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Psychological distress in coronary heart disease

*Risk indicators, treatment and cardiovascular
prognosis*

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Abstract

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The aims of this thesis were to: (1) explore factors associated with emotional distress; (2) investigate psychosocial stress as a risk factor for cardiovascular (CV) morbidity in patients with coronary heart disease (CHD); (3) investigate the impact of group-based stress management on psychological outcomes, and if that mediates risk of CV events; and (4) evaluate an internet-based cognitive behavioral therapy (iCBT) for emotional distress in patients with a recent myocardial infarction (MI).

In Study I, data from the national registry SWEDEHEART on 27,267 MI patients < 75 years was used. Study II was a prospective longitudinal study with 14,577 patients with stable CHD. Psychosocial stress was assessed with a questionnaire and patients were followed-up for clinical events on average 3.7 years. In Study III, a group-based stress management was evaluated in a randomized controlled trial of 362 CHD patients. Psychological outcomes (stress, somatic anxiety, depression and vital exhaustion) were assessed at five time-points over two years. Joint modelling for longitudinal and time-to-event data was used to analyze if reduction in the psychological outcomes mediated the positive effect the treatment had on later CV events. Study IV describes Study V and includes a pilot study investigating the acceptability of the intervention used. In Study V 239 MI patients were recruited to evaluate iCBT versus usual care in a randomized clinical trial.

In summary, in Study I, sociodemographic factors, previous psychiatric diagnosis and readmission for CV events were associated with incident and persistent emotional distress post-MI. In Study II, after multivariable adjustments, depressive symptoms, financial stress and living alone were all independently associated with CV death or the composite of CV death, non-fatal MI or non-fatal stroke. These results emphasize the importance of targeting psychosocial factors in order to optimize secondary prevention. In Study III, somatic anxiety was the only targeted psychological outcome affected positively by stress management, and may have in turn reduced subsequent CV events. Other mediating factors remain to be identified. Study IV indicated the intervention used in Study V was acceptable. Study V concluded that iCBT was not superior to usual care for emotional distress in post-MI patients and treatment adherence was unexpectedly low. Potential reasons for the low adherence require further exploration.

Keywords: psychological distress, myocardial infarction, coronary heart disease, depression, anxiety, stress, cognitive behavioral therapy, iCBT, stress management, cardiac rehabilitation

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Till Axel och Knut

List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

- I Norlund, F., Lissåker, C., Wallert, J., Held, C., Olsson, E.M.G. Factors associated with emotional distress in patients with myocardial infarction: Results from the SWEDEHEART registry. Submitted.
- II Hagström, E., Norlund, F., Stebbins, A., Armstrong, P.W., Chiswell, K., Granger, C.B., Lópezes-Sendón, J., Pella, D., Soffer, J., Sy, R., Wallentin, L., White, H.D., Stewart, R.A.H., Held, C., on behalf of the Stability Investigators (2017). Psychosocial stress and major cardiovascular events in patients with stable coronary heart disease. *J Intern Med*, 28(Cvd):1–10.
- III Norlund, F., Olsson, E.M.G., Pingel, R., Held, C., Svärdsudd, K., Gulliksson, M., Burell, G. (2017). Psychological mediators related to clinical outcome in cognitive behavioural therapy for coronary heart disease: A sub-analysis from the SUPRIM trial. *Eur J Prev Cardiol*, 24(9):917–25.
- IV Norlund, F., Olsson, E.M.G., Burell, G., Wallin, E., Held, C. (2015). Treatment of depression and anxiety with internet-based cognitive behavior therapy in patients with a recent myocardial infarction (U-CARE Heart): study protocol for a randomized controlled trial. *Trials*, 16(1):1–8.
- V Norlund, F., Wallin, E., Olsson, E.M.G., Wallert, J., Burell, G., von Essen, L., Held, C. Internet-based cognitive behavior therapy for symptoms of depression and anxiety among patients with a recent myocardial infarction: The U-CARE Heart randomized trial. Submitted.

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Abbreviations

CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CBT	Cognitive behavior therapy
CHD	Coronary heart disease
CI	Confidence interval
CV	Cardiovascular
ELSS	The Everyday Life Stress Scale
HADS	Hospital Anxiety and Depression Scale
HR	Hazard ratio
iCBT	Internet-based cognitive behavior therapy
MADRS-S	Montgomery-Åsberg Depression Rating Scale-Self-rating
MI	Myocardial infarction
OR	Odds ratio
PCI	Percutaneous coronary intervention
RCT	Randomized controlled trial
RIKS-HIA	The Register of Information and Knowledge about Swedish Heart Intensive care Admissions
SEPHIA	Secondary prevention after heart intensive care admission
STABILITY	Stabilization of atherosclerotic plaque by initiation of darapladib therapy
SUPRIM	The secondary prevention in Uppsala primary health care project
U-CARE	Uppsala University psychosocial care programme
WHO	World Health Organization

Introduction

Heart and mind

In 1898, William Osler, often called the father of internal medicine, described the typical patient at risk of coronary heart disease (CHD) as “a keen and ambitious man, the indicator of whose engine is always at full speed ahead.” The representation of a busy and stressed person suddenly stricken by a myocardial infarction (MI) still exists to some degree today. Research has proven Osler right in that behavior and stress matter in CHD. However, we just as often find the depressed, anxious, exhausted and abject CHD patient. One depressed patient with a recent MI described it to me as “It feels like I am in the middle of a lake and no matter how much I try to swim, I never make it to the shore.” These two patterns of psychological distress are related to increased risk of first and recurrent cardiac events. Indeed, the heart and mind are closely connected.

Since CHD is the leading cause of disability and death worldwide, many of us have direct and indirect experiences of MI. Perhaps we have also experienced the anxiety and depression that might follow an MI. Less well known is the role psychological distress plays in the development and maintenance of CHD. This thesis aims at filling the gap by addressing risk indicators of psychological distress, psychological distress in relations to disease prognosis and how patients with psychological distress can be supported.

Prevalence and pathophysiology of CHD

CHD includes stable angina, unstable angina, MI and sudden coronary death (Wong, 2014) and has become the leading cause of disability worldwide (Murray et al., 2012). CHD morbidity including chronic angina is estimated to affect up to 7% of the adult population (Roger et al., 2012). Furthermore, in Europe, 20% of all death can be attributed to CHD (Townsend et al., 2016). In Sweden, 25,700 individuals had an MI in 2016, meaning that every 20 minutes someone suffers an MI (Swedish National Board of Health and Welfare, 2017).

Coronary atherosclerosis results from a chronic inflammatory process in the coronary arterial wall and it comprises a series of complex cellular, mo-

lecular and immunological mechanisms prompted by an interplay between genetic factors and various metabolic risk factors (Nabel & Braunwald, 2012). The process starts with infiltration of low density cholesterol particles that undergo oxidation in the arterial wall, triggering an inflammatory response. The oxidized particles are then partially absorbed by macrophages which transforms them to foam cells, an important component of the atherosclerotic plaque and forming a fatty streak beneath the endothelium in the walls of the coronary arteries. The inflammation induces proliferation of smooth muscle cells that form a cap covering the developing arterial the plaque with an increasing necrotic core. This plaque may subsequently grow to partially obstruct the coronary vessel, thereby causing various degrees of impaired blood flow to the myocardium and as a result myocardial ischemia, leading to angina pectoris (Hansson, 2005; Montalescot et al., 2013; Ross, 1999).

However, stable plaques are rarely the cause of acute coronary syndromes, i.e. MI or unstable angina, which are more likely to occur as a result of a ruptured unstable plaque (Hansson, 2005). A stable plaque may change into an unstable when the core of the plaque is degraded and the covering fibrous cap becomes thinner with time and thus more prone to rupture. Once a plaque rupture occurs, a process of platelet activation starts and the coagulation cascade is activated. This leads to the formation of a thrombus, which can ultimately partially reduce the blood flow and cause ischemia, or to arterial occlusion causing irreversible necrosis of the myocardium, leading to an MI (Nabel & Braunwald, 2012).

Treatment of coronary heart disease

Acute treatment

Treatment of acute MI has changed dramatically over the last 30 years. New and more effective pharmacological drugs have developed, such as statins, ACE-inhibitors and more effective antiplatelet drugs that are often combined, i.e. double antiplatelet therapy, all leading to reductions in re-infarction rates and mortality. Also, more invasive strategies with routine angiography and revascularization either with percutaneous coronary intervention (PCI) or coronary artery by-pass graft operation (CABG) have further reduced the risk of post MI complications. These new treatments in combination with less smoking, is likely to have led to a reduction in mortality by 50% over the last 20 years (Szummer et al., 2017).

Cardiac rehabilitation and secondary prevention

After the acute phase of a coronary event, two types of treatment are needed: (1) cardiac rehabilitation (CR) to limit the negative effect of the MI and to restore maximum functionality and (2) secondary prevention to minimize the risk of new cardiac events. Many interventions serve both purposes, e.g. physical exercise and stress management. CR and secondary prevention are therefore sometimes used interchangeably. Guidelines recommend that MI patients are offered comprehensive interventions including clinical assessment, patient education, smoking cessation, exercise therapy, and psychosocial support in order to reduce risk of cardiovascular (CV) complications (Piepoli et al., 2016; Smith et al., 2011). Adherence to behavioral advice (diet, exercise, and smoking cessation) after acute coronary syndrome is associated with a markedly lower risk of recurrent CV events (Chow et al., 2010). Participation in an exercise-based CR have been associated with lower CV mortality and less hospital admissions but not to the risk of a new MI (Anderson et al., 2016). Furthermore, secondary prevention and CR has been shown to be cost-effective (Papadakis et al., 2008) and to improve quality of life (Clark, Hartling, Vandermeer, & McAlister, 2005). However, both secondary prevention (Hambræus, Tydén, & Lindahl, 2016; Vedin et al., 2012) and CR seem to be underused with poor referral and low participation rate and wide variations between countries (Kotseva et al., 2016; Martin et al., 2012).

Psychosocial factors involved in CHD

In addition to a number of lifestyle factors, including physical inactivity and smoking, several psychosocial risk factors has been identified and are included in the European guidelines for treatment of CV disease (Piepoli et al., 2016). A landmark study in showing the influence of lifestyle related risk factors, as mentioned above, as well as psychosocial factors is the large INTERHEART study (Yusuf et al., 2004). Nine modifiable risk factors were identified that jointly comprise approximately 90% of the total population attributable risk for MI. Psychosocial risks assessed in the INTERHEART were: stress (both at work and at home), financial stress, perceived control, occurrence of major life events, and depressive symptoms. Altogether they turned out to be largely associated with the risk of having an MI (population attributable risk was 33%) (Rosengren et al., 2004; Yusuf et al., 2004). In addition to the factors found in INTERHEART, low socioeconomic status, social isolation and vital exhaustion have also been identified and will be presented in more detail below.

Depression

Both diagnosed depression and depressive symptoms predict CHD in healthy populations (Rugulies, 2002; Wulsin & Singal, 2003) and worsen the prognosis in CHD patients (Barth, Schumacher, & Herrmann-Lingen, 2004; van Melle et al., 2004). In a recent meta-analysis the association between depression and CV events and mortality is attenuated if left ventricular ejection fraction (LVEF) is taken into account but still remains an independent risk factor (Meijer et al., 2013).

Depression is characterized by sadness, loss of interest or pleasure, feelings of guilt or low self-esteem, sleep disturbances, poor appetite, feelings of tiredness and impaired concentration (American Psychiatric Association, 2013). At its most severe, depression can lead to suicide. Lifetime prevalence varies widely, but in most countries the number falls within an 8–12% range (Andrade et al., 2003). In Sweden, a point prevalence of 5-8 % has been found (Dahlberg, Forsell, Damström-Thakker, & Runeson, 2007).

The first two weeks post MI, the prevalence of diagnosed depression is about 20%. The prevalence of self-reported depressive symptoms varies from 16 to 30% depending on the questionnaire and cut-offs used and whether somatic symptoms are included. Indeed, somatic symptoms used in diagnosing depression may be difficult to distinguish from symptoms secondary to medical illness or medical treatment (Thombs et al., 2006) and makes assessment of depression following an MI challenging.

Anxiety

Two recent meta-analyses have established that anxiety is an independent risk factor for incident CHD (Roest, Martens, de Jonge, & Denollet, 2010) and for adverse events following MI (Roest et al., 2010), however, different types of anxiety may have different impact on prognosis.

Symptoms of anxiety seem to be as common as symptoms of depression in CHD patients, ranging from 15-54% (Roest, Martens, Denollet, & de Jonge, 2010). However, existing prevalence rates are based on self-ratings and not diagnostic interviews. The prevalence of anxiety disorders, as opposed to symptoms, is therefore probably lower.

Even if the previous studies show that anxiety is generally associated with CHD prognosis, results are conflicting regarding the impact on prognosis, ranging from indicating that anxiety is a strong risk factor for new CV events to being protective of new events. Part of this discrepancy results might be due to the type of anxiety or anxiety diagnosis investigated.

Panic disorder is common among CHD patients and have been found to have a robust relationship to incident CHD and major adverse cardiac events, even when controlling for depression (Tully et al., 2015).

Generalized anxiety disorder (GAD) is much more prevalent in CHD patients than in the general population (Celano, Daunis, Lokko, Campbell, & Huffman, 2016). Whether GAD is good (for the prognosis) or not, in CHD patients, is not clear. Whilst some studies have demonstrated protective effects of GAD on CVD prognosis (Meyer, Buss, & Herrmann-Lingen, 2010; Parker, Hyett, Hadzi-Pavlovic, Brotchie, & Walsh, 2011), the majority of studies have found GAD to be associated with higher risk of mortality and morbidity (Frasure-Smith & Lespérance, 2008; Roest, Zuidersma, & de Jonge, 2012; Tully et al., 2015).

Post-traumatic stress disorder (PTSD) is associated with development of CHD in the general population (Edmondson, Kronish, Shaffer, Falzon, & Burg, 2013). However, in veterans with established CHD, PTSD has been found to be protective (Bradley et al., 2014; Copeland et al., 2014). The cause of this discrepancy is unknown, as well as whether this relation exists outside of the veteran population.

Specific cardiac anxiety, which is related to the fear of cardiac events, is also associated with adverse cardiac prognosis post MI, particularly for patients scoring high on anxiety-related avoidance of exercise (van Beek et al., 2016). In summary, conflicting results of risk of clinical outcomes in different anxiety studies have been found. A reason for this conflict could be the type of anxiety diagnosis. Moreover, anxiety might lead to increased appropriate help-seeking and self-caring behavior, but it can also lead to avoidant behavior patterns including less adherence to medication and avoidance of help-seeking (Benninghoven et al., 2006).

While anxiety and depression have distinct characteristics, they are moderately to strongly correlated. Indeed, it has been suggested that a general disposition toward psychological distress, including irritability, may be more important as a risk-factor in the CHD population, than the expression of any specific negative affect (Suls & Bunde, 2005; Tully, Cosh, & Baumeister, 2014).

Stress theories

Stress is a topic of everyday conversations and has been subject to a great deal of research, however, a simple unified definition is lacking (McEwen, 2005). Four stress approaches will be discussed below. First, stress can be defined as a biological adaptive response to threat. Stress makes the person (or animal) more prepared to fight, or flee from the threat. However, if the threat is impossible to handle with fight or flight, the stress response might become chronic and instead of being acute and adaptive, it becomes detrimental for health (Cannon, 1932). Hans Selye (1976) continued the research on chronic stress by describing three different phases of the stress reactions (general adaptation syndrome) where fight/flight is the first alarm phase, which is followed by the stage of resistance and stage of exhaustion if the situation is not resolved. Especially the last stage is detrimental to the health and might even

lead to death (Selye, 1976). A more recent development of these ideas is the allostatic load theory (McEwen, 2005).

Second, stress can be approached as being part of the environment; stress is thus seen as a stimulus (*a stressor*), such as death in the family or high job demands, or as a response, focusing on the psychological or physiological response to a stressor (*strain*) such as feeling nervous or having tense muscles. A third model in this framework is *transactional* stress model, where stress is a process between the stressors and the person's response to the stressor, which includes continuous adjustments and interactions (Lazarus, 1999). The transactional stress model takes into account that individuals differ in the amount of stress they experience from the same stressor.

Third, stress research in the CHD field has to a large extent focused on job-stress and built on Karasek's demand-control model defining stress as a combination of high demands and low control (Karasek, 1979). This combination seems to be detrimental for health, especially if low social support at work is added (Johnson & Hall, 1988). Central in the theory is that high control buffers the impact of job demands on strain and enhances the job satisfaction because of opportunity to engage in challenging tasks and learn new skills (Karasek, 1979).

A fourth stress model, the effort-reward imbalance model, defines work stress as perceived imbalance between the efforts spent and the rewards received at work (Siegrist, 1996). Rewards can be economical but also in terms of accomplishments, esteem, possibility for promotion and job security. An imbalance can be maintained when there is no alternative choice in the job market, for strategic reasons (e.g. expecting future gains) or when the individual has an excessive work-related over-commitment and need for approval, preventing them to accurately assess the cost-gain relationship (Siegrist, 1996; Siegrist et al., 2004).

Stress at work and at home

Most studies on stress and CHD have been performed in relation to work. A recent large meta-analysis found robust associations between exposure to job strain (i.e. high demands combined with low control) and first CHD event in a healthy population (Steptoe & Kivimäki, 2013). A meta-analysis found that imbalance in effort reward at work increases the risk of incident MI about 50% (Kivimäki et al., 2006). Furthermore, in patients with an established CHD, chronic job strain has been shown to be an independent predictor of recurrent CHD (Aboa-Eboulé et al., 2007; László, Ahnve, Hallqvist, Ahlbom, & Janszky, 2010). A low degree of effort-reward balance has also been associated with recurrent CV events, especially in women (Aboa-Eboulé et al., 2011). This association appeared to be explained by low reward rather than by high levels of effort. Moreover a heavy burden of caregiving to sick spouses, relatives or children (often grandchildren) or marital strain has been shown to

be associated with an increased risk of CHD (Eaker, Sullivan, Kelly-Hayes, D'Agostino, & Benjamin, 2007; Lee, Colditz, Berkman, & Kawachi, 2003a, 2003b; Orth-Gomér et al., 2000; Rosengren et al., 2004).

Stress assessed as strain (perceived stress) have in a meta-analysis of six studies been associated with risk of incident CHD (Richardson et al., 2012).

Vital exhaustion

Vital exhaustion refers to excessive fatigue, feelings of demoralization, and irritability (Appels, Höppener, & Mulder, 1987). Vital exhaustion symptoms overlap with depression symptoms but whether they represent different underlying constructs are not clear (Schnohr et al., 2015). Women seem more afflicted by vital exhaustion than men (Kopp, Falger, Appels, & Szedmak, 1998). Moreover, in women, high degrees of vital exhaustion seems to be associated with the double burden of both working and taking care of the household (Appels, Falger, & Schouten, 1993). Vital exhaustion has been associated with CHD and mortality even after multiple adjustments (Williams et al., 2010) and has been ranked as the strongest risk factor for men and second strongest after smoking for women. Furthermore, including vital exhaustion improved risk prediction of CHD (Schnohr et al., 2015).

Social support and marital status

Lack of social support is an important risk factor for premature death in general and the risk seems consistent across gender, length of follow-up, and world region, although initial health status has an influence (Holt-Lunstad, Smith, Baker, Harris, & Stephenson, 2015). Lower social support after CHD events affects the disease-specific quality of life outcomes, general physical functioning, and depressive symptoms more in women than men (Leifheit-Limson et al., 2010). Perceived social support seems to counteract the adverse effect of depression on CHD (Frasure-Smith et al., 2000).

Living alone, which may be considered a proxy for lack of social support, has also been linked to CV disease especially in younger patients (Udell et al., 2012). Living alone, if you are not among the eldest, might be a marker of a stressful psychosocial situation, such as isolation, with adverse neurohormonal effects on the CV system (Rozanski, Blumenthal, Davidson, Saab, & Kubzansky, 2005). Living alone might also lower the chance of seeking medical attention before lethal cardiac complication ensues (Atzema et al., 2011). Moreover, being married which might be considered a proxy for social support, has been found to be very beneficial to men (Ben-Shlomo, Smith, Shipley, & Marmot, 1993; Malyutina et al., 2004; Mendes de Leon, Appels, Otten, & Schouten, 1992) and lately also for women (Floud et al., 2014). On the other hand, marital stress can be negative for cardiac health, for

example it has been found to predict poor prognosis in women with CHD (Orth-Gomér et al., 2000).

Socioeconomic status

Socioeconomic status (SES) is one of the most investigated psychosocial factors related to CHD and usually refers to educational level, income, occupational class, wealth or a combination of these factors. Low SES is a risk of MI (Manrique-Garcia, Sidorchuk, Hallqvist, & Moradi, 2011) and mechanism for this may include exposure to environmental challenges, e.g. financial stress, insecure employment, low control over stressful life events and low self-esteem. The relation may also be reversed, in that health determines social and economic status (Marmot, Ryff, Bumpass, Shipley, & Marks, 1997).

Financial stress alone, in both a healthy population and in patients with established CHD is associated with CV morbidity and mortality (Eaker, Pinsky, & Castelli, 1992; Ferrie, Martikainen, Shipley, & Marmot, 2005; Georgiades, Janszky, Blom, László, & Ahnve, 2009; Rosengren et al., 2004). The suggested reasons for this are multiple, ranging from chronic stress due to worry or shame to not having energy and focus to take care of oneself. Generally, low education and financial stress seems to be more explicit risk factors in women than men (Prata, Ramos, Martins, Rocha-Gonçalves, & Coelho, 2014). Financial stress has a strong relation to low SES but can also occur independently.

Gender differences in psychological distress

Generally, psychosocial risk factors seem to be of greater importance for women than for men. A number of findings indicate systematic gender differences regarding psychosocial risks, in that they have more of the stress-related factors (such as depression and PTSD) that have been linked to CHD and in that they may be more vulnerable to the adverse effect of these factors on CHD, perhaps due to altered neurobiological physiology. This seems to be especially prominent in younger women (Vaccarino & Bremner, 2017).

Clusters of risks

Each of the previously mentioned psychosocial factors is a risk on its own but in reality individual risk factors often cluster in the same individual. Both women and men of lower socio-economic status and/or with chronic stress are more likely to be depressed, hostile, and socially isolated and also to have a more unhealthy lifestyle. Low SES patients are less adherent to cardiac medication regimes and are less likely to follow recommendations regarding behavior change (Albert, Glynn, Buring, & Ridker, 2006; Chandola et al.,

2008; Rozanski et al., 2005; Stringhini et al., 2010; Wamala, Mittleman, Schenck-Gustafsson, & Orth-Gomér, 1999; Whooley et al., 2008).

Clustering of psychosocial risk factors can be found also without low SES. For example it has been suggested that depression and stress together might create “the perfect storm” that increases the risk of MI (Alcantara et al., 2015).

Studies investigating several different psychosocial risk factors in a stable CHD on optimized secondary preventive therapy are lacking. Such research could evaluate the importance of psychosocial burden when traditional risk minimizing medication have been provided.

Psychological distress and emotional distress

Psychological distress is generally viewed as non-specific mental health problems and a state of emotional disturbance at different levels of severity, which reduces social functioning and daily activities (Drapeau, Marchand, & Beaulieu-Prevost, 2012). It has no official definition and has been criticized of being too vague to be useful (Ridner, 2004), but it usually includes emotional suffering characterized by symptoms of anxiety and depression (Mirowsky & Ross, 2002). In this thesis psychological distress refers to symptoms of depression and anxiety as well as various kinds of self-reported stress experiences, irritability, vital exhaustion and lack of social support. Moreover, emotional distress in this thesis, refers to symptoms of anxiety and depression.

Mechanisms connecting psychosocial distress and CHD

The mechanisms connecting psychosocial distress and CHD might involve several behavioral pathways, such as unhealthy lifestyle (smoking, alcohol, unhealthy diet, low physical activity), or low adherence to cardiac pharmacotherapy (Albert et al., 2006; Lissåker, Wallert, Olsson, & Held, 2017; Stringhini et al., 2010). It can also be biological, i.e. alterations of autonomic function (including reduced heart rate variability), in the hypothalamic–pituitary axis and in other endocrine markers, which affect endothelial function, hemostatic and inflammatory processes, and myocardial perfusion (Chandola et al., 2008).

Factors associated with depression and anxiety post MI

Who is at risk of depression or anxiety post MI? So far, most studies have focused on depression and results have been conflicting regarding which factors are associated with risk of emotional distress. Factors such as age, female gender, diabetes, LVEF, previous history of depression or anxiety and type D personality (a syndrome of negative affectivity including irritation and worry,

and social inhibition, such as low self-esteem and social isolation) have been found (Dickens et al., 2004; Doyle et al., 2015; Frasure-Smith et al., 2000; Lauzon et al., 2003; Lesperance, Frasure-Smith, & Talajic, 1996; Martens, Smith, Winter, Denollet, & Pedersen, 2008; Shiotani et al., 2002; Shiozaki et al., 2011; Spijkerman, van Den Brink, Jansen, Crijns, & Ormel, 2005; van Melle et al., 2006).

Anxiety has been much less studied, but one Dutch study found that Type D personality, depressive symptoms, negative affectivity and anxiety sensitivity, but not clinical factors such as LVEF, were associated with anxiety shortly post MI (Versteeg, Roest, & Denollet, 2015).

Studies on persistent depression and anxiety up to a year post MI are even scarcer. Young age and female gender have been found to be associated with persistent depression and/or anxiety in some studies (Dickens et al., 2004; Joergensen et al., 2016) but not in others (Kang et al., 2015; Martens et al., 2008; Versteeg et al., 2015). Moreover, a history of depression (Joergensen et al., 2016; Martens et al., 2008), frequent angina, recurrent MI (Dickens et al., 2004), type D personality (Martens et al., 2008; Versteeg et al., 2015) negative affectivity and anxiety sensitivity (Versteeg et al., 2015) are factors related to persistent depression and/or anxiety. However, these studies are frequently underpowered and have focused on personality aspects that require extensive skills and screening methods, which are rarely available in regular cardiac clinics. Furthermore, despite guidelines for managing psychosocial riskfactors, less than a third of depressed patients post MI are identified (Smolderen et al., 2011). Having better knowledge on which patients that have increased risk of psychological distress post MI enhances the chances for them to be detected and referred to appropriate care. So far, no study has investigated factors associated with incident and persistent symptoms of depression and anxiety in a large real world population with a recent MI.

Treatments of psychological distress in CHD patients

Psychological interventions may reduce the level of depression and anxiety in cardiac patients (Richards et al., 2017). Cognitive behavioral therapy (CBT) has shown the most favorable results among psychological interventions for depression in CHD patients (Dickens et al., 2013) but choice of treatment for anxiety in the CHD patient population is unknown.

Group based interventions focusing on a broader range of psychosocial risk factors seem to have beneficial results in the reduction of cardiac endpoints and mortality. These studies have all used CBT principles in a cognitive behavioral stress management program (Claesson et al., 2005; Friedman et al., 1986; Gulliksson et al., 2011; Kristina Orth-Gomér et al., 2009). Others, mostly individually based, have failed in showing a beneficial effect in reduction of CV events (Berkman et al., 2003; Frasure-Smith et al., 1997; Jones &

West, 1996). The hope of affecting cardiac prognosis through treatment of depression was particularly articulated in the well-known ENRICHD trial (Berkman et al, 2003), but that ambition failed. The CBT-intervention did however show a small but significant effect on depressive symptoms.

One of the successful group based CBT stress management programs was the SUPRIM (The secondary prevention in Uppsala primary health care project) trial (Gulliksson et al, 2011) including 362 patients with CHD. It found a large reduction of new CV event in the intervention group compared to usual care. The mechanism of this reduction is still unknown and the targeted psychological outcomes have not been investigated.

Moreover, since CBT is the most promising type of intervention for psychological distress in CHD patients it is of clinical importance to find a way of disseminating it to a larger patient population.

Internet-based cognitive behavioral therapy

Internet-based cognitive behavioral therapy (iCBT) is today an established alternative to traditional face-to-face therapy. Importantly, iCBT can be as effective as traditional CBT when it comes to reduction of anxiety and depressive symptoms in the general population (Cuijpers, Donker, van Straten, Li, & Andersson, 2010). Individual support by psychologists in iCBT is strongly recommended to achieve good compliance and results when delivering iCBT (Andersson & Cuijpers, 2009). Tailoring the intervention towards specific problems in the target population instead of using generic treatments also seems beneficial (Baasterlar, Pouwer, Cuijpers, Riper, & Snoek, 2011). In addition populations with various somatic disorders also seem to benefit from iCBT (Cuijpers, Van Straten, & Andersson, 2008).

iCBT has several logistic advantages over traditional face-to-face CBT. First, the treatment can be delivered at any preferred time and place and participants can work with the material at their own pace and review it as often as desired. Second, it is often possible to reduce the therapist time while maintaining efficacy (Cuijpers et al., 2010).

As such, iCBT has a great potential of easy and cost-effective dissemination and there has been a call within the cardiac community to integrate more e-health in the care (Cowie, Chronaki, & Vardas, 2013). Before implementation it is important to have evidence for a new type of treatment. With the exception of a promising iCBT trial in Australia with individuals at risk of cardiovascular disease and symptoms of depression (Glozier et al., 2013), iCBT has not been evaluated in CHD patients.

Concluding remarks

Even though symptoms of depression and anxiety are common post MI and known to be associated with low quality of life and higher risk of rehospitalization, no study has investigated factors associated with incident and persistent symptoms of depression and anxiety in a large real world patient population with a recent MI.

Furthermore, little is known about the CV prognosis associated with psychosocial stress in patients with established stable CHD. Methodologically, most studies to date have examined a single factor of psychosocial stress at a time in spite of the common clustering of psychosocial stressors or have used lengthy questionnaires (Rozanski et al., 2005).

The SUPRIM trial was one of the most successful secondary prevention trials in terms of improving cardiac prognosis, comparing group based stress management vs usual care in CHD patients. However, the mechanism of the effect on CHD prognosis is unknown.

iCBT seems promising for a wide range of psychological problems and populations. Still it has not been evaluated for post MI patients. Furthermore, few iCBT studies have prospectively recruited participants in a clinical setting for somatic patients, and to our knowledge, no randomized studies have been performed. This lack of externally valid studies is a limitation, and studies are needed to clarify the important questions about feasibility of iCBT for somatic patients.

Aims

Overall aim

The overarching aim of the current thesis was to evaluate prevalence and factors that might be associated with emotional distress, and the association between psychosocial factors and CV prognosis in patients with CHD. Furthermore, we aimed to increase the understanding of mediating factors explaining the positive effects of a stress management program on CV prognosis. Finally, in a randomized controlled trial we evaluated effects of an iCBT treatment to reduce symptoms of depression and anxiety in post MI patients.

Specific aims

Study I: To explore factors associated with incident emotional distress two and twelve months post- MI, respectively, and with persistent emotional distress, vs remittent emotional distress.

Study II: To investigate the association between self-reported psychosocial stress and long-term risk of clinical outcomes in patients with CHD.

Study III: To investigate the impact of a group based CBT stress management program on stress, somatic anxiety, depression and vital exhaustion, respectively, in patients with prior CHD.

Study IV: To describe the design and methods in the U-CARE Heart trial (Study V) and in addition, to evaluate the acceptability and participant activity in a pilot study.

Study V: To evaluate in a randomized controlled trial if iCBT towards depressive symptoms and anxiety vs usual care can improve self-reported symptoms of depression and anxiety in patients with a recent MI.

Methods

Design

Study I is a prospective longitudinal study with register data. Study II is a prospective longitudinal study STABILITY (Stabilization of atherosclerotic plaque by initiation of darapladib therapy), whereas Study III is an RCT (SUPRIM) as well as Study V (U-CARE Heart trial). Study IV is a study protocol and a pilot for Study V.

Table 1. Design, methods and participants and analyses of Studies I-V.

Study	Study design	Data collection	Study sample	Analyses
I.	Correlational	Questionnaire, register	27,267 patients with first time MI	Regression analysis
II.	Correlational	Questionnaire, clinical end-points	15,456 patient with stable CHD	Cox proportional hazards models
III.	RCT and observational	Questionnaire, register	362 CHD patients	Linear mixed model, Joint model for longitudinal and time-to-event data
IV.	Study protocol and pilot study (of Study V)	NA	20	NA
V.	RCT	Questionnaire	239 patient post MI with symptoms of depression and/or anxiety	Multiple linear modelling

Participants and procedures

Study I

The study was conducted using data from 27,267 and 22,911 first-time MI patients under 75 years registered with complete data at the first and second follow-up at 2 and 12 months post MI respectively in SEPHIA (The Secondary Prevention after Heart Intensive Care Admission) between 2006 and 2013.

The follow-up visits were done with interviews by a physician or nurse at outpatients visits or via telephone. Data were linked between two of the SWEDHEART registers (The Register of Information and Knowledge about Swedish Heart Intensive care Admissions [RIKS-HIA] and SEPHIA) and the National Patient Register, which records all diagnoses according to ICD-10 at inpatient and outpatient hospital visits. About 63% of the registered patients were men and mean age was 62 years.

Study II

A total of 15,828 patients were recruited in a prospective RCT (STABILITY) evaluating an Lp-PLA₂ inhibitor versus placebo, from 39 countries worldwide (White et al., 2014). All patients had stable CHD, defined as prior MI, prior coronary revascularization or multi-vessel CHD without revascularization. In addition, at least one additional indicator of CV risk such as age ≥ 60 years, diabetes mellitus requiring pharmacotherapy or high-density lipoprotein cholesterol was required. A total of 15,456 patients answered a life-style questionnaire at baseline and had a median follow-up of 3.7 years. About 80% were men and mean age was about 65 years.

Study III

Patients were included in the SUPRIM trial if under 75 years and discharged from Uppsala University Hospital after an MI, PCI or CABG between 1996 and 2002. Furthermore, they needed to be Swedish speaking, and willing to participate in the SUPRIM trial on stress treatment. There were no inclusion criteria regarding stress level. This resulted in 362 patients included, 77% men and mean age was about 62 years. The CBT stress management program (n=192) started between 0-11 months after inclusion and at the last measurement all participants had completed it. The control group was allocated to treatment as usual (n=190). The mean follow-up time for CV events and mortality was 94 months post randomization. Psychological outcomes was assessed with questionnaires every 6 month during 2 years.

Study IV and V

Eligible patients in the U-CARE Heart trial were under the age of 75 years, with a recent MI and above 7 on one or both of the two Hospital Anxiety and Depression Scale (HADS) subscales; HADS anxiety and HADS depression subscales (Zigmond & Snaith, 1983). Patients were excluded if scheduled for CABG, unable to use computer/internet/email/mobile phone, unable to read Swedish, life expectancy of less than one year, anticipated poor compliance, reporting severe depression or suicidal ideation or participating in another behavioral intervention trial.

During the 40 months recruitment period, 3928 patients were identified and screened for eligibility at 25 hospitals across Sweden one to eight weeks after their MI and then contacted by study personnel at the study center (Uppsala) 8 to 12 weeks post MI for more information. Patients were then given the opportunity to sign an informed consent and received login details via e-mail. After answering baseline questionnaires via the U-CARE portal, patients scoring above eight on any of the HADS subscales were randomized to either iCBT or usual care. Patients indicating signs of severe depression or suicidal ideation when answering the baseline assessments were excluded from the study and contacted via telephone by a psychologist and, if needed, referred to adequate treatment.

This procedure resulted in 239 (6% of the screened) patients (67% men, mean age 60 years) randomized to either therapist-guided, tailored, 14 week iCBT treatment (n=117), or treatment as usual (TAU) (n=122). Patients in the iCBT arm also had access to TAU. Almost half were included based on both HADS subscales, 11% were included based on HADS-D only and 38% were based on HADS-A only. More patients in the control group (94%) than in the treatment group (84%) completed the follow-up assessment (Pearson's $\chi^2 = 8.61$, $P < 0.01$). See Figure 1 for a study flowchart.

In Study IV, the first 20 patients in the RCT were included in an internal pilot study to investigate treatment acceptability and patient activity using two criteria; (1) at least 50% of eligible participants not meeting any exclusion criteria should accept participation in the study, and (2) at least 50% of the participants randomized to treatment should have submitted at least one homework assignment within three weeks.

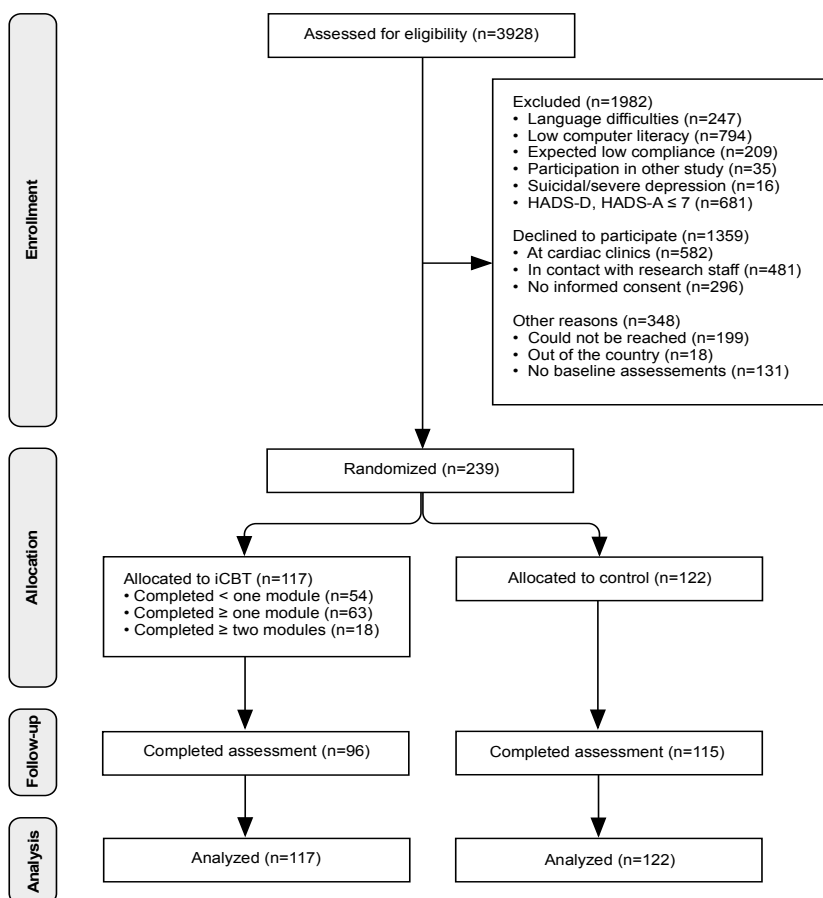


Figure 1. Flowchart of study V (U-CARE Heart)

The interventions

Study III

The stress management program was based on CBT principles and had five key components: education, self-monitoring, skills training, cognitive restructuring and spiritual development, and focused on reducing daily experiences of stress such as time urgency and hostility. It was in a group format (5-9 patients in each group), structured, following a treatment manual and lasting one year. The 20 two-hour sessions had specific theme, working material and homework assignment. Self-observation and behavioral skills training as well as relaxation training and discussion about possible values in life that are more health-beneficial were core content in the treatment. The sessions were led by specially trained psychologists, nurses and a lay welfare worker who were all supervised by the psychologist (Gunilla Burell) who designed the intervention.

Simple diaries were used for self-monitoring of behaviors, reactions and skills training. Behavioral exercises (“drills”) were introduced early and were monitored and discussed in every session. In addition to traditional CBT principles stress was approached using all theories mentioned in the introduction section. Cannon’s (1932) theory of fight/flight was the base when targeting stress reactivity, but also the general adaptation syndrome theory when targeting chronic stress. Principles from demand control theory and effort-reward theory were used when discussing stress including other people’s and own demands.

The main finding was a 41% reduction in fatal or non-fatal first recurrent CV events in the stress management group compared with the control group and a 45% reduction in recurrent MI during 94 months of follow-up. It could not be explained by differences in use of antihypertensive or lipid-lowering drugs, antidepressants or smoking habits (Gulliksson et al., 2011).

Study IV and V

The iCBT used in U-CARE Heart trial was inspired by face-to-face CBT for psychological problems and earlier iCBT-manuals. The mandatory introduction module comprised the CBT model and the patients’ description of their present concerns and goals with their participation in the treatment. Then the participants could, with help from their therapist, choose the problem area(s) on which they wanted to work. This self-tailored design is suggested to provide the participants more control while maintaining treatment quality, and can be especially useful in patient groups where comorbidity and overlapping symptoms are common (Andersson, Estling, Jakobsson, Cuijpers, & Carlbring, 2011).

There were 10 treatment modules designed specifically for the study to choose from after finishing the introduction module:

- Worry management
- Fear and avoidance after a MI
- Behavioral activation
- Problem solving
- Communication training
- Relaxation
- Cognitive restructuring
- Coping with insomnia
- Values in life
- Relapse prevention.

Each module contained two to four steps, and the participants were suggested to work with one step per week. Each step had text-based psycho-education, and one-or-two homework assignments. The iCBT treatment included a library with supplementary material and video clips of interviews conducted with post MI patients concerning coping with common psychological reactions post MI. Furthermore, a discussion forum was available where patients in the iCBT treatment had the possibility to communicate with each other.

Therapist support consisted of feedback on homework assignments and the possibility to contact the assigned personal psychologist at any time via the portal. Inactive patients were contacted via telephone after one week and if unable to reach, SMS and e-mail reminders were sent. The focus during the telephone calls were to identify and resolve barriers of treatment activity in a manner inspired by motivational interviewing.

Measurements

Study I

Outcome measures

The EuroQol-5D (EQ-5D) assesses health-related quality-of-life in five domains (EuroQol Group, 1990). Emotional distress is assessed with the following item: “Please indicate which statements best describe your own health state today”, (1) “I am not anxious or depressed”, (2) “I am anxious or depressed to some extent”, (3) “I am extremely anxious or depressed”. The second and third responses were combined to compare individuals reporting any emotional distress to those who reported none. Furthermore, persistent emotional distress was defined as patients reporting emotional distress at both

the 2 and 12 months assessments. Remittent emotional distress was defined as patients reporting emotional distress only at the 2 month assessment. The EQ-5D is considered a valid instrument in the CV patient population (Dyer, Goldsmith, Sharples, & Buxton, 2010). The EQ-5D domain on emotional distress has been validated and found to be moderately associated with the Beck Depression Inventory and Beck Anxiety Inventory (Konig et al., 2010), as well as diagnostic interviews for major depressive episodes and/or anxiety disorders (Supina, Johnson, Patten, Williams, & Maxwell, 2007). Further, it has been shown that reporting symptoms of emotional distress in the EQ-5D are more common among patients with major depression alone than those with anxiety disorders alone, but most common among those with both depression and anxiety (Supina et al., 2007).

Exposure variables

From the SWEDEHEART sub register RIKS-HIA registry data was obtained on sociodemographic and clinical factors potentially associated with emotional distress. Sociodemographic variables included age, gender, employment status (categorized into employed, retired, and other, of which the latter includes being on sick leave, unemployed or studying), and smoking (never, former smoker [quit > one month ago], or current smoker).

Medical history included diabetes, stroke, hypertension, and hyperlipidemia. Data obtained on admission to hospital included chest pain, dyspnea, Killip class, cardiac arrest and heart rate. Atrial fibrillation (AF) was estimated by electrocardiography (ECG) at discharge. LVEF was assessed during the hospitalization. Complications during hospitalization were defined as bleeding and/or cardiogenic shock under medical care. Length of hospital stay was defined as the time between dates of CCU admission and discharge. Discharge medication coverage consisted of: (1) beta blockers, (2) statins, (3) other lipid lowering drugs, and (4) angiotensin converting enzyme inhibitor or angiotensin II receptor blockers. Aspirin was not included since it was prescribed to more than 99% of the patients.

In-hospital interventions consisted of CABG, PCI, thrombolytics or no in-hospital intervention. In case a patient received first thrombolytics and then PCI, PCI was the selected intervention for that patient. Readmission was defined as any readmission due to angina, MI, heart failure, other cardiac disease, bleeding complication, or stroke within 30 days after discharge. Hospital size was based on its number of treated MIs the same year as the respective patient. Type of MI (STEMI/NSTEMI) was based on ECG at admission.

From the National Patient Register data was obtained on country of birth that was categorized into three regions: Sweden, the Nordic countries (Finland, Norway, Denmark and Iceland) and the rest of the world. Psychiatric diagnoses, given at specialized inpatient and outpatient care, within 6 months prior to the MI, obtained from the same registry, included depression and/or

anxiety (ICD-10 codes F30-39 and F40-48), substance abuse (F10-19), and schizophrenia or similar diagnosis (F20-29).

Study II

The lifestyle questionnaire completed at baseline, included questions about education, marital status, if they were living alone and several items on frequency of experiencing stress at work, at home and financial stress during the last year. Depressive symptoms were assessed by the questions “Have you felt sad, low in spirits or depressed?” and “Have you lost interest in hobbies or activities that previously gave you pleasure?” Each of the questions were scored as never/rarely, sometimes, often or always. Stress at work, home and financial stress were posed with similar alternative answers as well as questions on control at home or at work. The primary composite endpoint consisted of CV death, nonfatal MI, or nonfatal stroke. Furthermore, CV death, all-cause death, MI, stroke and hospitalization for heart failure were end-points. These were documented by the STABILITY study investigators and were settled by an independent clinical events committee (White et al., 2014).

Study III

Time urgency and hostility were assessed with The Everyday Life Stress Scale (ELSS). 20 statements about stress in daily life were ranked on a 4-degree scale (0-3) with higher points indicating a more stressful reaction (Gulliksson et al., 2007).

Anxiety was assessed with the Somatic Anxiety scale. The instrument consists of 21 items customized for the present study about bodily reactions to anxiety such as sweating, hyperventilation and headache.

Depression was assessed with The Depressive Mood Scale. The instrument consists of parts from the Hamilton Depression Scale (Hamilton, 1960) and the Beck Depression Inventory and has been validated in a study with MI patients (Anfält & Söderberg, 2010).

Vital exhaustion was assessed by Maastricht Vital Exhaustion Questionnaire (Appels et al., 1987).

Medical outcomes were obtained from National Hospital Discharge Registry and National Cause of Death Registry and included all deaths, irrespective of their cause, the first CV event (fatal or non-fatal) and the first MI (fatal or non-fatal) after baseline identified according to the International Classification of Diseases revision 8-10; for further details see Gulliksson et al (Gulliksson et al., 2011)

Study IV and V

The primary outcome was self-reported depression and anxiety assessed by

the HADS which comprises one subscale for anxiety symptoms (HADS-A) and one for depressive symptoms (HADS-D) developed for a medical population. Good internal consistency for the Swedish version has been found (Lisspers, Nygren, & Söderman, 1997). Reporting above 8 on either of the subscales has been suggested to identify possible cases of anxiety and depression among adults (Zigmond & Snaith, 1983). Furthermore, there were three secondary outcomes: (1) Depressive symptoms were assessed with Montgomery Åsberg Depression Rating Scale-Self-rating (MADRS-S) (Svanborg & Åsberg, 2001). The MADRS-S is also used to screen for severe depression and/or risk of suicide. (2) To assess another aspect of depression, passivity and avoidance, the instrument Behavioral Activation for Depression Scale-Short Form is used (Kanter, Mulick, Busch, Berlin, & Martell, 2007). (3) Cardiac anxiety is assessed by the Cardiac Anxiety Questionnaire (CAQ) (Eifert et al., 2000). CAQ measures fear of, avoidance of and focus on cardiac-related stimuli and sensations.

Statistical analyses

Study I

Logistic regression models were used in analyzing the relation between exposures and outcome. In the adjusted model all the exposure variables were included at the same time. Sensitivity analyses of the associations between exposures and outcome were performed after multiple imputation of exposure variables through mass imputation via chained equations and predictive mean matching (Buuren & Groothuis-Oudshoorn, 2011).

Study II

The relation of psychosocial variables and the clinical outcomes are analyzed with Cox proportional hazards models with the psychosocial stressors as categorical variables. Two models were used to analyze the data. The first model adjusted for randomized treatment, age and gender. The second model adjusted for model 1 and CV risk factors (previous MI, previous CABG, prior PCI, multivessel disease, renal dysfunction, polyvascular disease, systolic and diastolic blood pressures, low-density and high-density lipoprotein cholesterol, diabetes mellitus, smoking [current, former, never], body mass index, family history of CHD and years of education). Each psychosocial stress variable was fitted into the model separately. In a secondary analysis, a model fitting all psychosocial stressors into model 2 was performed.

Study III

The main parameter of interest was the fixed effect interaction term between groups and time, describing whether the patients in the two groups changed differently across the observation period. To estimate the parameters we used linear mixed models (LMM) for the continuous outcomes, with (restricted) maximum likelihood as the method of estimation. The maximum likelihood method is efficient since it uses all available observations and is independent of the dropout under the missing at random assumption (MAR) (Fitzmaurice, Laird, & Ware, 2004). To test for the inclusion of random effects, likelihood ratio tests were performed. To improve efficiency gender, age, education and previous MI were included in an adjusted regression model. All results were analyzed using an intention-to-treat approach.

To study the potential mediation effect of psychological outcomes on CV events an approach similar to Baron and Kenny was used. A psychological outcome was considered a mediator if: (a) The intervention has an effect on CV events. (b) The intervention is associated with the psychological outcome. (c) The psychological outcome is associated with CV events, while controlling for the intervention. (d) After inclusion of the psychological outcome, the hazard ratio (HR) of the intervention is smaller compared to the HR in (a). Criterion (a) was tested using Cox proportional hazards regression. Criterion (b) was tested by LMM. To test criterion (b) we used joint modelling of longitudinal responses and time-to-event data (Rizopoulos, 2012). The joint modelling approach allows for event-dependent drop-outs in a longitudinal analysis, while the longitudinal outcomes were modelled according to the previously specified LMMs. To account for death from causes other than a CV event, the time-to event data was modelled using a competing risks model with spline-approximated baseline risk function. Criterion (d) about the magnitude of the mediation, was presented on a descriptive basis and calculated as $(\text{HR for intervention in (a)} - \text{HR for intervention in (c)}) / (\text{HR for intervention in (a)} - 1)$ (Lin, Fleming, & De Gruttola, 1997).

Study IV

No statistical analyses were performed.

Study V

Multiple linear modelling was used to analyze the treatment effect on outcomes in the main analysis conducted according to intention-to-treat (ITT) principle for all outcomes. Age, gender and baseline HADS-T, were entered as covariates in order to achieve increased precision. Due to three reasons the ITT analysis was preceded with multiple imputation via chained equations and

predictive mean matching (Buuren & Groothuis-Oudshoorn, 2011). The reasons were: (1) 12% of the patients had missing values in the main outcome, (2) we could not expect values missing completely at random and (3) pre-planned analyses included multiple outcomes. Sensitivity analyses were performed with observed data and per protocol analyses were performed with data from the patients completing at least one homework assignment.

Results

Study I

Emotional distress was reported by 38% of the patients at 2-months follow up and by 33% at 12-months follow up. A previous diagnosis of depression or anxiety, female gender, being younger, born outside of the Nordic countries, current smoker and neither employed nor retired and having had a readmission due to a CV event had the strongest association with emotional distress at 2 months. A significant, albeit less strong, association, was found in being treated at large hospital, hospitalization >6 days and not having undergone PCI or CABG. Similar factors were related to emotional distress at 12 months post MI with similar strengths. Persistent emotional distress was reported by 22% of the total sample with complete data on both time-points. With the exception of previous diagnosis of depression, anxiety or substance abuse, sociodemographic variables were the only ones associated with persistent emotional distress when compared with remittent emotional distress; see Table 2.

Table 2. *Crude and adjusted odds ratios of associations of emotional distress in Study I*

	2 months post MI Emotional distress Crude OR (95% CI) N=27,267	2 months post MI Emotional distress Adjusted OR (95% CI) N=27,267	12 months post MI Emotional distress Crude OR (95% CI) N=22,911	12 months post MI Emotional distress Adjusted OR (95% CI) N=22,911	Persistent ED vs remitted ED Adjusted OR (95% CI) N=8,493
Socio-demographic factors					
Age (increase by 5 years)	0.87 (0.86, 0.88)	0.87 (0.85, 0.89)	0.89 (0.86, 0.91)	0.87 (0.85, 0.89)	0.92 (0.89, 0.96)
Female (vs Male)	2.26 (2.14, 2.39)	2.33 (2.19, 2.47)	2.22 (2.09, 2.36)	2.25 (2.11, 2.40)	1.54 (1.40, 1.70)
Employment: Retired (vs Employed)	0.88 (0.83, 0.92)	1.08 (1.01, 1.16)	0.98 (0.93, 1.04)	1.23 (1.13, 1.34)	1.38 (1.21, 1.56)
Employment: Other (vs Employed)	2.40 (2.16, 2.66)	1.77 (1.58, 1.98)	2.65 (2.35, 2.98)	2.01 (1.77, 2.27)	1.93 (1.61, 2.31)
Born Nordic country (vs Sweden)	1.16 (1.04, 1.30)	1.03 (0.92, 1.16)	1.07 (0.94, 1.20)	0.94 (0.82, 1.07)	0.95 (0.78, 1.15)
Born rest of the world (vs Sweden)	2.30 (2.12, 2.51)	1.95 (1.78, 2.13)	2.25 (2.05, 2.47)	1.94 (1.75, 2.14)	1.54 (1.33, 1.78)
Current smoker (vs never smoker)	1.58 (1.49, 1.68)	1.34 (1.25, 1.43)	1.57 (1.46, 1.68)	1.33 (1.24, 1.44)	1.15 (1.03, 1.29)
Former smoker (vs never smoker)	1.03 (0.97, 1.09)	1.10 (1.03, 1.17)	1.01 (0.94, 1.08)	1.07 (0.99, 1.14)	1.00 (0.90, 1.12)
Medical and psychiatric history					
Diabetes mellitus	1.18 (1.10, 1.27)	1.10 (1.01, 1.19)	1.22 (1.12, 1.32)	1.12 (1.02, 1.22)	1.09 (0.95, 1.25)
Hypertension	1.05 (1.00, 1.10)	1.08 (1.02, 1.14)	1.07 (1.01, 1.13)	1.08 (1.01, 1.15)	1.04 (0.95, 1.15)
Stroke	1.11 (0.98, 1.26)	1.09 (0.95, 1.24)	1.23 (1.06, 1.41)	1.16 (1.00, 1.36)	1.19 (0.94, 1.52)
Hyperlipidemia	1.12 (1.05, 1.19)	1.13 (1.05, 1.22)	1.14 (1.06, 1.22)	1.13 (1.04, 1.22)	1.08 (0.95, 1.22)
Depression & anxiety [a]	4.45 (3.79, 5.21)	3.41 (2.89, 4.03)	4.46 (3.75, 5.29)	3.46 (2.89, 4.15)	2.28 (1.80, 2.89)
Schizophrenia & similar [a,b]	1.59 (1.03, 2.46)	1.00 (0.63, 1.60)	1.82 (1.09, 3.02)	1.05 (0.61, 1.82)	1.29 (0.53, 3.16)
Substance abuse [a]	1.38 (1.27, 1.50)	1.07 (0.97, 1.18)	1.42 (1.29, 1.57)	1.12 (1.00, 1.25)	1.23 (1.04, 1.45)

Cardiac status and care					
Killip class at admission, II-IV (vs I)	1.10 (0.98, 1.23)	1.02 (0.90, 1.16)	1.09 (0.96, 1.24)	1.02 (0.88, 1.17)	1.00 (0.84, 1.19)
Chest pain at admission	0.94 (0.86, 1.03)	1.04 (0.92, 1.18)	0.95 (0.86, 1.06)	1.06 (0.92, 1.22)	1.04 (0.88, 1.24)
Dyspnea at admission	1.08 (0.94, 1.25)	0.93 (0.77, 1.14)	1.05 (0.89, 1.25)	0.93 (0.74, 1.18)	0.85 (0.64, 1.12)
Cardiac arrest at admission	0.90 (0.69, 1.17)	0.95 (0.70, 1.13)	0.98 (0.73, 1.31)	1.08 (0.77, 1.51)	0.94 (0.76, 1.18)
HR (per +10 bpm) at admission	1.03 (1.02, 1.04)	1.01 (1.00, 1.02)	1.03 (1.01, 1.04)	1.01 (0.99, 1.02)	0.99 (0.97, 1.01)
Atrial fibrillation at discharge	0.88 (0.74, 1.04)	0.97 (0.81, 1.16)	0.88 (0.72, 1.07)	0.98 (0.79, 1.20)	0.84 (0.61, 1.17)
LVEF at discharge <50% (vs ≥50%)	1.01 (0.95, 1.07)	1.01 (0.95, 1.08)	1.07 (1.00, 1.14)	1.09 (1.01, 1.16)	1.11 (0.99, 1.23)
LVEF not measured (vs ≥50%)	0.95 (0.88, 1.02)	0.99 (0.92, 1.07)	0.97 (0.90, 1.05)	1.01 (0.92, 1.09)	0.99 (0.87, 1.13)
Complication during intake [c]	1.38 (1.14, 1.68)	1.19 (0.96, 1.47)	1.36 (1.09, 1.69)	1.16 (0.91, 1.47)	1.02 (0.72, 1.44)
Teaching hospital (vs not teaching)	1.28 (1.22, 1.36)	1.15 (1.08, 1.23)	1.17 (1.10, 1.24)	1.03 (0.95, 1.11)	0.98 (0.87, 1.10)
Hospital size, medium (vs small)	1.11 (1.02, 1.20)	1.11 (1.01, 1.20)	1.02 (0.94, 1.19)	1.01 (0.92, 1.11)	0.93 (0.81, 1.08)
Hospital size, large (vs small)	1.29 (1.20, 1.39)	1.23 (1.13, 1.35)	1.18 (1.09, 1.28)	1.18 (1.07, 1.30)	1.14 (0.98, 1.32)
CABG (vs no treatment)	0.74 (0.65, 0.85)	0.78 (0.67, 0.90)	0.77 (0.66, 0.90)	0.82 (0.70, 0.97)	0.90 (0.69, 1.16)
PCI (vs no treatment)	0.81 (0.76, 0.86)	0.92 (0.86, 0.99)	0.85 (0.79, 0.91)	0.96 (0.88, 1.04)	1.07 (0.94, 1.20)
Thrombolytics (vs no treatment)	0.99 (0.73, 1.36)	1.09 (0.78, 1.53)	0.83 (0.58, 1.18)	0.88 (0.60, 1.29)	0.96 (0.56, 1.65)
Medication [d] ≤2/4 (vs 4/4)	1.21 (1.10, 1.34)	1.14 (1.02, 1.27)	1.10 (0.98, 1.23)	1.04 (0.92, 1.18)	1.19 (0.99, 1.44)
Medication [d] 3/4 (vs 4/4)	1.07 (1.02, 1.13)	1.04 (0.98, 1.10)	1.06 (1.00, 1.13)	1.04 (0.97, 1.12)	1.09 (0.98, 1.21)
Hospital stay, 3-5 days (vs 0-2 days)	1.16 (1.08, 1.25)	1.22 (1.12, 1.32)	1.00 (0.92, 1.09)	1.01 (0.93, 1.11)	0.99 (0.86, 1.14)
Hospital stay, ≥6 days (vs 0-2 days)	1.26 (1.16, 1.37)	1.35 (1.23, 1.49)	1.11 (1.01, 1.22)	1.15 (1.03, 1.28)	1.08 (0.91, 1.27)
Readmission due to cardiovascular event the first 30 days	2.17 (1.98, 2.39)	2.04 (1.85, 2.26)	1.61 (1.45, 1.79)	1.49 (1.33, 1.67)	1.03 (0.88, 1.20)

HR, heart rate; bpm, beats per minute; LVEF, left ventricular ejection fraction; CABG, Coronary Artery Bypass Grafting; PCI, Percutaneous Coronary Intervention. [a] Diagnosis within 6 months prior to MI. [b] ICD codes F20-29. [c] Bleeding and/or cardiogenic shock. [d] Medication coverage: 1) beta blockers, 2) statins, 3) other lipid lowering drugs, and 4) angiotensin converting enzyme inhibitor or angiotensin II receptor blockers.

Study II

The results of the model 2 adjusted for age, gender and CV risk factors are displayed in Table 3. Reporting depressive symptoms “feeling sad” and “lost interest” were both associated with increased risk of CV death, all-cause death and the primary composite end-point.

Table 3. *The association between psychosocial variables and outcomes*

	The primary composite end-point	Cardiovascular death	All-cause death
	HR (95% CI)	HR (95% CI)	HR (95% CI)
	Model 2	Model 2	Model 2
Feeling down	1.14 (1.06, 1.26)***	1.21 (1.09–1.34)***	1.22 (1.12, 1.32)***
Loss of interest	1.11 (1.04 1.18)**	1.16 (1.05–1.27)***	1.17 (1.08, 1.26)***
Stress			
At work	0.82 (0.69, 0.98)*	0.70 (0.53, 0.91)**	0.74 (0.60, 0.91)***
At home	1.06 (0.99, 1.14)	1.02 (0.91, 1.14)	0.99 (0.91, 1.08)
Financial	1.11 (1.04, 1.18)***	1.19 (1.08, 1.30)***	1.14 (1.06, 1.23)***
Control at work	0.96 (0.81, 1.13)	1.07 (0.83, 1.39)	1.02 (0.83, 1.26)
Control at home	0.99 (0.94, 1.04)	0.99 (0.92, 1.06)	0.99 (0.93, 1.05)
Living alone	1.28 (1.11, 1.48)***	1.68 (1.38, 2.05)***	1.48 (1.26, 1.73)***
Marital status			
Partner	0.81 (0.67, 0.97)*	0.64 (0.49, 0.82)***	0.71 (0.58, 0.87)**
Single	0.95 (0.72, 1.26)	0.83 (0.55, 1.25)	0.84 (0.60, 1.17)
Divorced	1.01 (0.78, 1.30)	1.10 (0.78, 1.56)	1.05 (0.79, 1.39)

Hazard ratio estimates and 95% CI for questions where the responses are listed never, sometimes, often and always, display a 1 unit change. Except for work-related stress which displays the association between experiencing any work-related stress to no work-related stress. Marital status HR compares reported status to widowed. Model 2: Adjusted for age, gender, treatment and CV risk factors (previous myocardial infarction, previous coronary artery bypass grafting, prior percutaneous coronary intervention, multivessel disease, renal dysfunction, poly vascular disease, systolic and diastolic blood pressures, low density and high density lipoprotein cholesterol, diabetes mellitus, smoking [current, former, never], body mass index, family history of CHD and years of education). *p<0.05, **p<0.01, ***p<0.001

Feeling stress at work sometimes, often or always, compared to never, decreased the risk of the composite end-point, CV death, and all-cause death but not MI. Financial stress was associated with higher risk of CV death, all-cause death, the composite end-point, compared to no stress. The risk was gradually increasing with the severity of the psychosocial stress factor, examples of this is seen in Figure 2 and Figure 3. There was no significant association between levels of control at work or at home and the risk of any of the outcomes.

Living alone was significantly associated with an increased risk of CV death, all-cause death and the primary composite end-point compared to not living alone. Being married/having a partner was associated with a lower risk of the composite end-point, CV death, and all-cause death compared to being

widowed. Being single or divorced, as compared to being widowed, was not associated with risk of any of the outcomes. Figure 2 below shows all the psychosocial factors in relation to CV death.

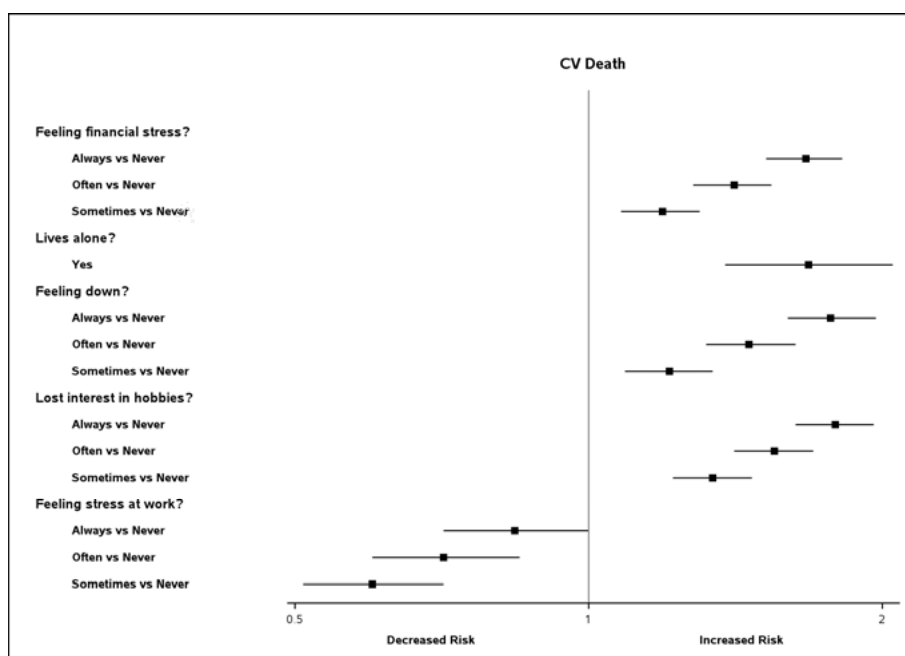


Figure 2. Association between psychosocial factors and CV death. Cox proportional hazards analysis for cardiovascular death by select psychosocial factors, adjusting for randomized treatment and clinical background characteristics.

An interaction analysis by gender was performed but no interactions were found in the fully adjusted model 2. Adding region of enrollment in the model did not change the results.

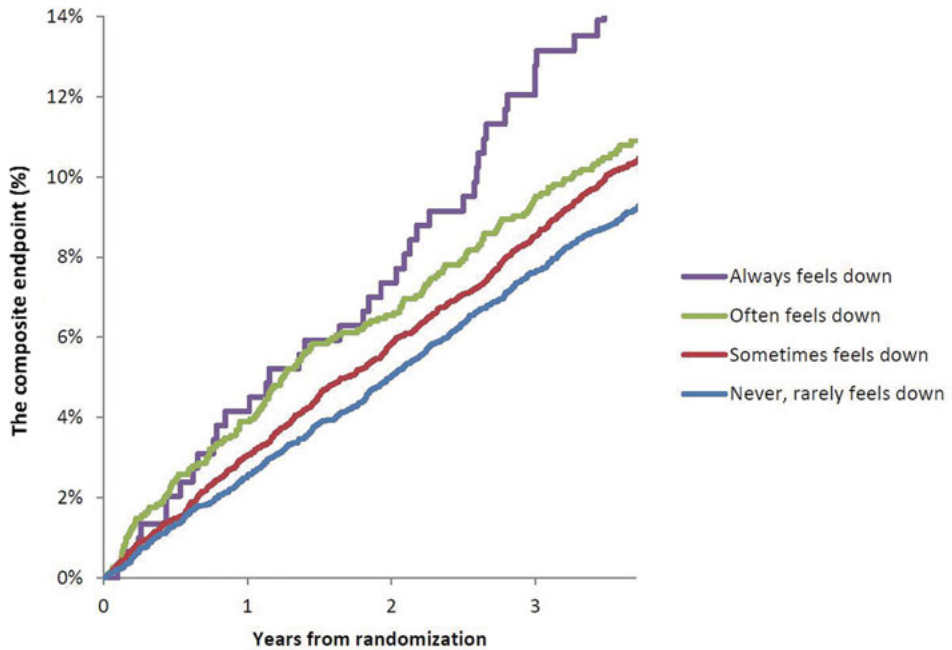


Figure 3. Cumulative incidence by outcome and depressive symptoms (feeling down) during 48 months in Study II. The outcome is a composite endpoint of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke.

Study III

The two study arms were well balanced in terms of baseline characteristics. There were no differences between the CBT stress management and control group regarding age, gender, marital status, educational level, retirement or any of the psychological outcomes. Further, there were no differences in medical history and in risk factor measurements between the groups at baseline.

Stress management had a small protective effect on somatic anxiety. The control group reported more symptoms of somatic anxiety over time while the group participating in the CBT stress management program did not change ratings over time. Furthermore, the effect size for somatic anxiety was small ($d_{corr} = 0.15$). No effects of the treatment were found in stress, vital exhaustion or depression. In both groups, participants had, on average, a decrease in stress over time. These main results are illustrated in Figure 4.

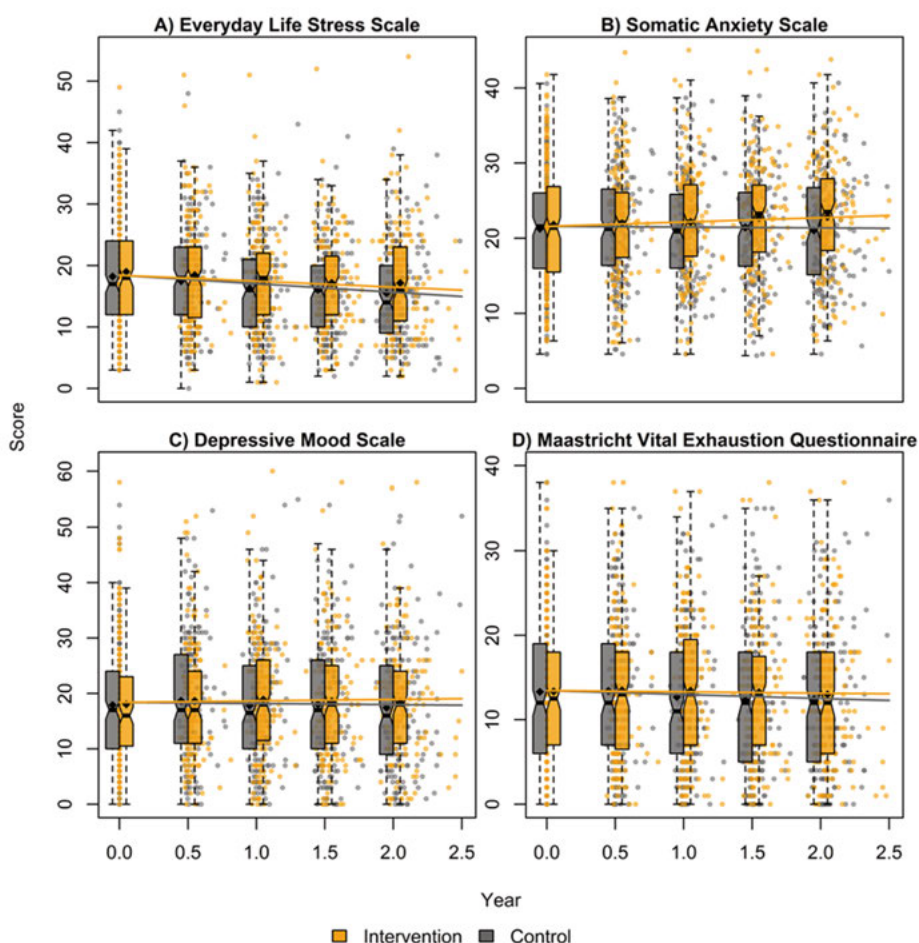


Figure 4. Development of the four outcomes over time for the study groups in Study III. The development is shown with estimated group means and 95% pointwise confidence intervals together with fitted curves from the crude linear mixed models in Study III.

Adjustments for the covariates age, gender, education and previous MI did not change the results compared to a crude model. The adjusted regression models showed female participants reported higher levels of somatic anxiety, vital exhaustion and depression. Furthermore, participants with a university education reported less somatic anxiety and older participants reported less stress reactivity. Exploratory analyses of social support and physical activity did not show any effect of treatment.

The results from the mediation analysis according to Byron and Kenny (Baron & Kenny, 1986) displayed in Table 5, showed that the intervention had

an association with lowered risk of fatal or non-fatal CV event (HR 0.64, 95% CI 0.46, 0.89). Furthermore, somatic anxiety was the only outcome fulfilling all four criteria and was thus considered a mediator. The magnitude of the mediation was 16 %. For details and exact numbers see paper III. (In the paper the value of 0.68 should be 0.70. An errata has been requested and the error has been fixed in Table 5 below)

Table 5. *Mediation analyses with estimates from Cox proportional hazards model for fatal or non-fatal cardiovascular events in Study III.*

	HR (95% CI)	Hazard ratio (95% CI) adjusted for:			
		Stress	Somatic Anxiety	Depressive mood	Vital exhaustion
Intervention	(a) 0.64** (0.46, 0.89)	0.63** (0.45, 0.88)	(d) 0.70* (0.50, 0.98)	(d) 0.68* (0.49, 0.94)	(d) 0.66* (0.47, 0.91)
Association of cardio-vascular events and psychological outcome		1.00 (0.98, 1.02)	(c) 1.04* (1.01, 1.06)	(c) 1.02* (1.01, 1.04)	(c) 1.04*** (1.02, 1.06)

CI = Confidence interval; a, c and d corresponds to three out of four mediator criterion according to Baron and Kenny (Baron & Kenny, 1986); a = the intervention has an effect on CV events; c = the psychological outcome is associated with CV events, while controlling for the intervention; d = after inclusion of the psychological outcome, the hazard ratio (HR) of the intervention is smaller compared to the HR in a. All models are adjusted for age, sex, education and previous myocardial infarction. HR for death due to other causes are not shown. *p<0.05; **p<0.01; ***p<0.001.

Study IV

The first criterion on acceptability of the study was met: 68% of the eligible patients not meeting any exclusion criteria accepted participation. The most common exclusion criterion was being unable or unwilling to use a computer or the internet (35%). Of the consenting participants that completed the baseline questionnaires, 21% had HADS scores above seven and were thus randomized. The second criterion about activity was also met: five participants (50%) submitted at least one homework assignment within three weeks from randomization. Another two participants submitted homework assignments later on. Three participants were not active at all. The first twenty patients were thus seamlessly included in the trial and the trial continued. Minor changes were made in order to improve information of the treatment portal and patient engagement.

Study V

Primary and secondary outcomes

Both the iCBT and the control group had a reduction in HADS-T over time (mean $\Delta=-5.1$; $t=12.92$, $p<0.01$). However, as seen in Table 6, the main analysis of HADS-T found no effect of treatment at follow up.

Table 6. *Study V, the U-CARE Heart trial outcomes at baseline and follow-up, change scores and treatment effect.*

	Baseline Mean (SD)	Follow-up Mean (SD)	Change	Effect β (95% CI)	<i>p</i>
HADS-T				-0.47 (-1.95 to 1.00)	0.53
iCBT	18.3 (4.9)	12.8 (5.9)	-5.5		
Control	18.6 (5.0)	13.6 (6.8)	-5.0		
HADS-A				-0.09 (-0.91 to 0.72)	0.82
iCBT	10.9 (2.4)	7.4 (3.2)	-3.5		
Control	10.8 (2.5)	7.3 (3.7)	-3.5		
HADS-D				-0.45 (-1.34 to 0.44)	0.32
iCBT	9.9 (2.2)	6.6 (3.3)	-3.3		
Control	10.3 (2.5)	8.0 (3.8)	-2.3		
MADRS-S				-0.58 (-2.20 to 1.04)	0.48
iCBT	14.8 (6.4)	12.0 (7.2)	-2.8		
Control	15.9 (7.2)	13.3 (7.6)	-2.6		
CAQ				-0.73 (-2.83 to 1.38)	0.50
iCBT	26.1 (10.3)	21.5 (10.2)	-5.4		
Control	25.3 (10.8)	22.0 (11.4)	-3.3		
BADS-SF				-0.50 (-2.31 to 1.30)	0.58
iCBT	21.2 (6.1)	21.4 (6.9)	0.2		
Control	21.4 (7.7)	21.6 (7.2)	0.2		

Mean, SD and Change are calculated from observed data. Effect estimates (β) are pooled adjusted coefficients for treatment (iCBT) versus Control (TAU) on follow-up outcomes adjusted for sex, age, and baseline levels of the respective outcomes after multiple imputation. BADS-SF indicates the Behavioral Activation for Depression Scale-Short Form; CAQ, Cardiac Anxiety Questionnaire; HADS-T, Hospital Anxiety and Depression Scale total score; HADS-D, Hospital Anxiety and Depression Scale depression subscale; HADS-A, Hospital Anxiety and Depression Scale anxiety subscale; MADRS-S, The Montgomery-Asberg Depression Rating Scale-Self Rated; CI, Confidence Interval; SD, Standard deviation

Furthermore, the main analysis showed that men scored lower on HADS-T compared to women at follow-up ($\beta=-2.04$ [95% CI = -3.60, -0.47], $p=0.01$), and there was a borderline significant reduction in HADS-T per unit increase in age ($\beta=-0.08$ [95% CI, -0.16, 0.01], $p=0.09$) at follow-up. There was no interaction between treatment and sex, or treatment and age, on HADS-T (p

for both >0.19). Robustly, separate exploratory analyses showed no effect of treatment on either HADS-A or -D subscales.

Two types of sensitivity analyses were performed; PP analysis and observed data analysis. Results from these did not differ from the main ITT analysis (PP, $\beta=-0.87$ [95% CI, -2.47, 0.72], $p=0.28$; observed data, $\beta=-0.55$ [95% CI, -2.04, 0.93] $p=0.46$) Analysis of the secondary outcomes of MADRS, CAQ or BADS-SF with multiple linear models did not show any effect of treatment either.

Adherence

Low treatment adherence was observed. About half of the patients completed the introductory module and 15 % completed additional modules. According to an earlier suggestion of a definition of adherence to tailored treatment (Păsărelu, Andersson, Bergman Nordgren, & Dobrea, 2017) only 1% completed the recommended number of 14 steps within the 14 weeks treatment period. Furthermore, there was no association between number of completed homework and change in HADS-T at follow-up ($r_s=0.07$, $p=0.53$).

Discussion

Summary of main findings

The aim in Study I was to explore which factors were associated with emotional distress post MI. We found that previous diagnosis of depression and/or anxiety, sociodemographic variables and readmission due to CV events were most strongly associated with symptoms of depression and anxiety 2 and 12 months post MI. Persistent, in comparison to remittent, emotional distress was even more strongly associated with sociodemographic factors and previous depression and anxiety.

The aim in Study II was to assess the association between psychosocial factors and clinical outcomes, especially ischemic events. Findings show that feeling down, loss of interest, living alone and financial stress were all associated with risk of a primary composite end-point, CV death as well as all-cause death. Moreover, higher exposure was associated with worse prognosis, when controlling for other traditional risk factors. In contrast, and somewhat unexpected, stress at work was found to be associated with lower risk of the primary composite end-point, all-cause death as well as CV death.

The aim in Study III was to investigate the impact of a group based CBT stress management program on stress, somatic anxiety, depression and vital exhaustion in patients with a prior CHD. Results from this study revealed that only somatic anxiety, but not stress, depression or vital exhaustion, was affected by the group based stress management ($d_{corr} = 0.15$). Furthermore, somatic anxiety had a small mediating effect on the stress management's positive effect on CV events.

The aim in Study IV was to describe the aims and design of Study V, and to evaluate the feasibility and acceptability of the intervention and study procedures in a pilot study. These were found to be overall acceptable and the pilot participants were thus seamlessly included in the main RCT. Minor adjustments were made in order to improve user-friendliness.

Finally, in Study V the aim was to evaluate the effects of an iCBT intervention targeting depressive and anxiety symptoms on patients with a recent MI, recruited from routine cardiac care. Findings showed that iCBT was not more effective than treatment as usual in reducing symptoms of anxiety and depression with both groups showing significant reductions in emotional distress from pre-to post treatment. iCBT treatment adherence was low.

Who is at risk of psychological distress post MI?

In Study I, previous depression or anxiety had the strongest association with incident distress among the investigated variables and had an even stronger association with persistent emotional distress post-MI. Indeed, these findings are in agreement with previous studies of MI patients showing that previous depression and anxiety is a risk indicator for emotional distress post MI (Dickens et al., 2004; Martens et al., 2008; Spijkerman et al., 2005). Generally, the risk of a depressive episode is much larger if you had a prior one. About 80% of those who experience two episodes will have another episode again, and the average is up to nine episodes in a life time (Kessler, Zhao, Blazer, & Swartz, 1997). Underlying mechanisms are unknown but it has been suggested that either depressive episodes increase the vulnerability for new depressive episodes (the scar theory), or persons at high risk of multiple episodes already had the crucial characteristics making them prone to depression even before their first episode. A review by Burcusa & Iacono (Burcusa & Iacono, 2007) argues that pathways to recurrent depression consist of underlying vulnerability, largely genetic in nature, that predisposes not only recurrent depressive episodes, but also to psychosocial risk factors that frequently coincide with recurrent depression. Given the age of the typical (depressed) CHD patients, it is likely that we are dealing with a recurrent episode of depression.

In Study I, women had a higher risk of having emotional distress post MI than men but in the general CHD literature results are conflicting, perhaps due to underpowered studies (Martens et al., 2008; Spijkerman et al., 2005; van Melle et al., 2006). In line with Study I, population studies worldwide find major depression to be about 1.7 times as common in women as in men, although the reasons for this are unclear. Suggested contributing factors have been genetics, hormonal, psychological risk factors and inequality between the genders, thus lower degree of perceived and real life control in women (Albert, 2015; Kuehner, 2003). However, the masked depression framework proposes that although men are reluctant to report (for men) socially unacceptable symptoms, like being sad or vulnerable, they might still experience psychological distress. The psychological distress is then rather expressed as anger, self-destructive behavior, risk-taking and self-distraction such as gambling, substance abuse or workaholism (Diamond, 2005). Including these alternative symptoms of distress when assessing prevalence of depressive symptoms, eliminates the gender disparities in prevalence of depression (Martin, Neighbors, & Griffith, 2013).

Study I explored a large range of possible predictive factors. Only a few medically related factors were associated with emotional distress including having a history of hypertension, hyperlipidemia or diabetes. Readmission due to CV event increased the risk of emotional distress later more than the other medical variables. Readmission due to CV events might be considered a stressor that elicits emotional distress. However, conversely, individuals with

emotional distress are more prone to seek help and, as such, readmission can be a consequence of experiencing distress. The possibility of an unknown confounder that is associated with both readmission and emotional distress must also be considered when interpreting the results. Furthermore, some of the factors aiming at measuring cardiac function such as LVEF are not stable but may improve during the first weeks post MI and moreover, some data were lacking (for example physical capacity, severity of angina or arrhythmias) which may have affected the results.

Apart from specific medical variables, the other factors that were shown to predict distress among MI patients are established risk factors for persistent distress in the general population, for example smoking, being born abroad and not being, employed nor retired and being a smoker. However, even if these factors are not unique to MI patients it is important to be aware of these vulnerable groups in cardiac care in order to identify patients at risk of emotional distress post MI.

Psychosocial factors and the relation to CV prognosis

Depressive symptoms and stress

Our findings of increased risk of CV outcomes and all-cause death in those reporting depressive symptoms support conclusions from several previous studies using more sophisticated methods to assess depression however with smaller samples (Frasure-Smith & Lespérance, 2008; Whooley et al., 2008). Findings from Study II showed that stress was inversely associated with CV risk. This finding was unexpected given previous studies showing stress at work to be a CV risk factor (Aboa-Eboulé et al., 2007; Aboa-Éboulé et al., 2011; László, Ahnve, Hallqvist, Ahlbom, & Janszky, 2010; Rosengren et al., 2004). One possible explanation to the conflicting findings is that participants in Study II were asked an open question about experiencing stress, with stress not being operationalized, leaving it open to personal interpretation, whereas in other studies it has been defined as irritation, anxiety or sleeping problems due to stress (Richardson et al., 2012; Rosengren et al., 2004). As such, in Study II, the report of job stress may be a proxy for feeling needed, being someone with social and professional significance and being engaged in meaningful activities, which are factors that have been shown to be beneficial to health (Britton, Shipley, & Horton, 2010). Another possible explanation for the negative association between stress and CV events in Study II is that the included participants might be less negatively affected by stress than non-participants considering they are willing to take on the commitment of participating in a study. The association between low reported work stress and higher risk of clinical outcome may also be due to that patients avoid stressful commitments because of their more severe cardiac condition.

Furthermore, the assessment of stress in this study only takes the stressor into account and not the strain. Most other studies finding a relation between stress and worsened CV prognosis or mortality have assessed stress defined as high demands and low control. This definition was not used in the current study.

No associations between stress at home and risk of any clinical outcomes were found. Comparisons with other studies are difficult since unspecified stress at home has not been frequently studied. Most other studies finding increased CV risk associated with stress at home have asked (women) about specific types of stress, such as care-giving burden (Lee et al., 2003a, 2003b; Orth-Gomér et al., 2000).

The finding of an increased risk of all-cause death and CV events in patients reporting financial stress are in accordance with findings from other studies (Eaker et al., 1992; Ferrie et al., 2005; Georgiades et al., 2009; Rosengren et al., 2004). The relation between financial stress and risk of CV events can have several reasons such as feelings of inferiority and shame which itself can be a powerful source of chronic stress and in turn affect the risk of negative CV outcomes (Wilkinson, 2002). Furthermore, financial stress might be preoccupying and lead to less attention and energy to focus on healthy behaviors (Carlsson et al., 2014). Probably there is no such thing as positive financial stress.

Social support

Being married and not living alone was associated with lower risk of CV death and all-cause death in Study II, which is in accordance with other studies (Floud et al., 2014; Udell et al., 2012). Living alone, if you are not elderly (younger than 80 years), might be a marker of a more stressful psychosocial situation, such as isolation with adverse neurohormonal effects on the CV system and larger impact on health behaviors compared to elderly (Udell et al., 2012, Rozanski et al., 2005). Further, living alone may be a proxy for low social support which is a known buffer against stress. Moreover, individuals living alone may be less likely to seek medical attention in case of severe disease (Atzema et al., 2011).

No significant associations between sense of control and clinical outcomes were found. One single question might not be sensitive enough to assess control. INTERHEART measured locus of control (which is another concept of control) with six questions and found it to be associated with having an MI. Findings from studies testing Karasek's model of demand control theory outside of the cardiac field has been inconsistent which might be due to the variation in instruments used (Kain & Jex, 2010).

Effect of group based stress management

Results from Study III indicate that somatic anxiety mediates the beneficial effect of stress management in reducing new CV events. This is interesting given previous research pointing to the importance of anxiety symptoms for CHD risk and prognosis. Two recent meta-analyses concluded that anxiety is an independent risk factor for both incident CHD and mortality in healthy populations, as well as an independent risk factor for adverse events following an MI (Roest et al., 2010; Roest et al., 2010). However, the nature of the relationship between anxiety and CV events is still unclear with a reversed relationship needed to be considered, where anxiety is only a signal of subclinical phase of a CV event.

Surprisingly none of the other targeted psychological outcomes were affected by the stress management treatment. An important factor when interpreting this result is that patients in Study III were not recruited based on specific criteria regarding levels of psychological distress. Their stress, depression and vital exhaustion levels were comparable to the general population (Gulliksson et al., 2007) which resulted in low baseline levels, leaving small room for improvement (Bower et al., 2013).

Group based psychological treatments for CHD patients seem more successful in reducing CV events than individual treatments, which strengthens the hypothesis that social support is an important part of the treatment. Social support and social isolation are well-known risk factors in both healthy individuals and as prognostic makers in patients with coronary heart disease (Rosengren et al., 2004; Steptoe & Kivimäki, 2013). Indeed, The CBT stress management group in the present study ran for an entire year and a clinical observation was that participants often bonded strongly with each other. In addition, a large part of the program content was about relationships to others, both directly through exercises in strengthening relations and indirectly, such as through anger management.

Reduction in somatic anxiety is presumably one of several factors, some not measured, or measured with insensitive questionnaires, which may explain the protective effect of the group based CBT stress management on CV events. Other mechanism are unknown. One can speculate that mediating factors of reduced CV events could be the aforementioned peer support from the group, but also better adherence to medication, more self-caring behaviors including physical activity, greater self-efficacy, health literacy and greater social skills. One recent study on approximately 1000 patients post PCI showed that most patients (67%) perceived they were cured, and 38% reported need to change their lifestyle (Perk et al., 2015). Perhaps the group stress management improved patients' understanding of the disease.

Internet-based psychological treatment for MI

In Study IV, the two pre-specified criteria of acceptability and activity were met, and thus the participants were included in the main study. However, the pilot indicated challenges both in recruitment and participant engagement with engagement being lower than expected. In response to the low engagement, Minor changes were made in the structure of the introduction module in the iCBT intervention to improve information and patient engagement. Following the pilot study, a crude estimation of the acceptability of the intervention and study procedures for the planned RCT was made. Although low adherence was identified as a concern in the pilot phase, adherence was assessed as sufficient to continue with the RCT. However, in hindsight, the low adherence would have needed to be further explored as it emerged as a significant problem in the RCT.

In Study V, 6% of the screened patients were randomized. The weighted prevalence of patients scoring >7 on HADS in one review (Thombs et al., 2006) was 16%. If considering the rather large proportion of patients not eligible due to low computer literacy and language difficulties, the inclusion of 6% might be considered rather high. Compared to other CBT studies in the CV field the recruitment rate in this study is the largest (Glozier et al., 2013; Lundgren et al., 2015).

Despite findings that face-to-face CBT is successful for CHD patients and that iCBT is promising for emotional distress and disease-related physical outcomes in various somatic patient populations (Dickens et al., 2013; van Beugen et al., 2014), the U-CARE trial was not successful in reducing symptoms of depression and anxiety. Possible explanations are low adherence and significant spontaneous improvement in the control group. The level of participant engagement is a recognized concern in iCBT, high attrition and low adherence can be a problem and the reason for this is not well understood (Christensen et al., 2009; Kelders, Kok, Ossebaard, & van Gemert-Pijnen, 2012) and patient motivation is considered the most important factor for engagement (Bendelin et al., 2011).

In the U-CARE trial, low adherence might be related to the recruitment method. Most iCBT studies with positive results are efficacy studies based on self-referral, in contrast to the U-CARE Heart study where patients were recruited in a routine care setting using screening methods. Being introduced to the study by a cardiac nurse at the same clinic where the MI was treated might positively influence a patient's willingness as well as motivation, to accept participation. Many patients expressed that their strongest argument for participating in the treatment was to assist in research rather than seeking help for their emotional distress. Furthermore, lower treatment adherence has been found in effectiveness studies on primary care samples which is more similar to the recruitment method in Study V than trials using self-referral (Allen et al., 2016; Newby et al., 2013).

The characteristics of the iCBT program might have influenced treatment adherence as well. Although it was developed in consultation with patients with

personal experience of psychological distress post MI, in retrospect it could be claimed that the U-CARE Heart trial was launched somewhat prematurely. It probably would have been useful to even more carefully follow the guidelines for development and evaluation of complex interventions as outlined by the British Medical Research Council (Craig et al., 2008). They stress the importance of testing the feasibility of the intervention and planned procedures before starting an RCT aiming at evaluating the efficacy of an intervention. This was partly done, but more concentrated efforts could have been made in the developmental phase to test the acceptability of the treatment content and delivery. Efforts were made to tailor the content to the MI population, including avoidance of psychiatric terms and including MI-relevant examples in the texts. However, this could probably have been done more systematically and to a greater extent. Moreover, the content and design of the intervention might not have been adjusted enough to the end-user needs, e.g. in terms of relevance and workload. Indeed, treatment burden and failure to tailor content adequately are associated with negative iCBT user experience (Knowles et al., 2015). Developing an effective and user-friendly iCBT is complicated and more knowledge on what is feasible for this group is needed.

The patients' characteristics need to be considered in relation to the low adherence in this study. The mean age of about 60 years in Study V was >10 years lower than the average MI population, but higher compared to other iCBT studies of patients with depression and anxiety (Hedman et al., 2014; Lindner, Nyström, Hassmén, Andersson, & Carlbring, 2015; Newby et al., 2013). Older age is correlated with lower computer literacy (Crabb et al., 2012). It is possible that patients experiencing technological difficulties were less active in the treatment. Furthermore, the level of education was somewhat lower compared to other iCBT studies (Hedman et al., 2014; Lindner et al., 2015; Newby et al., 2013), another factor that has been related to low adherence to psychological treatment (Christensen et al., 2009).

Both groups reported improved psychological well-being over time which might be explained by regression to the mean. It could also be due to that the control group accessed to other professional support for psychological distress in primary or cardiac care.

Methodological considerations

Design

Studies I and II were observational studies, and their designs thus preclude firm conclusions regarding causality. Moreover, even if multivariable adjustments were performed, residual confounding from unknown or unmeasured factors cannot be excluded. For example, in Study I there is a lack of socioeconomic status variables, however, occupational status which is a factor that

may affect both depression and anxiety was included. Furthermore, no factors assessing psychological vulnerability as risk indicators of symptoms of depression and anxiety, such as personality, anxiety sensitivity and previous negative life events, were considered, yet they have been identified as perhaps the most important factors for depression and anxiety post MI (Doyle, McGee, Conroy, & Delaney, 2011; Martens et al., 2008; Versteeg et al., 2015). On the other hand, all factors used in this study are more readily available for nurses and physicians in cardiac care, while assessing psychological vulnerability requires special competence and additional resources. The main strengths in Study I is the large sizes of the SWEDEHEART cohorts, the internationally unique good coverage of patients and the fact that data are collected prospectively in routine health care settings, which contributes to the robust generalizability of the results. In the exploratory design in Study I, a large range of factors were investigated. This first exploratory step prepares future studies to investigate causal relationships.

The main strength of the design of Study II, is that it is prospective and has a large sample size making it well powered.

Study III and V were RCTs, which generally allows for causal inferences regarding the effect of an intervention and the highly structured format enhances treatment integrity. A limitation in Study III was that the psychological assessments were timed with inclusion in the study and not with the onset of randomized treatment, which could mean a delay of treatment of up to a year after the first assessment. The timing of the assessments makes difficult to evaluate what is an effect of the treatment and what is an effect of passage of time.

In Study V, the initial cut-off >10 in any of the HADS subscales as an inclusion criterion was lowered early in the study to >7 in order to increase recruitment rate. Similar to Study III that had no inclusion criteria related to psychological distress, this leaves less room for improvement, making it less likely to detect a treatment effect. Furthermore, patients experiencing a low level of emotional distress might also have a low perceived need for psychological help and be less motivated to stay active in the treatment. Floor effects are a general problem in trials on psychological distress in somatic groups (Linden & Satin, 2007). One could question whether it is appropriate to treat patients with as low as 8 on one of the HADS subscales, especially given the large proportion of spontaneous readmission of psychological distress post MI. However, not all patients have remitting symptoms and not only diagnosed depression is related to impaired CV prognosis (Meijer et al., 2011).

Furthermore, treatment as usual was the control to the iCBT intervention. This was chosen since iCBT has never been evaluated in this patient population before, and the question was what it could add to already existing cardiac rehabilitation. However, the control group might have been affected by the Hawthorn effect (Cambell, 1995), suggesting that inclusion in a study might change participants' behavior. The mere screening of psychological distress

before allocation might have led to control group patients modifying their behavior and perspective, as well as their physicians' and nurses' behavior.

Measurement

Both in Study I and II crude measures of psychosocial stress were used. In Study I, emotional distress was not assessed with structured diagnostic interviewing or an established questionnaire. On the other hand, the question from EQ-5D pertaining anxiety and depression has been validated against established instruments with good results (Dyer et al., 2010; König et al., 2010). In addition, not only diagnosis but also sub-diagnostic symptoms of depression and anxiety are associated with a lower quality of life and risk of subsequent cardiac events and is therefore important to detect (Kaptein, de Jonge, van den Brink, & Korf, 2006; Moser et al., 2011).

In Study II, perceived work stress was not predefined as negative stress, and only assessed with one single item which may be too blunt. Detrimental job strain have been found when assessed as a quite complex concept, including job demands, decision latitude, perceived locus of control and amount of job hours (Steptoe & Kivimäki, 2013) and the single question included in this study could, of course, not capture the entire concept. The same applies for the assessment of stress at home, perceived control at home and at work which may explain the lack of association between these psychosocial stressors and the risk of CV events in Study II (Kivimäki et al., 2012; Rosengren et al., 2004). On the other hand, using simple questions enabled us to evaluate a very large population, which would have been difficult using more complex questionnaires requiring more time and competence. Additionally, the great advantage with using simple questions instead of lengthy questionnaires is the facilitation in implementation of assessment in regular care.

In Study III we did not succeed in identifying processes linking the intervention to the positive effect on cardiac outcomes. The stress measurement (ELSS) focuses on frequencies of stress reactivity (strain), but does not take the intensity or duration of the reactivity into account, or increased level of control in daily life due to better problem solving skills for example. On the other hand, the ELSS has been sensitive to change in other stress management programs (Blom et al., 2009; Burell & Granlund, 2002; Claesson et al., 2005). Furthermore, it should be noted that two of the four measurements were especially designed for this study, the Depression scale and the Somatic Anxiety Scale. It is thus not known how sensitive to change they are and the Somatic Anxiety Scale has not been validated. As somatic anxiety was identified as mediating factor, future studies should explore the validity of the measure and whether certain items capture aspects that seem especially important for explaining the relationship between stress management and cardiac outcomes.

In Study V the HADS total score was the main outcome. HADS has been criticized as a screener for distress due to inconsistent findings regarding its factor structure (Coyne & van Sonderen, 2012). However, it is widely used including the cut-off of above 7, and is considered a powerful instrument in predicting mortality in CHD patients (Doyle, Cosco, & Conroy, 2012).

Sample size and statistical analyses

In Study I, no formal power calculations were made since it was an exploratory analysis. In Study II, the sample size calculation was based on assumptions of a pre-specified effect on risk reduction of CV events by the study drug, and not primarily on associations between psychological variables and outcomes. However, the large sample sizes in Study I and II allowed for precise statistical modeling, and sufficient power to analyze a wide range of exposures. In Study III the power calculation was based on a pre-specified effect on a 5% risk reduction of recurrent CV events and not on psychological outcomes. However, the sample size in the study is enough to detect a small effect size of 0.2.

The sample size in Study V is large enough to detect a medium effect size ($d = 0.5$) but not a small size ($d = 0.3$) which was planned from the beginning.

The linear mixed model used in Study III are suitable in a longitudinal data set. The method is efficient since it uses all available observations and is independent of the dropout under the assumption of missing at random.

Generalizability

In Study I the data were collected in a setting of routine health care, in a national registry with a high-quality population database with high nationwide coverage of >90% of all MIs in Sweden. This helps reducing problems with selection bias and provides high generalizability. Registry data from almost an entire country is rare. Of course, this study reflects Swedish circumstances but it confirms similar findings from other countries. Moreover, Study I is based on self-reported symptoms of psychological distress and it is unknown if it is comparable with diagnosed depression or anxiety.

Study II was a global RCT including 39 countries and patients were recruited from all continents in the world. However, generalizability may be limited due to the underrepresentation of certain populations, for example ethnic minorities and lower socioeconomic groups often found in RCTs. Further, given the possibility that women, ethnic minorities and patients with low SES are underrepresented, and psychosocial stressors are more common within these groups, as well as clinical outcomes, the associated risk may be underestimated.

In Study III, patients were consecutively recruited at one cardiac clinic (Uppsala) with few exclusion criteria. The patients with most severe CHD

were not included since patients needed to be healthy enough to be referred to primary care one year post cardiac event. This aspect must be considered when assessing the generalizability of the findings.

In Study V, patients were recruited from 25 hospitals in both rural and urban areas in Sweden which improves the generalizability to an implementation of iCBT in cardiac clinics more than if the patients would have been self-referred.

All studies in this thesis, with the exception of Study II had an inclusion criteria of being under the age of 75, despite the fact that the proportion of elderly is increasing both in the community and in the CHD population, which limits the generalizability. Further, there is an overrepresentation of men compared to female in all studies however samples mirror the proportions of men and women with MI aged 60-65 years.

Ethical consideration

All participants in Study II and V provided written informed consent, and in Study III verbal informed consent was obtained, according to the standard requirement at the time. In Study I all participants, according to Swedish law, must be informed that they are registered in SWEDEHEART and that they have a right to delete their data from the register at any time. This has been very rarely used. All the studies have applied for, and were granted ethical approval.

A design where one group does not receive active treatment has been criticized from an ethical point of view as the design may involve withholding treatment from participants (Schwartz, Chesney, Irvine, & Keefe, 1997). However, since there are no prior studies of iCBT for MI patients it could be argued that it was important to obtain a controlled evaluation of the effect of participation in an intensive and time-consuming intervention. Informed consent is one way to approach this problem (Hart, 2001).

Conclusions

- Sociodemographic factors (younger age, born outside of Nordic countries, female, smoker, neither employed; nor retired), previous diagnosis of depression and anxiety and readmission for CV events were associated with incident and persistent emotional distress post MI.
- Depressive symptoms, financial stress and living alone were all independently associated with CV death or the composite of CV death, non-fatal MI or non-fatal stroke. These results emphasize the importance of targeting psychosocial factors in order to optimize secondary prevention.

- Somatic anxiety was the only targeted psychological outcome affected positively by stress management and that might in turn have had a reducing effect on CV events. Other mediating factors remain to be identified.
- Group based CBT stress management had a significant effect on somatic anxiety which in turn partly mediated the effect the stress management had on cardiac events. Stress management did not have an effect on other psychological outcomes.
- Recruitment and treatment adherence in the planned U-CARE Heart trial evaluating iCBT to reduce symptoms of anxiety and depression among MI patients were deemed feasible and acceptable in an internal pilot study.
- iCBT was not superior to usual care for symptoms of depression and anxiety in patients with a recent MI and treatment adherence was unexpectedly low. Potential reasons for these findings need to be further explored.

Clinical implications

The studies included in the current thesis suggest a range of clinical implications discussed below.

Patients that are born outside of the Nordic countries, female, smokers, younger, neither employed, nor retired, with a history of depression or anxiety diagnoses and a readmission due to CV events are at increased risk of emotional distress post MI, both in the short term and, more importantly, even stronger risk of persistent distress (both 2 months and 12 months). Taking these factors into account may improve identification of high risk patients who need further screening and subsequently, specific treatment. Furthermore, it provides an answer to patients with symptoms of depression and anxiety who asks themselves (and their psychologist), *“How come I feel so bad although it was only a small myocardial infarction?”* It seems like the size of the infarction does not matter, other things are more important!

Results from Study II confirms and expands previous results in other CHD populations that patients with psychosocial stress despite optimized medical secondary prevention, have a higher risk of CV events and death. These patients need to be better identified and may require special attention and support in order to avoid readmissions and premature death.

Regarding the evaluation of the target psychological outcomes in the stress management intervention in Study III, the only improvement was a small reduction in somatic anxiety, and this seems to reduce the risk of new CV events. Nevertheless, the group based stress management has been proven to reduce

CV events to a large extent compared to treatment as usual, so implementation of the program is still recommended.

Although a group-format, as in SUPRIM, enhances availability for psychological treatments in this patient group, an internet-based intervention would be even more accessible. This was tested in study V. Based on those results, iCBT, in the U-CARE Heart trial-format, was obviously not a feasible and effective treatment for patients with a recent MI recruited in a clinical setting.

Future research

Study I found a range of factors associated with emotional distress, but the predictive value of the factors is not known and need more research. It is also unknown if an accumulation of these factors in the same individual further increases the risk of emotional distress.

The mechanisms through which the stress management program influences CV prognosis is not fully understood. Future research needs to carefully assess, for example, social support, physical activity and medical adherence as mediators of reduced risk of CV events.

It is still unknown whether other types of iCBT are more feasible and thus promising in this patient population. Neither CBT nor iCBT is defined uniformly, and there are variations, even if they share basic principles; therefore, another package might work better. Furthermore, computer literacy rises in Sweden every year including among elderly (Davidsson & Thoresson, 2017), and thus the computer literacy in the cardiac population will change with time. Qualitative interviews about the experience of participating in the U-CARE Heart trial may clarify why there was such a low adherence. Potentially iCBT might work better in patients that actually ask for help and support, and new identification strategies are needed.

Given that most patients in Study V were included due to anxiety, this connection might be crucial. Exactly what this anxiety represents is yet to be explored in the data from the trial.

It is my hope that there will be continuous work to understand and develop treatments for psychological distress in CHD patients, perhaps succeeding in reducing new cardiac events but if not, at least reducing psychological distress.

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