whom cardiac anxiety persisted were less often employed, had more diabetes mellitus, a history of acute coronary syndrome, depressive symptoms, anxiety and avoidance at baseline and a lower quality of life at follow-up.

Conclusion – This first study addressing cardiac anxiety after an MI identified four trajectories. Future studies should focus on cardiac outcome and treatment strategies for cardiac anxiety in the subgroup with persistent high anxiety levels.

Keywords – anxiety, cardiac, heart, myocardial ischemia, myocardial infarction, acute coronary syndrome.

Introduction

While depression and its association with cardiac disease have been thoroughly studied [1], anxiety in cardiac patients has received far less attention. Recently, it has been suggested that anxiety disorders are independent risk factors for myocardial infarction (MI) [2]. In a large cohort of young men (n=49321), early-onset anxiety predicted acute MI (hazard-ratio (HR) = 2.51 (95% Confidence Interval (CI) 1.38-4.55) [3]. In two meta-analyses similar conclusions were drawn [4,5]. The first included 20 studies and confirmed that anxiety might be an independent risk factor for incident coronary heart disease (HR= 1.26 (95% CI 1.15-1.38) and cardiac mortality (HR=1.48 (95% CI 1.14-1.9) . The second meta-analysis included 12 studies and showed that higher anxiety levels increased the risk of adverse cardiac outcomes after a MI with 36%, with reported HRs of 1.23 (95% CI 1.03-1.47) for cardiac death, 1.47 (95% CI 1.02-2.13), for overall death and 1.71 (95% CI 1.31-2.23) for cardiac events [5]. Nevertheless, the actual number of studies remains small in comparison to studies examining depression in heart disease and, more importantly, confounding by cardiovascular risk factors cannot be fully excluded [4,5]. Furthermore, heterogeneity of individual study results included in the meta-analyses was substantial and hypothesized to be due to the diversity in anxiety measures. Therefore, which aspects of anxiety are related to cardiac outcome remains unknown and confounding by depression as overlapping construct cannot be excluded. Finally, most studies focus on the impact of anxiety measures at one time-point, whereas for depressive symptoms, it has been shown that longitudinally elevated symptom scores have the highest risk of a negative outcome [6]. The objective of the present paper is to identify patients with different courses of cardiac anxiety after a myocardial infarction.

Only two studies have explored the course of anxiety in cardiac patients [7,8] and yielded widely different results. The first study was conducted among female cardiac patients and identified two trajectories. The majority of patients had low anxiety levels, which improved during the one year follow-up. A small group started with relatively higher levels of anxiety and/or depression that worsened over the year [7]. The second study, conducted among exhausted cardiac patients after a Percutaneous Coronary Intervention, yielded five different trajectories. Four trajectories showed stable anxiety scores over time and were defined by their baseline levels of anxiety symptoms (no, mild, moderate, severe). A fifth trajectory was found including patients with severe anxiety that decreased over time [8].

These varying results might be explained by a different population, but also by the instruments used to measure anxiety. After a MI specific anxiety symptoms related to cardiac stimuli and sensations may develop. This is known as cardiac anxiety,

which can be reliably assessed by the Cardiac Anxiety Questionnaire (CAQ) [9-11]. Both previous studies, however, included only general measures of anxiety, respectively the Hospital Anxiety Depression Scale (HADS) [7] and the Spielberger State-Trait Anxiety Inventory (STAI) [8]. Moreover, the STAI does not clearly differentiate anxiety and depression [12].

The CAQ has been developed based on the assumption that specific fears about heart disease might be more important with regard to prognosis and need for interventions in cardiac patients than more general fears. Available studies indeed show that the CAQ is more sensitive than a general anxiety measure like the HADS in patients who are focused on chest pain [13,14]. In 90 cardiac patients, Hoyer et al. [13] assessed both general anxiety (HADS) and cardiac anxiety (CAQ) before and after cardiac surgery. While general anxiety decreased in all patients to levels similar to the general population, cardiac anxiety remained elevated in a subgroup of patients. This might help to identify cases in need for additional support in adjusting to their cardiac problems. This was further supported by a randomized controlled trial comparing cognitive behavioral therapy, antidepressant medication and placebo in patients with non-cardiac chest pain. Effectiveness of treatment was found to be mediated by the subscale "heart-focused anxiety" of the CAQ but not the HADS [14].

We conducted an exploratory prospective cohort study in cardiac patients hospitalized with myocardial infarction with follow up after discharge at one, three, six and twelve months. Aims of the current study were 1) to identify the different trajectories of cardiac anxiety over a 12-month period in patients hospitalized for a MI and 2) to compare the different trajectories in terms of socio-demographic, cardiac and psychiatric variables at baseline and quality of life at end of follow-up.

Methods

Study population

The study population consisted of all patients admitted between November 2006 and December 2007 to the department of cardiology of Radboud University Nijmegen Medical Centre, the Netherlands. All were screened for eligibility by a senior cardiologist within two days after admission. Inclusion criteria were a final diagnosis of Myocardial Infarction, both ST-Elevated MI (STEMI) and Non ST-Elevated MI (NSTEMI). The diagnosis was confirmed by the presence of a rise and fall of troponin I (>0.20 µg/l). Exclusion criteria were: age above 85 years, discharge out of hospital within two days of admission, and inability to fill in questionnaires (due to insufficient

knowledge of the Dutch language, cognitive impairment or being too ill to participate).

Procedure

Eligible patients received oral and written information about the study and were asked informed consent. Between day 2 and 7 after admission, patients completed a set of five self-report-questionnaires: the Cardiac Anxiety Questionnaire [9-11], the Agoraphobic Cognitions Questionnaire [15,16], the Mobility Inventory [17,18], the Beck Depression Inventory [19-21] and the EuroQol-5D [22,23]. In addition, socio-demographic data and information about the presence of cardiovascular risk factors hypertension, diabetes mellitus, hypercholesterolemia, and peripheral atherosclerotic disease, as well as a history of coronary artery disease and stroke and other somatic co-morbidity were extracted from the medical file.

At one, three, six and twelve months after discharge patients were sent the same questionnaires by post. If necessary, patients were contacted by phone two weeks later as a reminder. The study protocol was approved by the local Medical Ethics Committee.

Measures

Cardiac Anxiety Questionnaire (CAQ) - The CAQ is an 18-item self-report-questionnaire, designed to assess heart-focused anxiety, rated on a 5-point Likert scale ranging from 0 (never) tot 4 (always). In line with previous publications on the CAQ, the overall score as well as subscale scores are expressed as an average item score [10]. The original factor analysis identified three subscales: 1) heart-related fear (8 items e.g. "I worry that I may have a heart attack" and "If test come out normal, I still worry about my heart"); 2) avoidance (5 items e.g. "I take it easy as much as possible"); and 3) attention (5 items e.g. "I check my pulse") [10]. In a sample of 188 patients referred for angiography the CAQ had a good internal consistency of both total (Cronbach α =0.83) and subscale scores (Cronbach α of 0.83, 0.82 and 0.69 respectively). It also showed good convergent validity, with moderate correlations with established anxiety measures like the Anxiety Sensitivity Index (0.69) and the Body Sensations Questionnaire (0.66). The CAQ also successfully differentiated cardiac anxiety from general anxiety in psychiatric outpatients [10]. A recent cross validation in the Netherlands [9] identified four subscales (fear, avoidance, physical attention and safety seeking behavior) with a good internal consistency of both total (Cronbach α 0.84) and subscale scores (Cronbach α between 0.6-0.9) In this study the CAQ had a high test-retest-reliability (0.88, $p<.001$) and low to moderate correlations with questionnaires such as the ACQ (0.31), STAI-State (0.39) and the BDI (0.27).

Comparable results, including the four subscales, have been previously reported in an independent cross validation study in 658 persons referred for screening for coronary artery disease [11].

Agoraphobic Cognitions Questionnaire (ACQ) - The ACQ is a widely used 14-item scale assessing the frequency of catastrophic thoughts during the experience of anxiety and fear [15], rated on a 5-point Likert scale from (1) '*thought never occurs*' to (5) '*thought always occurs*'. The ACQ consists of two subscales: 1) social/ behavioral concerns (e.g. act foolish, hurt someone); and 2) physical concerns (e.g. heart attack, stroke). The ACQ has high internal consistency (Cronbach α=0.87), moderate test-retest reliability (r=0.67 for 1 month) and sensitivity to changes due to treatment [15,16]. The ACQ also differentiates between persons with and without anxiety disorders [24].

Mobility Inventory (MI) - The MI is a self-report-questionnaire to measure avoidance behavior. Patients are instructed to rate their level of avoidance (from 0 "never avoid" through 4 "always avoid") in 26 familiar situations (e.g. driving a car, going to supermarkets, being home alone). Patients score avoiding these situations in two conditions; when accompanied and when alone. The questionnaire has good internal consistency (Cronbach α=0.94), high test-retest reliability (r=0.90), and good convergent and discriminant validity [17,18].

Beck Depression Inventory (BDI) - Depression symptoms were measured on a 4 point scale with the BDI, a 21-item self-report-questionnaire. The total sum score (range 0-63) is indicative of the severity of depressive symptoms, a score of 10 or higher is indicative of mild to severe symptomatology [19,20]. The BDI has good internal consistency (Cronbach α=0.93) [17]. It is proven to be an acceptable screening instrument (Cronbach α=0.81) in somatic populations [21] including patients with MI [25].

Cardiovascular variables – The diagnosis of a MI was based on clinical history and a rise and fall of troponin I (>0.20 μ/l). Creatinin Kinase (CK) was determined with an enzymatic assay (ArchitectC16000 analyzer). Based on the electro cardiogram (ECG), patients were classified as having a ST-Elevated MI (STEMI: ≥0.2 mV in men or ≥ 0.15 mV in women in leads V2–V3 and/or ≥0.1 mV in other leads) or Non ST-Elevated MI (NSTEMI).

Medical history was retrieved from the medical dossier of either the general practitioner and/or hospital consultant. Hypertension was defined as repeatedly elevated blood pressure exceeding 140/90mmHg or the use of anti-hypertensive medication. Hypercholesterolemia was defined as a total cholesterol level higher than 240mg/dL or the use of cholesterol lowering medication. We prospectively

collected data whether patients were referred to a heart rehabilitation program after discharge. All cardiovascular variables were collected by a cardiologist in training and independently checked by a consultant cardiologist. This double check did not reveal any disagreement between the two.

Quality of life - Quality of life was measured using the EuroQol EQ-5D [22]. The EQ-5D measures quality of life in five dimensions, including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The dimensions are divided into three response levels: no problems, some/moderate problems, and extreme problems/unable to. The combination of scores is weighted to arrive at a single index score between -0.33 (worst imaginable health state) and 1.00 (best imaginable health state). Dutch norm scores were used to calculate the mean EQ-5D index values [23].

Statistical analysis:

Conventional growth models assume that individuals come from a single population and that a single growth trajectory can approximate the entire population. This assumption, however, does not automatically apply for all research domains, and currently new methods are available to model such heterogeneity of growth trajectories [26]. Latent class growth analysis (LCGA) tries to identify different homogeneous groups within the larger heterogeneous population, each with its own growth trajectory. The total CAQ score was taken as the primary outcome and we performed a LCGA in Mplus 6.11, using maximum likelihood parameter estimator with robust standard errors, starting with a one class model (which in fact reflects the homogeneous model), and expanding the number of classes (introducing heterogeneity), until the best model fit was found. LCGA tries to fit the data on a model in which each class represents a group of patients which have more or less the same severity and course of cardiac anxiety. The course over time is modeled using polynomials with a maximum order of three, and it was assumed that the total scores follow a Poisson distribution, meaning that in the Mplus-model these had to be defined as count variables. The best model fit is determined by the lowest BIC value and still a significant difference in the Vong-Lo-Mendell-Rubin likelihood ratio test (VLMR) [27]. Subsequently, the procedure was repeated using the different subscales of the CAQ [9,10], in order to check whether the different symptom cluster results in similar trajectories or whether trajectories are subscale specific.

Finally, classes were compared with regard to relevant socio-demographic, cardiac and psychiatric variables at baseline and quality of life endpoint, by performing ANOVA for continuous variables or X^2-tests for categorical variables using SPSS17.0. Normal distribution was checked for continuous variables, and if needed variable was

transposed to log or tested non parametrically by KrussKal Wallis or Mann-WhitneyU tests. Due to the large number of tests, the level for statistical significance should be adapted to less than .05. However, as correction for multiple comparisons may increase the risk of type II errors, we have chosen to present all individual statistics and p-values [28].

Results

Sample

During the study period, 398 patients with a MI had been admitted, of which 135 patients after primary PTCA were relocated to a hospital in their home area within two days of admission. Of the 263 patients who were still present at the time we asked informed consent, 203 patients (77%) agreed to participate. Nine persons had to be excluded from the analysis because more than 3 items of the CAQ were missing (n=3) or because the CAQ was only available for one assessment (n=6).

The average age of the study sample (n=194) was 61.8 years (SD=11.5; range 24-85) and the male-female-ratio 2:1 (130/64). A total of 65/194 (32%) had a history of coronary artery disease.

The overall average item score of the CAQ was 1.35 (SD=0.60). Correlation of scores of the CAQ with cardiac disease severity was low. Spearman rank correlation of CAQ with STEMI/NSTEMI was r=-0.18, p=.004, with troponin levels r= -0.13, p=.06 and with CKmax level r=-0.13, p=.06.

Latent class growth analyses

The CAQ data of the 194 patients were imported in Mplus and analyzed. Using quadratic polynomials with the LCGA, showed better results compared to a linear model. A cubic model did not obtain better results when compared to the quadratic model. Therefore, having less free parameters, we chose the quadratic model. Its decision parameters (BIC, VLMR, P-value, Entropy) are shown in table 1. The decision parameters show that a solution with 4 classes was the most optimal, i.e. it had the lowest BIC value and the VLMR test showed a significant improvement of the model when compared to 3 classes. Although the entropy of 4 classes was just above 0.70, it was significantly better than the entropy of 5 classes.

Table 1: CAQ latent class growth analysis decision parameters.

Classes	BIC	VLMR P-value	Entropy
1	5143	-	-
2	4619	0,0000	0,763
3	4554	0,0035	0,760
4	4516	0,0004	0,716
5	4519	0,4088	0,627

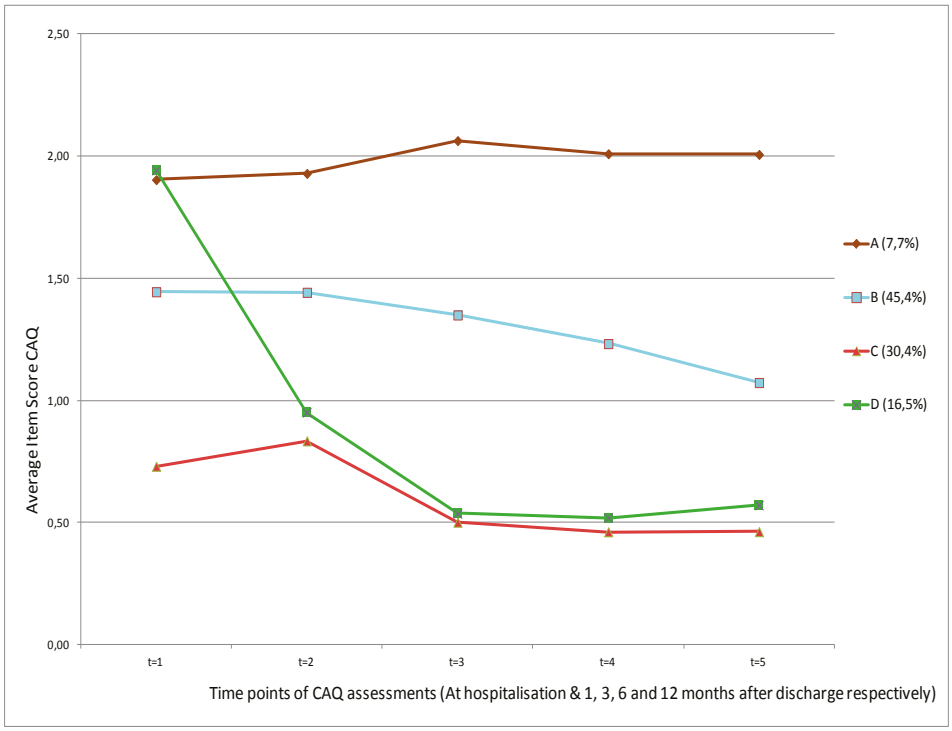

Figure 1: The total CAQ score of the four groups based on the Latent Class Analysis at baseline, and 1, 3, 6, and 12 months after discharge.
Best fit model in Mplus showing the four classes with their course on CAQ score during one year (admission, one month after discharge, three months, six and twelve months after discharge). On y-axis CAQ-total score on Cardiac Anxiety Questionnaire.

In our model we thus identified four classes of different courses of cardiac anxiety (average CAQ item scores) during one year. These different courses of cardiac anxiety were already apparent after three months (retention rate 65%, 127/194). Overall retention rates for CAQ were 72% (149/194) after one month, 65% (127/194) after three months, 49% (95/194) after six months, and 24% (46/194) after one year.

The first group "A"(n=15, 7.7%) started with a high average CAQ item score (and stayed high on cardiac anxiety level). The second "B"(n=88, 45.4%) had a continuously intermediate CAQ level (labeled as "continuously medium"), the third group "C" a continuously low CAQ level (n=59, 30.4%), and a fourth group "D" (n=32, 16.5%) with patients who started with high anxiety levels at hospitalization, that diminished in the course of a year to a low score at one year follow up (see figure 1).

The CAQ can be divided in three [10] or four [9,11] clinically relevant subscales, targeting fear, avoidance, attention and the fourth safety seeking behavior. When doing a LCGA on a model using the average item score of these subscales, the individual trajectories of each subscale followed the same latent class growth pattern as the 4 groups described above, based on the total average CAQ item score. Assignment to a class was checked for stability; each class showed the same number of persons and no person switched into another class. Thus, even with a model with more free parameters, we obtained the exact division of persons into classes and the sub-scale-trajectories resembled very close.

Baseline characteristics per Cardiac Anxiety Class

Differences between patients with the four trajectories on demographic characteristics, cardiac measures and risk factors, and psychiatric parameters at baseline are shown in Table 2. Significant differences between the four classes were age, employment, diabetes mellitus, coronary heart disease, and all psychiatric symptom scales (see table 2).

For clinical practice, the differences between subjects in trajectories A and D are interesting, as these may differentiate patients with spontaneous remission of high anxiety scores from those who might benefit from treatment. Post hoc comparison of these two groups on those overall significant variables, showed that patients in whom cardiac anxiety persisted over time had significantly less employment (χ^2=5.8, p=0.016,), more diabetes mellitus (χ^2=6.2, p=0.013) and more often a history of acute coronary syndrome (χ^2=8.9, p=0.003) (see Table 1). They also reported significantly more depressive (t=2.3, p= 0.029) and anxiety symptoms (t=2.3, p=0.026), and more

avoidance (t=2.2, p=0.032). As the number of persons in the subgroups was too small, no multivariate analyses were conducted.

Quality of life at end of follow-up

Due to low retention rates at the end of follow-up (see above), last-observation carried forward (LOCF) was applied to the EQ-5Dscores obtained at follow-up (baseline values were not carried forward as these values are supposed to be confounded by being hospitalized). LOCF was deemed reliably as all pairs of follow-up measures did not differ significantly in patients with complete data (mean difference between follow-up measures ranged from 0.002 through 0.030 points (all p-values>.22). One-way-ANOVA showed significant differences between the four groups (F=3.5; 3,149; p=.017). Post-hoc comparisons showing that group A (high) had significantly lower EQ-5Dscores compared to group B (intermediate, p=.047), group C (low, p=.004) and group D (high-low, p=.006) (see figure 2). Group D (high-low) did neither differ from group B (intermediate, p=.16), nor from group C (low, p=.88).

Table 2 Baseline characteristics of the four subclasses based on CAQ course

Variable	Total Sample	Low (C)	Medium (B)	High (A)	High-Low (D)	Statistics
	(n=194)	(n=59)	(n=88)	(n=15)	(n=32)	
Demographics						
Age (years), mean (SD)	61.8 (11.5)	60.0 (11.8)	61.0 (11.5)	69.3 (10.8)	63.6 (10.3)	F=3.0; 3;p=.030
Male sex, n (%)	130 (67%)	38 (36%)	58 (66%)	12 (80%)	22 (69%)	X^2=1.4; 3;p=.70
Stable relationship, n (%)	155 (80%)	46 (78%)	70 (80%)	14 (93%)	25 (78%)	X^2=1.9; 3;p=.60
Higher education, n (%)	50 (26%)	16 (27%)	21 (24%)	2 (13%)	11 (36%)	X^2=3.0; 3;p=.40
Employment, n (%)	86 (46%)	24 (43%)	44 (51%)	2 (13%)	16 (50%)	X^2=7.8;3;p=.051
Somatic history of						
Hypertension, n (%)	85 (44%)	23 (39%)	44 (50%)	7 (47%)	11 (34%)	X^2=3.1; 3;p=.37
Hypercholesterolaemia, n (%)	55 (28%)	15 (26%)	32 (36%)	3 (20%)	5 (16%)	X^2=6.1; 3;p=.11
Diabetes mellitus, n (%)	33 (17%)	5 (9%)	19 (22%)	6 (40%)	3 (9%)	X^2=11.3; 3;p=.010
Peripheral atherosclerosic disease, n (%)	28 (14%)	8 (14%)	14 (16%)	1 (7%)	5 (16%)	X^2=1.0; 3;p=.81
Stroke, n (%)	7 (4%)	2 (3%)	4 (5%)	1 (7%)	0 (0%)	X^2=1.8; 3;p=.61
(history) Coronary artery disease, n (%)	62 (32%)	13 (22%)	32 (37%)	10 (67%)	7 (22%)	X^2=13.3;3;p=.004
Assigned for heart rehabilitation, n (%)	84 (43%)	22 (37.3%)	44 (50.0%)	3 (20.0%)	15 (46.9%)	X^2=6.0, 3;p=0.11
Cardiac disease status						
Troponin, n (%) above median	96	31 (53%)	41 (47%)	9 (60%)	15 (47%)	X^2=1.3; 3;p=.74
CKmax, median (P_{25} – P_{75}) *	571 (158-1594)	752 (180 - 1577)	531 (161 - 1388)	546 (117 - 1644)	579 (188 - 2188)	F=0.3;190,3; p=.83
Non-ST elevated MI, n (%)	92 (47%)	25 (42%)	41 (47%)	8 (53%)	18 (56%)	X^2=1.3; 3;p=.74
Duration of hospitalization (days), median (P_{25} – P_{75}) *	6 (4-8)	5 (4 - 8)	6 (5 - 8)	5 (4 -10)	6 (4 - 8)	F=0.6l; df=190; p=.64

Variable	Total Sample	Low (C)	Medium (B)	High (A)	High-Low (D)	Statistics
Psychological symptoms						
BDI sum score, median (P_{25} – P_{75})	6 (3-10)	4 (2 - 7)	6 (4 - 10)	12 (7 - 16)	7 (4 - 12)	X^2= 21.7;3; p<.001
BDI >=10, n (%)	54 (28%)	10 (17%)	23 (26%)	11 (73%)	10 (32%)	
ACQ sum score, median (P_{25} – P_{75})	1.21 (1.00-1.50)	1.14 (1.00 – 1.36)	1.21 (1.07 – 1.50)	1.43 (1.29 - 1.71)	1.14 (1.00 - 1.43)	X^2=18.6;3; p<.001
ACQ social/behavioral, median (P_{25} – P_{75})	1.29 (1.00-1.71)	1.14 (1.00 – 1.41)	1.43 (1.00 - 1.71)	1.71 (1.29 – 2.00)	1.29 (1.00 – 1.57)	X^2=17.9;3; p<.001
ACQ physical, median (P_{25} – P_{75})	1.00 (1.00-1.29)	1.00 (1.00 – 1.14)	1.00 (1.00 – 1.14)	1.29 (1.14 – 1.57)	1.00 (1.00 – 1.14)	X^2=18.7;3; p<.001
MI together, median (P_{25} – P_{75})	0.17 (0.0-0.7)	0.03 (0.00 -0.31)	0.21 (0.00 – 0.69)	0.72 (0.37 – 1.69)	0.21 (0.00 – 0.90)	X^2=16.6; 3; p=.001
MI alone, median (P_{25} – P_{75})	0.14 (0.0-0.48)	0.03 (0.00 – 0.31)	0.14 (0.00 – 0.41)	0.72 (0.29 – 1.39)	0.14 (0.00 – 0.72)	X^2=1.63; 3; p=.001

Statistics based on Log-transformed CKmax values analyzed with ANOVA
Variables low-medium-high-high low are the classes based on course of total Cardiac Anxiety Questionnaire (CAQ) score;

n=number; SD=standard deviation; CKmax= maximum level of Creatinin Kinase; P25;=value at the 25th percentile; P75=value at the 75th percentile; MI=myocardial infarction; BDI-=Beck Depression Inventory: ACQ=Agoraphobic Cognitions Questionnaire; MI Mobility Inventory; MI together=subscale of MI measuring avoidance behavior with others; MI alone=subscale of MI measuring avoidance behavior alone

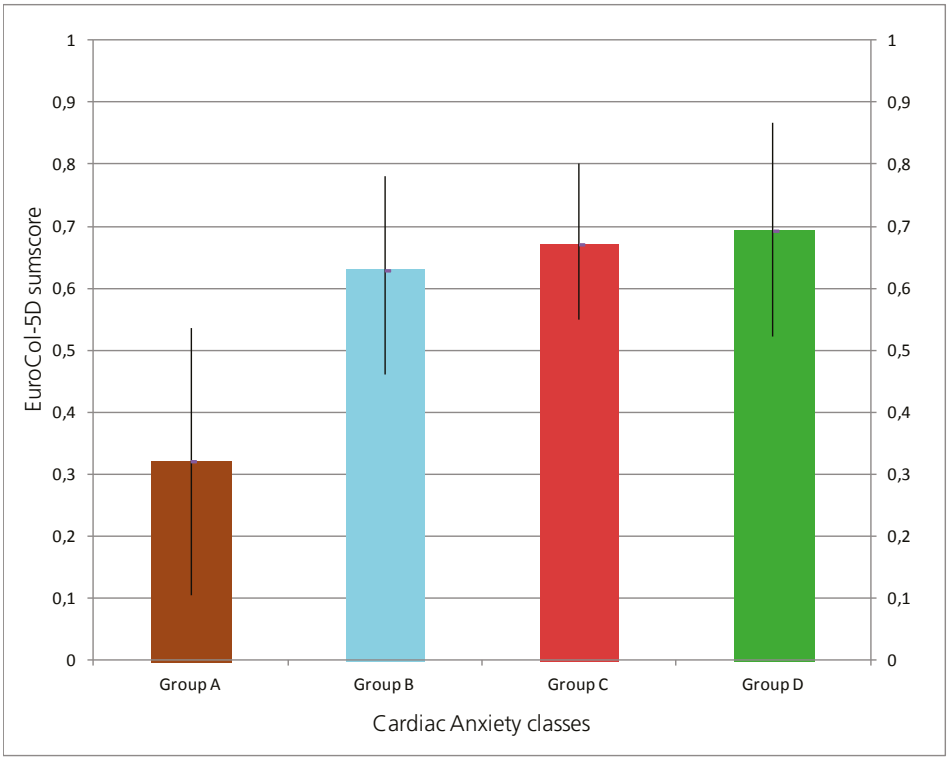

Figure 2 Quality of life as assessed with the EuroQol-5D at end of follow-up for the four groups with a different trajectory of cardiac anxiety

Legend:

Group A: Stable levels of high cardiac anxiety during follow-up

Group B: Stable levels of intermediate levels of cardiac anxiety during follow-up

Group C: Stable levels of low levels of cardiac anxiety during follow-up

Group D: High initial levels of cardiac anxiety which decrease during follow-up

Discussion

Main finding

In addition to the few studies of trajectories of anxiety in cardiac patients, the present study is the first to examine the trajectories of specific cardiac anxiety in patients hospitalized for myocardial infarction, including both ST-elevated and non-ST-elevated MI. We identified four latent classes with distinctive courses of cardiac anxiety; during the one-year follow up three groups stayed at about the same level of cardiac anxiety as they started (with respectively a low, intermediate and high level of cardiac anxiety), and the fourth group had a high but decreasing level of cardiac anxiety. Although we acknowledge that the retention rate decreased over time, the differences in CAQ course are already determined at time 2 and 3, when the retention was still substantial. The finding of multiple trajectories instead of one anxiety trajectory is consistent with previous researches reporting multiple trajectories on anxiety, depression and quality of life in cardiac patients [6-8,29], although none of these studies specifically addressed cardiac anxiety.

Remarkable was the distinct course of group D with high but diminishing cardiac anxiety symptoms over the one year follow-up period. A similar subgroup that started high but showed declining general anxiety levels in the follow up period, was seen in women followed up to 12 months after a MI or coronary artery bypass graft surgery [7] and in a study of exhausted cardiac patients after a percutaneous coronary intervention during an 18-months follow up period [8]. The relevance of our findings of different trajectories of specific cardiac anxiety is indicated by a study of Hoyer et al. [12] who assessed both general anxiety (HADS) and cardiac anxiety (CAQ) before and after cardiac surgery in 90 cardiac patients. While general anxiety decreased to levels comparable with the general population, cardiac anxiety decreased but still remained elevated for a subsample, indicating that measures of specific heart anxiety, in contrast to global psychosocial indicators, may help to identify cases in need for additional help in adjusting to their cardiac problems.

For clinical practice it is indeed relevant to get more information about the people in whom the anxiety persists, particularly as their quality of life at one-year follow-up is significantly lower than that of the other groups. Unfortunately, the CAQ has not yet an established cut-off score to identify cases with clinically relevant cardiac anxiety. The average CAQ item score in our population (1.35 (SD=0.60) was lower than that in other populations demonstrating mean CAQ item scores of 1.67 (SD=0.81) in 30 post-angiography and 12 outpatients [10] and 1.87 (SD=0.55) in 90 cardiology pre-surgery patients [13]. The included patients in above mentioned studies may not be entirely

comparable with our population. In the first study the 12 outpatients were selected because of a diagnosis of anxiety disorder. Furthermore, in 47.6% of the patients referred for angiography coronary artery disease was not established, implying a higher level of psychiatric symptoms in this subgroup. In the latter study, the CAQ was assessed 2 weeks before scheduled cardiac surgery. The CAQ scores of groups A and D based on the LCGA in our sample (1.90 (SD=0.56) and 1.94 (SD=0.36), respectively) were higher than in the previously reported studies [10,13]. Although preliminary, these data suggest that a clinically relevant cut-off lies somewhere in between the average item score in the group with intermediate CAQ item scores (i.e.1.45 (SD=0.40) and these higher average item scores of 1.90.

A closer look at the differences between the two subgroups with high baseline cardiac anxiety levels, is therefore of clinical importance. Previous studies, focusing on factors associated with a continuing high anxiety or depression level, reported mixed results. Reported determinants of persistent anxiety or depressive symptoms were psychosocial characteristics like educational level and perceived social support [7,8,30], as well as the presence of somatic diseases like a previous acute coronary syndrome (ACS) or cardiac risk factors like diabetes mellitus (DM) [31-33]. Our study replicates the association with somatic diseases: the subgroup of patients which experienced high cardiac anxiety over time had a significantly higher frequency of DM and more often a history of ACS than the subgroup of patients who had a high but declining level of cardiac anxiety. Interestingly, baseline characteristics of the group with decreasing cardiac anxiety levels most closely resembled the group with stable low cardiac anxiety. One may hypothesize that a higher level of somatic co morbidity may trigger a negative attitude towards newly developed somatic symptoms as patients had negative experiences before.

Importantly, cardiac anxiety did not represent a more severe cardiac injury as it was hardly related to the actual severity of cardiac injury. The correlation coefficients between CAQ score and three indicators of cardiac injury were not clinically relevant (range r=-.13 through-.18) and only the association with STEMI/NSTEMI reached statistical significance.

Furthermore, our study replicates the association with psychological determinants; the subgroup of patients which experienced high cardiac anxiety over time also reported significantly higher depressive symptoms as well as avoidance behavior than the subgroup of patients who had a high but declining level of cardiac anxiety. One may hypothesize that inactivity, which can be associated with depression, as well as avoidance behavior may maintain cardiac anxiety. Targeting this avoidance, for example by exposure, may therefore be of importance in the treatment of these

patients. This is also supported by studies in chronic back pain patients, in which anxiety for physical activity and the associated avoidance are shown to be important determinants for the maintenance of symptoms. Treatment of chronic back pain, targeting this avoidance by exposure has been shown to be effective [34].

Methodological considerations

A strength of this study is the use of repeated CAQ assessments and the LCGA method toidentify different courses of cardiac anxiety symptoms after MI, which has not been applied previously in this context. The follow up period of 12 months provides clinically relevant information about the course of anxiety and depressive symptoms after the initial stressful cardiac event and hospitalization.

In a LCGA analysis each person is assigned to the class with the best fit. It is recommended that the number of class members of each class is at least equal to the number of free parameters of the model. For our quadratic LCGA with 4 classes there are 15 free parameters, where the minimum class membership is also 15 (in one class). However, we must be aware that significant group differences are not the same as clinically relevant individual predictors. Nevertheless, the significant differences between the four classes, and especially the differences between the two classes with persons who scored high on cardiac anxiety levels at hospitalization, provide a first insight in possible relevant factors for clinical practice.

Although the recruitment rate was relatively high, generalization of our results is compromised by the fact that we could not include patients who were transferred after intervention to other hospitals within two days and those with the greatest illness severity. As we did not include the most ill and those being healthy enough for early transportation to other hospitals, we cannot estimate whether this has biased our results and if so, in what direction. The mean CAQ score in our population was indeed slightly lower than that in other cardiac populations [10,13], suggesting that we might not have included the most anxious patients. Nevertheless, the number of patients (n=194) and response rate (77%) was reasonably high, particularly given the practical difficulties conducting a study of psychological symptoms in a patient population with a severe somatic condition like MI. Unfortunately the number of persons in the two subgroups of interest were too small to control for possible confounders in a multivariate analysis. We consider the comparison as a first step in exploring possible confounders. It would be interesting to re-examine the somatic and psychological variables in a bigger independent sample of cardiac patients with high CAQ levels, in order to interpret and weigh the clinical relevance of the found predictors better.

Final conclusion/implications

This study identified four different courses of cardiac anxiety in MI patients in a 12 months follow up. Of those patients presenting with high level on cardiac anxiety, those with high levels of general psychological distress and a more complicated history of somatic diseases, had persistent levels of cardiac anxiety during follow-up and a significantly lower quality of life at the end of follow-up. These findings may be a first step in providing tools for the clinician to decide which patients deserve attention for their anxiety levels and may benefit from early interventions. Furthermore, reassessment after one month may also identify patients with initially high cardiac anxiety levels, but a much more favorable course. In addition, as the class of patients with intermediate CAQ scores does not improve during follow-up either, we are not able to exclude the possibility that they might be in need of additional treatment for their symptoms as well. Interestingly, a recent RCT study in patients who were discharged for coronary heart disease showed that a cognitive behavioral therapy intervention focused on stress management on emotional factors as anxiety decreased the risk of recurrent myocardial infarction compared to traditional care [35]. The potential determinants identified in the present study may guide the development of such interventions. For example coping strategies with and realistic expectancies about somatic co morbidity may be important.

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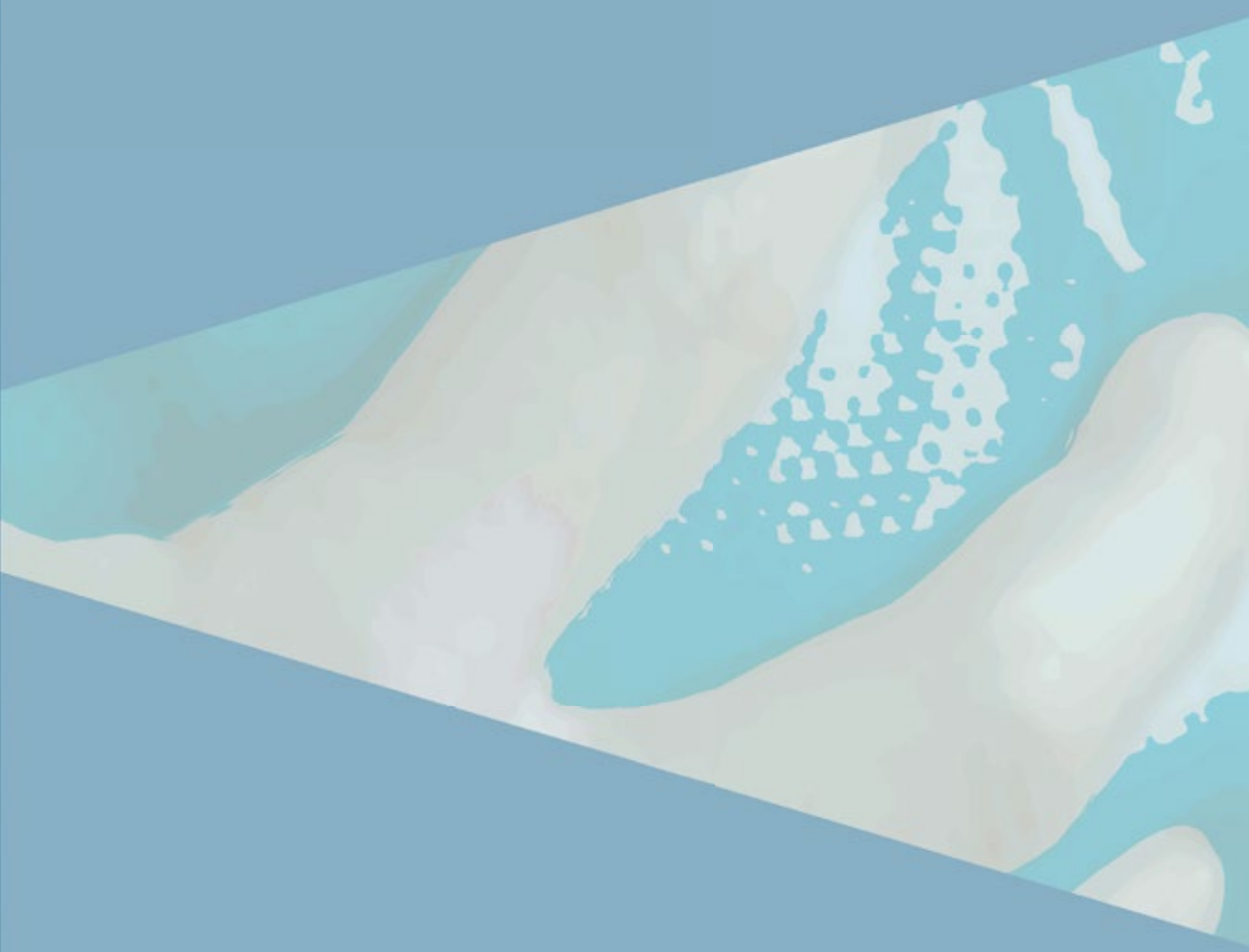
CHAPTER 5

Impact of cardiac anxiety on cardiac prognosis after myocardial infarction



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Abstract

Background – General anxiety and depressive symptoms following a myocardial infarction are associated with a worse cardiac prognosis. However, the contribution of specific aspects of anxiety within this context remains unclear.

Aim – To evaluate the independent prognostic association of cardiac anxiety with cardiac outcome after myocardial infarction (MI).

Methods – We administered the Cardiac Anxiety Questionnaire (CAQ) during hospitalization (baseline, n=193) and four months (n=147/193) after discharge. CAQ-subscale-scores reflect fear, attention, avoidance and safety-seeking behavior. Study-endpoint was a major adverse cardiac event (MACE): readmission for ischemic cardiac disease or all-cause-mortality. In Cox regression analysis, we adjusted for age, cardiac disease severity, and depressive symptoms.

Results – The CAQ-sum-score at baseline and at 4 months significantly predicted MACE ($HR_{baseline}$= 1.59, 95% CI 1.04-2.43; $HR_{4\text{-months}}$= 1.77, 95%CI 1.04-3.02) with a mean follow-up of 4.2 (sd=2.0) years and 4.3 (sd=1.7) years respectively. Analyses of subscale-scores revealed that this effect was particularly driven by avoidance (HRbaseline 1.23, 95% CI 0.99-1.53, HR4-months=1.77, 95% CI 1.04-3.02).

Conclusions – Cardiac anxiety, particularly anxiety-related avoidance of physical exercise, is an important prognostic factor for MACE in MI-patients, independent of cardiac disease severity and depressive symptoms.

Keywords – anxiety, cardiac, myocardial infarction, cardiovascular prognosis, depression, heart.

Introduction

Potential factors that determine cardiac prognosis after a myocardial infarction (MI) include demographic and clinical parameters, health behaviors, and psychiatric morbidities. Recently, the impact of anxiety symptoms on cardiac prognosis in heart disease patients has gained more attention. In a meta-analysis, post-MI anxiety was associated with a 36% increased risk of adverse cardiac outcomes [1]. Although this meta-analysis could not adjust for measures of disease severity, effect estimates of included studies that did adjust for measures of disease severity were only slightly or not attenuated [1]. Also, generalized anxiety disorder (GAD) was related to adverse outcomes in MI patients and this relationship was not explained by cardiac disease severity parameters [2]. In contrast, other studies described no association [3-5] or even a beneficial association in MI patients [6,7] and stable coronary artery disease (CAD) patients [8] between anxiety and cardiac prognosis. Furthermore, a recent study in CAD patients undergoing coronary artery bypass graft surgery showed different associations of different types of anxiety with cardiac prognosis: no association of the fear and panic disorders and their symptom dimensions, but an adverse association with GAD [9]. These controversy findings suggest that different types of anxiety may be differently related with cardiac prognosis.

As it remains unclear which specific aspects of anxiety are associated with cardiac prognosis, the need to examine the unique contribution of types of anxiety on cardiovascular risk has been advocated [1,10]. Recently, a population-based study found that worry predicted non-fatal cardiac outcome over a three-year follow-up, whereas panic and phobia did not [11]. Another population-based study suggested that in women phobic anxiety may predict fatal but not nonfatal cardiac events [12].

After a MI, cardiac stimuli and sensations may trigger specific anxiety symptoms, conceptualized as cardiac anxiety. This can be assessed reliably by the Cardiac Anxiety Questionnaire (CAQ) [13,14]. CAQ subscale scores in MI patients reflect fear, attention, avoidance of physical exercise, and safety-seeking behavior [14]. Higher cardiac anxiety is shown to be associated with lower quality of life in MI patients [15]. To our knowledge, the association between cardiac anxiety and cardiac outcome has not been examined previously.

Furthermore, in most studies anxiety symptoms are measured directly after hospitalization or surgery [1], which may inflate the rates of psychopathology due to the temporary distress of hospitalization. Long-term functional outcome may only be affected by psychopathological symptoms that persist, or develop during the first weeks as has been demonstrated for depressive symptoms [16]. Previously, we showed

that trajectories of cardiac anxiety after a MI are largely determined within the first three to four months after the event [15].

The aim of the present study was to explore the impact of self-reported cardiac anxiety at both hospitalization and at four months after discharge on cardiac prognosis after a MI. We hypothesized that patients reporting elevated symptoms of cardiac anxiety had the worst cardiac prognosis independent from potential confounders like cardiac disease severity and depressive symptoms.

Methods

Study population

For the present analysis we included MI-patients enrolled in an exploratory prospective cohort study described previously [15]. Patients consecutively hospitalized with MI between November 2006 and December 2007 to the department of cardiology of Radboud University Medical Centre, the Netherlands, were recruited within two days after admission. Eligible patients had to be diagnosed with ST-Elevated (STEMI) or Non ST-Elevated MI (NSTEMI). The diagnosis was confirmed by the presence of a rise and fall of troponin I (>0.20 µg/l). Exclusion criteria were: age above 85 years, discharge out of the hospital within two days of admission, and inability to fill out questionnaires (due to insufficient knowledge of the Dutch language, cognitive impairment or being too ill to participate).

The study protocol was approved by the local Medical Ethics Committee, and all patients provided written informed consent.

Procedure

Between days 2 and 7 after admission (baseline), patients completed a set of self-report-questionnaires including the Cardiac Anxiety Questionnaire (CAQ) [13,14] and the Beck Depression Inventory (BDI) [17]. At four months after discharge patients were sent the same questionnaires by post. If necessary, patients were contacted by phone as a reminder.

Measures

Assessment of Cardiac Anxiety

Cardiac anxiety was assessed with the 18-item self-report-questionnaire CAQ, rating each item on a 5-point Likert scale ranging from 0 (never) tot 4 (always) [13]. In line

with previous publications, the overall score as well as subscale scores are expressed as an average item score, which was computed by summing the score on the relevant items and dividing it by the number of items. The CAQ is well-validated in different populations, originally by Eifert et al. (2000) [13,14,18] . Recently we cross-validated the CAQ in MI patients and identified a factor structure of four subscales: assessing fear (e.g. "When I have chest discomfort, or when my heart is beating fast: I get frightened"), attention (e.g. "I pay attention to my heart beat"), avoidance of (physical) activity (e.g. "I avoid activities that make my heart beat faster") and safety seeking behavior (e.g. "When I have chest discomfort or when my heart is beating fast, I like to be checked out by a doctor") respectively [14]. Our study showed a good internal consistency of both total and subscale scores (Cronbach α 0.84 and 0.6-0.9 respectively), a high test-retest-reliability (0.88, p<.001) and low to moderate correlations with questionnaires such as the Agoraphobic Cognitions Questionnaire (0.31), the State-Trait-Anxiety Inventory (0.39) and the Beck Depression Inventory (0.27). Comparable results, including the four subscales, have been previously reported in an independent cross validation study in 658 persons referred for screening for coronary artery disease [18].We confirmed the four subscales factor solution on the present data. In the present study, our main predictors were the continuous overall mean item score of the CAQ (i.e. total score divided by number of items), as well as the mean item score of the subscales.

Assessment of covariates

Socio-demographic and cardiac-related variables

Socio-demographic and clinical data concerning the severity of the cardiac disease (left ventricular ejection fraction (LVEF) and a history of MI), as well as relevant cardiac risk factors (including smoking, hypertension, hypercholesterolemia, diabetes mellitus, history of stroke, peripheral atherosclerotic disease, history of cardiac disease other than MI) were collected by the cardiologist during hospitalization for the MI. LVEF was determined by echocardiography according to the modified Simpson's rule [19]. Information on possible treatment with PCI and assignment for cardiac rehabilitation after admission was retrieved from the hospital files.

Psychiatric comorbidity

Anxiety often coincides with depression in MI patients [20]. Two meta-analyses have identified depression in MI-patients as a risk factor for all-cause mortality, cardiac mortality, and cardiac events [21,22]. In order to adjust for depression as a covariate, depressive symptoms were measured with the Beck Depression Inventory (BDI), a

21-item self-report-questionnaire rating each item on a 4-point Likert scale, which is well-validated in MI patients [17,23].

Assessment of adverse outcomes

The primary outcome was a major cardiac adverse event (MACE), defined by all-cause mortality or a re-admission for a major cardiac event, occurring after the CAQ assessment at baseline or four months after discharge respectively.

Hospital re-admissions with discharge diagnoses with ICD-9 codes 410, 411, 413, 414 (ischemic heart disease); 427.4 (Ventricular fibrillation and flutter), 427.5 (cardiac arrest) and/or readmissions for an acute (unplanned) coronary intervention (coronary artery bypass graft/ percutaneous coronary intervention) were included as a major cardiac event [24]. Data on all-cause mortality were obtained up until 01 January 2013 from the Dutch Central Bureau of Statistics by linkage to the municipal personal records database. Data concerning hospital admissions came from the Dutch national registry of hospital discharges and were obtained up until 01 January 2012 from the Dutch Central Bureau of Statistics by linkage to the municipal personal records database. Furthermore, in order to obtain more complete data, we also examined the administration and patient records of the Radboud University Medical Centre on readmissions for MACE and/or mortality. These data were obtained up until 01 January 2013.

Statistical analysis:

Multiple Imputation Model:

In order to use all available data for survival analysis, we performed multiple imputations in patients with data on MACE. Rubin's rules were used to pool the data [25]. Linear and logistic regression for multiple imputations was performed with all variables to be included in the final analysis model, as well as other relevant variables that were not included in the analyses, including cardiac risk and disease variables, PCI treatment and assignment to cardiac rehabilitation. These variables were examined for normal distribution and if needed transposed before the imputation was run: BDI was Natural Log-transformed. In total, 7.0% of all values in the imputation model were missing. 67 datasets were created, because 67.0% of the cases had at least one missing value [26]. For each imputed file, SPSS calculated in 100 iterations the best model fit.

Baseline:

Baseline demographic and clinical characteristics were compared with logistic

regression (for categorical variables), Student's t-test, or when continuous variables were not normally distributed with the Mann Whitney U test.

Correlation and Survival analysis:

The correlation between sum scores of the CAQ and the BDI was evaluated with Spearman's rho.

Cox regression was used to evaluate risk of MACE associated with CAQ sum scores at baseline and at four months after discharge. Next, using Cox regression the association between each of the four CAQ subscales at baseline and at four months after discharge with MACE was evaluated. For analyses with CAQ at hospitalization as determinant, the follow-up period for the primary endpoint started at hospitalization for index-MI. For analyses with CAQ at 4 months after index-MI as determinant, the follow-up period for the primary endpoint started at the date of this CAQ assessment. In all analyses the follow-up period for primary endpoints ended at 01-01-2013, and patients who did not have the outcome of interest until 01-01-2013 were censored on 01-01-2013.

In the basic model, adjustments were made for age and gender. A priori we decided to adjust for a history of MI and LVEF as objective parameters of cardiac disease severity, as both have been shown to be consistently related to worse cardiac prognosis. In addition, since cardiac related hospital readmissions between baseline and four months also reflect cardiac disease severity, we adjusted for this characteristic when examining the CAQ score at 4 months after discharge. In the final model, we also adjusted for BDI-scores.

Sensitivity analyses:

Post-hoc sensitivity analyses were performed in order to further adjust separately for possible confounders. In the basic model we tested those characteristics that at baseline differed between patients with and without a MACE.

Furthermore, sex-effects were explored post-hoc as depression has a higher impact on mortality in males compared to females [27], although other studies with respect to cardiac prognosis did not find sex-specific effects [28,29]. For the latter sensitivity analysis, we included this interaction variable in the regression model for multiple imputations.

For all analyses, SPSS 20 for Windows was used and significance level was set at 0.05, two-tailed.

Results

Sample

Of 398 MI patients admitted at the cardiology ward, 135 patients were after primary PCI relocated to a hospital in their home area within two days of admission. Of the 263 patients who were still present at the time we asked informed consent, 203 patients (77%) agreed to participate. Ten persons had to be excluded because of missing data on MACE, leaving 193 patients to be analyzed for the association between CAQ at baseline and MACE. Baseline characteristics, resulting from the imputational model, for the 193 patients stratified according to occurrence of MACE are shown in Table 1.

Please note that four persons died before the assessment four months after discharge, leaving 189 persons to be analyzed for the association between CAQ at four months after discharge and MACE.

The mean (SD) duration of assessment of CAQ and BDI was at baseline 3.7 (3.8) days from hospitalization (or index MI). The follow-up assessment took place 138.8 (59.4) days from hospitalization. A total of 77.8% (n=147/189) patients completed the CAQ at follow up. Sum scores of CAQ and BDI were moderately correlated at hospitalization (Spearman $\rho=0.332$, $p<0.001$)) and highly at four months after discharge (Spearman $\rho=0.501$, $p<0.001$).

Predictors of MACE

During a mean (SD) follow-up period of 4.2 (2.0) years, 77 (39.9%) of 193 patients had a MACE after baseline (36 of them (46.8%) died). During a mean (SD) follow-up period of 4.3 (1.7) years, 67 (35.4%) of 189 patients had a MACE after four months (32 of them (47.8%) died). Patients who had an event during the follow-up period were significantly older ($p<0.001$), had significantly higher CAQ scores at baseline ($p=0.018$) and were significantly more likely to have a comorbid cardiac disease ($p<0.001$), diabetes mellitus ($p=0.002$), lung cancer ($p=0.029$) and a positive cardiac history ($p<0.001$) (see Table 1).

Table 1: Baseline characteristics of 193 MI patients divided according to incidence of MACE (yes/no) [a]

	MACE	No MACE	Test statistic			
	(n=77)	*(n=116)*	*OR [b]*	*t-test*	*U-test*	*P*
Age, mean (SD)	66.0 (11.6)	58.7 (11.0)		4.394		<0.001***
Male (%)	46 (59.7%)	83 (71.6%)	0.590,			0.089
Stable relation	57 (74.0%)	97 (83.6%)	1.791			0.107
High education[1] (%)	20 (26.0)%	30 (25.9%)	0.981			0.953
Hypertension (%)	40 (51.9%)	45 (38.8%)	0.586			0.072
Diabetes Mellitus (%)	21 (27.3%)	12 (10.3%)	0.308			0.003**
Hypercholesterolemia (%)	22 (28.6%)	33 (28.4%)	0.994			0.985
History of MI (%)	41 (53.2%)	21 (18.1%)	0.194			<0.001***
History of cardiac disease other than MI [c] (%)	30 (39.0%)	11 (9.5%)	0.164			<0.001***
Peripheral atherosclerotic disease (%)	14 (18.2%)	14 (12.1%)	0.618			0.241
History of stroke (%)	3 (3.9%)	4 (3.4%)	0.881			0.871
Smoker at inclusion (%)	38 (49.4%)	45 (38.8%)	1.58			0.157
Family history of cardiac disease (%)	34 (44.2 %)	51 (44.0%)	0.993			0.982
LVEF%, mean(SD)	51.9 (12.7)	54.2 (10.3)		1.164		0.245
CAQ hospitalization, mean (SD)	1.5 (0.6)	1.3 (0.6)		2.333		0.020*
CAQ 4 months post MI, mean (SD)	1.3 (0.7)	1.0 (0.6)		2.908		0.004**
BDI hospitalization (IQR)	6.8 (4.0-12.0)	6.0 (3.9-9.5)			3484	0.257[3]
BDI 4 months post MI (IQR)	7.0 (4.8-11.0)	4.0 (2.0-8.0)			1758.5	0.002[3]**
PCI (%)	44 (57.1%)	73 (62.9%)	1.28			0.412
Assigned for cardiac rehabilitation (%)	35 (45.5%)	87 (75.0%)	3.56			0.001**

a. Rubin's rules were used to pool the data of the imputed datasets[25]
SD=Standard deviation; T=T test ; OR=Odds ratio; IQR=interquartile range; PCI=Percutaneous Coronary Intervention
b. We report OR (based on univariate analysis) for all categorical variables
[1]The categorical variables high education, smoker at inclusion and family history of cardiac disease were (party) imputed.
c. Including e.g. stable angina pectoris, endocarditis, heart failure and atrial fibrillation

*p<0.05; **p<0.01; ***p<0.001

CAQ sum score and risk of MACE

CAQ at baseline was significantly associated with a higher risk of MACE, independent of age and sex, LVEF and cardiac history, and BDI. CAQ at four months after discharge was also significantly associated with a higher risk of MACE, even when adjusted for age, sex, LVEF, cardiac history, cardiac related hospital readmissions between the index event and CAQ assessment and BDI (see Table 2 for Hazard Ratios (95% CI).

Subscales of CAQ at four months after discharge and risk of MACE

Only the subscale "Avoidance" at four months after discharge was significantly associated with MACE independent from all previously mentioned covariates. The prognostic association of "Avoidance" at baseline lost significance after adjusting for severity of cardiac disease (see Table 3 for HR's (95% CI)).

Sensitivity analyses potential cardiac risk factors

In sensitivity analyses, we tested whether characteristics that differed at baseline between patients with and without MACE and were not included in our model, might have influenced our results. Adding these variables (see Table 1) to model 2 did virtually not affect the association between overall CAQ score and adverse prognosis. The only exception was the presence of a history of cardiac disease other than MI: in this model the HR for CAQ at baseline and MACE was attenuated to just non-significant (HR: 1.43 (0.96-2.11); p=0.076).

Sensitivity analyses sex differences in overall CAQ score and risk of MACE

We found an interaction effect between sex with overall CAQ score in the prognostic model (included variables: CAQ, sex, age, interaction sex-CAQ) at baseline ($HR_{baseline}$ 2.16, 95% CI 1.03-4.56, p=0.043; $HR_{fourmonths}$ 2.78, 95% CI 1.00-7.72, p=0.050). Stratified analyses showed larger HRs and more significant results in the females compared to the males. Only in females, the full model remained significant for the CAQ at baseline (HR 3.04 (1.47-6.28); p=0.003; n=64 of which n=31 had a MACE during follow-up), whereas the HR for the CAQ at four months lost significance after additional adjustment for BDI (HR 2.17 (0.78-6.07); p=0.139; n=62 of which n=27 had a MACE during follow-up) (see supplemental Tables A-C).

Table 2: Hazard ratio's (95% CI) for MACE associated with scores on the CAQ during hospitalization and at 4 months after discharge

	Hazard ratio (95% CI)					
	CAQ sum score at hospitalization N=77/193			**CAQ sum score at approximately 4 months after discharge N=67/189**		
		p	R^2 (%)		**p**	**R^2(%)**
Model 1	1.70 (1.16-2.46)	0.006**	4.1	2.09 (1.38-3.17)	0.001**	8.0
Model 2	1.64 (1.14-2.38)	0.008**	13.1	2.04 (1.30-3.19)	0.002**	12.9
Model 3	1.52 (1.03-2.23)	0.034*	22.6	2.00 (1.24-3.23)	0.005**	20.3
Model 4	1.59 (1.04-2.43)	0.033*	22.8	1.77 (1.04-3.02)	0.036*	21.1

*p<0.05; **p<0.01; ***p<0.001
Rubin's rules were used to pool the data of the imputed datasets (Rubin 1987)
The explained variance (R^2) for Cox regression was estimated according based on the log likelihood as proposed in Hosmer at al. [30].
Model 1: unadjusted;
Model 2: adjusted for age and sex
Model 3: Model 2 + LVEF, history of MI, and hospital readmissions between the index event and CAQ assessment four months after discharge in the model evaluating HR at four months.
Model 4: Model 3 + transformed BDI-score at same time as cardiac anxiety assessment (i.e. at baseline or 4 months after discharge, respectively)
BDI: Beck Depression Inventory; CAQ: Cardiac Anxiety Questionnaire; CI: confidence interval; LVEF: left ventricular ejection fraction; MACE: major adverse cardiac event; MI: myocardial infarction; baseline assessment 3.7 (3.8) days from hospitalization; assessment 4 months after discharge 138.8 (59.4) days from hospitalization

Table 3: Hazard ratio's (95% CI) for MACE associated with scores on the four CAQ subscales during hospitalization and at 4 months post-MI

	Baseline (77 persons out of a total of 193 had a MACE during follow- up)				**4 months after discharge** (67 persons out of a total of 189 had a MACE during follow- up)			
	Fear	**Avoid-ance**	**Atten-tion**	**Safety seeking**	**Fear**	**Avoidance**	**Attention**	**Safety seeking**
Model 1	1.29 (0.95-1.75); p=0.104; R^2=1.3%	1.34 (1.10-1.64); p=0.003** R^2=5.0%	1.02 (0.73-1.42); p=0.917 R^2=0.0%	1.29 (1.01-1.66); p=0.046* R^2=2.1%	1.27 (0.95-1.70); p=0.114 R^2=2.7%	1.64 (1.32-2.04); p<0.001** R^2=10.3%	1.41 (0.93-2.12); p=0.106 R^2=1.9%	1.13 (0.85-1.50); p=0.416 R^2=0.6%
Medel 2	1.33 (0.98-1.80); p=0.067 R^2=11.2%	1.31 (1.08-1.59); p=0.007** R^2=13.5%	1.08 (0.78-1.50); p=0.625 R^2=9.9%	1.20 (0.94-1.54); p=0.137 R^2=10.8%	1.24 (0.93-1.66); p=0.138 R^2=8.6%	1.60 (1.26-2.02); p<0.001*** R^2=14.2%	1.54 (0.99-2.39); p=0.054 R^2=9.0%	1.07 (0.80-1.42); p=0.665 R^2=6.6%
Model 3	1.30 (0.94-1.81); p=0.119 R^2=21.7	1.23 (1.00-1.51); p=0.053 R^2=22.4%	1.05 (0.76-1.46); p=0.761 R^2=20.8%	1.25 0.97-1.61); p=0.084 R^2=22.0%	1.25 (0.93-1.68); p=0.146 R^2=17.1%	1.51 (1.18-1.95); p=0.001** R^2=20.4%	1.52 (0.98-2.36); p=0.062 R^2=17.3%	1.10 (0.80-1.50); p=0.557 R^2=15.5%
Model 4	1.32 (0.92-1.90) p=0.1436 R^2=21.8%	1.23 (0.99-1.53); p=0.060 R^2=22.5%	1.04 (0.74-1.45); p=0.843 R^2=20.8%	1.25 (0.96-1.62); p=0.093 R^2=22.0%	1.09 (0.78-1.53); p=0.616 R^2=19.0%	1.41 (1.07-1.86); p=0.014* R^2=21.7%	1.45 (0.92-2.28); p=0.111 R^2=20.2%	1.07 (0.78-1.46); p=0.690 R^2=18.8%

*p<0.05; **p<0.01; ***p<0.001
The explained variance (R^2) for Cox regression was estimated according based on the log likelihood as proposed in Hosmer et al. [30].
Model 1: unadjusted;
Model 2: adjusted for age and sex
Model 3: Model 2 + LVEF and history of MI, and hospital readmissions between the index event and CAQ assessment four months after discharge in the model evaluating HR at four months.
Model 4: Model 3 + transformed BDI-score at same time as CAQ assessment (i.e. baseline or 4 months after discharge respectively).

Supplemental Table A: Hazard ratio's (95% CI) for MACE (and n with event/n) associated with scores on the CAQ during hospitalization and at 4 months after discharge in 193 MI patients

	Male patients (n=129)		Female Patients (n=64)	
	Hazard ratio (95% CI)		Hazard ratio (95% CI)	
	Cardiac anxiety at hospitalization	Cardiac anxiety at 4 months post-MI	Cardiac anxiety at hospitalization	Cardiac anxiety at 4 months post-MI
Model 1	1.42 (0.88-2.29); p=0.156; n= 46/129 R^2=1.1%	1.94 (1.17-3.24;) p=0.011*; n=40/127 R^2=4.1%	2.54 (1.41-4.57); p=0.002**; n=31/64 R^2=4.9%	2.63 (1.13-6.10); p=0.025*; n=27/62 R^2=4.8%
Model 2	1.24 (0.78-1.95); p=0.364; n=46/129 R^2=6.7%	1.90 (1.11-3.25); p=0.019*; n=40/127 R^2=7.1%	2.55(1.40-4.65); p=0.002** n=31/64 R^2=6.9%	2.41 (1.03-5.86); p=0.043*; n=27/62 R^2=5.4%
Model 3	0.09 (0.55-1.47); p=0.671; n=46/129 R^2=17.9%	1.65 (0.92-2.97); p=0.094; n=40/127 R^2=14.0%	2.75 (1.47-5.17); p=0.002**; n=31/64 R^2=8.9%	2.79 (1.09-7.11); p=0.032*; n=27/62 R^2=8.4%
Model 4	0.96 (0.55-1.68); p=0.880; n=46/129 R^2=18.0%	1.56 (0.80-3.04); p=0.194; n=40/127 R^2=14.4%	3.04 (1.47-6.28); p=0.003**; n=31/64 R^2=9.1%	2.17 (0.78-6.07); p=0.139; n=27/62 9.7%

*p<0.05; **p<0.01; ***p<0.001
Model 1: unadjusted;
Model 2: adjusted for age
Model 3: Model 1 + LVEF and cardiac history**,** and hospital readmissions between the index event and CAQ assessment four months after discharge in the model evaluating HR at four months.
Model 4: Model 3 + transformed BDI-score at same time as cardiac anxiety assessment
BDI: Beck Depression Inventory; CAQ: Cardiac Anxiety Questionnaire; CI: confidence interval; LVEF: left ventricular ejection fraction; MACE: major adverse cardiac event; MI: myocardial infarction

Supplemental Table B: Hazard ratio's (95% CI) for MACE (and n with event/n) associated with scores on the 4 CAQ subscales during hospitalization

	MALES				FEMALES			
	Fear	**Avoidance**	**Attention**	**Safety seeking**	**Fear**	**Avoidance**	**Atten-tion**	**Safety seeking**
Model 1	1.12 (0.77-1.64); p=0.548; n=46/129 R^2=0.2%	1.30 (1.00-1.68); p=0.046*; n=46/129 R^2=2.3%	0.95 (0.63-1.45); p=0.819 n=46/129 R^2=0.0%	1.12 (0.80-1.57); p=0.499; n=46/129 R^2=0.2%	2.06 (1.16-3.68); p=0.014*; n=31/64 R^2=3.0%	1.47 (1.10-1.97); p=0.009**; n=31/64 R^2=3.7%	1.21 (0.68-2.18); p=0.518; n=31/64 R^2=0.2%	1.61 (1.33-1.94); p=0.012*; n=31/64 R^2=3.2%
Model 2	1.10 (0.76-1.58); p=0.621; n=46/129 R^2=6.4%	1.19 (0.92-1.54); p=0.192; n=46/129 R^2=7.3%	1.03 (0.70-1.54); p=0.868; n=46/129 R^2=6.3%	1.00 (0.72-1.37); p=0.975; n=46/129 R^2=6.3%	2.05 (1.15-3.69); p=0.016*; n=31/64 R^2=5.0%	1.49 (1.11-1.99); p=0.008**; n= 31/64 R^2=5.9%	1.20 (0.68-2.13); p=0.526; n=31/64 R^2=2.4%	1.51 (1.25-1.83); p=0.030*; n=31/64 R^2=4.5%
Model 3	0.92 (0.61-1.39); p=0.698; n=46/129 R^2=17.9%	0.99 (0.75-1.32); p=0.963; n=46/129 R^2=17.9%	0.89 (0.59-1.35); p=0.584; n=46/129 R^2=18.0%	0.92 (0.65-1.31); p=0.655; n=46/129 R^2=17.9%	2.16 (1.16-3.99); p=0.015*; n=31/64 R^2=6.9%	1.49 (1.10-2.01); p=0.010*; n=31/64 R^2=7.3%	1.30 (0.73-2.232); p=0.369; n=31/64 R^2=4.3%	1.59 (1.08-2.33); p=0.018* n=31/64 R^2=6.7%
Model 4	0.97 (0.61-1.54); p=0.904; n=46/129 R^2=18.0%	1.03 (0.76-1.39); p=0.864; n=46/129 R^2=18.1%	0.91 (0.60-1.39); p=0.657; n=46/129 R^2=18.1%	0.95 (0.66-1.37); p=0.780; n=46/129 R^2=18.0%	2.14 (1.10-4.16); p=0.026*; n=31/64 R^2=7.0%	1.50 (1.06-2.11); p=0.022*; n=31/64 R^2=7.4%	1.19 (0.64-2.24); p=0.584; n=31/64 R^2=4.7%	1.58 (1.06-2.35); p=0.023*; n=31/64 R^2=7.0%

*p<0.05; **p<0.01; ***p<0.001
Model 1: unadjusted;
Model 2: adjusted for age
Model 3: Model 1 + LVEF and cardiac history
Model 4: Model 3 + transformed BDI-score at same time as cardiac anxiety assessment
BDI: Beck Depression Inventory; CAQ: Cardiac Anxiety Questionnaire; CI: confidence interval; LVEF: left ventricular ejection fraction; MACE: major adverse cardiac event; MI: myocardial infarction

Supplemental Table C: Hazard ratio's (95% CI) for MACE (and n with event/n) associated with scores on the 4 CAQ subscales at 4 months after discharge

	MALES				FEMALES			
	Fear	**Avoidance**	**Attention**	**Safety seeking**	**Fear**	**Avoidance**	**Attention**	**Safety seeking**
Model 1	1.26 (0.80-1.99); p=0.316; n=40/127 R^2=1.5%	1.60 (1.22-2.10); p=0.001**; n=40/127 R^2=6.2%	1.03 (0.60-1.79); p=0.904 n=40/127 R^2=0.1%	1.28 (0.91-1.79); p=0.158; n=40/127 R^2=1.3%	1.28 (0.83-1.97); p=0.264; n=26/62 R^2=1.6%	1.85 (1.15-2.97); p=0.011**; n=26/62 R^2=4.8%	2.22 (1.05-4.71); p=0.038*; n=26/62 R^2=3.9%	0.93 (0.57-1.51); p=0.762; n=26/62 R^2=0.2%
Model 2	1.28 (0.79-2.08); p=0.311; n=40/127 R^2=5.2%	1.53 (1.16-2.03); p=0.003**; n=40/127 R^2=8.3%	1.15 (0.64-2.07); p=0.631; 40/127 R^2=3.9%	1.20 (0.86-1.68); p=0.286; n=40/127 R^2=4.3%	1.24 (0.82-1.86); p=0.307; n=26/62 R^2=2.9%	1.76 (1.08-2.85); p=0.022**; n= 26/62 R^2=5.4%	2.13 (1.01-4.52); p=0.049*; n=26/62 R^2=5.2%	0.90 (0.54-1.47); p=0.663; n=26/62 R^2=1.9%
Model 3	1.23 (0.75-2.01); p=0.413; n=40/127 R^2=13.4%	1.34 (0.98-1.84); p=0.065; n=40/127 R^2=14.1%	1.07 (0.58-1.97); p=0.832; n=40/127 R^2=12.5%	1.21 (0.83-1.75); p=0.322; n=40/127 R^2=12.9%	1.29 (0.84-1.98); p=0.249; n=26/62 R^2=5.3%	1.85 (1.10-3.10); p=0.020*; n=26/62 R^2=7.9%	2.22 (1.08-4.55); p=0.030*; n=26/62 R^2=7.7%	0.99 (0.58-1.69); p=0.959 n=26/62 R^2=4.0%
Model 4	1.14 (0.66-1.96); p=0.646; n=40/127 R^2=13.9%	1.30 (0.92-1.84); p=0.140; n=40/127 R^2=14.6%	1.02 (0.54-1.91); p=0.961; n=40/127 R^2=13.4%	1.17 (0.80-1.71); p=0.419; n=40/127 R^2=13.7%	1.05 (0.65-1.70); p=0.837; n=26/62 R^2=8.1%	1.61 (0.92-2.82); p=0.098; n=26/62 R^2=10.0%	2.15 (1.08-4.31); p=0.030*; n=26/62 R^2=11.1%	0.94 (0.51-1.74); p=0.850; n=26/62 R^2=8.1%

*p<0.05; **p<0.01; ***p<0.001
Model 1: unadjusted;
Model 2: adjusted for age
Model 3: Model 1 + LVEF and cardiac history + hospital readmissions between the index event and CAQ assessment four months after discharge
Model 4: Model 3 + transformed BDI-score at same time as cardiac anxiety assessment
BDI: Beck Depression Inventory; CAQ: Cardiac Anxiety Questionnaire; CI: confidence interval; LVEF: left ventricular ejection fraction; MACE: major adverse cardiac event; MI: myocardial infarction

Discussion

Main finding

This study was the first to address the independent prognostic association of cardiac anxiety following myocardial infarction with adverse cardiac prognosis. Patients reporting higher cardiac anxiety were at increased risk of adverse prognosis after adjustment for age, gender, cardiac disease severity parameters and depressive symptoms; with each point increase on the CAQ, which has a possible range of 0 to 4, the risk of a new cardiac event increased from 56% (at baseline) to 71% (at 4 months after discharge). This effect seemed to be particularly driven by avoidance behavior.

Our findings are in line with previous research reporting the prognostic impact of anxiety [1] and anxiety disorders [2,29,31] in MI patients. These heterogeneous studies used different anxiety measures and the reported HRs in the meta-analysis (around 1.30) 1 were based on dichotomous cut off points of anxiety (present or not) which makes it difficult to compare the reported HRs with ours. One study evaluated the prognostic association of separate dimensions of anxiety in MI patients. It also described an adverse prognostic association: significant associations for somatic anxiety (HR 1.29) and total anxiety (HR 1.38), with a trend for psychological anxiety [32]. However, these anxiety dimensions were derived from a questionnaire assessing general anxiety (Hamilton Anxiety and Depression Rating Scales) and all dimensions are more or less associated with avoidance behavior. These general findings are extended by our findings showing the most specific results for avoidance behavior related to cardiac stimuli, especially at four months after discharge.

For depression the reported HRs are even higher [33], especially when not adjusted for cardiac disease severity. In our study, after adjustment for parameters of cardiac disease severity, the association remained significant, and more importantly the HRs hardly attenuated, implying a prognostic effect of cardiac anxiety independent from cardiac disease severity. Adjustment for depressive symptoms did not affect the effect size of the cardiac anxiety on adverse cardiac prognosis. This is consistent with other studies assessing the association between general anxiety or anxiety disorder and cardiovascular events independent from depression [2,31,34].

Potential mechanisms

The association between anxiety and ischemic heart disease might be explained by both behavioral and biological mechanisms. First, anxiety appears to be associated with unhealthy behavior (e.g. physical inactivity and smoking) in individuals at risk of coronary heart disease [35]. Our finding that the main prognostic effect of cardiac

anxiety was driven by the subscale assessing avoidance of physical activity supports this. Surprisingly though, in our study patients reporting higher anxiety less often smoked. Although this is in contrast with a recent finding suggesting less adherence of anxious MI patients to risk reducing recommendations like cessation of smoking [36], this difference might be caused by the type of anxiety (general versus cardiac) examined, or by differences in coping strategies of individual patients.

Unfortunately, our data do not provide any insight into potential biological mechanisms explaining the negative association between anxiety and cardiac disease, like reduced heart variability, cardiac arrhythmias, and increased platelet activity or inflammation [37-39]. For example, increased anxiety levels may trigger ventricular tachycardia's in a dose-dependent way and are among patients with implantable cardioverter defibrillators associated with a higher number of shocks [40].

Methodological considerations

A strength of the present study is that cardiac anxiety was assessed not only at hospitalization but also at four months post-MI, when the possible inflating impact of the stressful hospitalization and event itself on anxiety parameters is expected to be settled down [15]. Importantly, although our sample size was relatively small, it was large enough to adjust for several important confounders simultaneously. Nonetheless, we were not able to address all indicators of cardiac disease severity. Therefore, we adjusted for the two most important indicators, LVEF and a history of a MI, in line with previous studies on this topic. However, since cardiac anxiety was inversely correlated with cardiac disease severity, as previously reported by our group [41], it seems unlikely that our results are driven by residual confounding due to cardiac disease severity.

In line with previous studies we chose as primary outcome a combination of all-cause mortality and cardiac readmissions. However, while previous studies included a rather broad range of cardiovascular events [1,2,21], we only evaluated readmissions for ischemic events. We consider this as an advantage. As patients with high cardiac anxiety might be more likely to consult their doctor and be admitted to the hospital with cardiac complaints, this might partly explain the association between cardiac anxiety and cardiovascular-related hospital readmissions. By only including readmissions due to acute ischemic events, this risk is minimized.

Although the prognostic association of cardiac anxiety with MACE was particularly driven by avoidance of physical activity, it is important to realize that physical activity was not assessed in the present study and some of the other dimensions of cardiac

anxiety (fear and attention respectively) showed even higher HRs than avoidance. The prognostic associations of these subscales were not significant in the final model, but this may be explained by a power problem (type two error). Studies in larger populations are needed to examine this more closely. Future studies should include physical activity as a mediating mechanism when studying the prognostic impact of cardiac anxiety.

Limitations of the present study are that we did not assess the presence (and/or history) of a formal diagnosis of an anxiety and/or depressive disorder, nor did we have information on possible psychiatric treatment. Therefore we do not know how cardiac anxiety is related to psychiatric diagnosis. As (some) anxiety disorders have been associated with the development of coronary heart disease in the general population [12,42] and prognosis in patients with heart disease [2,28,29], this would have been interesting. Nevertheless, we did adjust for depressive symptoms, which is an important possible confounder [21,22].

Our study had a high response rate of 77% [15], even though we had to exclude the most severely ill patients. As on the other hand, patients with milder symptoms who were transported to other hospitals within two days were not eligible for the present study, it is questionable whether this limits generalization of our results.

In our study, the association between cardiac anxiety and adverse prognosis could not be explained by cardiac disease severity parameters, including LVEF and cardiac history. Nevertheless, it is still possible that the association is confounded by disease severity, especially since some symptoms of cardiac anxiety, such as chest pain, might also be symptoms of heart disease. However, most items in the CAQ focus on the impact of these symptoms on affect (anxious), thought (worrying) or behavior (avoidance and safety seeking behavior).

Although the HRs were particularly large for women, the sex-specific findings should be considered preliminary due to lack of statistical power. Moreover, the sex-effect was opposite to that found for the association between depression and mortality in cardiac patients [27] and two smaller studies with underrepresentation of women did not find sex-effects [28,29]. Therefore, future studies examining anxiety should preferably examine possible interaction effects with sex.

Clinical implications

The present findings of a prognostic association with MACE, independent from cardiac disease severity and depressive symptoms, stress the potential clinical impact of cardiac anxiety. Interestingly, when looking at the CAQ score alone, the explained

variance increased in the follow up model compared to the baseline measurement (4% and 8% respectively), indicating the importance of identifying (persisting) cardiac anxiety symptoms in the months post MI. Diagnosing elevated cardiac anxiety symptoms and its specific subtypes can be helpful in developing specific interventions reducing maintaining or exacerbating factors such as avoidance of cardiac stimuli and physical exercise. Cognitive behavioral therapy (CBT) may target anxiety-related avoidance behavior which may even result in a better cardiac outcome. General CBT focused on stress management has been shown to improve cardiac outcome over 8 years post MI [43].

For this reason, cardiac anxiety should be explicitly addressed in cardiac rehabilitation programs. Whereas there is awareness for general anxiety in cardiac rehabilitation and recent studies did pay attention to specific types of anxiety recognized by the DSM like generalized anxiety disorder [9], cardiac anxiety may in fact be relatively unexplored. Outcomes of cardiac rehabilitation programs might even further improve if physical exercise is used as a behavioral experiment to test out specific cardiac fears patients may have. So, the findings of the present study indicate the need to evaluate and target cardiac anxiety- in addition to depression and general anxiety- in the future.

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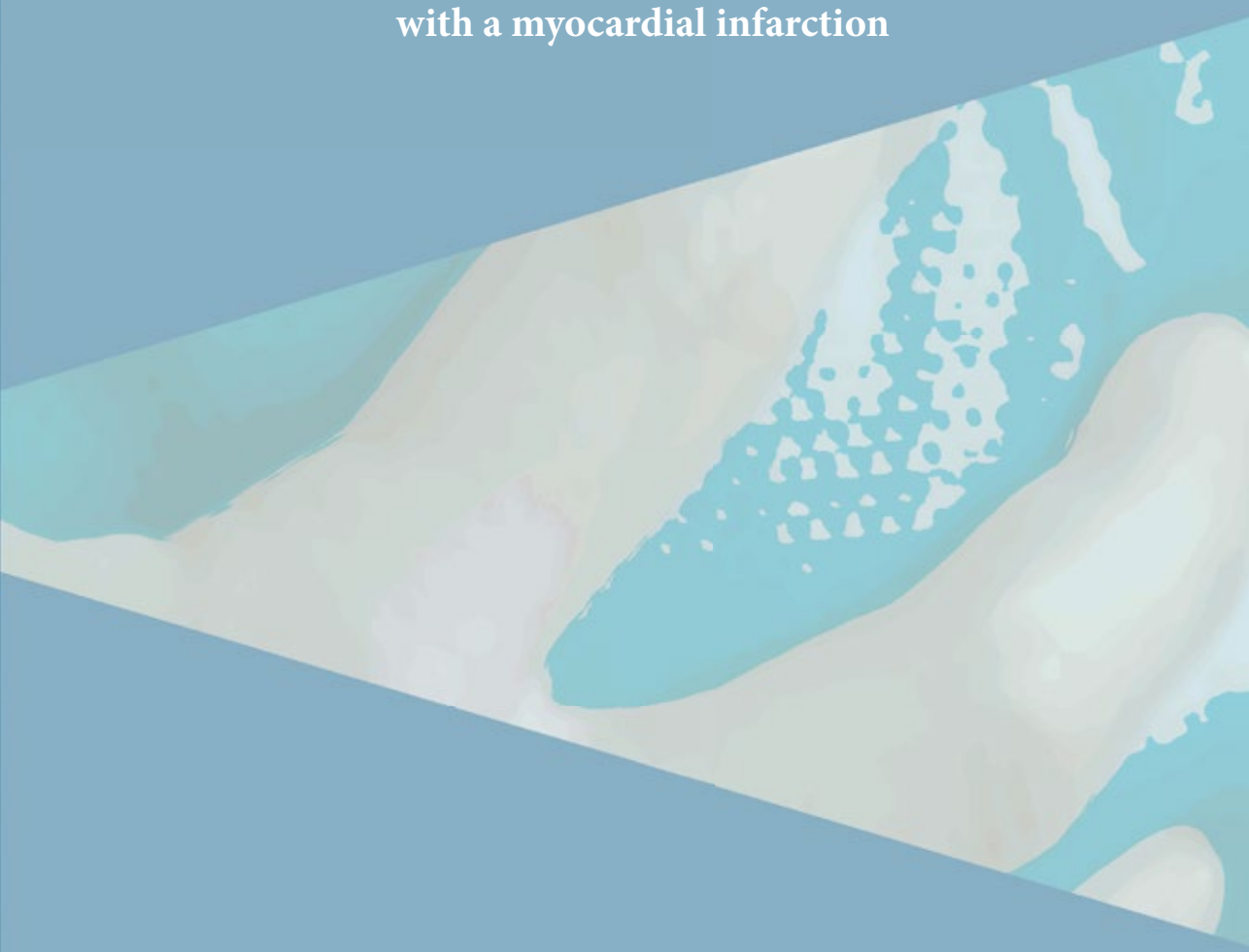
CHAPTER 6

The prognostic impact of physical health complaints with new cardiac events and mortality in patients with a myocardial infarction



submitted

M.H.C.T. van Beek, A.M. Roest, K. J. Wardenaar, A.J.L.M. van Balkom, A.E.M. Speckens, R.C. Oude Voshaar, M. Zuidersma.

Abstract

Background – Self-rated general health has been associated with worse outcome after a myocardial infarction (MI). In previous research, however, concurrent depression or anxiety were not taken into account.

Objective – To evaluate the impact of physical health complaints on the prognosis of MI adjusting for cardiac disease severity, depression and anxiety.

Methods – The somatic subscale of the Health Complaints Scale (HCS) was administered to 424 MI-patients at 3 and 12 months post-MI. Types and trajectories of health-complaints were identified with latent-transition-analysis (LTA). The prognostic impact of HCS-sum-score at 3 months, and of types and trajectories of health-complaints on combined endpoints of new cardiac events and mortality was evaluated with Cox-regression. Adjustments were made for age, sex, education-level, history of MI, left ventricular ejection fraction, depressive symptoms and generalized anxiety disorder.

Results – 192 (45.3%) MI-patients, had a new cardiac event or died during a mean follow-up of 5.7 (3.1) years. In the fully adjusted model HCS-sum-score predicted outcome (HR=1.03 [95% CI: 1.01-1.05]). LTA distinguished 5 groups at both 3 and 12 months characterized by 1) no/minimal symptoms, 2) cardiac complaints, 3) lack of energy, 4) sleep-problems, and 5) mixed health-complaints, resulting in 25 transition-classes. Patients with cardiac complaints at 3 months (HR=1.55 [1.15-2.10]) and those with new or persistent cardiac, energy and mixed complaints over time had a worse prognosis (HRcardiac=1.55 [1.11- 2.16], HRmixed=1.71 [1.19- 2.47], HRenergy=1.50 [1.09-2.07]).

Conclusions – Physical health-complaints are predictors of cardiac outcome independent from cardiac disease, depression and anxiety. Type and trajectories of health-complaints may have additional prognostic significance.

Keywords – myocardial infarction, energy complaints, cardiac complaints, sleep complaints, cardiovascular prognosis, depression, anxiety, physical health.

Introduction

Cardiovascular disease, in particular myocardial infarction (MI), is one of the leading causes of death in industrialized countries [1]. Numerous studies identified factors that are associated with cardiac prognosis, including demographics, like age and gender, and clinical factors such as hypertension, diabetes and severity of the MI. A systematic review describing 34 prospective cohort studies showed that self-rated physical health status predicts an adverse cardiac prognosis, even when adjusted for objective disease severity [2]. In the 7 studies specifically conducted in MI-patients [3-9], neither the severity of the MI nor the follow-up time had impact on the predictive value of self-rated health status. This suggests a robust predictive effect of self-rated physical health status on adverse prognosis in MI patients over and above traditional objective cardiac disease severity measures [2]. Therefore, health complaints might serve as a valuable low-cost addition in the process of risk-stratification, particularly because they are not always in agreement with what clinicians observe [10,11]. However, self-rated health status is not yet mentioned in clinical guidelines for the secondary prevention of cardiovascular disease [12,13].

A limitation of previous studies on self-rated health status and cardiac prognosis is that they did not take depression and/or anxiety into account [2,14]. Depression and anxiety are associated with worse cardiac prognosis following MI [15,16]. These findings are robust and based on both self-reported depressive or anxiety symptoms and clinical diagnoses, like post-MI depression or generalized anxiety disorder. Since patients with affective symptoms rate their physical health more negatively [17], the impact of self-rated health status on cardiac prognosis may be confounded by affective symptoms.

Another limitation of most previous studies on self-rated health after MI and cardiac prognosis is that they did not distinguish between different types of health complaints, while there is evidence that different types of complaints can be distinguished in MI patients. Factor analysis on the somatic subscale of the Health Complaints Scale (HCS) yielded three dimensions: cardiac complaints, sleep complaints, and fatigue/energy complaints in MI patients [18,19]. In another study, in 418 MI patients, principal components analysis on the Hospital Anxiety Depression Scale yielded a distinction between cardiopulmonary/autonomic symptoms, sleep problems and fatigue/energy complaints. Of these three somatic dimensions, only cardiopulmonary/autonomic symptoms were related to worse cardiac prognosis [20]. These findings suggest that, of the different types of somatic health complaints after MI, particularly cardiac complaints may be predictive of cardiac prognosis.

Finally, most previous studies used only one assessment of self-rated health status. However, a single assessment of self-rated physical health may be more prone to bias caused by the stress of a recent vascular event. For example, some patients may perceive their health in a less positive way shortly post-MI, but their self-rated health perception may improve during time. Therefore, the course over time in self-rated health status may be a more accurate predictor of cardiac prognosis. In support of this, a recent study in 640 MI patients showed that patients who reported an improvement in their physical health status from before to after the MI were more likely to survive event-free throughout the next 13 years [14]. This effect remained significant when adjusted for multiple cardiac risk factors, including cardiac severity and self-rated physical health in the year before the MI. Additionally, in two other studies in heart failure and MI patients respectively, changes over time in self-rated health provided additional predictive value for adverse cardiac outcomes and mortality beyond a single assessment of self-rated health [6,21].

The aim of the present study was to evaluate whether physical health complaints predict cardio-vascular events and all-cause mortality in MI-patients, when adjusted for both cardiac disease severity as well as depressive and anxiety comorbidity. In addition, the type of physical health symptoms as well as their trajectories over time were explored.

Methods

Study design, participants and procedures

For the present analysis MI patients enrolled in the Depression after Myocardial Infarction study (DepreMI) were included. DepreMI is a naturalistic cohort study evaluating the effects of depression on cardiovascular prognosis up till 10 years follow-up in MI patients. Details of this study have been described elsewhere [22-24]. The study protocol was approved by the local medical ethics committee of each of the four participating hospitals.

Patients hospitalized with MI between September 1997 and September 2000 were recruited consecutively from four hospitals in the north of the Netherlands. Eligible patients had to meet at least 2 out of the 3 following criteria; (1) chest pain for at least 20 minutes, (2) increased cardiac enzyme levels, (3) new pathological Q-waves on the electrocardiogram in at least two leads. Excluded were those patients with a life expectancy of less than a year due to a non-cardiac condition, and inability to fill in questionnaires (due to poor physical function, cognitive dysfunction, inability to speak

or read Dutch, and/or when follow-up visits were scheduled in a nonparticipating hospital). Eligible patients received oral and written information about the DepreMI study and were asked to sign informed consent.

A total of 1166 patients hospitalized for MI were screened on eligibility, of which 284 did not meet inclusion criteria, and 354 gave no informed consent. The remaining 528 patients were included in the study.

At 3 and 12 months post-MI patients underwent a face-to-face interview with a trained research assistant, and filled out questionnaires to assess demographic, psychosocial, biological and mental health parameters. In addition, the medical status of the participants was examined to determine cardiac disease severity parameters and presence of comorbid medical disorders.

Assessment of cardiac outcomes

Data on all-cause mortality were obtained up until 31 December 2007 from the Dutch Central Bureau of Statistics by linkage to the municipal personal records database. Data concerning hospital admissions came from the Dutch national registry of hospital discharges and were obtained from the Dutch Central Bureau of Statistics by linkage to the municipal personal records database. Hospital readmissions with ICD-9 codes 410, 411, 413, 414 (ischemic heart disease including recurrent MI and unstable angina pectoris); 427.1, 427.4, 427.5 (cardiac arrhythmia); 428, 398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93 (heart failure); 433, 434, 435, 437.0, 437.1 (cerebrovascular disease); and 440, 443.9 (peripheral vascular disease) were included as cardiovascular events.

The primary end-point of this study was a combined end-point of cardiovascular events and all-cause mortality occurring between the self-rated health assessments (respectively 3 or 12 months after the index MI) and 31 December 2007. If no event or death occurred, the patient was censored at 31 December 2007 in the survival analyses.

Assessment of self-rated health status

Self-rated health status was assessed with the Health Complaints Scale (HCS) at 3 and 12 months post-MI. The HCS is a self-report questionnaire including 12 items assessing somatic complaints (e.g. "pain in heart and chest", "trouble falling asleep", "fatigue") and 12 items assessing cognitive health complaints (e.g. "worrying about health"; [18]. In the present study, only the 12-item somatic subscale was administered. This somatic subscale has high internal consistency (Cronbach's alpha was 0.89, 0.91

and 0.90 in the study of Denollet [18], Pedersen & Denollet [19] and the present sample respectively), adequate test-retest reliability (r=0.69 in the study of Denollet [18], r=0.76 in the present study), and is sensitive to improvements during cardiac rehabilitation [18]. In previous studies, factor analysis on the 12 items of the somatic subscale of the HCS yielded three symptom dimensions comprising cardiac complaints, sleep complaints and energy complaints [18,19].

Patients rated each health complaint on a 5-point scale ranging from 0 (not at all) to 4 (extremely), yielding a possible score range of 0-48, with higher scores reflecting more health impairment. For the latent class analysis (LCA) and latent transition analysis (LTA) the answers on the items were dichotomized into 'not present' (HCS response 0) or 'present' (HCS responses 1 till 4). This was done because especially the higher responses were rarely endorsed, leading to problems when computing the (polychoric) item correlation matrix used for latent variable modeling.

Types and trajectories of health complaints

Latent transition analysis (LTA) was performed to investigate both quantitative change (in experienced severity) and qualitative (in experienced symptom patterns) change in self-rated health status between 3 and 12 months post-MI. Based on the LTA, patients were classified into a LCA-class at 3 months post-MI and a LCA-class at 12 months post-MI. In addition, the probabilities of transitioning between the classes between 3 and 12 months post-MI were calculated (see Box 1 for details).

Socio-demographic variables, psychiatric comorbidity and cardiac variables

Demographic data, smoking status and comorbid depressive and anxiety disorder were assessed during the face-to-face interview at 3 months post-MI. The presence of a post-MI depressive episode and/or current anxiety disorder (including generalized anxiety disorder, panic disorder, agoraphobia, social phobia) were established with the Composite International Diagnostic Interview (CIDI) during the face-to-face interview at 3 months after the index MI. The CIDI is a structured clinical interview designed for use in research settings with high validity for depressive and anxiety disorders [25,26]. Self-reported depressive symptoms were assessed with the Beck Depression Inventory (BDI) at 3 months post-MI [27]. This 21-item-questionnaire is well-validated in MI patients [28].

Severity of the index-event was assessed by a history of MI, anterior location of the MI, the kind of treatment for the index MI and heart failure as indicated by Killip class (a standardized four-point clinical assessment of the degree of heart failure) at hospitalisation. Furthermore LVEF was determined by wall motion score index,

gated single photon emission computed tomography, magnetic resonance imaging angiography, or clinical judgment by the treating cardiologist and was dichotomized at 40%. Co morbid medical disorders and conditions were extracted from the medical status of the patients.

Statistical Analyses

Characteristics

Baseline characteristics were compared between study completers and those who dropped out with t-tests and chi-square tests. Baseline demographic and clinical (i.e. somatic and psychiatric) characteristics were compared between patients with and without a combined endpoint with t- tests and chi-square tests. The variables which differed significantly between the two groups ($p<0.10$) were included as covariates in the survival analyses.

Prognostic impact of HCS sum-score at 3 months post-MI

The prognostic impact of the total HCS-score at 3 months post-MI on the risk of combined events was evaluated with Cox regression. Models adjusted for socio-demographic covariates only, for socio-demographic and somatic covariates, for socio-demographic and psychiatric covariates and for all covariates are presented. Adjustments were made for variables that were associated with combined endpoint univariately ($p<0.10$), and included age, sex, education-level, history of MI, LVEF, anterior location of MI, Killip Class, diabetes mellitus, peripheral vascular disease, cerebrovascular disease, having received treatment for psychiatric symptoms post-MI, depressive symptoms (BDI-sum-score) and generalized anxiety disorder.

Prognostic impact of types and trajectories of health complaints

With Cox regression, the prognostic impact on combined events was evaluated for (1) the type of health complaints at 3-months post-MI, and (2) the trajectories of health complaints from 3 to 12 months after MI, which were obtained with LTA. In these survival analyses, the models adjusted for sex, age and education level were presented. Because of small group sizes additional covariates (those with $p<0.10$ in table 1) were entered separately.

Sensitivity analysis

In a population of MI patients which consisted partly of the DepreMI cohort, the somatic-affective dimension of the BDI was associated with adverse cardiac outcomes [29]. Therefore, in sensitivity analyses we adjusted for the somatic-affective dimension

of the BDI instead of the total BDI score. A confirmatory factor analysis revealed very good fit for the model found by de Jonge et al [29] on the present sample (CFI: 0.983; TLI: 0.989; RMSEA: 0.037).

Descriptive and survival analyses were conducted with SPSS 22 [30] for Windows with alpha=0.05 (two-tailed). The confirmatory factor analysis, LCA and LTA were conducted with Mplus (version 5.2) [31].

Results

Study sample

A total of 424 out of 528 DepreMI patients were available for analyses, due to missing values on HCS scores at three months (n=82), the cardiac outcomes (n=20) or both (n=2). The 104 patients with missing data did not differ from the 424 patients with respect to age (t=0.26, 526, p=.79), sex (χ^2=0.22, 1, p=.64), education-level (χ^2=0.86, df=1, p=.35), history of MI (χ^2=0.49, 1, p=.49),), Killip class (χ^2=0.059, df=1, p=.82), anterior location of the MI(χ^2=0.68, df=1, p=.41), comorbid diabetes mellitus (χ^2=0.32, df=1, p=.57), comorbid peripheral (χ^2=2.30, df=1, p=.13) and cerebro-vascular disease (χ^2=0.53, df=1, p=.47), psychiatric diagnosis of any anxiety/ depressive disorder (χ^2=1.53, df=1, p=.22), diagnosis of generalized anxiety disorder (χ^2=0.29, df=1, p=.59) , depressive symptoms (t=0.99, df=511, p=.92) and having received psychiatric treatment (χ^2=0.02, df=1, p=.88). Baseline characteristics of the study sample are presented in table 1.

Characteristics and combined events

A total of 192/424 (45.3%) experienced a combined endpoint during a mean (sd) follow-up of 5.7 (3.1) years. Baseline characteristics of the study sample stratified according to occurrence of a combined endpoint are presented in table 1. Those with combined endpoint were significantly older and lower educated and had significantly more often a lower LVEF , a higher Killip class, an anterior location of the MI, a history of a MI, comorbid peripheral and cerebro-vascular disease, and depressive symptoms, and were less likely to have received treatment for psychiatric symptoms post-MI than those without combined endpoint.

Table 1: Baseline characteristics of 424 MI patients divided according to incidence of combined endpoint (yes/no)

Variables	Combined endpoint (n=192; 45,3%)	No combined endpoint (n=232; 54.7%)	Test statistic; p-value		
			T, χ^2	Df	R
Socio-demographic variables					
Age (mean, SD)	63,4 (11,2)	58.4 (10.7)	T=-4.737	422	<0.001***
Gender (male, n%)	152 (79,2%)	191 (82.3%)	0.679	1	0.410
Higher education (n/%)	50 (26%)	93 (40.1%)	9.271	1	0.002**
Living alone (yes, n/%)	30 (15-6%)	25 (10.8%)	2.188	f=1	0.139
Cardiac disease status& treatment					
LVEF <40 (n/%)	61 (31,9%)	39 (16.8%)	13.279	1	0.001**
Anterior location of MI (n/%)	73 (38%)	63 (27.2%)	5.693	1*	0.017
Killip class >2 (n/%)	43 (22,5%)	15 (6.5%)	22.632	1	0.001**
PCI during hospitalisation (n/%)	40 (22,7%)	61 (27.7%)	1.287	1	0.257
CAG during hospitalisation (n/%)	39 (22,2%)	62 (28.2%)	1.867	1	0.172
CABG during hospitalisation (n/%)	4 (2,3%)	10 (4.5%)	1.481	1	0.224
Trombolysis during hospitalisation (n/%)	88 (45,8%)	100 (43.3%)	0.275	1	0.600
Somatic cardiac risk factors and comorbidity					
Previous MI (yes, n/%)	38 (19,8%)	20 (8.6%)	11.103	1	0.001**
Fam History of CAD (yes, n/%)	72 (37,5%)	87 (37.5%)	0.000	1	1.000
Hypercholesterolemia Yes (n/%)	70 (36,5%)	79 (34.1%)	0.267	1	0.605
Hypertension Yes (n/%)	55 (28,6%)	65 (28%)	0.020	1	0.886
Previous smoker (n/%)	62 (36,5%)	77 (35.8%)	0.018	1	0.894
Current smoker (n/%)	90 (52,9%)	110 (51.2%)	0.120	1	0.729
BMI	26,8 (3,5%)	26.6 (4.4%)	T=0.323	347	0.747
Peripheral vascular disease (n/%)	23 (12%)	6 (2.6%)	14.547	1	< 0.001***
Cerebrovascular disease (n/%)	14 (7,3%)	5 (2.2%)	6.476	1	0.011**
Diabetes Mellitus (n/%)	24 (12,5%)	17 (7.3%)	3.218	1	0.073
Psychiatric morbidity					
GAD 3 months post MI (n/%)	15 (7,8%)	9 (3.9%)	3.044	1	0.081
Any anxiety disorder 3 months post MI (n/%)	26 (13,5%)	25 (10.8%)	0.759	1	0.383
Depression 3 months postMI (n/%)	31 (16,1%)	32 (13.8%)	0.460	1 P	0.498
Received any treatment for psychiatric complaints post MI (n/%)	11 (5,7%)	32 (13.8%)	7.496	1	0.006**
HCS 3 months (mean, SD)	21,7 (8,8%)	19.7 (6.9%)	T=-2.462	422	0.009**
BDI 3 months (mean, SD)	7,9 (6,7%)	6.4 (5.5%)	T=2.552;	420	0.011*

MI=myocardial infarction; GAD=generalized anxiety disorder; SD=Standard deviation; T=T test ; χ^2=Chi square test; Degrees of freedom; PCI=Percutaneous Coronary Intervention; CAG=coronary angiogram; CABG=coronary bypass graft

*p<0.05; **p<0.01; ***p<0.001

Self-rated health complaints at 3 months post-MI and adverse cardiac outcomes

Results of the survival models are presented in table 2. Total HCS score was significantly associated with an increased risk of combined endpoint, after adjustment for age, sex, history of MI, LVEF, anterior location of MI, Killip Class, presence of diabetes mellitus, comorbid peripheral and cerebro-vascular disease, having received treatment for psychiatric symptoms post MI, depressive symptoms (total BDI score) and generalized anxiety disorder (HR 1.03 [95% CI: 1.01 – 1.05] (p=.025)).

Table 2: Hazard ratio's (95% CI) for combined endpoint associated with HCS sum-scores at 3 months post-MI

	HCS sum score at hospitalization N=192/424 with combined endpoint	
	HR	**P**
Model 1	HR= 1.03 (1.01-1.05)	0.001**
Model 2	HR=1.02 (1.00-1.04)	0.025*
Model 3	HR=1.03 (1.01-1.06)	0.003**
Model 4	HR=1.03 (1.00-1.05)	0.025*
Model 4b	HR=1.03 (1.00-1.05)	0.032*

*p<0.05; **p<0.01; ***p<0.001
Mean follow-up time (sd) for a combined end-point after HCS at 3 months post-MI was 5.7 (3.1) years.
Model 1: adjusted for age, sex and education level
Model 2: Model 1 + LVEF, history of MI, anterior location of MI, Kilip Class, Diabetes Mellitus, Peripheral vascular disease, Cerebrovascular disease
Model 3: Model 1 + Diagnosis of GAD, BDI, having received treatment for psychiatric complaints post MI
Model 4: Model 3 + LVEF, history of MI, anterior location of MI, Killip Class, Diabetes Mellitus, Peripheral vascular disease, Cerebrovascular disease
Model 4 b: Model 4 but instead BDI adjusted for somatic-affective BDI
HCS Health Complaints Scale; CI: confidence interval LVEF: left ventricular ejection fraction; MI: myocardial infarction; GAD: Generalized Anxiety Disorder; BDI: Beck Depression Inventory.

Type and trajectories of different health complaints by Latent Transition analysis (LTA)

LTA analyses included 392 patients, due to missing HCS data at 12 months for 32 patients. LTA distinguished 5 groups at both 3 and 12 months, characterized by 1) no/minimal, 2) cardiac, 3) energy, 4) sleep, and 5) mixed health complaints, resulting in 25 transition-classes (see box 1 for detailed information).

Type and trajectories of different types of health complaints and adverse cardiac outcomes

During a mean (SD) follow-up period of 5.5 (2.5) years, 153 (39.0%) of the 392 patients had an a combined event. Table 3 presents the number of patients with a combined event in each of the 25 transition classes to give an exploratory overview.

Table 3: Number of patients with the adverse cardiac outcome in each transition class according to type and trajectory of health complaints[1]

	Low 12	Cardiac12	Energy12	Sleep12	Mixed12	Total
Low3	**30/81 (37%)**	1/3 (33%)	)0/0	0/2 (0%)	0/1 (0%)	31/87 (35.6%)
Cardiac3	6/12 (50%)	**12/28 (43%)**	1/12 (8%)	3/3 (100%)	1/1 (100%)	23/56 (41%)
Energy3	4/14 (29%)	2/4 (50%)	**24/51 47%)**	1/1(100%)	5/7 (71%)	36/7747%)
Sleep3	6/14 (43%)	0/2 (0%)	0/2 (0%)	**16/64 (25%)**	0/1 (0%)	22/83 (27%)
Mixed3	0/1 (0%)	0/0	5/13 (39%)	2/9 (22%)	**34/66 (52%)**	41/89
Total	46/123 (37%)	15/37 (41%)	30/78 (38%)	22/79 (28%)	40/76 (53%)	**153/392 (39%)**

[1] Follow-up period for adverse cardiac outcomes started after HCS at 12 months

Table 4 shows the results of the survival analysis evaluating the risk of combined events according to the type of health complaints at 3 months post-MI and their trajectory over time from 3 to 12 months post-MI. Cardiac complaints at 3 months post-MI were significantly associated with combined events after adjustment for sex, age and education level (HR 1.55 (95% CI 1.15-2.10), p=0.004)). Adding one-by-one the variables that were univariately associated with combined endpoint with p<0.10 (see table 1) did not change the association between cardiac complaints and combined events.

As shown in table 4, new or persistent cardiac complaints, as well as new or persistent lack of energy and new or persistent mixed complaints were associated with an increased risk of combined endpoints. Adding one-by-one the variables that were univariately associated with combined endpoint with p<0.10 (see table 1) did not change these associations (data not shown), but for two exceptions: (1) The HR for new and persistent energy complaints attenuated to non-significant after adjusting for cerebrovascular disease (1.38 [1.00-1.92], p=0.052) (2) The HR for new and persistent

energy complaints attenuated to non-significant after adjusting for depressive symptoms ((1.37[0.96-1.96], p=0.081)

Sensitivity analysis: the role of somatic-affective depressive symptoms

HCS-sum-score was moderately to highly correlated with the somatic-affective BDI (r=0.567, p<0.001) at 3 months post MI. However, after adjusting for somatic-affective BDI instead of total BDI score in the fully adjusted model the association between HCS sum-score and combined endpoints remained significant (HR=1.03 (1.00-1.05), p=0.032).

After adjustment for the somatic-affective BDI the impact of cardiac complaints at 3 months post-MI on combined endpoint was attenuated to non-significant (HR 1.38 [0.99-1.92], p=0.055).

Adjustment for the somatic-affective BDI attenuated the associations of new or persistent cardiac complaints, mixed complaints and energy complaints with combined endpoint toward non-significant (HRcardiac 1.39 [0.96-2.01], p=0.082, HRmixed 1.43 [0.92-2.23], p=0.113), HRenergy 1.32 [0.90-1.93] p=0.163 respectively).

Table 4: Risk of combined endpoint associated with (types of) self-rated health at 3 months post MI and their course from 3-12 months post MI in 392 MI patients

	Model 1	
	HR [95% CI]	P-value
Three months post MI1:		
• Cardiac complaints	1.55 [1.15-2.10]	.004**
• Energy complaints	1.33 [1.00- 1.78]	.055
• Sleep complaints	1.11 [0.82- 1.50]	.517
• Mixed complaints	1.43 [0.99- 2.07]	.055
Trajectory from 3-12 months post MI2:		
• New or persistent vs no or transient cardiac complaints3	1.55 [1.11- 2.16]	.009**
• New or persistent vs no or transient energy complaints3	1.50 [1.09-2.07]	.013*
•New or persistent vs no or transient sleep complaints3	0.74 [0.51- 1.09]	.128
• New or persistent vs no or transient mixed complaints3	1.71 [1.19- 2.47]	.004**

*p<0.05; **p<0.01; ***p<0.001
Model 1: adjusted for sex, age, education level
1 Follow-up period for adverse cardiac outcomes started after HCS at 3 months
2 Follow-up period for adverse cardiac outcomes started after HCS at 12 months; reference group comprised those with no or transient complaints
3 Patients with cardiac complaints included those with cardiac complaints and mixed complaints, patients with energy complaints included those with energy complaints and those with mixed complaints, patients with sleep complaints included those with sleep complaints and mixed complaints, patients with mixed complaints included those with mixed complaints only
MI=Myocardial Infarction; Vs=versus; LVEF= Left Ventricular Ejection Fraction; CIDI=Composite International Diagnostic Interview; BDI=Beck Depression Inventory

Discussion

Main finding

In the present study, self-rated worse physical health status at 3 months post-MI was a significant predictor of new cardiovascular events and all-cause-mortality after adjustment for demographic variables, cardiac disease severity as well as depression and anxiety and depression. With each point increase on the somatic subscale of the HCS (range 0 to 48), the risk of a new cardiac event increased with 3% in line with previous studies [2]. Our results extend previous findings [3-9] by having adjusted the results for depression and anxiety.

With LTA we showed that subgroups of patients can be classified based on the type of complaints they report, showing that health complaints can be divided into cardiac complaints, lack of energy and sleep problems. This is consistent with the results of previous studies in MI patients on the HCS which reported on these three types of physical health complaints [18, 19]. In line with the findings of a previous study [20], cardiac complaints at 3 months post-MI were associated with worse cardiac outcome. Although the impact of lack of energy and mixed complaints did not reach statistical significance, this might be due to limited statistical power.

Patients with new or persisting cardiac complaints, new or persisting lack of energy and new or persisting mixed complaints during the first year post-MI showed an increased risk of adverse cardiac outcomes. These findings are in line with previous research showing that changes in self-reported physical health from before to after a myocardial infarction have prognostic value [14]. Our findings imply that the course of physical health complaints after a MI may provide additional information on prognosis as well.

Adjustment for the somatic-affective BDI in sensitivity analyses attenuated the hazard risks of both types and trajectories of physical health complaints to non-significant. This suggests an overlap between physical health complaints and somatic-affective BDI. Indeed, we found a moderate to high correlation of these scores three months post-MI ($r=0.567$, $p<0.001$) as can be expected considering the overlap in items of these questionnaires; e.g. insomnia (BDI) versus feeling you can't sleep (HCS) and somatic preoccupation (BDI) versus tightness of chest/shortness of breath (HCS) and fatigue (BDI) versus exhausted without reason/fatigue (HCS). Nevertheless, the sum-score of physical health complaints three months post-MI was still predictive of cardio-vascular prognosis independent of the somatic-affective BDI. This stresses the clinical impact of physical health complaints, independent of depression, anxiety and

cardiac disease severity.

Methodological considerations

An important strength of this study is that we evaluated the prognostic impact of physical health complaints adjusted for multiple covariates, including several markers of cardiac disease severity, psychiatric comorbidity as well as having received treatment for psychiatric symptoms post-MI. With regard to psychiatric comorbidity we took both diagnosed and self-reported depression and diagnosed anxiety into account. Unfortunately, we did not assess self-reported anxiety symptoms, which may have been interesting as we recently showed the prognostic impact of self-reported cardiac anxiety post-MI [32]. Nevertheless, we did adjust for a diagnosed anxiety disorder.

In contrast to some studies which measured reported health almost immediately after the index MI [7] or one year later [3], we chose, like others [5, 9], to assess baseline HCS three months post-MI. We consider this an advantage as the immediate impact of the initial stressful cardiac event and hospitalization is settled down and a more representative view of which complaints persist can be made. Supportive of this, we previously reported that only after 3 months post-MI symptoms of cardiac anxiety stabilized in patients with mild, moderate and severe symptom levels of cardiac anxiety [33]. A potential limitation is that the dropout rate might affect the generalization of our results. However, no differences were found between included and excluded patients on the parameters of interest. Another potential limitation of the current study is that there was no information on objective measures of cardiac disease severity at 12 months. Therefore we cannot exclude the possibility that the associations in the present study could be partly explained by objective cardiac disease severity measures at 12 months. Another limitation is the low number of patients in the subgroups with new and persisting complaints. Therefore, to avoid over-fitting we could not adjust for all covariates simultaneously in these analyses.

Implications

Taken together, to identify patients at high risk of adverse cardiac outcomes, physical health complaints have an added value over and above severity of both cardiac morbidity and comorbid anxiety and depression. In the recent decades, much attention has been given to the potential impact of depression and anxiety on cardiac prognosis [12; 13] and clinicians become more aware of the associated risks. However, the present study suggests that self-reported physical health status should also be taken into account by clinicians. Our findings indicate that cardiac, energy and mixed symptoms become especially informative when they increase or persist over

time. This implies that subjective experiences of physical health post-MI should be monitored regularly. Overall, our results suggest that the prognostic impact of self-reported physical health complaints should be mentioned in clinical guidelines, as it may serve as an (additional) inexpensive and non-invasive prognostic marker.

Box 1 Description of the Latent Transition Analysis

The preparatory analyses and the LTA itself were conducted in several steps: (1) subtype-identification based on the HCS data at 3- and 12-month follow-up by preliminary Latent Class Analyses (LCA), (2) investigation of the stability of the identified model over time (measurement invariance), and (3) fitting the LTA model.

Step 1) Preliminary Latent Class Analyses

To gain preliminary insight into the latent groupings in the data and to decide how many classes would be included in the LTA, separate LCA's were run on the 3- and 12-month HCS item-level data using robust maximum likelihood estimation package. For each time point, LCA's were run with increasing numbers of classes. The best fitting model was determined by comparison of the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) between the models, with the lowest AIC/BIC indicating the best fit. In addition, the Bootstrapped Likelihood Ratio Test (BLRT) was used to test whether adding a kth class led to a significant improvement in model fit compared to the k-1 class model. Eventually, both for 3- and 12-months post-MI, the best model was selected based on both model-fit and interpretability (sufficient differentiation between classes and no overly small classes [n<20]).

Step 2) Investigation of measurement invariance

Before transition between latent classes over time can be investigated, measurement invariance of the classes had to be established in order to be sure that class-models represented the same concepts at both time-points, and thus, that class-transitions can be meaningfully determined. In the context of LTA, measurement invariance is investigated by comparison of the log-likelihood of LTA-models with constrained and unconstrained model-parameters. The Likelihood-Ratio Test can be used to test whether loosening constraints (allowing for measurement non-invariance) significantly increases model-fit. If this is not the case, we can assume (partial) measurement invariance and interpret transition-probabilities between the classes across time.

Step 3) Fitting the LTA model

In case of (partial) measurement invariance, the LTA can be used to define latent

transition classes based on the (k3-month by k12-month) matrix of transition patterns. All patients were allocated to these latent groups based on their highest posterior class probability.

Results of the Latent Transition Analysis

LTA analyses included 392 patients, due to missing HCS data at 12 months for 32 patients. Latent Class Analyses (LCA) at 3- and 12 months post-MI showed decreasing AIC/BIC values with each class-addition up to 7 classes and significant BLRT values (with 100 bootstraps) for each class-addition. However, from the 5-class model on, adding more classes only resulted in very small BIC changes (3 months:ΔBIC=8; 12 months: ΔBIC =10). Additional inspection of the response patterns, suggested that adding more classes only resulted in more intermediate classes but no additional qualitative differentiation. Therefore, a 5-class model was selected for both 3 and 12 months after MI.

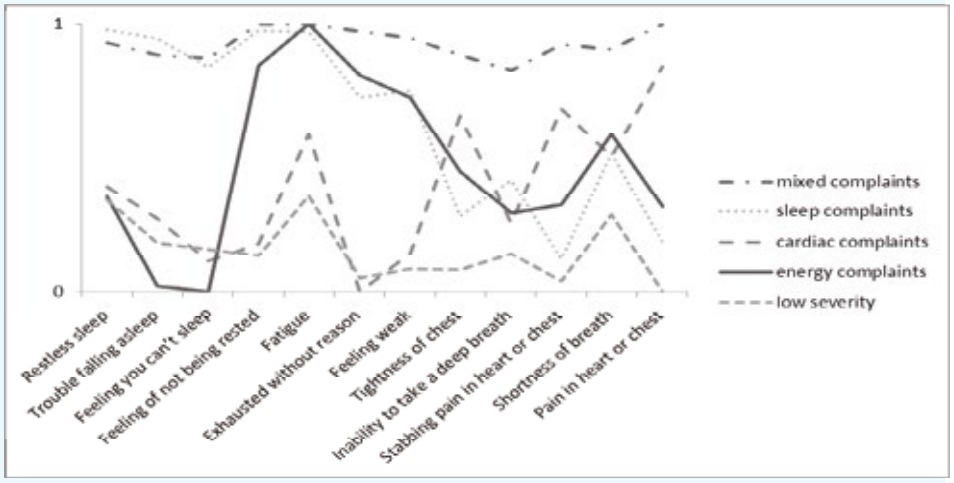
The five classes (see figure 1) included three classes with more specific symptom patterns (respectively scoring predominantly on complaints of "cardiac", "energy", or "sleep complaints") and two with similar scores on all symptoms, thus reflecting mainly quantitative severity groups (respectively one group scoring on all factors ["mixed complaints"] and one group reporting hardly any complaints ["low severity"]). These results indicated that a 5-class model could be included in the LTA.

No significant difference in model fit was found between a 5-class LTA model with constrained parameters over time and an LTA model with class-specific thresholds (-2 log-likelihood difference (D)=42.2; with 60; p=0.96). This suggested that (partial) measurement invariance could be assumed and it was possible to look directly at the transition-probabilities between the classes at 3 and 12 months post MI.

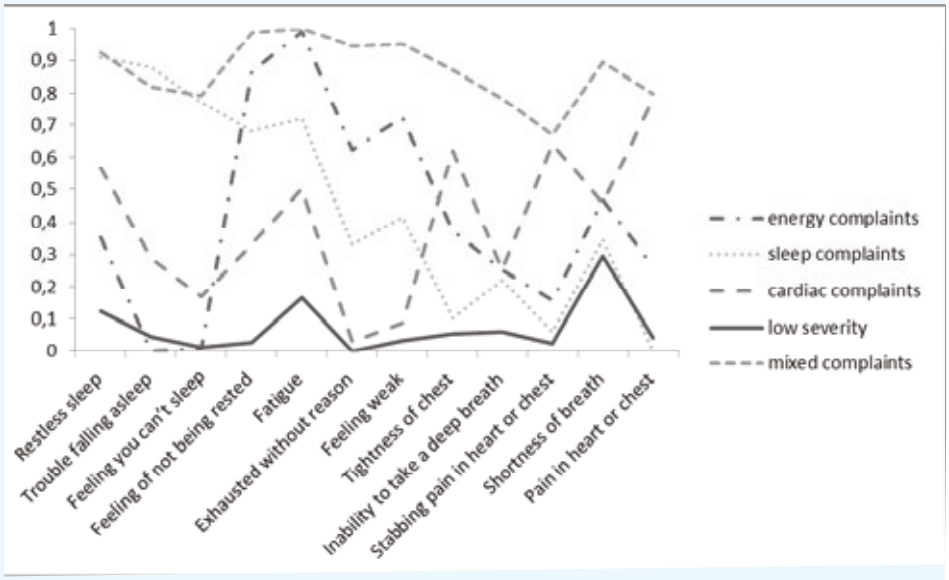
Because 5-classes were modeled at each time-point, the LTA yielded an estimated model of 25 latent transition classes. All patients were classified in one class based on the highest posterior class probabilities.

Figure 1: Latent Class Models based on the Health Complaints Scale at 3 and 12 months post MI

3 months post-MI



12 months post-MI



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CHAPTER 7

A brief cognitive-behavioral intervention for treating depression and panic disorder in patients with non-cardiac chest pain: a 24-week randomized controlled trial

published
M.H.C.T. van Beek, R.C. Oude Voshaar, A.M. Beek, G.A. van Zijderveld, S. Visser, A.E.M. Speckens, N. Batelaan, A.J.L.M. van Balkom.
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Abstract

Background – Most patients with non-cardiac chest pain experience anxiety and depressive symptoms. Commonly they are reassured and referred back to primary care, leaving them undiagnosed and untreated. Some small studies have suggested efficacy of twelve cognitive behavioral therapy (CBT) sessions. Our aim was to examine efficacy of brief CBT in reducing anxiety and depressive symptoms in patients with non-cardiac chest pain and comorbid panic and/or depressive disorders.

Methods – In this 24-week randomized controlled trial comparing CBT (n=60) versus treatment as usual (TAU, n=53) we included all adults who presented at the cardiac emergency unit of a university hospital with non-cardiac chest pain, scored ≥8 on the Hospital Anxiety and Depression Scale (HADS) and were diagnosed with a comorbid panic and/or depressive disorder with the Mini International Neuropsychiatric Interview. CBT consisted of six individual sessions. Main outcome was disease severity assessed with the Clinical Global Inventory (CGI) by a blinded independent rater.

Results – ANCOVA in the intention-to-treat and completer sample showed that CBT was superior to TAU after 24 weeks in reducing disease severity assessed with CGI ($p<0.001$). Secondary outcomes on anxiety (HADS-Anxiety, State Trait Anxiety Inventory (STAI)-Trait) and depressive symptoms (Hamilton Depression Rating Scale) were in line with these results except for HADS-Depression ($p=.10$), Fear Questionnaire ($p=.13$) and STAI-State ($p=.11$).

Conclusions – Brief CBT significantly reduces anxiety and depressive symptoms in patients with non-cardiac chest pain who are diagnosed with panic and/or depressive disorders. Patients presenting with non-cardiac chest pain should be screened for psychopathology and if positive, CBT should be considered.

Keywords – anxiety, depression, cardiac, heart, chest pain, cognitive behavioral therapy.

Introduction

Chest pain is one of the most frequent reasons for patients to visit an emergency department [1,2], yet only one-quarter of patients who experience chest pain actually present to a hospital [3]. In more than half of these patients there is no underlying cardiac or other somatic cause, and the diagnosis at discharge is non-cardiac chest pain [1,4]. It is common practice to reassure these patients and refer them back to primary care, thus ignoring that their complaints could have other origins, for example a psychiatric disorder. The prognosis of non-cardiac chest pain is poor: despite reassurance by emergency physicians and cardiologists, more than half of patients continue to report chest pain and remain concerned about having a serious heart disease [1,5], resulting in high medical care utilization [6].

High prevalence rates of psychiatric symptoms, predominantly anxiety and depressive symptoms, have been reported in patients with chest pain, irrespective of an underlying cardiac illness [7,8,9]. In patients whose chest pain has an atypical origin, i.e. those diagnosed with non-cardiac chest pain, the prevalence of psychiatric co-morbidity is reported to be as great as 50% [10,11], with high levels of anxiety, depression, catastrophic thinking, and physical disability [12-15]. Often patients are diagnosed with either depression or an anxiety disorder. Among the anxiety disorders, panic disorder is frequently reported [5,16]. This is understandable, as the symptoms of a panic attack may mimic a myocardial infarction. Since psychiatric symptoms are associated with persistent chest pain and continuing functional incapacity [5], these symptoms may provide a good starting point for interventions. Furthermore, studies have demonstrated the effects of both depression and anxiety on subsequent cardiovascular events in both cardiac patients [17-22] and non-cardiac patients [23-25]. This makes it relevant to devote specific attention to the subgroup reporting psychiatric symptoms.

Previous studies have evaluated a range of different psychological interventions for non-cardiac chest pain (NCCP); including relaxation therapy, hypnotherapy and cognitive behavioral therapy at both group and individual level. [1,26,27] In most studies, the primary outcome was a reduction in chest pain, although some also reported a reduction in self-reported depressive symptoms [12,28-33] or anxiety symptoms [28,29,31-34]. However, these studies included NCCP patients both with and without comorbid psychiatric disorders. Some even excluded patients with a comorbid psychiatric disorder [12,35,36]. A drawback of such studies is that they include a mixture of patients with mild and severe symptoms. In clinical practice, however, the challenge is to detect and treat those patients who need treatment. Patients who are likely to have a favorable course (i.e. those without a psychiatric disorder) should not be over treated.

NCCP patients with comorbid anxiety and depressive disorders should be treated according to general guidelines. In such cases, cognitive behavioral therapy (CBT) is the treatment strategy to be evaluated. First of all, a wealth of studies have shown the efficacy and effectiveness of CBT for treating psychiatric symptoms such as anxiety, depression and unexplained physical symptoms [37-40]. Second, considering the population of patients with non-cardiac chest pain, evidence suggests that CBT may be effective in reducing anxiety symptoms [1]. Unfortunately, these conclusions were based on only five studies with relatively small sample sizes. Furthermore, the CBT intervention often consisted of twelve sessions, while a shorter intervention may also be effective [1,30,41].

The objective of the present study was to examine the effectiveness of brief CBT on anxiety and depressive symptoms after six months in patients presenting at a cardiac emergency unit with non-cardiac chest pain with comorbid panic and/or depressive disorders. The present randomized controlled trial (RCT) adds value to the five previous CBT studies because it 1) examines CBT consisting of six sessions rather than twelve, 2) was conducted with a large sample almost equal to the total number of subjects in the five previous studies combined (n=113 vs. n=136), 3) was conducted over a longer period (six months vs. three months) [1] and 4) addressed the most severe cases to specifically target, NCCP patients with a comorbid psychiatric disorder.

Methods

Study design

A 24-week RCT was conducted, comparing brief cognitive behavioral therapy (CBT) with treatment as usual (TAU) in patients presenting with non-cardiac chest pain at a cardiac emergency unit. We generated the two comparison groups by using simple randomization, with an equal allocation ratio, by referring to a table of random numbers (to which all researchers and physicians were blinded). The study was approved by the VU University Medical Center Ethical Review Committee.

Study population

Recruitment took place at the cardiac emergency unit of the VU University Medical Center. The target population consisted of all subjects aged 18 years or older who presented with chest pain and were convinced they were experiencing a heart attack. Eligible patients were subjects in whom full medical examination revealed no cardiopulmonary, gastrointestinal or endocrinal explanation for their complaints

(and thus were diagnosed with "non-cardiac chest pain") and who scored 8 or higher on either or both subscales of the Hospital Anxiety and Depression Scale (HADS) [42]. A cutoff score of 8 is frequently used for both subscales because it provides the optimal balance between sensitivity and specificity (for both subscales approximately 0.80) [43]. Eligible patients were asked to provide informed consent for a psychiatric interview using the Mini-International Neuropsychiatric Interview (MINI) [44].

The final inclusion criteria were 1) meeting the DSM-IV criteria for panic disorder and/or depressive disorder, and 2) providing signed informed consent after an oral and written explanation of the procedures and purpose of the study. Subjects who were excluded included 1) those with insufficient knowledge of the Dutch language, and 2) those who, in the month before screening, received systematic psychotherapy or used antidepressants. Benzodiazepine usage was allowed during the trial, up to a maximum of 50 mg of oxazepam or equivalent doses of other medications. Patients who used benzodiazepine were required to keep their dosages constant throughout the study.

Intervention

Patients randomized to TAU were reassured by the cardiologist that their complaints were not caused by cardiac disease. TAU was tailored to the individual needs of the patients. However, TAU did not include psychotherapy, including CBT, or antidepressants.

CBT consisted of a total of six individual sessions with a duration of 45 minutes. The CBT protocol was based on the cognitive model developed by Clark and consisted of a combination of psycho-education, cognitive restructuring and influencing avoidance behavior, according to the basic concept of CBT that physical complaints can be cognitively mediated [45,46]. Since the protocol developed by Clark concerns the treatment of panic disorder, the CBT protocol was also adjusted to the treatment of depressive complaints. At the beginning of the treatment the emphasis was on the cognitive model and on cognitive restructuring of the automatic anxiety-provoking or depressive mood-provoking cognitions; after that, behavioral interventions were added. The treatment was matched to the subject's diagnosis, so that, if needed, more attention was given to psycho-education on the physical symptoms of anxiety or physical symptoms associated with depressed mood. For patients with panic disorder, with or without agoraphobia, the rationale of exposure in vivo was explained and exposure in vivo homework assignments were given. For patients with depression, reactivation was explained and reactivation homework assignments were given.

The therapists were two clinical psychologists trained in CBT, who received specific training for the treatment of patients with non-cardiac chest pain. Extensive manuals were used to guide CBT. All CBT sessions were recorded on audiotape. A registered supervisor from the Dutch Association for Behavioral Therapy (S.V.) supervised them. During supervision, adherence to the treatment protocol was checked and assistance was provided in planning future sessions. No formal fidelity ratings were used. The supervisor reviewed parts of all audiotapes from all patients to ensure the method's fidelity to the principles of cognitive therapy. In the vast majority of cases, the therapists adhered strictly to the therapeutic methodology.

Measures

At baseline and after 24 weeks the patients were assessed by an independent rater, who was blinded to the condition to which the patients were allocated.

Primary outcome measure

Because we included patients with depressive disorder and/or panic disorder, we chose the assessor-rated Clinical Global Impression Severity Scale (CGI-Severity) as the primary outcome measure. CGI-Severity scores the global severity of the illness, varying from normal to severe, on a scale of 1-7 [47], with 1 indicating "normal, not at all ill", 4 "moderately ill" and 7 "among the most extremely ill patients". The CGI is widely used in psychiatric clinical trials and has been shown to correlate with standard drug-efficacy scales in diseases such as major depressive disorder, panic disorder, social anxiety disorder [48] and generalized anxiety disorder [49]. Various studies have tested the reliability of the CGI scale [50-53] and have demonstrated good inter-rater reliability for the above diseases. The standard CGI scale has been demonstrated to be just as effective as an improved CGI scale in depression [50]. However, less convincing data have also been published [54], emphasizing the need for secondary outcome measures (see below).

Secondary outcome measures

The presence and severity of anxiety and depressive symptoms were measured with:

1) The assessor-rated 17-item Hamilton Depression Rating Scale (HDRS) [55].

2) The self-rated Hospital Anxiety and Depression Scale (HADS), assessing the severity of anxiety and depression in subjects in non-psychiatric hospital settings [42] and in subjects with non-cardiac chest pain [56]. Anxiety (HADS-A) and depression (HADS-D) are assessed as separate subscales.

3) The self-rated State-Trait Anxiety Inventory (STAI), which consists of two subscales: STAI-S, the state subscale, which assesses transient emotional symptoms evoked by a stressful situation and the STAI-T, the trait subscale which assesses proneness to anxiety in an individual [52].

4) The self-rated 21-item Fear Questionnaire (FQ), yielding three subscales (agoraphobia, social phobia and blood phobia) [58,59].

5) In the completer sample, at 24 weeks the assessor-rated Clinical Global Impression-Improvement Scale (CGI-Improvement) was administered. The CGI-Improvement measures change in the clinical condition over time. This scale has a range of 1-7, with 1 indicating "much improvement," 4, "no change" and 7, "much deterioration" of the clinical condition [47].

Power considerations

For CBT targeting patients with panic and/or depressive disorders, large effect-sizes of about .80 and higher can be expected [26,28,29]. However, although all the subjects included had to meet the diagnostic criteria for panic and/or depressive disorders, they were also diagnosed with non-cardiac chest pain. Therefore, acknowledging the more difficult population under study and the reported moderate effect-sizes, we a priori expected an effect-size of 0.6. Assuming a two-sided α set at 0.05 and a β of 0.20, we required an intent-to-treat sample size of 45 subjects per condition. Assuming a dropout rate of 30% (n=27), a total of 117 persons had to be included.

Statistical analysis

Baseline characteristics were compared between groups with chi-square tests in case of categorical variables and t-tests in case of continuous variables.

The primary analyses were conducted on the intent-to-treat sample including patients who refused treatment sessions (treatment dropouts) and those who did not complete the outcome measurements (data dropouts) on an "as-randomized basis" (n=113; CBT n=60; TAU=53). In the intent-to-treat sample missing measures were imputed with the Last Observation Carried Forward method.

The primary analyses were repeated in the completer sample, to evaluate the treatment effect in those subjects who really had undergone the treatments to which they were assigned. Subjects were included in the completer sample in CBT when they had attended at least four CBT sessions and had completed the outcome assessment and in TAU when they had completed the outcome assessment. The completer sample

consisted of 75 subjects (CBT n=41; TAU n=34).

Differential treatment outcome after 24 weeks was analyzed with analyses of covariance (ANCOVA) with the posttest as dependent variable and the pretest as covariate. Because of differences found at baseline between CBT and TAU, the following other covariates were included in all of the ANCOVAs: pretest CGI-Severity, pretest HADS-A, and pretest STAI-T (see under results). Time effects were analyzed with paired t-tests (pretest vs. posttest) within each condition.

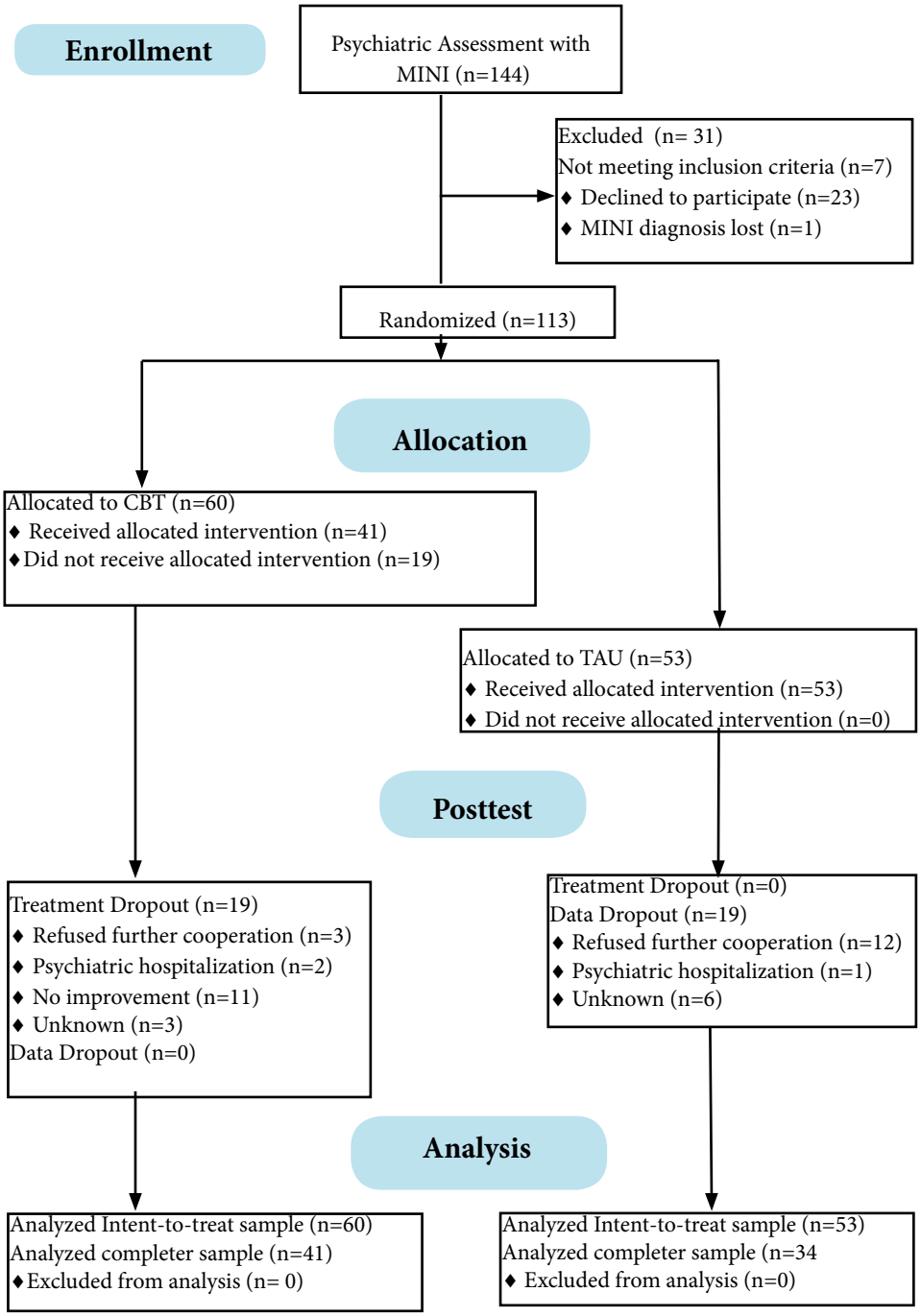
DSM-IV diagnoses were not evenly distributed over the two conditions. Therefore we repeated ANCOVA on the primary outcome variable in two subsamples: 1) all patients with panic disorder, with or without depression, and 2) all patients with depression, with or without panic disorder. Analyses were conducted in SPSS version 18 (SPSS Inc., Chicago, IL) with a two-tailed alpha=0.05.

Results

Attrition

Figure 1 shows the flow of participants throughout the study. In total, 38 of 113 participants (34%) dropped out, respectively 19/60 (32%) in the CBT group and 19/53 (36%) in TAU. The dropout percentages did not differ significantly over the two conditions (χ^2 (1)=0.22; p=0.64). When comparing the completer sample with the sample consisting of treatment dropouts plus data dropouts on the baseline characteristics, the completer sample appeared to be somewhat less depressed (score on HADS-D for completer: mean:17.1, SD:3.9; for dropouts/refusers: mean: 18.6, SD:3.6; t=1.96; 110; p=0.05).

Figure 1 CONSORT Diagram



Baseline characteristics

The sociodemographic and clinical status variables of the intent-to-treat sample are presented in Table 1. When comparing the CBT and TAU group at baseline, the TAU group had significantly more males. Moreover, in comparison to the CBT group, in the TAU more subjects suffered from panic disorder with or without agoraphobia and fewer subjects were diagnosed with a depressive disorder. With respect to the other clinical status variables, the patients in CBT appeared to have significantly higher scores on the CGI severity scale. In addition, a trend to significance was found with respect to scores on the HADS-A and STAI-T, indicating greater severity among patients in CBT.

Primary outcome measures

The means and SDs of CGI-Severity are presented in Table 2. ANCOVA yielded significant results ($F(4,91)=14.3$; $p<0.001$), indicating the superiority of CBT over TAU in decreasing clinical severity. Time effects were analyzed with paired t-tests within each condition, indicating that the symptoms in CBT improved significantly ($t(53)=6.12$; $p<0.001$), in contrast to no significant improvement in TAU ($t(47)=0.70$; $p=0.49$).

Since the TAU and CBT groups differed significantly at baseline with respect to the distribution of MINI diagnoses, we repeated the ANCOVA with 1) all patients with a diagnosis of panic disorder, with or without comorbid depression (ANCOVA: $F(4.78)=9.5$; $p=0.003$), and 2) all patients with a diagnosis of depressive disorder, with or without comorbid panic disorder (ANCOVA: $F(4.54)= 9.5$; $p=0.003$). The ANCOVA results did not change critically and indicated the superiority of CBT over TAU, suggesting that the results could not be explained by differences in MINI diagnoses between the groups.

Table 1: Baseline characteristics of intent-to-treat sample (n=113)#

	CBT		TAU		Statistics	
	n=60		n=53			P value
Sociodemographics						
Male (n, %)	26	(43.3)	38	(71.7)	$\chi2(1)=9.20$	0.002
Single (n, %)	24	(40.0)	17	(32.1)	$\chi2(1)=0.76$	0.38
Paid employment (n, %)	39	(65.0)	32	(60.4)	$\chi2(1)=0.14$	0.70
Higher education (n, %)	23	(38.3)	14	(26.4)	$\chi2(1)=1.81$	0.18
Age (year) (Mean, SD)	48.7	(13.0)	49.9	(11.0)	t(110)= .53	0.60
Psychiatric status						
MINI Diagnosis					$\chi2(2)=6.95$	0.003
Panic disorder + agoraphobia (n, %)	18	(30.0)	28	(52.8)		
Depressive disorder (n, %)	9	(15.0)	8	(15.1)		
Co morbid Panic + Depression (n, %)	33	(55.0)	17	(32.1)		
Previous psychiatric treatment (n, %)	17	(28.3)	15	(14.9)	$\chi2(1)=0.10$	0.75
Previous use of antidepressants (n, %)	17	(28.3)	14	(26.4)	$\chi2(1)=0.08$	0.77
Benzodiazepine use (n, %)	27	(45.0)	16	(30.1)	$\chi2(1)=1.70$	0.19
Positive family history (n, %)	13	(21.3)	20	(37.7)	$\chi2(1)=3.11$	0.08
CGI severity (Mean, SD)	4.2	(1.0)	3,8	(0.7)	t(100)=2.28	0.03
HADS-A (Mean, SD)	19.9	(3.3)	18.6	(3.8)	t(110)=1.82	0.07
HADS-D (Mean, SD)	18.2	(4.0)	17,3	(3.7)	t(110)=1.22	0.22
HAM-D (Mean, SD)	19.2	(5.9)	17.3	(5.4)	t(91)=1.59	0.12
FEAR-Q (Mean, SD)	34.9	(23.6)	35,8	(26.5)	t(106)=0.19	0.85
STAI-S (Mean, SD)	52.1	(11.7)	48,7	(12.2)	t(106)=1.49	0.14
STAI-T (Mean, SD)	54.8	(11.0)	50,9	(11.7)	t(106)=1.77	0.08
Somatic Status						
Heart disease (n, %)	6	(10.0)	6	(11.3)	$\chi2(1)=0.03$	0.86
Hypertension (n, %)	22	(36.6)	19	(35.8)	$\chi2(1)=0.05$	0.83
Previous stroke (n, %)	0	0	1	(1.9)	$\chi2(1)=1.11$	0.29
Renal disease (n, %)	1	(1.6)	0	(0)	$\chi2(1)=0.92$	0.34
Lung disease (n, %)	8	(13.3)	6	(11.3)	$\chi2(1)=0.15$	0.70
Diabetes mellitus (n, %)	3	(5.0)	1	(1.9)	$\chi2(1)=0.86$	0.36
Thyroid disease (n, %)	8	(13.3)	2	(3.8)	$\chi2(1)=3.38$	0.07

# Not all measures were available for all patients; the n of several measures may vary.
CBT = Cognitive Behavioral Therapy; TAU = Treatment as Usual
CGI severity= Clinical Global Impression Severity Scale; HADS= Hospital Anxiety Depression Scale; HADS-D Hospital Anxiety Depression Scale, depression subscale; HADS-A Hospital Anxiety Depression Scale, anxiety subscale; HAM-D=Hamilton Depression Rating scale; FEARQ=Fear Questionnaire; STAI-S State-Trait Anxiety Inventory, state part; STAI-T; State-Trait Anxiety Inventory, trait part.

Table 2 Means and standard deviations and ANCOVA outcomes of intent-to-treat sample (n=113)[a]

	CBT (n=60)				TAU (n=53)				ANCOVA	
	Pretest		Posttest		Pretest		Posttest			
Measure	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*F(df)*	*p*
Primary Outcome										
CGI severity	4.2	1.0	3.1[b]	1.6	3.8	0.7	3.8	1.1	F(4,91)= 14.3	<0.001
Secondary Outcomes										
-HADS-D	18.1	4.0	15.7[b]	4.9	17.3	3.7	16.1[b]	4.5	F(4,91) = 1.6	0.20
-HADS-A	19.8	3.4	16.7[b]	5.3	18.6	3.8	17.2[b]	4.4	F(4,91) = 4.0	.048
HAM-D	19.2	5.9	13.5[b]	9.8	17.6	5.6	16.6	6.5	F(4,91) = 4.0	.001
FEARQ	34.9	23.4	28.5[b]	25.6	35.8	26.5	33.9	27.1	F(4,92) = 3.7	0.56
-agora	11.6	10.8	9.8[b]	12	10.5	11.2	10.6	12.2	F(4,97) = 1.9	0.18
-blood	10.7	9.7	7.9[b]	9.0	10.5	9.6	9.6	9.3	F(4,92) = 4.1	0.045
-social	12.6	9.6	10.7	10.2	14.8	9.8	13.7	9.7	F(4,92) = 1.6	0.20
STAI-S	52.4	11.8	46.6[b]	14.4	48.7	12.2	46.2	13.0	F(4,93) = 1.7	0.19
STAI-T	55.1	11.0	49.0[b]	12.6	50.9	11.7	50.0	12.8	F(4,91) = 4.5	0.004

[a] Not all measures were available for all patients; the n of several measures may vary.
[b] Paired t-test (pretest versus posttest) revealed a significant decrease of symptoms within condition.
ANCOVA = Analysis of CoVariance. Posttest served as dependent variable. Covariates were: pretest variable and: pretest CGI severity, pretest HADS-A and pretest STAI-T.
CBT = Cognitive Behavioral Therapy; TAU = Treatment as Usual; HADS= Hospital Anxiety Depression Scale; HADS-D Hospital Anxiety Depression Scale, depression subscale; HADS-A Hospital Anxiety Depression Scale, anxiety subscale; HAM-D=Hamilton Depression Rating scale; FEARQ=Fear Questionnaire; subscales agoraphobia, blood/injury phobia and social phobia; STAI-S State-Trait Anxiety Inventory, state part; STAI-T; State-Trait Anxiety Inventory, trait part; CGI Clinical Global Impression scale (subscales severity and improvement); n.a.=not applicable.

Secondary outcome measures

Means, standard deviations and outcomes of the ANCOVAs on the secondary outcome easures are presented in Table 2. As follows from this table, after 24 weeks CBT improved significantly in contrast to TAU on HAM-D, HADS-A and STAI-T. Time effects, analyzed with paired t-tests within each condition, indicated that the symptoms in CBT improved significantly on HAM-D ($t(59) = 4.68$; $p<0.001$), HADS-A ($t(58)=5.24$; $p<0.001$) and STAI-T ($t(56)=3.85$; $p<0.001$), while none of the paired t-tests in TAU was significant. As follows from Table 2, ANCOVA did not reveal significant differences between the two treatment conditions on HADS-D, STAI-T and FQ.

Completer analyses

The completer analyses of both the primary and secondary outcome measures were in line with the results of the intent-to-treat analyses and are therefore not reported here.

In addition, in the completer sample, the CGI-Improvement at 24 weeks revealed the superior effect of CBT (mean=2.3; SD=1.1) over TAU (mean=4.0; SD=1.1). When dichotomizing the CGI improvement score ('very much' or 'much mproved' vs. 'minimally improved or less') CBT appeared to be superior to TAU (CBT 12 responders among 42 patients s TAU 2 responders among 34 patients; 2(1)=33.11; p<0.001).

Discussion

This study reports the results of BT compared to TAU in a patient population that visited a cardiac emergency unit for non-cardiac chest pain and was diagnosed with panic and/or depressive disorder. In accordance with our hypothesis, CBT was found to be superior to TAU in the improvement on the primary outcome measure CGI-Severity after 24 weeks. In addition, on the secondary outcome measures of anxiety and depressive symptoms, CBT showed superior results compared to TAU. For the secondary outcome measures HADS-D, Fear Questionnaire and STAI-S, we did not find CBT to be superior to TAU. The results in the completer sample were in line with those in the intent-to-treat sample.

These findings are in line with the findings of five previously performed trials evaluating psychological symptoms and included in a Cochrane review 1. In that review, reporting on psychological interventions in subjects with non-cardiac chest pain, CBT improved anxiety and depressive symptoms [12,33,34,36,] Our study, however, adds to this literature for the following reasons.

Firstly, three [12,34,36,] of the four studies included up to twelve individual CBT sessions, whereas our study offered a maximum of six sessions. The only other study also offering six sessions [33] offered CBT within a group format. Although a group format may be more costeffective compared to individual therapy and may therefore be promising, that study did not reach significance based on the Cochrane criteria. Interestingly, a small pilot study recently suggested efficacy on the experience of bodily sensations of only three CBT sessions in a combined group of patients suffering from non-cardiac chest pain and benign palpitations 30. However, the CBT was conducted by one therapist and ratings were not blinded. Very recently, an intervention cohort study in NCCP patients diagnosed with a panic disorder compared three interventions

with supportive care, including a seven-session CBT intervention. There was an improvement in the severity of panic disorder, relative to supportive care. Although the sample size was small (n=19) this promising result was in line with the results of our study [41,60].

Secondly, the inclusion criteria of the five studies in the Cochrane review [1] were largely based on non-cardiac chest pain irrespective of the presence of psychiatric pathology. None of the studies selected cases based on the presence of psychiatric comorbidity, which may have led to floor effects of CBT on general measures of depression and anxiety. Moreover, three studies even excluded patients suffering from major depressive disorder [12,35,36] which may have seriously limited the generalization acknowledging the high prevalence of depressive isorder among patients with non-cardiac chest pain [9,10,13]. In contrast, we included noncardiac chest pain patients with comorbid psychiatric disorders as CBT has been shown to be particularly effective in this subgroup, whereas floor effects can be expected when there is a low severity of depression and anxiety symptoms.

Although we acknowledge that limiting the included anxiety disorders to panic disorder alone may have consequences for the generalization of ur results, the validity of our choice is strengthened by data suggesting panic disorder is the most prevalent anxiety disorder in a non-cardiac chest pain population [5,16]. As we focused exclusively on patients with NCCP and comorbid depression and/or panic disorder, our results cannot be generalized to NCCP patients without these conditions. Interestingly, our effect-size is indeed larger than the pooled effect-size of the five studies in the Cochrane meta-analysis. This is a promising finding for cost-effectiveness, although not specifically addressed by our study.

A disadvantage of combining both depressed and anxious subjects in our study is that we cannot demonstrate the effectiveness of CBT on both groups separately. However, we repeated the main analysis in these subgroups post hoc. The results were in line with the analysis of the primary outcome measure. An advantage of the mixed group approach is that it enhances external validity of the trial results.

Some methodological issues should be mentioned. Although our population almost equals the total number of subjects in the five studies combined within the Cochrane study [1] (n=136), we do have to acknowledge the high dropout rate of 35%. The dropout percentages did not differ significantly over the two conditions. When comparing the baseline haracteristics of the completer sample with patients who dropped out prematurely or who refused to cooperate, the per-protocol sample appeared to be somewhat less depressed. The non-significant results on the Depression subscale of

the HADS, the Fear Questionnaire and the STAI Trait, may represent insufficient statistical power due to the heterogeneity of the included sample.

In the review of Kisely et al. [1], most studies included patients with and without established psychiatric comorbidity. Therefore, lower dropout rates might be caused by a differential dropout between cases with and without psychiatric comorbidity, as people may feel stigmatised by receiving a psychiatric diagnosis. Nonetheless, as long as we do not know the reasons for this relatively high dropout rate, it remains an interesting point whether our focus on psychiatric cause may have consequences for the engagement of those patients with a somatic attribution.

Some methodological limitations concern the outcome parameters used. 1) Our primary outcome measure was the Clinical Global Impression Scale (CGI). Although the psychometric properties of the CGI are questioned by some authors, in our study outcome assessed using the CGI paralleled the outcome assessments using the well-validated and disorder-specific instruments we applied. The CGI was chosen because we included patients with two types of psychiatric disorders. 2) Perhaps we should have stratified for type of MINI diagnosis since that was significantly different between both conditions. However, post-hoc analyses with subgroups did not change the results. If all, the effect may be an underestimation because of more comorbidity in the CBT condition as opposed to more "simple" anxiety problems in the TAU group. Unfortunately we did not repeat the MINI at follow-up. As a result, no evaluation was made of the number of patients who fulfilled the diagnostic criteria of panic and/or depressive disorder after six months. However, when dichotomizing our sample into responders versus non-responders on the CGI improvement scale, CBT appeared to be superior to TAU, which corroborates our dimensional outcome measures. 3) Regretfully we did not evaluate the frequency and severity of non-cardiac chest ain at follow-up. We focused on the presence and severity of panic and depressive symptoms, which are aspects of the differential diagnosis of NCCP. We consider chest pain just one symptom of a broader problem (i.e. panic and/or depressive disorder) that we plan to target. We have demonstrated a significant and clinically relevant amelioration of panic and depressive symptoms, suggesting an improvement in NCCP symptoms as well [34,61]. 4) A disadvantage of combining both depressed and anxious subjects in our study is that we cannot demonstrate the effectiveness of CBT on both groups separately. However, we repeated the main analysis in these subgroups post hoc. The results were in line with the analysis of the primary outcome measure. An advantage of the mixed group approach is that it enhances external validity of the trial results.

We conclude that CBT of up to six individual sessions significantly reduces anxiety and depressive symptoms in patients with non-cardiac chest pain who are diagnosed

with panic and/or depressive disorders. The high prevalence of affective disorders among patients with non-cardiac chest pain and the effectiveness of our intervention argue for psychiatric screening in this specific population. Taking into account the reduced quality of life due to untreated anxiety and depression, high levels of persistent medical consumption, and finally the higher risk of subsequent vascular events, non-screening in this specific population or issing important psychiatric diagnoses should be considered as an omission that carries a high risk of iatrogenic damage.

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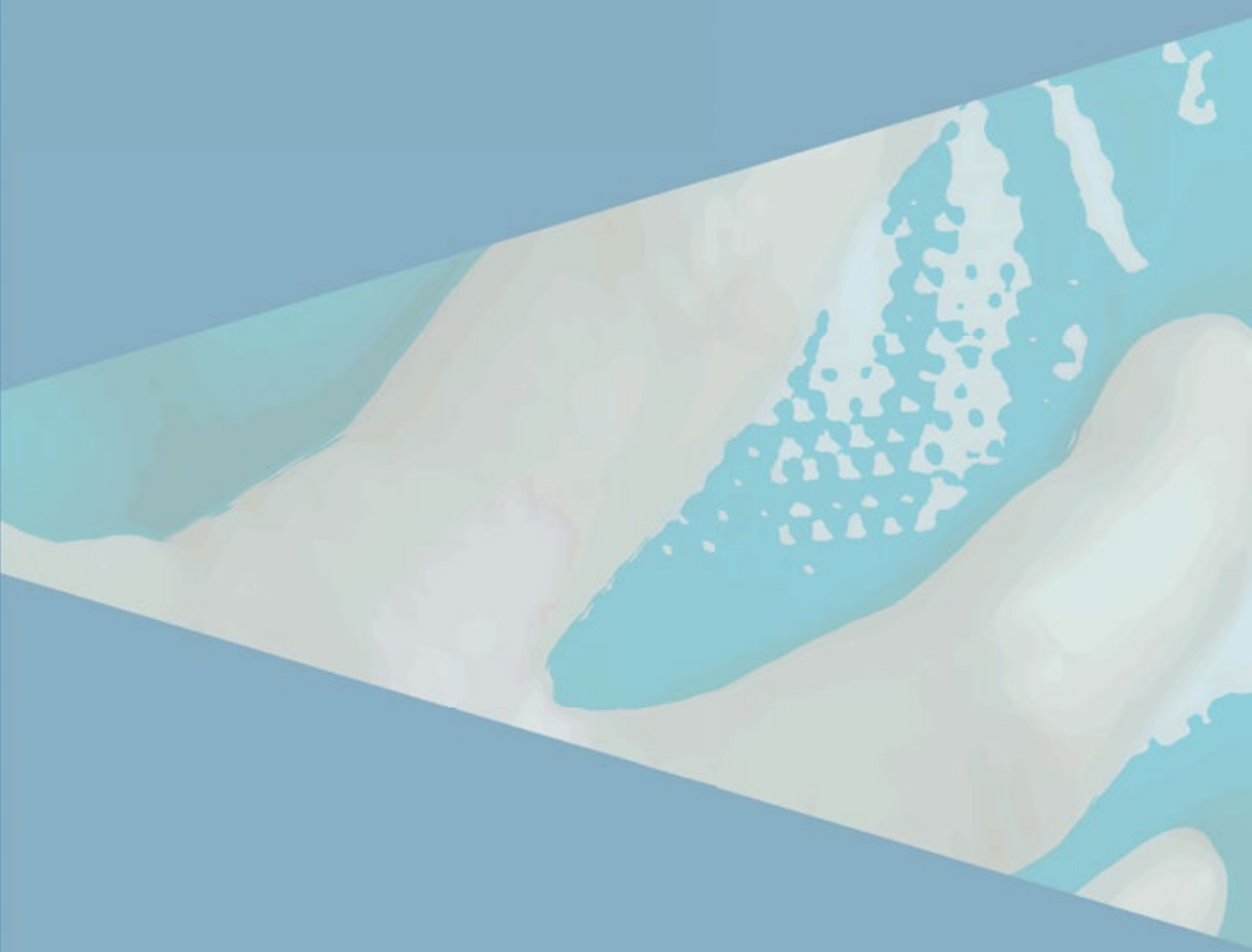
CHAPTER 8

Summary



Summary

Anxiety is a common emotion to a perceived threat. When the heart is thought to be in danger, this can be experienced as life-threatening and as such provoke a specific fear related to the heart: cardiac anxiety.

Two diseases in which patients may experience cardiac anxiety are a myocardial infarction (MI) and non-cardiac chest pain (NCCP). MI patients suffer from symptoms of cardiac disease, most frequently chest pain or chest discomfort, caused by blockage of the coronary arteries which supply the heart of oxygen: a well-known type of coronary artery disease (CAD). In contrast, NCCP patients experience symptoms of cardiac disease (i.e. chest pain) in the absence of a diagnosed cardiac origin.

In case anxiety is disproportionate, and limits a person to function adequately in daily life, it becomes pathological. At the pathological end of the spectrum are the anxiety disorders, like a panic disorder, which is characterized by sudden and repeated panic attacks. Pathological anxiety often coincides with depression: a state of low mood and/or anhedonia (loss of interest in activities formerly found amusing) that influences wellbeing and interferes with daily life.

Post MI, both depression and anxiety are shown to be associated with a worse quality of life and with adverse cardiac outcome [1,2]. However, considering the latter, findings are inconsistent. Various attempts to treat depressive symptoms post MI did not result in improving effects on cardiac outcome [3-5]. Several explanations can be put forward. One is that measurements of depression and/or psychological stressors might not be specific enough, as constructs related to mood and anxiety disorders may party overlap. Recent findings suggest that different types of anxiety and depression may be related to different outcomes in terms of increased mortality and increased incidence of cardiac events [6-10]. Therefore, the focus on a specific construct –i.e. cardiac anxiety- may be of help in disentangling the specific roles of anxiety.

Only few studies have evaluated cardiac anxiety in cardiac patients (mainly heterogeneous populations of both CAD and non-CAD patients) and all but one [11] had a cross-sectional design [12-14]. To date, no studies in a homogeneous sample of MI patients have focused on cardiac anxiety.

NCCP patients report similar to higher levels of cardiac anxiety compared to patients with established CAD [15]. Despite reassurance by medical professionals, the majority continues to report chest pain and remains concerned about having a serious heart disease [16,17]. Perhaps avoidable, since psychiatric disorders like panic disorder and depressive disorder can be treated effectively, e.g. with cognitive behavioral therapy [18,19].

The present thesis aimed to evaluate cardiac anxiety comprehensively by evaluating 1) the validity and reliability of an assessment tool for cardiac anxiety in patients with a myocardial infarction (MI), 2) the prevalence and characteristics of cardiac anxiety during hospitalization for an MI, 3) the course and trajectories of cardiac anxiety in the year after an MI and its association with quality of life, 4) the prognostic impact of cardiac anxiety on cardiac prognosis in terms of new cardiac events and all-cause mortality post MI, 5) the effect of a short cognitive behavioral therapy (CBT) intervention in non-cardiac chest pain (NCCP) patients assumed to experience cardiac anxiety. Three independent samples were used: a cohort of patients hospitalized for an MI at the Radboud UMC, a cohort of MI patients included in the Depression after Myocardial Infarction (DepreMI) study [20,21] - and a sample of NCCP patients who presented themselves at the emergency department of the VU and were diagnosed with a panic and/or depressive disorder.

Assessment of cardiac anxiety

Chapter 2 described a cross-validation study of the self-report Cardiac Anxiety Questionnaire (CAQ) in 237 patients admitted for a myocardial infarction (MI). The CAQ and five other well-established self-report questionnaires, assessing general anxiety, avoidance and depression, were administered. Confirmatory factor analysis revealed that the original three-factor solution of the CAQ as described by Eifert et al. (2000) [12], consisting of the three subscales fear, attention and avoidance, was acceptable. However, our data were better explained by a model including a fourth subscale reflecting safety seeking behaviors. This is consistent with the findings of a previous study in a mixed sample of both patients with and without coronary atherosclerosis [22]. Internal consistency and test-retest reliability in our sample were good. The CAQ had moderate correlations with the other questionnaires, reflecting reasonable to good convergent validity. Entering the subscales of all questionnaires in a factor analysis identified different factors, including one that contained all CAQ subscales. This implies that cardiac anxiety is a separate construct distinct from depressive and general anxiety symptoms. Patients who were recently admitted with MI had significantly higher scores than patients with rheumatoid arthritis, even after controlling for general anxiety and depressive symptoms. Therefore, divergent validity was good.

In conclusion, the findings of this validation-study imply that the CAQ is a reliable and valid self-report-instrument to assess cardiac anxiety in patients hospitalized with MI.

Prevalence and characteristics of cardiac anxiety post MI

Chapter 3 showed the findings of a cross-sectional study in the same cohort MI patients as described in chapter 2. Cardiac anxiety was assessed with the CAQ and information on socio-demographic, psychological and cardiac disease characteristics was gathered. Univariate and multivariate logistic and linear regression analyses were conducted to determine which characteristics were associated with cardiac anxiety. Cardiac anxiety was not associated with socio-demographic variables. However, cardiac anxiety did appear to be associated with psychological distress such as depressive symptoms, agoraphobic cognitions and avoidance behaviour. Interestingly, there was an inverse relationship between cardiac anxiety and severity of cardiac injury - as indicated by ST-Elevated Myocardial Infarction (STEMI) and troponin level. Two possible explanations seem likely for this latter finding. Anxious persons might seek help earlier, thus being more often diagnosed with minor cardiac pathology. Secondly, cardiac anxiety might partly be caused by diagnostic uncertainty. Although there has to be noted that the size of the correlations in this study seemed rather small, these postulated underlying explanations may be of impact for clinical practice. Communication strategies to reassure patients efficiently should be developed as these might be relevant for the subgroup of patients placed in a situation of uncertainty due to minor cardiac injury as well as the subgroup of patients with higher levels of cardiac anxiety in general.

To conclude, these cross-sectional findings showed that in patients admitted for MI higher cardiac anxiety was associated with more psychological distress but lower severity in cardiac injury.

The course of cardiac anxiety and its predictors

Chapter 4 reported on a longitudinal cohort study in the subsample (n=194) of the cohort of MI patients described in chapter 2 which filled out the CAQ after admission. Follow-up assessments took place at approximately one, three, six and twelve months after discharge. Latent class analysis identified four trajectories of cardiac anxiety; three groups had continuous CAQ levels of respectively high, intermediate and low intensity, while the fourth group had high scores at the beginning, but these decreased with time. Between group differences were of particular interest for the two subgroups which started high in cardiac anxiety, since these may differentiate patients with spontaneous remission from those who might be in need of treatment. Patients in whom cardiac anxiety persisted were more frequently unemployed, had more often diabetes mellitus and previous MI, and had higher baseline levels of depressive symptoms, anxiety and avoidance.

Unfortunately the number of persons in the two subgroups of interest were too small to control for possible confounders in a multivariate analysis. Therefore, we consider the comparison as a first step in exploring possible confounders.

Overall, this longitudinal cohort study addressing cardiac anxiety during the year post MI, identified four trajectories of cardiac anxiety. Future research should focus on cardiac outcome and efficacy of treatment strategies for cardiac anxiety especially in the subgroup of patients with persistent high cardiac anxiety levels.

Impact of cardiac anxiety on cardiac outcome

Chapter 5 assessed the prognostic impact of cardiac anxiety -measured with the CAQ -on cardiac outcome in the same cohort of MI patients as described in chapter 4. In previous studies anxiety symptoms were measured directly after hospitalization or surgery [23]. However, temporary distress due to hospitalization or surgery may inflate the rates of psychopathology whereas long-term functional outcome may only be affected by psychopathological symptoms that persist, or develop during the first weeks as has been demonstrated for depressive symptoms [24]. Furthermore, we showed in chapter 4 that trajectories of cardiac anxiety after a MI are largely determined within the first three months after the event. Therefore, we chose to investigate the prognostic association of the CAQ at both hospitalization and approximately four months after.

Study endpoint was a major adverse cardiac event (MACE) defined as a readmission for ischemic cardiac disease or all-cause mortality within approximately 4-5 years after the index-MI. The prognostic impact of CAQ on MACE was evaluated with Cox regression analysis, adjusted for age, cardiac disease severity (Left Ventricular Ejection Fraction, cardiac history), and depressive symptoms (Beck Depression Inventory). CAQ overall score both at hospitalization and after four months significantly predicted the occurrence of MACE over the 4 to 5 year follow-up period. Subsequent analyses of subscale scores revealed that this effect was particularly driven by "Avoidance", especially at four months post MI. These results imply that anxiety and its related behavior (especially avoidance of physical exercise) should be addressed, e.g. in rehabilitation programs. It could be targeted with cognitive behavioral therapy (CBT).

In conclusion, cardiac anxiety in MI patients, particularly anxiety-related avoidance of physical exercise, seemed an important prognostic factor for cardiac outcome in MI patients, independent of cardiac disease severity and depressive symptoms.

Chapter 6 tried to capture the prognostic impact of cardiac anxiety by investigating the association of patient-reported physical health with cardiovascular prognosis. In MI patients of the DepreMI cohort the somatic subscale of the self-report Health

Complaints Scale (HCS) was filled out at 3 and 12 months post-MI. Unfortunately, the CAQ was not administered. As previous research in cardiac patients undergoing planned surgery [25] showed that (negative) correlations of cardiac anxiety-assessed with CAQ- were stronger related with physical quality of life than with psychological quality of life, we hoped that (some type of) physical health could serve as a surrogate marker for cardiac anxiety. The prognostic impact of the HCS on a combined endpoint of new cardiac events and mortality was evaluated with Cox regression analysis adjusted for all socio-demographic, cardiac and psychiatric variables that were associated with combined endpoint univariately ($p<0.10$), including age, sex, education-level, history of MI, left ventricular ejection fraction, anterior location of MI, Killip Class, diabetes mellitus, peripheral vascular disease, cerebrovascular disease, having received treatment for psychiatric symptoms post-MI, depressive symptoms (BDI-sum-score) and generalized anxiety disorder. In addition, the type of physical health symptoms as well as their trajectories over time were explored.

Latent transition analysis (LTA) on the HCS yielded five groups of patients with 1) no/minimal symptoms, 2) cardiac complaints, 3) lack of energy, 4) sleep-problems, and 5) mixed health-complaints respectively, resulting in 25 latent transition classes.

In contrast to what we hoped, none of these groups seemed to resemble cardiac anxiety specifically. Nevertheless, we found interesting results. Of 424 MI-patients, 192 (45.3%) experienced a cardiac event or died during a mean (sd) follow-up of 5.7 (3.1) years. Physical health complaints 3 months post MI were associated with adverse cardiac outcome, even when adjusted for cardiac and psychiatric morbidity. Considering type of complaints, particularly cardiac complaints were important predictors of cardiac outcome, whereas mixed and energy complaints showed a trend of being a predictor. With respect to their course over time, new or persistent mixed, cardiac and energy complaints showed significant prognostic impact. However, obviously, replication of these findings in an independent sample, large enough to adjust not only for baseline cardiac and psychiatric disease severity but also for their changes during follow-up, is needed to see if this information from the patient's history may indeed serve as a prognostic marker.

Overall, although we failed to construct a measure for cardiac anxiety in this DepreMI cohort, research findings were interesting. Physical health complaints after a heart attack are predictors of cardio-vascular outcome independent from cardiac disease, depression and anxiety. These physical health complaints post- MI can be classed into different type and course over time, consisting of cardiac complaints, lack of energy, sleep problems, mixed and minimal health complaints. Type and trajectories of health-complaints may have additional prognostic significance.

Impact of cognitive behavioral therapy on cardiac anxiety

Chapter 7 showed the results of a 24-week randomized controlled trial comparing cognitive behavioral therapy (CBT) (n=60) versus treatment as usual (TAU, n=53) in adults who presented at the cardiac emergency unit of a university hospital with non-cardiac chest pain, who scored ≥8 on the Hospital Anxiety and Depression Scale (HADS) and were diagnosed with a comorbid panic and/or depressive disorder. CBT consisted of six individual sessions. Main outcome was global functioning assessed with the Clinical Global Inventory (CGI) by a blinded independent rater. ANCOVA in the intention-to-treat and completer sample showed that CBT was superior to TAU after 24 weeks in reducing disease severity assessed with CGI. Secondary outcomes on anxiety (HADS-Anxiety, State Trait Anxiety Inventory (STAI)-Trait) and depressive symptoms (Hamilton Depression Rating Scale) were in line with these results except for HADS-Depression, Fear Questionnaire and STAI-State.

In short, this randomized controlled trial showed that brief CBT significantly improves global functioning and reduces anxiety and depressive symptoms in patients with non-cardiac chest pain who are diagnosed with panic and/or depressive disorder.

Main Finding/Overall conclusion

The four studies in a cohort of MI patients as described in chapters 2-5 of this thesis indicate that cardiac anxiety can be reliably assessed with the self-rated CAQ, that patients report different trajectories of cardiac anxiety over time following a MI, and that higher cardiac anxiety is associated with more general anxiety and depressive symptoms, a worse quality of life one year post MI, and a worse cardiac prognosis up to five years after the MI. The study reported in chapter 6 in another cohort of MI patients showed that it is difficult to approximate cardiac anxiety when it is not explicitly assessed. Finally, the randomized controlled trial presented in chapter 7 of this thesis found that a CBT intervention in NCCP with a comorbid panic and/or depressive disorder can significantly reduce disease severity, anxiety and depressive symptoms. A logical follow-up would be to treat cardiac anxiety post MI.

Overall, these results imply that cardiac anxiety is relevant as it affects quality of life, psychiatric and cardiac outcome and is potentially modifiable. As such, cardiac anxiety may be a useful construct to detect persons at risk and to guide treatment.

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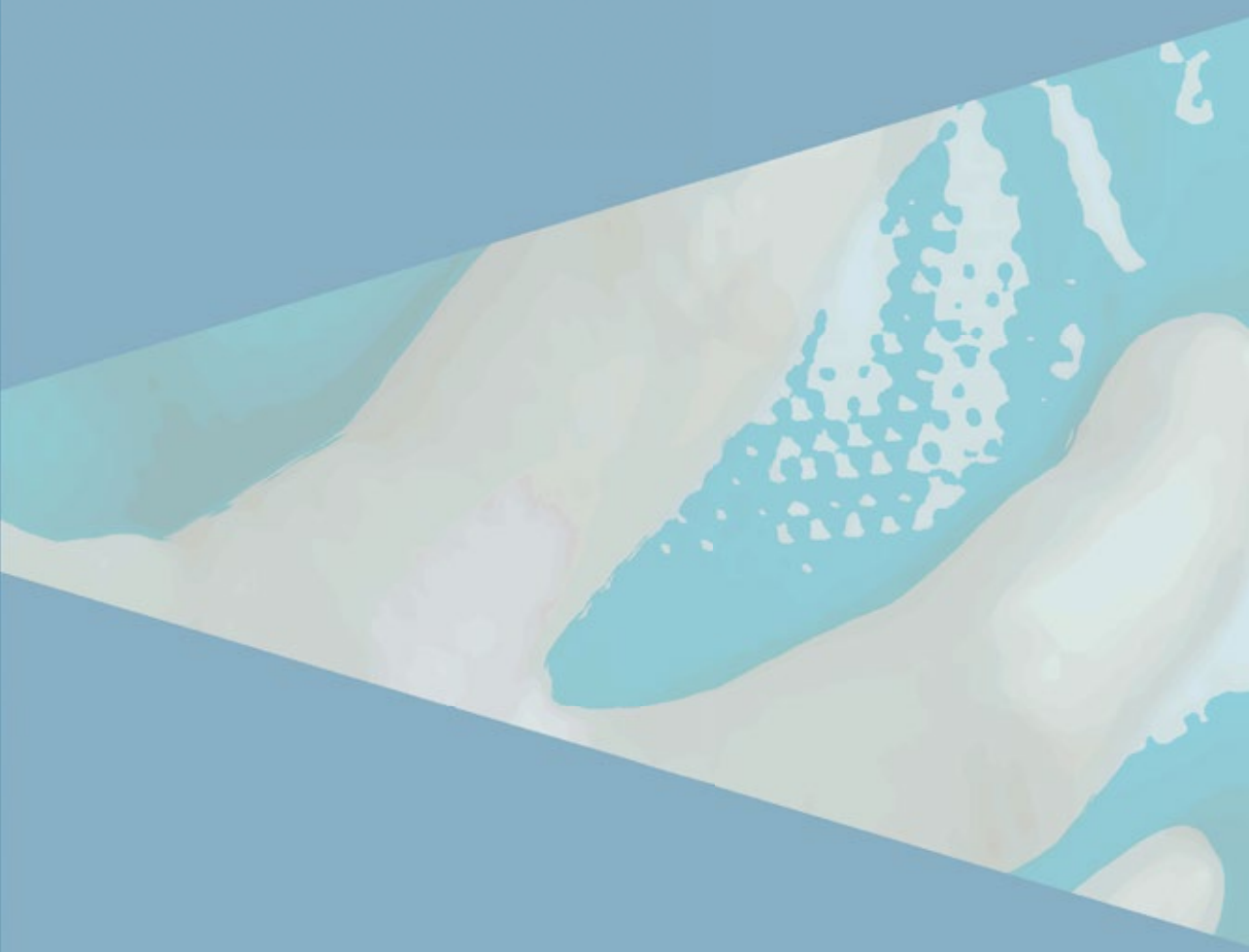
CHAPTER 9

General Discussion



General discussion

Findings of the present thesis show that cardiac anxiety post MI is relevant as it can be persisting, and is associated with other psychiatric symptomatology like more depressive symptoms and avoidance, with a worse quality of life and with a worse cardiac prognosis.

Historically, the main focus of research of psychiatric symptoms and their prognostic significance in MI patients used to be on depression rather than anxiety. As explained in chapter 1 of this thesis, depression post MI has been shown to be common and to have a negative impact on quality of life and cardiovascular outcome [1,2]. However, most studies evaluating antidepressant treatments in MI patients did not find beneficial effects on cardiac prognosis [3-5]. Secondly, some studies suggest that in particular somatic-affective but not cognitive-affective depressive symptoms are associated with cardiac prognosis [6-9]. Thirdly, pooled odds ratios in meta-analysis of studies evaluating the association between depression and cardiac prognosis were attenuated when adjusting for left ventricular function as marker for cardiac disease severity [1]. Therefore, it has been suggested that the effect of depression on post MI prognosis may be partly due to cardiac disease severity.

As post MI depression often co-occurs with anxiety [10], over the last decade the research focus has been extended to anxiety. Indeed, a meta-analysis of previous studies on anxiety found that post MI anxiety was associated with a 36% increased risk of adverse cardiac outcomes [11]. In this meta-analysis outcome was not adjusted for measures of cardiac disease severity. However, in the studies which did control for disease severity effect estimates appeared to be only slightly or not attenuated [12-14]. This suggests that the relationship between anxiety and cardiac prognosis might be less confounded by cardiac disease severity than that between depressive symptoms and cardiac prognosis. In a more recent-analysis evaluating the association of anxiety post-MI and in stable CAD with cardiac outcome, results were varying, depending on the operationalization of both the anxiety and the outcome variables [15]. A significant association was found between anxiety as a continuous predictor with a worse cardiac prognosis defined as a composite outcome, which is similar to our design. In the corresponding analysis adjusted for relevant covariates a one-standard increase in anxiety was associated with a 21% increase risk of a new cardiac event or death. Our results are consistent with these previous findings, demonstrating a prognostic association of anxiety with cardiac outcome independent from several cardiac severity parameters. As we have shown that cardiac anxiety was inversely related to other variables of cardiac disease severity (chapter 3), it seems unlikely that these findings were driven by residual confounding due to cardiac disease severity. Moreover, we

demonstrated that after additional adjustment for depressive symptoms, next to age, sex and parameters of cardiac disease severity, higher cardiac anxiety still increased the risk of adverse prognosis. Summarizing, the findings of this thesis show that anxiety post MI matters.

In line with the previously mentioned results for depression showing different prognostic associations for different types of depressive symptoms, the question can be raised which type of anxiety matters or matters the most. As reported in chapter 1, a recent study in CAD patients undergoing coronary artery bypass graft surgery showed different types of anxiety had a different relationship with cardiac prognosis: fear and panic disorders did not have an adverse association with cardiac prognosis, but generalized anxiety disorder did [16]. Commonly used anxiety questionnaires predominantly assess general anxiety, avoidance behavior, worrying and fear of bodily sensations. After a MI, cardiac-related stimuli and sensations may trigger specific anxiety symptoms, based upon their assumed negative consequences [17]. These specific fears and anxiety-related behaviors like increased attention, avoidance and safety-seeking behavior can be conceptualized as cardiac anxiety. The present thesis focused on cardiac anxiety rather than general anxiety and confirmed its association with cardiac prognosis, implying that cardiac anxiety indeed matters.

Unfortunately, the present thesis did not examine whether a focus on cardiac anxiety has additional value over general anxiety. However, the present findings do show that cardiac anxiety has an adverse association to cardiac outcome independent from depression. Given this fact, it would be worthwhile to hypothesize if and how cardiac anxiety post MI could be treated. In line with medical reasoning and common sense, one might argue that the more specific the problem, the more specific the treatment, the more effective the treatment might be. This could be further investigated in randomized controlled trials comparing cardiac outcome of specific interventions for cardiac anxiety with those of interventions targeting more general anxiety.

Methodological Considerations

Study type/design

This thesis tried to explore cardiac anxiety in a comprehensive way by using several research designs; observational studies, with either a cross-sectional (chapter 3) or longitudinal design (chapters 4-6) and an intervention study (chapter 7). The cross-sectional data enabled us to descriptively explore prevalence and associations of cardiac anxiety at one specific time point (immediately after a MI), whereas the longitudinal designs made it possible to explore the course of cardiac anxiety and

its prognostic association with cardiac outcome. Both indicated cardiac anxiety was associated with a worse outcome in terms of psychological distress and cardiac morbidity. A disadvantage of the longitudinal design used in this study is that the timing of the assessments was determined and the course of cardiac anxiety in between those time points was not taken into account. However, we did assess cardiac outcome for the whole period. Furthermore, we tried to target this issue by assessing cardiac anxiety for five times at regular intervals during the year post-MI (see chapter 4). More frequent assessments might have led to more drop-outs or to learning effects and both might have led to less valid findings. Although the RCT had a shorter follow-up period than the observational studies, the use of this experimental design provided additional value with respect to treatment outcome, although unfortunately we did not assess effects of CBT on reported chest-pain.

As the study designs in the three independent populations were different, their results may complement each other in the present thesis. Ideally, research implications of one study are addressed in the next. Unfortunately, as the studies were developed independent of each other and at other points in time, this was not possible. If they had been, we would have assessed cardiac anxiety with the CAQ in all studies including the RCT (chapter 7) and the Depremi study (chapter 6). Furthermore, we would have done a structured psychiatric interview in all studies in order to diagnose relevant psychiatric disorders, as was done in the RCT with the Composite International Diagnostic Interview (CIDI) and in the DepreMI cohort with the Mini-International Neuropsychiatric Interview (MINI). Next, we would have administered a general anxiety measure in addition to a cardiac anxiety measure. Finally, the cardiovascular outcome parameters of the DepreMI study (chapter 6) would have been defined more strictly, excluding minor non-ischaemic cardiac pathology, as they were in the prognostic CAQ study (chapter 5).

Population and generalizability

A clear strength of the present thesis and an indication of the external validity is that its findings are based on three independent populations: 1) MI patients recruited at the Radboud UMC (chapters 2 to 5); 2) MI patients included in the Depremi study (chapter 6); and 3) NCCP patients recruited at the VU University Medical Center (chapter 7). Two of the studies described a population recruited in university medical centres. The exception was the DePreMI study (chapter 6) which described a mixed sample of MI patients recruited in both academic as well as non-academic hospitals. As patients admitted to an academic setting may suffer from more complex pathology compared to patients in non-academic hospitals, their results may not automatically

be generalized to patients in non-academic hospitals. However, the cardiology department of the Radboud UMC (chapters 2-5) has a major regional function in the acute care of MI. Consequently, the pathology of many of the patients admitted for a MI in the Radboud UMC may in fact be comparable to non-academic hospitals. Nevertheless, replication of our findings in a multicenter study is needed.

Cardiac anxiety: A neglected psychiatric problem?

Cardiac anxiety is a specific type of anxiety not (yet) recognized by the DSM. Consequently, in most (psychiatric) research it has not been assessed explicitly, as is the case in the DepreMI study (chapter 6) and the RCT (chapter 7). Therefore, in this thesis several strategies to address cardiac anxiety were used: a dimensional approach (chapters 2 to 6) versus a categorical approach (chapter 7); and explicit assessment with a self-report questionnaire (chapters 2 to 5) versus trying to examine cardiac anxiety more implicitly (chapter 6 and 7). Obviously, when aiming to explore cardiac anxiety, the preferred method is to assess it directly, e.g. with an instrument like the CAQ. Such a standardized approach would have made it easier to relate the research results to each other. Even though we tried our best to use measures assessing similar constructs as the CAQ, the underlying inconsistencies obviously hampered relating the findings of the different studies to each other. The Health Complaints Scale (HCS) (chapter 6) and panic disorder in patients with non-cardiac chest pain (NCCP) (chapter 7) are reasonable measures as both are associated with cardiac anxiety. However, both constructs are broad and may in fact only partly capture the concept of cardiac anxiety. Therefore, in the future replication of these findings with the CAQ as direct measure of cardiac anxiety in these populations is desirable. Preferably, the CAQ should be assessed together with psychiatric diagnoses and general measures of psychopathology, in order to evaluate the specific contribution of each of these concepts.

Psychometric aspects

Cardiac anxiety is a multidimensional construct as can be seen by the different subscales of the CAQ (chapter 2). This thesis showed that the association with cardiac outcome is especially mediated by avoidance behavior, which may provide a focus for treatment. On the other hand, the association of higher cardiac anxiety with worse quality of life, seemed to apply to all dimensions of cardiac anxiety. These findings point to the relevance of a dimensional approach.

A recent German study tried to set percentiles based on a normative sample of the general population for the CAQ [18]. However, these cut-offs are based on statistical

norms only and lack confirmation by a gold standard. For clinical care, the lack of a gold standard is less relevant as it is most useful to know the predictive validity of cardiac anxiety with respect to its association with quality of life, its course over time, and cardiac prognosis. The optimal cut-off points probably differ for these different endpoints. Acknowledging the limited empirical data on cardiac anxiety, we prefer the dimensional approach to support clinical (and shared) decision making.

Cardiac aspects

In the cohort studies evaluating the prognostic association, several cardiac disease severity parameters were assessed and taken into account, which is a clear strength of these studies. Ideally, these parameters should have been assessed repeatedly during follow up for a more accurate adjustment of cardiac disease severity on the prognostic association of cardiac anxiety.

Furthermore, although the longer follow-up period is an advantage, during the years inevitably clinical guidelines and as such preferred cardiac treatment may change due to progressive insight. This is particularly relevant for the outcome of the DepreMI cohort, which was performed in the era before the treatment of choice for MI was a primary percutaneous intervention (PCI), which was been shown to improve outcome when compared to thrombolytic medication [19]. However, the effect on prognostic impact of cardiac anxiety may be minimal: in the cohort of the Radboud UMC we performed a sensitivity analysis in which we included "having received PCI treatment (yes/no)", in the model with CAQ, sex and age, which hardly affected the association between overall CAQ score and adverse prognosis.

Interestingly, the prognostic association of cardiac anxiety on cardiac outcome in our study seemed to be mediated by avoidance. In light of these findings, the role and effect of cardiac rehabilitation is important. In recent years, more attention has been given in the national guidelines of cardiac rehabilitation to awareness and treatment of anxiety and depression. In our prognostic study on the CAQ (chapter 5), we adjusted in sensitivity analysis for "being assigned to cardiac rehabilitation", and although assignment in fact was an independent predictor of cardiac outcome in this model, it hardly affected the association between overall CAQ score and adverse prognosis. Furthermore, in the latent class analysis-study (chapter 4) assignment for cardiac rehabilitation did not significantly differ between the four latent groups of patients with different course of cardiac anxiety, implying that despite cardiac rehabilitation cardiac anxiety may still be present. More research is needed to evaluate which patients profit from cardiac rehabilitation and which ones do not with respect to both general and more specific cardiac anxiety. This may provide starting points to

optimize treatment

Future directions and implications

Research directions

Future research in MI and NCCP patients should address how cardiac anxiety relates to psychiatric diagnoses and general anxiety by combining these variables in assessments. By identifying the overlap between these different constructs, cardiac anxiety could be further delineated.

The findings of this thesis suggest a behavioral mechanism of cardiac anxiety on cardiac prognosis as particularly anxiety-related avoidance of physical exercise predicted future cardiac events in MI patients, which was independent of cardiac disease severity and depressive symptoms. More research investigating possible biological mechanisms of cardiac anxiety, such as rhythm disturbances due to increased sympathetic or decreased parasympathetic nervous activity or atherosclerosis promoting abnormalities like increased platelet activity and inflammation, is needed.

Although the results of the RCT (chapter 7) might imply that CBT could decrease cardiac anxiety and avoidance in NCCP patients, more research explicitly assessing cardiac anxiety in this population is needed. Preferably this could be done with the CAQ, as a recent study that cross-validated the CAQ in NCCP patients [20] indicated good psychometric properties for this instrument. As our study findings in NCCP patients cannot automatically be generalized to MI patients, future studies should examine the effect of a CBT intervention or related treatments in reducing cardiac anxiety in MI patients specifically.

Clinical implications

The findings of the present thesis give an indication of the clinical relevance of cardiac anxiety post MI. When translating these results into clinical practice, we should acknowledge that more information about cardiac anxiety is needed on when best to assess it, whether it is amenable to treatment and the potential beneficial effects of this treatment on psychological and cardiac outcome. With respect to treatment options, it is interesting that the present thesis showed that anxiety indeed can be targeted with CBT in a NCCP population (Chapter 7). Although the CAQ was not administered in this trial and replication is needed in a population with established high levels of cardiac anxiety, it is likely that NCCP patients experience a certain level cardiac anxiety (chapter 7). One might assume such an intervention could also be helpful for anxiety with a cardiac origin (i.e. anxiety post MI), especially since we showed

an association between cardiac anxiety and cardiac prognosis independent of cardiac disease severity. However, we should acknowledge that the NCCP patients who received CBT in our RCT (chapter 7) were diagnosed with a panic disorder and/or depressive disorder. As such, their treatment was based on the cognitive model of panic disorder developed by Clark [21], if needed extended with the treatment of depression. It consisted of a combination of psychoeducation, cognitive restructuring and reduction of avoidance behavior [22]. When hypothesizing about the appropriate treatment for cardiac anxiety, it is important to realize that patients experiencing cardiac anxiety may not necessarily fulfill the criteria of a panic and/or depressive disorder. Some may meet the criteria for hypochondriasis, their CBT may need to consist of elements of hypochondriasis: health anxiety with an emphasis on maintaining this anxiety by safety seeking behavior. Others may not fulfill the criteria of a psychiatric disorder, but may nevertheless profit from treatment, as CBT has previously been shown to be effective for sub syndromic anxiety symptoms [23]. As this thesis demonstrated that the prognostic association of cardiac anxiety was particularly explained by avoidance behavior, and it is common knowledge that avoidant behavior can be (unintendedly) maintained by significant others, another suggestion may be to explicitly involve family members in treatment programs.

Using the subscale scores of the CAQ, it may be possible to identify which specific aspects of cardiac anxiety are important. This can be of help in tailoring interventions to the specific processes which each could elevate or maintain anxiety: increased attention to cardiac stimuli, catastrophic worries and interpretations, avoidance of cardiac stimuli and physical exercise, and safety seeking behaviors. Cognitive behavioral therapy (CBT) techniques may target anxiety-related avoidance behaviors which may even result in a better cardiac outcome. An efficacy study examining CBT, paroxetine and placebo in patients with non-cardiac chest pain, showed that an early reduction of cardiac anxiety (assessed with the CAQ) mediated pain reduction afterwards [24]. This may also be the case for MI patients. A multi-center-RCT in MI patients is planned investigating the effect of internet-based CBT on anxiety and interestingly, cardiac anxiety (assessed with CAQ) will be one of the secondary outcomes [25].

In the future, the assessment of cardiac anxiety may be helpful in identifying patients at risk for developing high and persisting levels of anxiety with negative consequences [17,26]. High levels of cardiac anxiety may indicate the need for therapeutic interventions targeted at reduction of anxiety [18]. However, even when all the necessary evidence is available, implementing such screening programs is still quite a challenge. A Dutch study trying to implement screening on panic disorder in NCCP patients attending

the emergency department demonstrated that implementation was limited because screening frequently conflicted with provision of acute care and because patients showed relatively high refusal rates [27]. As several heterogeneous psychiatric disorders in this particular cohort were diagnosed, the authors call for a more personalized approach, instead of a screening program aimed at identifying only those with panic disorder. Considering the findings of the present thesis, the assessment of cardiac anxiety within this context might be more acceptable and possibly of more use.

Final remarks:

Cardiac anxiety may be a valuable construct to further explore the role of anxiety in MI and NCCP patients and its association with cardiac prognosis. In the future it may be used as a feature to optimize risk assessment and guide treatment. Just like psychologists and psychiatrists should be aware of cardiac diseases and risk factors in their patients, cardiologists should acknowledge and treat anxiety in theirs.

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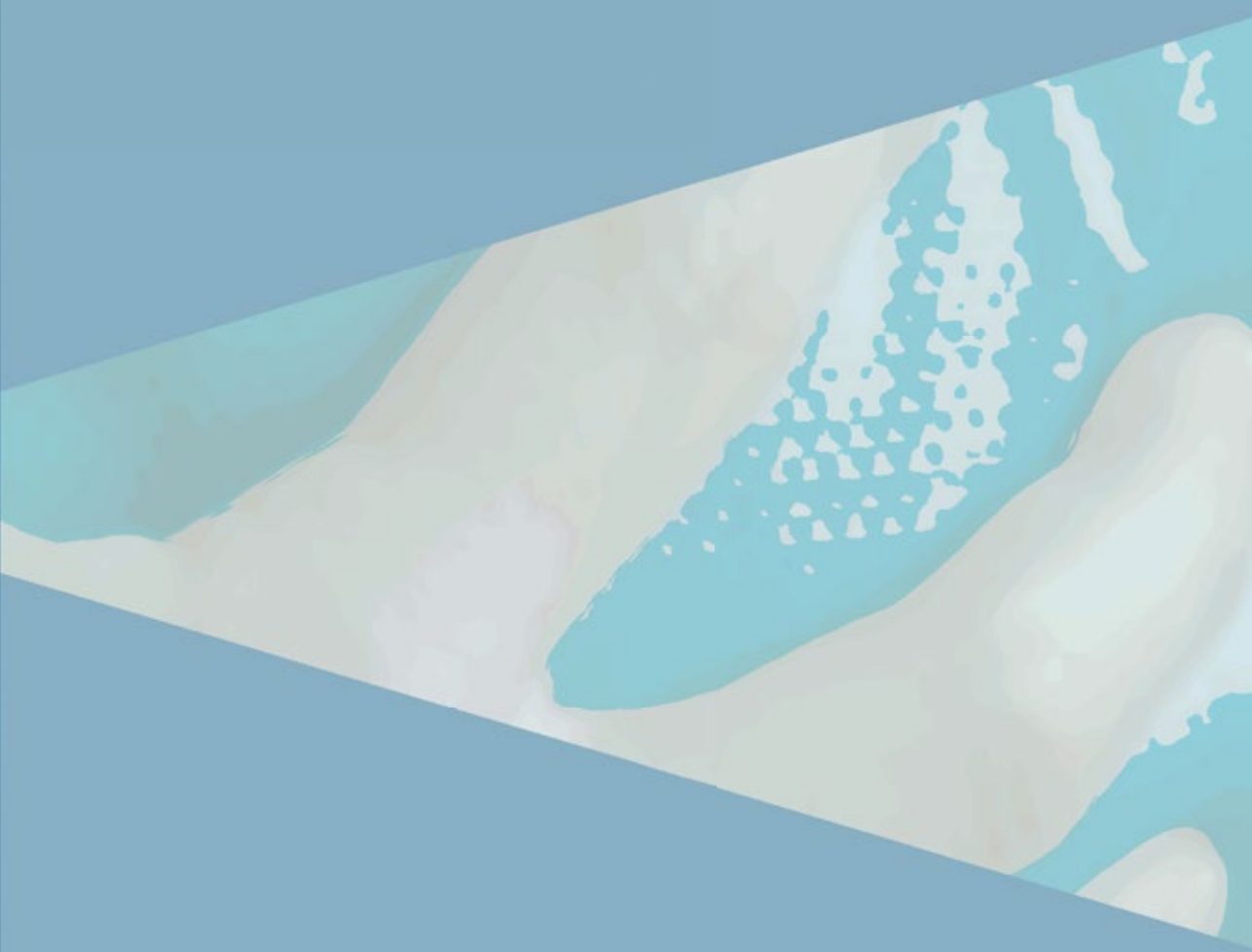
CHAPTER 10

Appendix



Appendix

Cardiac Anxiety Questionnaire

Cardiale Angst Vragenlijst

Acronyms

Summary in Dutch | Nederlandse samenvatting

About the author

List of publications

Acknowledgement in Dutch | Dankwoord

Cardiac anxiety Questionnaire

Please rate each item by circling the answer (number) that best applies to you:

		Never	Rarely	Sometimes	Often	Always
1.	I pay attention to my heart beat	0	1	2	3	4
2.	I avoid physical exertion	0	1	2	3	4
3.	My racing heart wakes me up at night	0	1	2	3	4
4.	Chest pain/discomfort wakes me up at night	0	1	2	3	4
5.	I take it easy as much as possible	0	1	2	3	4
6.	I check my pulse	0	1	2	3	4
7.	I avoid exercise or other physical work	0	1	2	3	4
8.	I can feel my heart in my chest	0	1	2	3	4
9.	I avoid activities that make my heart beat faster	0	1	2	3	4
10.	If tests come out normal, I still worry about my heart	0	1	2	3	4
11.	I feel safe being around a hospital, physician or other medical facility	0	1	2	3	4
12.	I avoid activities that make me sweat	0	1	2	3	4
13.	I worry that doctors do not believe my symptoms are real	0	1	2	3	4

When I have chest discomfort or when my heart is beating fast:

14.	I worry that I may have a heart attack	0	1	2	3	4
15.	I have difficulty concentrating on anything else	0	1	2	3	4
16.	I get frightened	0	1	2	3	4
17.	I like to be checked out by a doctor	0	1	2	3	4
18.	I tell my family or friends	0	1	2	3	4

- G.H. Eifert et al. / Behaviour Research and Therapy 38 (2000) 1039-1053

Cardiale Angst Vragenlijst

Omcirkel aub het antwoord (nummer) dat het beste past volgens u:

		Nooit	Zelden	Soms	Vaak	Altijd
1.	Ik let op mijn hartslag	0	1	2	3	4
2.	Ik vermijd lichamelijke inspanning	0	1	2	3	4
3.	Mijn hartslag maakt me 's nachts wakker	0	1	2	3	4
4.	Pijn op de borst/ een gespannen gevoel maakt me wakker 's nachts	0	1	2	3	4
5.	Ik doe het zo rustig mogelijk aan	0	1	2	3	4
6.	Ik controleer mijn pols	0	1	2	3	4
7.	Ik vermijd inspanning of fysieke arbeid	0	1	2	3	4
8.	Ik kan mijn hart in mijn borstkas voelen	0	1	2	3	4
9.	Ik vermijd activiteiten die mijn hartslag versnellen	0	1	2	3	4
10.	Als onderzoeken goede resultaten hebben, maak ik me toch zorgen om mijn hart	0	1	2	3	4
11.	Ik voel me veilig in een ziekenhuis, bij een arts of andere medische voorziening	0	1	2	3	4
12.	Ik vermijd activiteiten die me laten zweten	0	1	2	3	4
13.	Ik maak me zorgen dat de artsen niet geloven dat mijn klachten echt zijn	0	1	2	3	4

Als ik pijn op de borst voel, of een drukkend gevoel heb, of als mijn hartslag snel is

14.	……maak ik me zorgen dat ik een hartaanval heb	0	1	2	3	4
15.	…heb ik moeite me op iets anders te concentreren	0	1	2	3	4
16.	…word ik bang	0	1	2	3	4
17.	…wil ik onderzocht worden door een arts	0	1	2	3	4
18.	…vertel ik het mijn familie of vrienden	0	1	2	3	4

Acronyms

ACQ	Agoraphobic Cognitions Questionnaire
ACS	Acute Coronary Syndrome
AIC	Akaike Information Criterion
ANCOVA	Analyses Of Covariance
ANOVA	Analysis of Variance
BAI	Beck Anxiety Inventory
BDI	Beck Depression Inventory
BIC	Bayesian Information Criterion
BLRT	Bootstrapped Likekihood Ratio Test
CAD	Coronary Artery Disease
CAQ	Cardiac Anxiety Questionnaire
CBS	Statistics Netherlands (Centraal Bureau voor de Statistiek)
CBT	Cognitive Behavioral Therapy
CFA	Confirmatory Factor Analysis
CFI	Comparative Fit Index
CGI	Clinical Global Inventory
CGI-Severity	Clinical Global Impression Severity Scale
CI	Confidence Interval
CIDI	Composite International Diagnostic Interview
CK	Creatine Kinase
CPK max	Maximum Creatinin PhosphoKinase level
CRP	C-Reactive Protein
DALYs	Disability Adjusted Life Years
DepreMI	Depression after Myocardial Infarction
DM	Diabetes Melitus
ECG	Electrocardiogram
EFA	Exploratory Factor Analysis
EQ-5D	EuroQol- 5 dimensions
FQ	Fear Questionnaire
GAD	Generalized Anxiety Disorder
HADS	Hospital Anxiety and Depression Scale
HADS-A	Hospital Anxiety Depression Scale, anxiety subscale
HADS-D	Hospital Anxiety Depression Scale, depression subscale
HCS	Health Complaints Scale
HDRS	Hamilton Depression Rating Scale
HPA-axis	Hypothalamic–Pituitary–Adrenal axis

HR	Hazard Ratio
ICD	International Classification of Diseases
LCGA	Latent Class Growth Analysis
LOCF	Last-Observation Carried Forward
LTA	Latent Transition Analysis
LVEF	Left Ventricular Ejection Function
MACE	Major Adverse Cardiac Event
MI	Myocardial Infarction (chapters 1, 3-6, 8, 9)
MI	Mobility Inventory (chapters 2, 4)
MINI	Mini-International Neuropsychiatric Interview
NA	Not Applicable
NCCP	Non-Cardiac Chest Pain
NSTEMI/Non-Stemi	Non-ST Elevated Myocardial Infarction
PCI	Percutaneous Coronary Intervention
PTCA	Percutaneous Transluminal Coronary Angioplasty
PTSD	Post-Traumatic Stress Disorder
RA	Rheumatoid Arthritis
RCT	Randomized Controlled Trial
SPSS	Statistical Package for the Social Sciences
STAI	State-Trait Anxiety Inventory
STAI-S	State-Trait Anxiety Inventory, state part
STAI-T	State-Trait Anxiety Inventory, trait part
STEMI	ST-Elevated Myocardial Infarction
TAU	Treatment As Usual
TLI	Tucker-Lewis Index
VLMR	Vong-Lo-Mendell-Rubin ratio test
WHO	World Health Organization

Summary in Dutch | Nederlandse samenvatting

Cardiale angst - als je vreest dat je hart in gevaar is -

Achtergrond (hoofdstuk 1)

Angst is een emotie die wordt opgeroepen bij dreigend gevaar. Angst stelt je lichaam in staat van paraatheid, waardoor je kunt vechten tegen of vluchten van gevaar. Als de angstreactie onevenredig is met het gevaar (in type, duur of intensiteit), wordt het afwijkend (of pathologisch), zeker als een persoon hierdoor niet meer adequaat in het dagelijks leven kan functioneren. Aan het pathologische eind van het angstspectrum staan de angststoornissen, zoals een paniekstoornis, die gekenmerkt wordt door onverwachte en herhaalde paniekaanvallen. Pathologische angst gaat vaak gepaard met depressie [1-3] ; een staat van verminderde stemming en/of anhedonie (het verlies van interesse in activiteiten die eerder als plezierig werden ervaren) die interfereert met het welzijn en het functioneren in het dagelijks leven.

Als je (vreest dat je) hart in gevaar is, kun je dat als levensbedreigend ervaren. Dit kan specifieke angst uitlokken: cardiale angst. Cardiale angst omvat alert zijn op hart-gerelateerde sensaties (zoals pijn op de borst), catastrofale gedachten hierover (bijvoorbeeld "ik heb een hartaanval"), het vermijden van activiteiten die deze sensaties kunnen oproepen (zoals lichamelijke inspanning), en het zoeken naar geruststelling (bijvoorbeeld het controleren van je pols).

Twee ziektes waarbij mensen die hieraan lijden cardiale angst kunnen ervaren, zijn een hartaanval, ook wel myocardinfarct (MI) genoemd, en niet-cardiale-pijn-op-de-borst (NCPB). MI patiënten lijden aan symptomen van een hartziekte, met name pijn of een drukkend gevoel op de borst. Dit wordt veroorzaakt door vernauwing en/of blokkade van de kransslagaders, die het hart van zuurstof voorzien: een welbekende vorm van coronaire hartziekte. Daarentegen ervaren NCPB patiënten symptomen van een hartziekte, te weten pijn op de borst, zonder dat er een cardiale oorzaak is gediagnostiseerd die hieraan ten grondslag ligt.

In eerdere onderzoeken is aangetoond dat angst en depressie na een hartaanval samenhangen met een slechtere kwaliteit van leven [4,5] en een ongunstiger cardiaal beloop, namelijk meer kans op het krijgen van een nieuwe hartaanval [6,7] of op overlijden 6-8 . Echter, in tegenstelling tot wat je op basis hiervan zou verwachten, hebben verschillende pogingen om depressieve klachten na een hartaanval te behandelen niet geresulteerd in een verbetering van de cardiale prognose voor de patiënten die deze

klachten rapporteerden [9-11]. Daarvoor zijn verschillende verklaringen te bedenken. Een mogelijke verklaring is dat instrumenten waarmee depressie en/of psychologische stress wordt gemeten niet specifiek genoeg zijn. Recente onderzoeksbevindingen suggereren dat verschillende typen angst en depressie samenhangen met een verschillende cardiale prognose [12]. Het focus specifiek op cardiale angst geeft mogelijk meer inzicht in de bijdrage van verschillende typen angst aan het geheel.

Slechts in enkele studies is cardiale angst bij hartpatiënten bekeken. Dit betrof vooral gemêleerde onderzoekspopulaties van zowel patiënten met als zonder coronaire hartziekte. Voor deze onderzoeken [13-15] met uitzondering van één [16] geldt bovendien dat cardiale angst slechts op één tijdstip en niet op meerdere momenten is gemeten. Tot op heden zijn er geen studies verschenen waarin cardiale angst in een homogene groep van patiënten met een hartaanval is onderzocht.

Patiënten met NCPB rapporteren vergelijkbare tot zelfs meer symptomen van cardiale angst dan patiënten met aangetoonde coronaire hartziekte [17]. Ondanks de geruststelling door artsen dat er geen cardiale oorzaak is gevonden, blijft de meerderheid van de patiënten last houden van pijn-op-de-borst en blijven ze bezorgd een ernstige hartziekte te hebben. Misschien kunnen we hier iets aan doen, aangezien psychiatrische stoornissen zoals een paniekstoornis en depressie effectief behandeld kunnen worden met bijvoorbeeld cognitieve gedragstherapie (CGT). CGT is een psychologische behandeling die gebaseerd is op twee principes. Disfunctioneel gedrag -dat leidt tot problemen- kan worden aangeleerd, maar is ook weer af te leren (de gedragskant). Dit gedrag kan het gevolg zijn van het feit dat je slecht over jezelf denkt en je vervolgens ook slecht voelt (de cognitieve kant). CGT pakt zowel de gedachten en gevoelens als het in standhoudend gedrag aan.

Vraagstelling proefschrift (hoofdstuk 1)

Het doel van dit proefschrift is om cardiale angst te onderzoeken aan de hand van de volgende vragen:

1. a. Hoe is de validiteit (meet het wat je wilt dat het meet?) en betrouwbaarheid (hoe nauwkeurig wordt het gemeten?) van de Cardiale Angst Vragenlijst (zie appendix 2) - een vragenlijst die cardiale angst beoogt te meten- in patiënten met een hartaanval ?

1. b.Wat is het vóórkomen en wat zijn de kenmerken van cardiale angst gedurende de ziekenhuisopname wegens een hartaanval ?

2. a. Hoe is het beloop van cardiale angst in het jaar na een hartaanval en hangt het

samen met kwaliteit van leven?

2.b. En (hoe) hangt cardiale angst samen met de cardiale prognose als het gaat om nieuwe cardiale incidenten of overlijden?

3 Wat is het effect van een korte cognitieve gedragstherapie voor patiënten met NCPB die verondersteld worden cardiale angst te ervaren?

Methode

Om deze vragen te beantwoorden werkten we met drie onafhankelijke groepen:

-een groep van 237 patiënten die met een hartaanval opgenomen waren op de afdeling cardiologie in het Radboud Universitair Medisch Centrum (RadboudUMC) te Nijmegen. Zij vulden de CAV en enkele andere vragenlijsten in tijdens de ziekenhuisopname (vraag 1: beschreven in hoofdstukken 2 en 3) en diverse keren in het jaar na ontslag (vraag 2: beschreven in hoofdstukken 4 en 5). Ook werden gegevens omtrent de ernst van de hartziekte en sociaal-demografische gegevens verzameld. Tevens werd bij hen gekeken of en zo ja wanneer ze gedurende de vijf jaar na ontslag opnieuw werden opgenomen met een hartaanval (of soortgelijke problematiek) of overleden waren (vraag 2: beschreven in hoofdstuk 5).

-een groep van 424 patiënten opgenomen met een hartaanval die deel hadden genomen aan het Depressie na Myocardinfarct (DePreMI) onderzoek, geworven uit vier Groningse ziekenhuizen te weten het Universitair Medisch Centrum Groningen (UMCG), het Martini ziekenhuis te Groningen, het Refaja ziekenhuis in Stadskanaal en het St. Lucasziekenhuis te Winschoten (vraag 2: beschreven in hoofdstuk 6). Zij vulden na 3 en 12 maanden een gezondheidsklachten vragenlijst in. Tevens werd beoordeeld of de diagnose van een depressieve en/of angststoornis bij hen gesteld kon worden en vulden patiënten een vragenlijst in over depressieve klachten. Daarnaast werden ook bij hen gegevens over de ernst van de hartziekte en sociaal-demografische gegevens verzameld en werd bekeken of en zo ja wanneer ze gedurende de vijf jaar na ontslag opnieuw werden opgenomen met een hartaanval (of soortgelijke problematiek) of overleden waren (vraag 2).

-een groep van 113 patiënten met NCPB die zich melden bij de eerste hulp van Vrije Universiteit Medisch Centrum (VUMC), 8 of meer punten scoren op een screenende vragenlijst voor depressieve en/of angstige klachten (de HADS) en gediagnostiseerd werden met een paniek- en/of depressieve stoornis (vraag 3: beschreven in hoofdstuk 7). Zij werden verdeeld over twee groepen: 60 patiënten kregen zes individuele

sessies cognitieve gedragstherapie (CGT) en 53 patiënten kregen de gebruikelijke behandeling. De twee groepen werden met elkaar vergeleken op het effect van de behandeling. De hoofduitkomstmaat was het globale functioneren zoals gemeten met de Clinical Global Inventory (CGI) door een onafhankelijke beoordelaar. Tevens werden depressieve en angstklachten in kaart gebracht middels vragenlijsten.

Bevindingen

De resultaten van de studies zijn in hoofdstukken 2 tot en met 6 van dit proefschrift beschreven. Hieronder volgt een korte opsomming van de belangrijkste bevindingen per vraagstelling/hoofdstuk.

(1a) Hoe is de validiteit en betrouwbaarheid van de Cardiale Angst Vragenlijst in patiënten met een hartaanval ?

In hoofdstuk 2 is een validatie-onderzoek beschreven naar de Cardiale Angst Vragenlijst (CAV), een vragenlijst die oorspronkelijk is ontwikkeld door Eifert en anderen [13]. Onze bevindingen hebben we vergeleken met de resultaten van de eerste studie naar deze vragenlijst [13], waarin drie subschalen van de vragenlijst werden beschreven die respectievelijk angst, aandacht en vermijding meten. In onze populatie paste een verdeling in vier subschalen beter, net als in een andere studie [15]. De vierde categorie werd gekenmerkt door geruststelling zoekend gedrag. Als je de CAV een aantal dagen na de eerste keer nog een tweede keer af nam, waren de resultaten consistent. Dit duidt erop dat de vragenlijst betrouwbaar is. Als we alle vragenlijsten met elkaar vergeleken, zagen we dat de CAV aansluit bij andere vragenlijsten die psychische klachten meten, maar dat cardiale angst wel een aparte factor was. Ook was duidelijk dat een controlegroep van patiënten die last hadden van reuma lager op de CAV scoorden dan de patiënten met een hartaanval, zelfs als we rekening hielden met hun niveau van algemene angst.

Deze resultaten duiden erop dat de CAV bij patiënten met een hartaanval inderdaad cardiale angst lijkt te meten en dat op een betrouwbare manier doet.

(1b) wat is het vóórkomen en wat zijn de kenmerken van cardiale angst gedurende de ziekenhuisopname wegens een hartaanval ?

In hoofdstuk 3 worden de bevindingen gerapporteerd van een studie naar cardiale angst in dezelfde groep patiënten als beschreven in hoofdstuk 2. Met behulp van regressie-analyses werd bekeken welke variabelen samenhingen met cardiale angst. Er was geen samenhang tussen cardiale angst en sociaal-demografische gegevens.

Wel hing meer cardiale angst samen met meer psychische klachten zoals depressie, algemene angst en vermijdingsgedrag. Interessant genoeg vonden we een omgekeerd verband tussen cardiale angst en ernst van de hartziekte. Ernstigere hartziekte was gedefinieerd volgens een bepaalde afwijking, te weten (1) een verhoging van het ST segment, op het hartfilmpje (STEMI) en (2) een hoog troponine gehalte, een enzym in het bloed dat duidt op hartschade. Patiënten met minder ernstige hartziekte bleken meer angst te hebben. Hiervoor zijn twee mogelijke verklaringen. Patiënten die angstig zijn, zouden eerder hulp kunnen zoeken, waardoor ze ook eerder gediagnostiseerd worden met een minder ernstige hartziekte. Ten tweede kan cardiale angst mogelijk uitgelokt worden door onzekerheid over de diagnose. Hoewel we moeten erkennen dat de correlaties in deze studie klein zijn, kunnen de twee voorgestelde verklaringen toch van invloed zijn op de klinische praktijk. Communicatie strategieën om patiënten effectiever gerust te stellen zouden voor zowel de subgroep die zich in een situatie van onzekerheid over de diagnose bevindt, als voor de subgroep van patiënten die sowieso hoger scoren op cardiale angst relevant kunnen zijn.

Concluderend laten deze resultaten zien dat bij patiënten die opgenomen zijn met een hartaanval cardiale angst samenhangt met meer psychische klachten maar minder cardiale schade.

(2a) hoe is het beloop en de trajecten van cardiale angst in het jaar na een hartaanval en de samenhang met kwaliteit van leven?

Hoofdstuk vier toont de resultaten van een onderzoek in een deel van de patiënten die in hoofdstuk 2 werden beschreven en met een hartaanval waren opgenomen. Deze subgroep werd gevraagd op meerdere momenten de cardiale angst vragenlijst in te vullen: tijdens de opname, en ongeveer na één, drie, zes en twaalf maanden na ontslag uit het ziekenhuis. Met behulp van een statische analyse methode die latente klasse analyse heet, identificeerden we vier mogelijke beloopstrajecten van cardiale angst na een hartaanval: drie groepen hadden gelijkblijvende niveaus van cardiale angst met hoge, middelmatige en lage intensiteit van de cardiale angst, en één groep scoorde hoog op cardiale angst in het begin, maar in deze groep daalden de klachten gedurende de follow-up.

De groepen die het hoogst scoorden op cardiale angst na één jaar, rapporteerden ook de slechtste kwaliteit van leven. Verschillen tussen de groepen zijn vooral interessant voor de subgroepen patiënten die veel cardiale angst in het begin rapporteerden, omdat deze verschillen aanwijzingen kunnen geven over wie wellicht behandeling van cardiale angst verdient en bij wie cardiale angst vanzelf herstelt in de loop van de tijd. Patiënten bij wie de angst persisteerde, waren vaker werkeloos, hadden vaker

suikerziekte of een eerdere hartaanval gehad, en hadden tijdens de opname meer last van symptomen van depressie, algemene angst en vermijding. Jammer genoeg was het aantal personen in deze twee subgroepen te klein om te controleren voor mogelijke verstorende variabelen.

Al met al, zijn door deze studie met meerdere meetmomenten van cardiale angst in het jaar na een hartaanval, vier mogelijke beloopstrajecten van cardiale angst geïdentificeerd. Toekomstig onderzoek zou zich moeten richten op cardiale prognose en de effectiviteit van behandelingen op cardiale angst met name in de subgroep van patiënten met persisterende cardiale angst.

(2b) (hoe) hangt cardiale angst samen met de cardiale prognose als het gaat om nieuwe cardiale gebeurtenissen of overlijden?

In hoofdstuk 5 wordt de voorspellende invloed van cardiale angst op cardiale prognose beschreven in dezelfde groep patiënten als waarover in hoofdstuk 4 is gerapporteerd. In eerdere soortgelijke onderzoeken werd angst meteen tijdens de ziekenhuisopname of na de operatie gemeten [7]. Door tijdelijke stress ten gevolge van deze opname of operatie kan het angst niveau echter tijdelijk verhoogd zijn, terwijl lange termijn uitkomsten vooral beïnvloed worden door klachten die blijven bestaan, of pas ontwikkelen gedurende de eerste maanden na een hartaanval zoals is aangetoond voor depressieve klachten [18]. Bovendien werd in hoofdstuk 4 van dit proefschrift aangetoond dat beloopsvormen van cardiale angst met name in de eerste drie maanden na het hartaanval bepaald worden. Daarom kozen we ervoor om de voorspellende invloed van cardiale angst op cardiale prognose zowel voor angst tijdens de opname als na vier maanden erna te bestuderen.

Als maat voor cardiale prognose namen we een gecombineerd eindpunt, te weten het optreden van een nieuwe acute ziekenhuisopname voor een coronaire hartziekte of overlijden binnen een periode van ongeveer 5 jaar na de start. Dit werd geanalyseerd middels Cox-regressie-analyse, waarbij gecorrigeerd werd voor geslacht, leeftijd, ernst van de hartziekte (pompkracht van het hart en of er al eerder een hartaanval was geweest) en de mate van depressieve klachten, omdat al deze variabelen het mogelijke verband zouden kunnen beïnvloeden. De cardiale angst tijdens de ziekenhuisopname en die vier maanden erna bleken voorspellend voor het optreden van een gecombineerd eindpunt. Aanvullende analyses van de sub schalen van de cardiale angst vragenlijst lieten zien dat dit effect vooral werd veroorzaakt door vermijdingsgedrag, met name drie maanden na het ontslag. Deze resultaten impliceren dat angst en het daaraan gerelateerde gedrag (vooral vermijding van fysieke activiteit) aangepakt moet worden. Cognitieve gedragstherapie zou hierbij een goede behandelstrategie kunnen zijn.

Concluderend lijkt het dat cardiale angst na een ziekenhuisopname voor een hartaanval, en dan met name de angst-gerelateerde vermijding, een belangrijke voorspellende factor is voor de cardiale prognose, onafhankelijk van de ernst van de hartziekte en depressieve klachten.

In hoofdstuk 6 onderzochten we het verband tussen patiënt-gerapporteerde fysieke gezondheid en cardiovasculaire prognose. Patiënten uit het DePreMI cohort vulden de vragenlijst Health Complaints Scale (HCS) in op 3 en 12 maanden na het hartaanval. De cardiale angst vragenlijst (CAV) was helaas niet afgenomen in dit onderzoek en konden we dus niet gebruiken. Omdat in eerder onderzoek in hartpatiënten (Hoyer 2008) aangetoond werd dat de CAV meer samenhing met de fysieke dan met de psychische kwaliteit van leven, hoopten we dat fysieke gezondheid - in ons geval gemeten met de HCS - zou kunnen dienen als surrogaat marker voor cardiale angst. Als maat voor cardiale prognose namen we het optreden van een gecombineerd eindpunt binnen een periode van ruim 5 jaar na de start: hetzij een nieuwe acute ziekenhuisopname voor een cardiovasculaire aandoening, hetzij overlijden. Dit werd geëvalueerd met behulp van cox-regressie-analyse, waarbij gecorrigeerd werd voor geslacht, leeftijd, opleidingsniveau, ernst van de hartziekte en andere relevante somatische parameters, alsmede relevante psychiatrische klachten, in dit geval depressieve symptomen en het al dan niet hebben van een gegeneraliseerde angststoornis.

Latente klasse analyse op de HCS liet op beide tijdstippen vijf groepen zien van patiënten die respectievelijk (1) geen of weinig, (2) cardiale, (3) energie, (4) slaap en (5) gemengde gezondheidsklachten rapporteerden. Met twee meetmomenten resulteerde dat in 25 opties (25 latente transitie klassen). In tegenstelling tot wat we hadden gehoopt, leek geen deze groepen het begrip cardiale angst te vertegenwoordigen. Toch waren de resultaten interessant.

Op drie maanden na de hartaanval, bleken vooral cardiale klachten belangrijke voorspellers, terwijl gemengde gezondheidsklachten en een gebrek aan energie wel een trend maar geen statistisch significant verband lieten zien. Wat betreft het beloop van de klachten, waren nieuwe en persisterende klachten van het gemengde, cardiale en energie-type voorspellend.

Terugkijkend kunnen we stellen dat hoewel we er niet in slaagden een maat voor cardiale angst in dit DePreMi cohort te construeren, de onderzoeksresultaten wel interessant waren. Fysieke gezondheidsklachten na een hartaanval voorspellen de cardiovasculaire prognose onafhankelijk van hartziekte, depressie en angst.

Deze klachten na een hartaanval kunnen verdeeld worden in verschillende types en beloopsvormen, bestaande uit cardiale, energie, slaap, gemengde en geen tot weinig klachten. Het soort gezondheidsklachten en hun beloop zijn mogelijk van meerwaarde in het voorspellen van cardiovasculaire prognose.

(3) wat is het effect van een korte cognitieve gedragstherapie behandeling voor patiënten met niet-cardiale-pijn-op-de-borst die verondersteld worden cardiale angst te ervaren?

Hoofdstuk 7 gaat over de bevindingen van een 24-weken-durend gerandomiseerd gecontroleerd onderzoek naar het effect van cognitieve gedragstherapie in vergelijking met de gebruikelijke behandeling in volwassenen die zich op de eerste hulp presenteerden met NCPB, 8 of meer punten scoorden op een screenende vragenlijst voor depressieve en/of angstige klachten (de HADS) en vervolgens werden gediagnostiseerd met een paniekstoornis en/of depressieve stoornis. CGT bestond uit zes individuele sessies. De hoofduitkomstmaat was het globale functioneren zoals gemeten met de Clinical Global Inventory (CGI) door een onafhankelijke beoordelaar, die niet wist in welke groep de patiënten waren ingedeeld.

ANCOVA analyses naar de primaire uitkomstmaat in zowel de gehele groep als de groep patiënten die de volledige studie afmaakten toonden aan dat CGT na 24 weken superieur was aan de gebruikelijke behandeling. De uitkomsten van de secundaire maten op angst (HADS-A, STAI-T) en depressieve symptomen (HDRS) kwamen hiermee overeen, met uitzondering van de HADS-D, Fear Questionnaire en Stai-State. Ook als in de analyses rekening werd gehouden met variabelen die vooraf verschillend waren tussen de beide groepen patiënten, bleven deze bevindingen overeind. Ondanks dat cardiale angst in deze studie niet expliciet gemeten werd en replicatie van deze bevindingen in een groep patiënten met hoge cardiale angst gewenst is, ligt het voor de hand dat NCPB patiënten met een paniek en/of depressieve stoornis veel cardiale angst ervaren.

Samenvattend liet dit gerandomiseerd gecontroleerd onderzoek in NCPB patiënten die gediagnostiseerd zijn met een paniek en/of depressieve stoornis zien dat kortdurende cognitieve gedragstherapie het globaal functioneren significant verhoogt en depressieve en angstklachten vermindert.

Hoofdbevinding/Algehele conclusie

De vier onderzoeken in myocardinfarct (MI) patiënten zoals beschreven in

hoofdstukken 2-5 van dit proefschrift laten zien dat cardiale angst valide en betrouwbaar kan worden gemeten met de door patiënten in te vullen Cardiale Angst Vragenlijst, dat patiënten gedurende het jaar na een hartaanval verschillende beloopstrajecten van cardiale angst vertonen, én dat meer cardiale angst samenhangt met meer algemene angst en depressieve klachten, een slechtere kwaliteit van leven één jaar na het hartaanval en een slechtere cardiale prognose tot vijf jaar na het hartaanval. Cardiale angst is dus relevant. Of het relevanter is dan algemene angst, is in dit proefschrift niet onderzocht. Door het onderzoek in de andere groep MI patiënten (hoofdstuk 6) werd duidelijk dat het moeilijk is conclusies te trekken over cardiale angst als cardiale angst niet specifiek gemeten wordt. Tenslotte toonde het gerandomiseerd gecontroleerde interventie-onderzoek, beschreven in hoofdstuk 7 van dit proefschrift, aan dat kortdurende cognitieve gedragstherapie in patiënten met Niet-Cardiale Pijn op de Borst (NCPB) die gediagnosticeerd zijn met een paniek en/of depressieve stoornis het globaal functioneren significant verhoogt en depressieve en angstklachten vermindert. Hoewel in deze laatste studie cardiale angst niet expliciet gemeten werd, en replicatie van deze bevindingen in een groep patiënten met hoge cardiale angst wenselijk is, ligt het voor de hand dat NCPB patiënten met een paniek en/of depressieve stoornis veel cardiale angst ondervinden. Als CGT bij hen effectief is, zou je kunnen aannemen dat CGT ook behulpzaam kan zijn voor angst mét een cardiale origine, zoals cardiale angst bij MI patiënten. Dit zou verder onderzocht moeten worden.

Slot Overwegingen

Net zoals psychologen en psychiaters zich bij hun patiënten bewust moeten zijn van eventuele cardiale aandoeningen en cardiale risicofactoren, behoren cardiologen bij hun patiënten cardiale angst te onderkennen en waar nodig te (laten) behandelen.

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About the author

Maria Helena Catharina Theodora (Marleen) van Beek was born on April 30th, 1979 in Tilburg, the Netherlands. She grew up in Gilze, a small town in the west of Brabant. She graduated from high school (gymnasium) at the Sint-Odulphuslyceum in Tilburg. From 1997 to 2003 she studied medicine at Maastricht University in Maastricht. During her studies she participated in the research track. As part of her internships she worked at the department of psychiatry in Syracuse, New York, USA. In 2003 she graduated as a medical docter and started her clinical career in psychiatry at the Reinier van Arkel Groep in 's-Hertogenbosch. From 2004 to 2008 she followed her residency training in psychiatry at the department of Psychiatry at the RadboudUMC Nijmegen, the Netherlands. In 2008 she started working as a staff psychiatrist at the same department, at first in the open inpatient unit and as of 2013 until now mainly in outpatient clinic/care (mood disorders/ psychiatric and somatic co-morbidity/ old age psychiatry).

In 2008 she started the research presented in this thesis at the RadboudUMC department of psychiatry, under supervision of prof. Dr. Anne Speckens (RadboudUMC), prof. Dr. Richard Oude Voshaar (previously RadboudUMC and currently UMC Groningen) and prof. Dr. Ton van Balkom (VU/GGzinGeest). She combined these research activities with her clinical work and teaching activities as a staff psychiatrist. In January 2016 she was appointed as coordinator of the medical master education program in psychiatry and member of the examination board of the faculty of medicine. In the future she aims to extend her current research activities in the area of psychiatric and somatic co-morbidity.

List of publications

Manuscripts included in this thesis:

Chapter 2
van Beek MH, Voshaar RC, van Deelen FM, van Balkom AJ, Pop G, Speckens AE. The cardiac anxiety questionnaire: cross-validation among cardiac inpatients. *Int J Psychiatry Med* 2012; 43(4): 349-364.

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Chapter 6
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Oude Voshaar RC, van Beek MHC, Speckens AEM, Van Balkom AJLM. Scared to death! The impact of (cardiac) anxiety on vascular health. *International Psychogeriatrics* 10/2013; 25: S25-S26..

Scientific National presentations in the context of the present thesis (in Dutch):

October 6th 2016. Vergadering Landelijke Werkgroep Cardiopsychologie, Nederlands Instituut voor Psychologen, Utrecht, the Netherlands. Cardiale angst na een hartaanval.

January 20th 2016. PAO Heyendael nascholing psychiatrie, Nijmegen, the Netherlands. Als de angst je om het hart slaat.

June 18th 2015. Verpleegkundig Vizier, Nijmegen, the Netherlands. Cardiale Angst; Consequenties en mogelijkheden.

March 30th 2015. Voorjaarscongres Psychiatrie 2015 "Psychiatrie op Maat", Maastricht, the Netherlands. Subjectieve gezondheidsklachten en cardiale prognose na een hartaanval.

April 4th, 2012. Voorjaarscongres Psychiatrie 2012 "Als angst regeert", Maastricht, the Netherlands. Het beloop van cardiale angst na een acuut coronair syndroom.

April 4th 2012. Voorjaarscongres Psychiatrie 2012 "Als angst regeert", Maastricht, the Netherlands. Kortdurende cognitieve gedragstherapie (CGT) voor affectieve stoornissen met niet-cardiale pijn-op-de-borst.

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