Doctorial Thesis for the Degree of Doctor of Philosophy, Faculty of Medicine.

Psychosocial and stress-related aspects on Ischemic Heart Disease

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The practice of medicine is an art

based on science

William Osler

To the men in my life;
To Jacob, Thomas,
Magnus and Kjell
and to the memory
of my father.

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Abstract

Objective: To study different aspects of ischemic heart disease (IHD) i.e. stress-related risk factors, biochemical markers of stress, in particular the cortisol awakening response (CAR) and outcome in terms of health related quality of life (HRQoL).

Methods: 72 myocardial infarction (AMI) patients took part in the HRQoL studies. From a subsample of a population-based cohort of Swedish adults 194 men and women, 15% with the metabolic syndrome (MetS), took part in awakening cortisol sampling. The risk factor study was conducted on 290 previous chest pain patients. Assessment of HRQoL was via questionnaires (SF-36, CHP, Zung). CAR was performed by measuring salivary cortisol and medical records or death certificates were read identifying ischemic heart or cerebrovascular disease during 14-years of follow-up.

Results: Patients < 59 years improved in SF-36 Physical Component scores (PCS) but not in Mental Component scores (MCS), and scored significantly below community norms in both PCS ($\overline{x}$=44.7, CI 40.6–48.7 vs. $\overline{x}$=50.3, CI 49.3–51.4) and MCS ($\overline{x}$=45.9, CI 41.8–49.9 vs. $\overline{x}$=51.3, CI 50.3–52.4) at 6 months. Predictors for MCS were age (p=0.03) and Vitality (p=0.02). Predictors for PCS were Physical Function (p=0.01) and CCS angina scores (p < 0.001). Angina was negatively related to HRQoL. Patients < 59 years reached community norms in PCS after 2 years but scored significantly below norms in MCS throughout with an effect size of -0.5 (CI -0.88 to -0.14) at 2 years. In patients ≥ 59 years, no changes took place after 6 months. A significant difference in CAR% was found between men and women with MetS, $\overline{x}$ (±SE) = 38.5 (13.1) % and 91.4 (17.0) %, p=0.02. Women with the MetS awoke with the lowest cortisol level $\overline{x}$ (± SE) = 8.92 (0.96) nmol.L^{-1}. Women without MetS had a CAR% of 36.5 (5.7) % and a awakening cortisol level of 12.33 (0.69) nmol.L^{-1}. The values for men were 38.5 (13.1) % and 36.0 (6.1) %. 74 patients had died or been hospitalised with a diagnosis of IHD or cerebrovascular disease. Age (OR 1.1, CI 1.1–1.2), previous history of angina pectoris (OR 9.7, CI 2.1–71.6), pathological ECG at ED (OR 3.3, CI 1.2–8.7), hypertension (OR 5.0, CI 1.9–13.8) and smoking (OR 3.0, CI 1.3–7.6) were all associated with future IHD or cerebrovascular events. Noradrenalin (NA) levels were highest in the event group compared with the non-event group, $\overline{x}$ ± SD 2.44 (1.02) versus 1.90 (0.75) and lowest in the non-participants 1.80 (0.61) nmol.L^{-1}. Cortisol values were lowest in the event group, $\overline{x}$ ± (SD) 377(133) nmol.L^{-1}.

Conclusion: Inferior health in younger compared to older AMI patients in mental health domains of HRQoL was detected as was a sex difference in the cortisol awakening response between men and women with MetS. Traditional risk factors were found to predict future diagnosis of ischemic heart or cerebrovascular disease 14 years after a hospital visit for chest pain.

Key-words: *Ischemic heart disease, risk factors, stress, cortisol awakening response, HRQoL*

List of original papers

I. Bengtsson I, Hagman M, Wedel H. Age and angina as predictors of quality of life after myocardial infarction: a prospective comparative study. Scand Cardiovasc J. 2001; 35(4):252-8.

II. Bengtsson I, Hagman M, Währborg P, Wedel H. Lasting impact on health-related quality of life after a first myocardial infarction. Int J Cardiol. 2004; 97(3):509-16.

III. Bengtsson I, Lissner L, Ljung T, Rosengren A, Thelle D, Währborg P. The cortisol awakening response and the metabolic syndrome in a population-based sample of middle-aged men and women. Metabolism. 2010; 59(7):1012-9.

IV. Bengtsson I, Karlson BW, Herlitz J, Evander MH, Währborg P. A 14-year follow-up study of chest pain patients including stress hormones and mental stress at index event. Int J Cardiol (2010). In press.

Abbreviations

ACS	acute coronary syndrome
AMI	acute myocardial infarction
ANS	autonomic nervous system
CABG	coronary artery bypass grafting
Catecholamines	adrenalin (A), noradrenalin (NA), dopamine (D)
CAR/CAR%	absolute and relative cortisol awakening response
CARi	change of cortisol from the level recorded on waking
CARauc	overall cortisol released over the waking period
CCS	Canadian cardiovascular society angina score
CHP	cardiac health profile
CV	coefficient of variance
CVD	cardiovascular disease
DALYs	disability adjusted life years, (YLL+YLD)
ECG	electrocardiogram
HPA	hypothalamic pituitary adrenal/adrenocortical
HRQoL	health related quality of life
ICD 10	international classification of diseases 10
IHD	ischemic/ischaemic/heart disease
MetS	metabolic syndrome
NSTEMI	non ST-segment elevation myocardial infarction
PCI	percutaneous coronary intervention
PTSD	post traumatic stress disorder
QoL	quality of life
SAM	sympathetic adrenomedullary
SF-36	Medical outcomes study short form 36
SNS	sympathetic nervous system
STEMI	ST-segment elevation myocardial infarction
UA	unstable angina pectoris
VAS	visual analogue scale
YLL	years of life lost
YLD	years of lived disability
Zung/ZDI	Zung depression inventory

1. Introduction

This thesis focuses on psychosocial and stress-related aspects on ischemic heart disease (IHD). In a global perspective, IHD is a major cause of premature death. This is especially so in the developed world but in later years it has become an increasing cause in the developing world as well. Despite remarkable advances in treatment and preventive measures, IHD is still a widespread and life threatening disease. For those who survive, the disease imposes a considerable burden on the individual and on society. Life-time medication and/or surgical interventions such as percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) are costly. Prolonged sick leave or pensions further add costs to society. The increased morbidity after an acute myocardial infarction (AMI) encompasses both physical and mental disorders of varying severity. In the physical sphere, chest pain or angina pectoris, chronic heart failure and reinfarction are the most common. In the mental sphere depression and anxiety are frequent.

As chronic diseases shape patients' whole life situation, a wider perspective, than the traditional morbidity and mortality indicators, is needed. By integrating patients' perception or assessment of their health and well-being, a more comprehensive picture can be obtained as to the impact of disease on peoples' lives and measures can be instituted to decrease suffering and lessen the burden of disease for both individuals and society. Patients' views on their health can be investigated through several means where interviews using qualitative and/or quantitative methods (usually self-administered questionnaires) are employed. Health related quality of life (HRQoL) questionnaires measure the subjectively perceived effects of illness, disease or treatments on pre-selected areas or domains of a person's life. Since the 1980's these measures have become increasingly frequent in medical research. The first part of this thesis investigates HRQoL over time in an AMI population. At the time of the start of the present study, little was known about long term effects on HRQoL after an acute myocardial infarction and the predictive properties of such instruments. Due to the clinical observation that younger patients seemed more adversely affected by their myocardial infarction exploring possible age group differences became a main issue.

Added to traditional risk factors for AMI stress has now firmly been linked to atherosclerosis and ischemic heart disease both in clinical and in experimental studies. The mechanisms behind stress and IHD are complex and to date not fully known. Substantial interest has been directed at identifying biochemical markers of stress and to find questionnaires sensitive enough to capture stress both in patients but also in the general population in order to identify individuals at risk of disease. However, many factors can elicit the stress response and there are a number of bidirectional interacting systems taking part in the stress response with various transmitters, hormones and peptides involved. The most studied are the sympathetic-adrenomedullary (SAM) system, the hypothalamic-pituitary-adrenocortical (HPA)-axis, the immune and coagulation systems making catecholamines, cortisol, metabolic and also inflammatory markers commonsense. In this thesis, in addition to traditional risk factors, cortisol and catecholamines were investigated jointly with items from a pool of stress related questions. Also explored was the cortisol awakening response (CAR) in relation to the metabolic syndrome, a cluster of known risks for IHD.

2. Background

2.1 Ischemic Heart Disease (IHD)

In the western world, public health efforts and clinical medicine have successfully reduced both incidence and mortality in coronary heart disease. About two thirds of the decline has been estimated to be due to lower incidence and one third to improved treatment [1]. Despite these advances with a reduction in incidence and death especially premature death in IHD, the AMI incidence in 2008 in Swedish men was 619/100.000 and in women 440/100.000 in the ages above 20 years. The age-standardised incident AMI level 2008 compared to 2001 was 20% lower in men and 15% lower in women. Mortality data for 2008 showed 169 deaths/100.000 men and 131 deaths/100.000 women [2]. For AMI incidence and mortality changes in Sweden since 1987, see Figure 1.

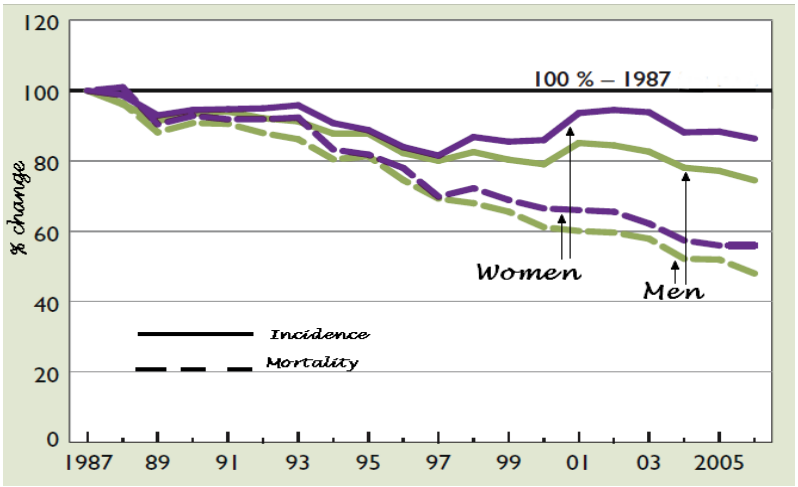

Figure 1. Percent change in AMI incidence and mortality 1987 - 2006 by men and women 20 years and older. Age standardized. Source: National Board of Health and Welfare [3].

In 1990, case fatality rate was 42% in men and 46% in women within 28 days post infarction. Comparable figures for 2008 were 29% and 32% respectively. For hospital treated AMI cases during 2007-2008, the fatality rate was 13% for men and 16% for women within 28 days post infarction. This is a 50% reduction since the 1980´s. Mortality data from Europe (Figure 2.) show higher mortality in northern compared to southern Europe and also an east-west gradient where there is an eight-fold difference in AMI mortality between France and Latvia. For men there were 72 deaths/100.000 and for women 16/100.000 in France and 555 deaths/100.000 Latvian men and 167/100.000 Latvian women [4].

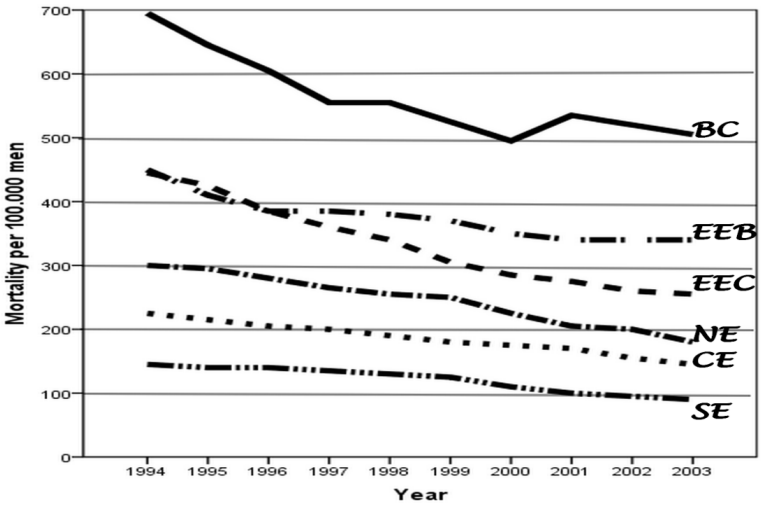

Figure 2. Age-standardized mortality rates per 100,000. Trends for ischemic heart disease in men aged 35-74. Redrawn from Giampaoli [5]. BC = Baltic countries, EEB = East Europe Balkan, EEC = East Europe Central, NE = Northern Europe, CE = Central Europe, and SE = Southern Europe.

In an international perspective the incidence of IHD in Sweden is still high. More than 878.000 incident AMI cases occurred between 1987 and 2008 and 322.000 died with AMI as cause of death. Estimated cost for inpatient coronary care was 4-6 billion SEK in 2007 [6].

In 1998 it was estimated that IHD accounted for 19.2 % of disability adjusted life years (DALYs) in Swedish men and 13.7 % in women [7]. In 2006, IHD was shown to account for 13.5% and 8.5% respectively [8]. DALYs are measures of disease burden and are made up of years lived with disability (YLD) plus years of life lost (YLL). One year of premature death is equivalent to one year lost. However disability is graded (0-1) from full health i.e. no disability to death. Thus disabilities contribute less to DALYs in most cases except when there is a heavy disability burden like in neuropsychiatric disease. A reduction in deaths will lower DALYs but YLD is likely to increase somewhat. However, the net result will be a reduction in DALYs. Thus, decline in coronary deaths have left survivors with functional impairment and risk of future events.

2.2. Pathophysiology

Behind the manifestation of IHD is coronary atherosclerosis [9, 10]. Inflammation is now regarded as one of the main factors in the pathogenesis of atherosclerosis and both the innate and adaptive immune systems are involved in the process [11-15]. Monocytes adhere to activated endothelial cells, enter the arterial wall intima and mature into macrophages. By means of scavenger receptors these macrophages engulf lipid particles and turn into “foam

cells". They sustain the atherosclerotic process by releasing cytokines and growth factors. Moreover, T-lymphocytes are activated by plaque antigens and move into the atherosclerotic plaque where they too produce proinflammatory cytokines. Disruption of atherosclerotic plaques with subsequent thrombus formation commonly leads to the serious complications of ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI), unstable angina (UA) or sudden death [16]. STEMI follows an abrupt complete occlusion of the blood vessel by a so called red or fibrin rich clot. NSTEMI/UA shows a white i.e. a platelet rich clot, which only partially occludes the artery. Thus, some preservation of antegrade blood flow is present. The clinical presentation and outcome depend on the severity and duration of ischemia.

As pathogenesis of STEMI, NSTEMI and UA are essentially the same but vary to degree, the clinical presentation is today termed Acute Coronary Syndrome (ACS). The most prominent features assessing the likelihood of ACS are the nature of the chest pain, a prior history of coronary artery disease, male sex, older age and the number of risk factors [17]. ACS is classified into STEMI/NSTEMI/UA depending on symptoms, ECG and cardiac enzyme features. The classification is important as PCI/CABG or if not available immediate thrombolytic therapy is crucial in STEMI to normalise flow and minimize myocardial necrosis [18]. High risk NSTEMI/UA patients may also be in need of emergency intervention. In NSTEMI/UA the thrombolytic treatment is aimed at preventing further clotting. Medical therapies include antiischemic medication (ß-receptor blockers, nitrates, calcium antagonists and renin-angiotensin-inhibitors (ACE), antiplatelet (aspirin etc) and antithrombin (low molecular weight heparin) treatments [17]. An international consensus document was published in 2007 defining five AMI types [19]. Type 4a, 4b and 5 are applicable for infarctions in connection with interventions, type 3 in sudden death, type 1 in acute or primary infarction due to plaque rupture/erosion/fissure and type 2 in secondary ischemia due to emboli, spasm, anaemia, arrhythmias etc. European recommendations on prevention of IHD in clinical practice, was published in 2007 [20].

2.3 Risk factors and indicators of IHD

Over 200 risk factors/indicators for IHD have been reported in medical literature. This figure is distressing as such large numbers of proposed risks fail to add practical substance to public health actions and also increases the possibility of unnecessary medicalisation. The term risk factor implies an indication of causal relationship to the disease in question. When there is a statistical association but causality is not proven the term risk indicator is usually chosen.

Experimental and epidemiological studies have long established a number of important risk factor in IHD. Already in 1950´s the first results from the Framingham study identified hypertension, hypercholesterolemia, and overweight as risks for arteriosclerotic heart disease [21]. In later years psychosocial and socioeconomic factors and stress have been added to the list of risk factors [22-28]. To capture "stress" has been regarded as an elusive task. However, it has been shown that a few relatively simple questions can liberate this state [24]. From the INTERHEART study it was concluded that abnormal lipids, smoking, hypertension, diabetes,

abdominal obesity and psychosocial factors or stress show increased risk of AMI. Consumption of fruits, vegetables, alcohol in moderation, and regular physical activity reduced this risk. This holds true for both sexes, at all ages and worldwide [29]. Anand et al. found some difference in risk factors between men and women where women differed in hypertension, diabetes, physical activity, and moderate alcohol use [26]. For the other risk factors (smoking, dyslipidaemia, abdominal obesity, unhealthy diet and psychosocial stress factors) the risks were equal between men and women.

2.3.1 Traditional risk factors

The traditional or classical risk factors for ischemic heart disease, as described above, can be found independently but often in combination e.g. obesity, high blood pressure, high total cholesterol, excessive alcohol and tobacco use are found in the same individual. A special cluster of these risk factors is termed the metabolic syndrome (MetS) and is made up of at least three of the following findings according to National Cholesterol Education Program (NCEP) criteria [30]; plasma glucose > 6.1 mmol.L^{-1}, HDL-C < 1.04 mmol.L^{-1} for men and < 1.29 mmol.L^{-1} for women, serum triglycerides > 1.7 mmol.L^{-1}, hypertension = systolic blood pressure of at least 130 mm Hg or diastolic blood pressure of at least 85 mm Hg or treatment for hypertension, waist circumference > 102 cm for men and > 88 cm for women. Increased risks of cardiovascular events and death have been found in MetS, RR 1.78 (CI 1.58 - 2.00) and the risk is higher in women than men. Furthermore, the risk exceeds that of the individual components of the syndrome [31]. The MetS prevalence in middle aged Swedes both men and women are circa 15% [32]. In that study the incidence increased with increasing age in women but not in men.

In the past these traditional risk factors have been estimated to account for less than 50% of the IHD risk. However, later studies have shown high serum total cholesterol, high blood pressure and cigarette smoking to account for 80% Coronary Heart Disease (CHD) risk in middle aged men [33] and in the INTERHEART [29] study the population attributable risk (PAR) for 9 risk factors were 90% for men and 94% for women.

2.3.2 Psychosocial risk factors

The psychosocial factors that have been found related to CHD are work environment, social isolation and lack of emotional or social support, socioeconomic status, life stress, personality (type D) or behaviour (type A), post traumatic stress disorder (PTSD) and depression/anxiety [34-36]. Also acute mental stress such as life stress, natural disasters, warfare among civilians, or intense anger can lead to ischemic events [37, 38]. Greater oxygen demand, effects of tachycardia and raised blood pressure, may trigger ischemia and malignant arrhythmias causing sudden death. Acting via primarily the HPA-axis, chronic stress has profound metabolic consequences with ability to hasten atherosclerotic processes [39]. The increased susceptibility to diseases in socioeconomically disadvantaged individuals have been attributed to dysfunction of the HPA-axis with inability to respond to new challenges and diminished recovery [40]. Recently, experimental evidence has suggested that there are differences

between physical and psychosocial stress where the latter increased atherosclerosis via proinflammatory cytokines (TNFα, IL1, and IL6 among others). Further the atherosclerotic process was diminished by a β-blocker indicating sympathetic nervous system (SNS) involvement [41].

2.3.2.1 Work

In contrast to men where job strain (high demand and low job control) is a main determinant, family stress substantially account for the social gradient in CHD in women [42]. About 1/10 of acute myocardial infarctions among people of working age is estimated to depend on factors of stress, low control at work and other social incapacitating situations [43]. Health inequalities due to socio-economic differences occur not only between regions and countries but also within countries, even within towns. Socio-economic status is inversely associated with coronary heart disease. In Sweden, the risk to be afflicted with an AMI during 2000-2005 was double that in people with basic compared with university education (2.4 for women and 1.8 for men). Generally there has been a more favourable development in men with different educational levels during the past 15 years while there has been smaller changes in women with basic education and no change in university educated women since 1991 [3].

2.3.2.2 Behaviour/Personality

Type A behaviour has been characterised by extremes of competitiveness, achievement striving, aggressiveness and time-urgency. However, the relation between Type-A behaviour and CHD has been found to be inconsistent. In later studies, hostility has been identified and has been significantly associated with AMI [44]. The type-D personality is characterised by a tendency to suppress emotional distress (chronic suppression of negative emotions). Type-D individuals are further characterised by low perceived social support, anxiety, unhappiness, irritability and depressive symptoms. These individuals carry a four times increased mortality risk compared to non-type-D coronary heart disease patients [45].

2.3.2.3 Depression and anxiety

In primary prevention and in epidemiological and clinical studies associations have been found between depression and IHD with a 2-3 fold increased risk of suffering an AMI [46, 47]. Clinical depression and depressive symptoms have been shown to predict the occurrence of CHD in previously healthy people [48]. Depression has been regarded as a factor in the aetiology of IHD. Several mechanisms have been proposed to account for the association between depression and IHD. These mechanisms include personality, behavioural and psychosocial factors. Also, depression may act directly on biological systems for example the hypothalamic-pituitary-adrenal axis, the sympathetic nervous system, the coagulation and the immune systems [49]. Individuals with panic disorders also run an increased risk of cardiovascular disease.

Moreover, depression in the post infarction period has been found in a high proportion and has been seen as a consequence of the infarction. It is also an important source of subsequent

morbidity and long acting reduced quality of life. A feeling of tiredness and lack of energy can be important indicators of post AMI depression. Depression has been estimated to occur in 15-20% of AMI patients and has been associated with a worse prognosis i.e. increased mortality risk [50, 51]. However, lately there have been reports where these associations could not be found [52, 53] and in 2002 it was reported that instead of symptoms of depression and anxiety following a myocardial infarction, disease severity predicted mortality [54].

Anxiety in the early post infarction period has also been associated with increased risk of ischemic complications [55]. Symptoms of anxiety has been found to exceed depression as a risk for subsequent cardiovascular events [56]. During hospital stay for AMI, anxiety and depression predicted poor outcome after one year on all SF-36 dimensions but did not predict mortality [57]. An overview on depression or depressive symptoms in relation to HRQoL can be found in an article by Stafford et al. [37].

2.3.3. Stress

The feeling of time urgency has long been the layman's definition of stress. Already nearly 100 years ago William Osler[1] was convinced, on the bases of observations, that "nothing is more certain than that the pace of modern life kills many prematurely through the complications of arterio-sclerosis" [58]. Since then, time urgency has not lessened. However, the stress concept and knowledge of stress have evolved.

2.3.3.1. Overview

The perception of actual or potential challenges or threats to an individual is called 'stress'. Stress is thus "threatened homeostasis" by external or internal forces. The key feature is threat/threatened. The 'stressor' is the stimulus i.e. the internal or external environmental change perceived, identified, anticipated or recalled by the brain and the 'stress responses' are all the underlying physiological/behavioural or in long-lasting stress pathophysiological reactions initiated by the stressor/s. Stressors can be physical and chemical or psychosocial in a broad sense and duration and type of stressor as well as previous experiences of the stressor/s are of great importance for the effects. Time stress, life events such as death of a spouse or divorce or abuse in childhood, noise, trauma but also internal processes like changing osmolarity or hypovolemia are examples of types of stressors. Possibly, some individuals are more prone to stress than others and there may be individual/gene variations especially to psychosocial stressors.

Hans Selye´s concept of stress as a fairly uniform response involving primarily the HPA-axis [59, 60] has now been broadened and several fine tuned complex biological responses to

[1] Sir William Osler, M.D., C.M., (1849–1919), Canadian-born physician and classical scholar. He was professor of medicine at four universities, and his *Principles and Practice of Medicine* (1892) became the chosen clinical textbook for medical students. *The New Zealand Oxford Dictionary*. Tony Deverson. Oxford University Press 2004. *Oxford Reference Online*. Oxford University Press.

stress have been identified [61]. The long and short-term effects are also different. Activation commonly involves the autonomic nervous system (ANS) especially the sympathetic nervous system and its sympathetic-adrenomedullary part, the HPA-axis and the immune and coagulation systems (Figure 3.). Multiple mediators are involved such as neurotransmitters, peptides and hormones and the systems are interconnected. Thus, there are many stress reactions in the body, several of which are bidirectional.

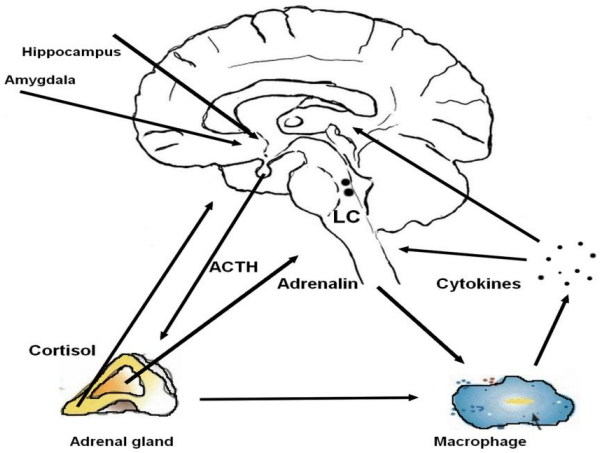

Figure 3. Schematic outline of the main stress systems, the sympathetic nervous system, including the SAM branch, HPA-axis and immune system (here represented by the macrophage) and some of the central connections, LC = Locus Coeruleus.

Thus, via the brain sets of systems are activated and interact with each other [62, 36]. Environmental external stimuli, for example, are mediated via the telereceptors and underlying physiological reactions are initiated in different parts of the CNS (amygdala, hypothalamus, hippocampus, prefrontal cortex and others), Figure 4. Depending on the type of stressors different responses are initiated. However, there is cross talk between areas. For example physical stressors may have a strong emotional component as well, and both the hypothalamus and the amygdala will be involved in the initial stress response. The effects of chronic stress are also depending on when throughout life it strikes. During childhood hippocampus still maturing seems to be extra vulnerable, in adolescence the frontal cortex and in adulthood and in aging again the hippocampus [63]. Reduced hippocampal size has been reported and has been attributed to neurotoxicity from severe chronic stress and/or to vulnerability owing to early trauma or genetics [63].

The amygdala is considered the emotional or the fear centre of the brain. Sensory stimuli are directed either via the thalamus acting as a relay station to the relevant parts of the cortex where they are interpreted and sent back to the amygdala to be acted upon or they may also go directly to the amygdala.

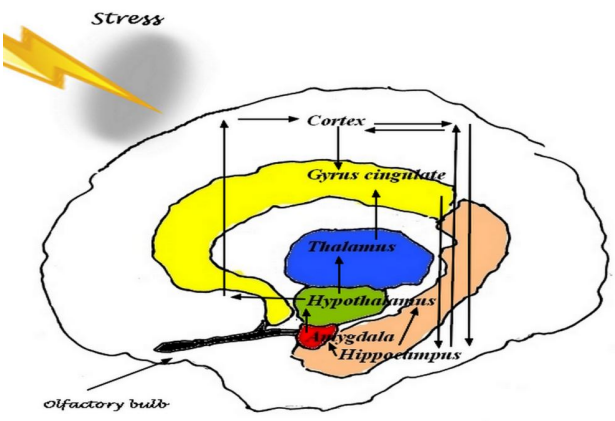

Figure 4. Schematic representation of some important brain areas related to stress and some of the interconnections (black arrows).

From the amygdala via hypothalamus and the brain stem the SNS especially the SAM system is rapidly activated and the catecholamines adrenalin (A) and noradrenalin (NA) are produced from the adrenal medulla (80%A, 20% NA) and noradrenalin is also released from sympathetic nerve endings. NA and A from the adrenal medulla have 5 to 10 times longer effect than NA released from the sympathetic nerve endings. These catecholamines have partly overlapping actions. The action of noradrenalin is mainly directed at the α-receptors and adrenalin at both α and β-receptors [64].

Adrenalin is 5 to 10 times more potent than noradrenalin when it comes to the metabolic and cardiac effects. Adrenalin can vastly increase the metabolic rate of the body and has effects on several metabolic parameters; increase in free fatty acids (adipose tissue lipolysis), blood glucose (liver glyconeogenesis and glycogenolysis) and in serum cholesterol (through reduced degradation). Diminished insulin secretion through the α-receptor leading to hyperglycaemia is another major metabolic effect. Stimulation of the α-receptor also leads to increased platelet aggregation. Adrenaline has a number of important additional effects i.e. increased cardiac output through increased heart rate and contractility. Through effects on β_2 receptors adrenalin produces bronchodilatation and dilatation of blood vessels in coronary circulation and skeletal muscle. Noradrenalin increases blood pressure through contraction of arteriolar smooth muscle redirecting blood from skin and viscera to skeletal muscle.

Noradrenalin also has important immune effects. SAM can both inhibit and stimulate cytokines via β-receptors causing suppression of the innate immune system and of cellular immunity but stimulate humoral immunity (antigen/antibody system) [65]. Of the cytokines TNFα, IL1 and IL6 activate the HPA-axis via corticotrophin releasing hormone (CRH) and vasopressin or antidiuretic hormone (AVP) neurons in the hypothalamus [66]. Cytokines can also stimulate the central noradrenergic stress system.

The amygdala and hypothalamus are also connected and the Locus Coeruleus releasing noradrenalin into the brain facilitating brain alertness and also activating the SAM. Other important loci are the hippocampus involved in learning and memory and the paraventricular nucleus (PVN) in the hypothalamus where corticotrophin releasing hormone (CRH) and vasopressin (AVP) are released into the portal circulation of the pituitary. The fast stress response involving the fight and flight response and the HPA-axis is mediated via the CRHR1 receptor and the more recently described urocortins work via the CRHR2 receptors. This is a mode that promotes recovery and adaptation and urocortins have anxiolytic properties [67]. CHR and AVP stimulate the release of adrenocorticotropic hormone (ACTH) from the pituitary gland which in turn binds to receptors in the adrenal cortex and in humans release mainly cortisol from that adrenal cortex. The HPA-axis has a well developed feedback system acting on three brain levels; the pituitary, the hypothalamus and the hippocampus. Evidence also suggests CRH to exert direct effects in several areas of the brain including the amygdala.

Neuroendocrine activation thus regulates the well known defence or alarm reaction, the defeat reaction, the "playing dead" and the freezing reactions [68]. The two last named are usually short or extremely short in duration. However, the defeat reaction can be long lasting and thus exert harming effects on organ and organ systems. The harming effects of stress may be manifested as disturbances of the circulatory, metabolic and immune and coagulation systems and by the brain itself (depression and anxiety). This type of stress has also been called submissive stress. The defence reaction is usually acute and aggressive in character with a limited length depending on how the CNS interprets the threat. Memory of previous stress episodes colour the appraisal of the current situation and is of great importance and the reaction is graded. From fighting or running for one's life to being a bit annoyed or being challenged or just feeling stimulated. Stress reactions generally are adaptive safeguarding survival and working to achieve balance, allostasis. But if systems get out of balance due to allostatic load i.e. too frequent, too intense and or too long lasting stress periods disease will follow. The effects or manifestations of stress are appraisal of stress and emotional, cognitive or behavioural reactions and if long lasting or intense, i.e. when adaptation no longer can be maintained, somatic or mental diseases. Thus, in chronic stress in humans increased anxiety, hypertension, metabolic disturbances and immune suppression are recognized.

2.3.3.2 Cortisol

Cortisol is an important hormone in mobilising energy (glucose and fatty acids) for muscular, heart and CNS utilisation in acute situations. However, in chronic stress of today the need of large amounts of "fuel" for muscular activity is limited. The main effects of cortisol are its anti-inflammatory and immunosuppressive effects and its metabolic effects where it stimulates gluconeogenesis (liver). It also inhibits insulin effects promoting insulin resistance with increased blood sugar as a consequence. Further, cortisol induces protein catabolism (muscle) and lipolysis (adipose tissue). Plasma levels of lipids (cholesterol, LDL, HDL, triglycerides and fatty acids) increase shortly after stress stimuli. Thus, glucose is made available and fat and proteins mobilised to serve as energy supply. However if little or no extra energy is needed accumulation occurs that can be seen as visceral fat accumulation [65]. There is growing evidence suggesting that behind abdominal obesity lays central

dysregulation of the HPA-axis activity and possibly also peripheral alterations of cortisol metabolism giving raise to inappropriate feedback signals [69, 70].

Cortisol exerts its effects via binding to cortisol receptors (mineral (MR) and glucocorticoid (GR) receptors) in the body (mainly GR) and in CNS (both GR and MR). These receptors are found in several areas of the brain and body. The mineral corticoid receptors are occupied by cortisol in the basal state and the glucocorticoid receptors mainly in states of stress. MR maintains for example the circadian rhythm and blood pressure, aid glucose availability in CNS and enhances synaptic plasticity. GR have opposite effects on glucose utilisation and plasticity. It is also the GRs that are involved in the HPA feedback system i.e. shutting off the stimuli to the adrenal cortex thus terminating the stress response. It is in chronic stress states that the GR effects become damaging.

Cortisol also takes part in modulating the immune system strengthening it the short term and suppressing it if the increase in cortisol is of long duration. Acute stress leads to immune enhancement or immune protection due to increase in leucocyte mobilisation, and in the innate response. The reverse is seen in chronic stress where dysregulation of the system leads to decreased immuneprotection [71]. Associations between immune suppression and psychosocial stress or in conditioning have been seen in animal experiments [72].

2.3.3.3. Stress markers

Several biological markers of stress linked to respective stress system have been or are in use in stress research [73, 74]. For the SNS and SAS catecholamines have been used, for the HPA-axis cortisol, for the inflammatory system various cytokines and C-reactive protein and for the coagulation system several components of that system. However, given the complex nature of the stress responses, interactions between systems and diurnal variations make it improbable that a single comprehensive measure will accurately assess the state or the activity of these systems. Single measurements of for example circulating catecholamines and cortisol are thus problematic to interpret. Catecholamines are short acting, and NA for instance is dependent on physical activity and posture. Also, noradrenalin levels are determined by spill-over and clearance and both these mechanisms are influenced by the state of the circulation [75]. They also show diurnal variation. They may not mirror the state of the whole body but rather local production at the site of puncture. To get a more representative sample arterial puncture is required but this is a stressful procedure in itself. Urine collection of NA will bypass some methodological problems [76].

Cortisol in saliva bypass stressful blood vessel puncture and can be handled by the study subjects themselves, after receiving detailed instructions. Further, salivary cortisol represents the biologically active fraction of that hormone. It is in effect free. It rapidly mirrors the circulating free fraction and is not dependent on salivary flow. Plasma cortisol, on the other hand, is bound to proteins (transcortin 75% and albumin 15%) and only 5-10% is free. Thus, in conditions where plasma proteins vary, for example pregnancy and oestrogen therapy, cortisol levels will also vary [77]. Today several salivary cortisol samples at strictly defined times or time intervals and ideally over several days are recommended. A minimum

requirement is three samples, the first at wakening, the second as close as possible to the morning peak (30-45 minutes later) and a third at bedtime. This will enable calculation of the awakening response, slope and bedtime level. Some commonly used cortisol indices of HPA-axis function, by level or dynamics, are listed in Table 1.

The cortisol awakening response (CAR), the area under the curve (AUC), the cortisol decline pattern or slope, the late evening (bedtime) value and the result of the dexamethasone test are the most common. The first sample at awakening (S_0) as a measure of the pre-awakening cortisol secretion and AUC_i or the mean increase (MnInc) as measures of dynamics have been proposed as a standard for quantification [78].

Table1. Some commonly used cortisol measures. Calculations that require several samples may or may not include the morning peak sample.

Level measures	**Dynamic measures**
1st awakening sample (S_0)	Absolute difference CAR (S_1-S_0)
Mean of awakening (S_0+S_1)/2	Percentage change CAR (S_1-S_0)/S_0 x 100
Mean of diurnal/total (S_0+.....S_n)/n	AUC_i with respect to increase (trapezoid method)
AUC_0 with respect to baseline (trapezoid method)	Diurnal slope (S_0-S_n) alt. (S_0-S_n)/hours i.e. decline per hour or linear regression on time
Late evening (bedtime) value (S_n)	Dexamethasone suppression test (DST) (S_0 pre and post 0.5 mg of Dexamethasone)
	Laboratory performed standardised stress test (assesses reactivity of the HPA-axis)

The CAR is considered a distinct and separate part of the circadian cortisol rhythm. There seem to be respondents, ca 20% in a general population, who do not react with an increase in the morning cortisol. If this can be considered a "normal" response in some people or if it indicates perturbed HPA-axis or if it simply depends on non compliance is not known [79]. Age and sex seem to play a minor role in CAR as does menstrual cycle phase and oral contraceptives. However, wake up time clearly has an effect, as does cigarette smoking (increased CAR but relatively small effect). In a variety of health disorders both increase and decrease in CAR have been reported. An increase has been found in visceral obesity, depression, and early wake up time. A blunted CAR has been reported in hypertension, CVD, pain, PTSD, depression and in women with increased carotid media thickness, for review see Fries et al. [80]. CAR has been reported to be flattened for men, subjects with CVD, people with late awakening times and longer sleep duration [81]. Both chronic and acute stress has been implicated to influence CAR as anticipation of forthcoming demanding tasks seems to play an important role in the response. About 30% of the cortisol level at a specific time point has been estimated to be due to trait or basic cortisol production and 70% to state or situational factors [82].

Workdays have shown a CAR increase larger than on weekends. In a meta-analysis CARi was reported to be positively associated with job and general life stress. However, it was negatively associated with fatigue, burnout, or exhaustion [27]. People with worries, with work overload and in socially difficult situations have an increased CAR. Total cortisol exposure has been shown to be associated with atherosclerosis of carotid arteries [83]. Hippocampal volume has also been associated with CAR which indicates that hippocampus may regulate the magnitude of CAR as low such a volume has been associated with no CAR.

High salivary cortisol in the morning has been found in subjects with high stress exposure and low morning values have been associated with cardiovascular risk factors or disease [84-87]. The evening value has been suggested to be a measure of the resting state of the HPA-axis. High evening values indicate lack of recovery. Low differences between morning and evening cortisol levels (a flattened slope) have been found in chronic stress and in men and women with psychosocial risk factors [88, 89]. A dexamethasone test with low cortisol values the following morning indicates an adequate HPA-axis regulation via the feedback system. Reports from a recent large community study show cortisol secretion indices to differ depending on wake up time (CAR and slope), gender (AUC), social support (AUC and slope) and smoking (slope). Unexpectedly no association was found between depressive symptoms and cortisol. Neither were there associations with diabetes, CAD or hypertension [90]. There are both inter- and intraindividual variations in cortisol levels. Norm values have been published but are yet to be firmly established [91, 92]. In the laboratory, response or the reactivity of the HPA-axis can be assessed by standardised stress tests such as the Trier social stress test (TSST).

2.3.3.4. Interpreting cortisol measurements

The many advantages of salivary cortisol measurements as a stress marker over cortisol in plasma and the relative ease with which it can be sampled have expanded cortisol measurements into both old and novel research areas. For example large field studies are now possible. Crucial in order to interpret results properly, are rigorous attendance to details performing the tests not least the problem of compliance, the relatively large variations within and between also healthy study subjects, proper choices of indices appropriate to the research question/s and adjustments to confounders [93].

2.3.3.5. Stress and IHD

It is these highly interacting bidirectional brain and bodily systems that make the study of stress so intricate. From the above it becomes clear that several identified risk factors for CHD can essentially be labelled stressors. Any stressor striking a vulnerable individual being sufficiently strong and or long lasting and stimulating the SAM, HPA, coagulation or immune systems may possibly be linked to CHD. It may not be the stressor per se but the cardiovascular, metabolic and immune effects of the stressor that determines the relation to silent or manifest cardiovascular disease. The mechanism/s behind stress and atherosclerosis and hence CVD are not fully known [94]. However, subacute inflammation seems to be a core factor in atherosclerosis and reduction of an inflammation biomarker (hsCRP) by a statin has been shown to reduce cardiovascular events [14]. In addition to conventional risk factors

stress, especially mental stress/psychosocial stress has been found to be associated with IHD [22, 23, 34]. In the INTERHEART study, stress was estimated to account for 30% attributable risk of AMI [24]. However, not only chronic stress but also acute stress can trigger an AMI [95, 96].

3. Health related quality of life (HRQoL)

In health care research the QoL concept has been judged to be too broad as there are clearly more determinants of a person's overall QoL than health or health problems. The purpose of medicine is about health of body and mind, not quality of life generally. The relationship between health and QoL is complex. For instance, health may not be sufficient for a good life nor does impaired health necessarily mean lack of QoL. Under normal circumstances, health is an important domain or dimension of a good life. If health is improved QoL is likely to change for the better. The need of an extended or more salutogenic health concept in health care and this inferred relation between health and QoL has led to the current interest in measuring QoL in health care research.

By introducing HRQoL, which is a more restricted definition than QoL, the centre is now on the effect of health conditions on an individual's quality of life. It discards aspects other than health or health care. HRQoL is thought of as a complement to traditional measures such as mortality and morbidity i.e. as an outcome measure. HRQoL has also been regarded as a risk factor for disease and as an instrument for policy making and in the evaluation of health care services. A drawback with HRQoL is that this concept is made up of two equally elusive constructs i.e. QoL and health. Not only that, but there is an overlap between health and QoL, as both concepts at least partly incorporate well-being. "The domains of health and QoL are complementary and overlapping" WHO states.

3.1 Definitions of HRQoL

"Subjective health status measurement" is one definition of HRQoL. Subjective meaning that it is the person/patient who makes the assessment i.e. judges his or her own health. This definition equals HRQoL with health status. A more comprehensive definition is "HRQoL is the value assigned to the duration of life as modified by the impairments, functional states, perceptions and social opportunities that are influenced by disease, injury, treatment and policy" [97]. Generally, HRQoL is regarded as a multidimensional construct usually containing some measurements of general health, physical and mental health and social well-being [98]. There should be both negative and positive aspects of health. The EuroQol instrument [99] uses five dimensions mobility, self-care, usual activities, pain/discomfort and anxiety/depression. There are three levels for each dimension. The respondents are also asked to mark their own current health state on a "thermometer" calibrated from zero (worst imaginable health state) to 100 (best imaginable health state).

HRQoL can be viewed as located somewhere along an imaginary spectrum that starts with clinical medicine and extends over health in a more holistic or pluralistic sense and ends in some evaluation of the overall goodness of life or life satisfaction. Next to clinical medicine is functional status, thereafter health status, HRQoL and finally QoL. The closer to the left of this spectrum the more traditionally medical indicators will be found in the instruments and the more to the right global indicator/s capturing well-being and life satisfaction will be included. One example of a questionnaire that contains an item of global QoL is the EORTC QLQ-C30 which is a 30-item cancer specific instrument [100]. If measuring HRQoL solely means linking different health related domains together it is in practise equivalent to assessing a person's health. If it is viewed as an estimation of the contribution of a person's health to his or her overall well-being then the problem of delineating health and non-health dimensions of QoL remains [101].

3.2 HRQoL and IHD

HRQoL measurements in IHD have been performed since the late 1980's. Initially, fairly good HRQoL after AMI was reported. For example Wiklund et al. [102] concluded that "5 years after AMI most patients seemed well-adjusted". But patients suffering from angina pectoris, dyspnoea and emotional distress reported impaired quality of life. Glasziou [103] concludes that quality of life is generally high six months after an AMI. Yet, it has also shown that both physical disease and emotional distress continue to be a substantial part of patients' assessment of HRQoL after an AMI [104].
There is a fair agreement that the presence of angina pectoris is associated with poorer HRQoL and that patients with congestive heart failure experience a generally low HRQoL. van Jaarsveld et al. [105] reported no recovery in HRQoL in a group elderly post-AMI patients after 24 months and concluded that the negative consequence of an AMI on HRQoL is not temporary. Thus, an acute coronary event can have long lasting effects physically and emotionally [106]. There also seems to be a difference between men and women in perceived HRQoL [107, 108].

The influence of age on HRQoL has varied in different studies. Thus, Beck et al. [109] did not find age to be a predictor of HRQoL after myocardial infarction. In contrast, Bosworth et al. [110] found age positively associated with increased SF-36 dimensions Mental Health, Vitality and Role Emotional in a study of social support, QoL and coronary artery disease (CAD). Six months after percutaneous coronary revascularization the SF-36 mental component summary score (MCS) was dependent on age and pre-intervention MCS in a study by Nash et al. [111].

As can be seen from the above, reported results have varied. Different studies have used different questionnaires with little ability to compare between studies and with population norms. Also, several of these earlier studies were part of clinical trials and/or had incorporated patients in different stages of CHD i.e. patients with no previous to one or more previous infarctions. Studies have also been cross sectional in design in many cases. In some studies focus has been directed to physical health and in others to mental health.

3.3 Interpreting HROoL measures

Generally quality of life measures are subject to some specific issues. The lack of a true baseline or zero and the possibility of a response shift are examples. The comparisons with a reference population will aid in handling the first issue. Response shift or psychological adaptation is a known phenomenon in serious disease [112] and needs to be kept in mind when interpreting change over time. Placebo and Hawthorne effects may also be present in experimental studies [113]. The effect of the natural history of disease is another factor to consider. The choice of quality of life instrument is also important and it should have been tested for reliability and validity. Whether the choice is a more general or more specific instrument depends on the research question. But the instrument must be sensitive enough to detect important change if patients are to be followed over time. To be able to compare with the general population is a great advantage as age, sex, and education may clearly influence results.

4. Aims

The general aim of this thesis was to study different aspects of ischemic heart disease with focus on risk factors for IHD, biochemical markers of stress and outcome of IHD.
More specifically:

- to explore predictive properties of classical, psychosocial and stress-related risk factors (Paper IV) for future diagnosis of ischemic heart or cerebrovascular disease by performing a 14 years follow-up study of chest pain patients.

- to describe a biochemical marker of stress (Paper III) by measuring the cortisol awakening response (CAR) in a randomly sampled adult Swedish population acting as reference population and compare with the cortisol response in a subgroup of men and women at risk of IHD i.e. men and women with the metabolic syndrome.

- to investigate outcomes after an AMI in terms of quality of life (Papers I and II) over time (1, 3, 6, 12 and 24 months) and compare this outcome between younger and older patients, and also with an age and sex adjusted reference population. Moreover to test predictive properties of illness and initial quality of life measures.

5. Methods

5.1 Patients and participants

5.1.1 Papers I and II

Over an 18-month period (March 1st 1995 - August 31st 1996) 80 consecutive men and women, with a first documented myocardial infarction, Swedish speaking and with an age below 70 were invited to take part in a study on quality of life after a first AMI. The patients

were treated at a 4-bed medical intensive care unit, Kungälvs Hospital and were initially followed for six months (Paper I). Criteria for inclusion in the study were no previous history of myocardial infarction and either 1) ECG with a pathological Q-wave in two parallel leads or 2) typical symptoms and a biochemical marker or 3) suspect ECG changes and a biochemical marker. A creatine kinase-MB > 15 μkat.L^{-1} was considered abnormal. The same physician assessed all ECG's. No patient had had percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass grafting (CABG) performed prior to inclusion in the study.

Informed consent was obtained usually on the fourth - fifth hospital day. Two patients did not consent to participate and six patients died during the hospital stay. Thus the in-hospital mortality was 7.5%. The remaining 72 patients constituted the study population for this investigation. One patient died after one month and over the six months follow-up period a total of 10 patients left the study because of referral to their general practitioner commonly after the second follow-up visit. One patient declined further participation. Thus 17% were lost to complete follow-up. For administrative reasons not all patients completed all questionnaires. A total of 54 patients completed both the first and third questionnaire.

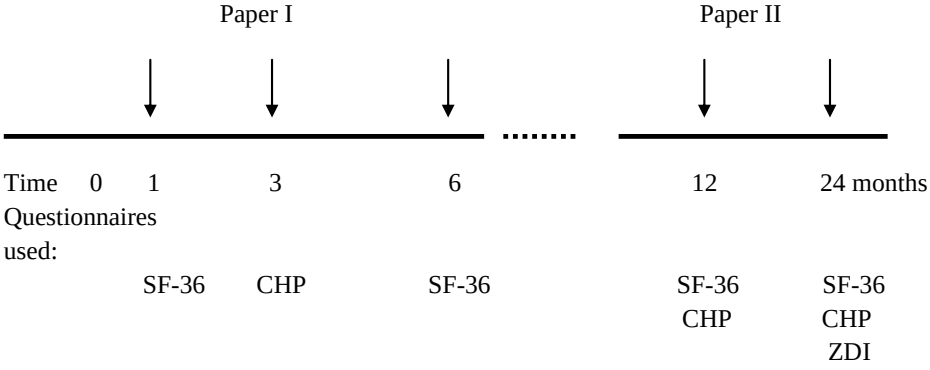

Figure 5. Overview of questionnaires used at different time points in Papers I and II.

Despite efforts to retain all enrolled patients at the continuation of the study (Paper II), one and two years after the index event, no questionnaire data existed for 3 patients due to early withdrawal of consent (1 patient) and living outside the hospital's catchment area (2 patients). One patient had died and 3 patients did not renew their consent. Consequently, at the one-year follow-up the number of possible responders was 65 and 63 patients actually responded. At the two-year follow-up there were 63 possible responders as another two deaths had occurred. At this time-point there were 56 actual responses. The time line is illustrated in Figure 5.

Questionnaires used in Papers I and II for investigating the patients perspective on their health related quality of life were the Medical Outcomes Study short form 36 (SF-36), the Cardiac Health Profile (CHP) and the Zung Depression Inventory (for a description of these see below).

5.1.2 Paper III

The participants in Paper III were recruited from a sub-sample from the INTERGENE program a randomly sampled population-based cohort of Swedish adults [114]. The focus in this study was on the cortisol response at awakening as a marker of stress.

In addition to a comprehensive health check-up, 194 men and women aged between ≥ 45 and ≤ 70 years were asked to perform salivary cortisol testing at awakening on an ordinary weekday. The participants were recruited consecutively, from a mixture of rural and suburban populations, from April 1st 2003 to April 30th 2004 at five different municipalities in Western Sweden. There were no participants from the main city of Gothenburg. The exclusion criteria were no consent, pregnancy and insufficient cortisol testing. Twelve subjects declined participation (mean age 52.6 ± 6.7 years). There were no pregnancies. Of the remaining 182 study subjects, seven had insufficient cortisol testing (too little saliva, discoloured sample or high values (>75 $nmol.L^{-1}$) indicating contamination with blood). They were therefore excluded giving a final participation rate of 90%. Thus, 175 participants, 91 women and 84 men with a mean age of 56.9 ± 7.0 years were included in the final analysis.

The metabolic syndrome was defined according to NCEP criteria (see page 13) for two reasons. The NCEP has more of a cardiovascular profile than the definitions by the World Health Organisation and the International Diabetes Federation (IDF). These latter profiles are more diabetic orientated. Further, the INTERGENE protocol did not contain any specific measures of disturbed glucose metabolism other than raised plasma glucose.

5.1.3 Paper IV

In Paper IV, the patients had initially been enrolled in a study on chest pain conducted at Sahlgrenska University Hospital, Gothenburg, Sweden. The long term outcome in this patient population was the objective of this prospective follow-up study. The patients had been recruited from January 1992 to March 1993 at the emergency department (ED). In short, 778 patients seeking the ED due to acute chest pain or symptoms suggestive of an AMI, but where an AMI was ruled out, were approached. These patients had been offered a revisit at a cardiac outpatient clinic after approximately a week. The clinic was staffed with experienced cardiologists. Of the 778 patients, 294 were excluded for various reasons [115].

Thus, 484 patients (295 men and 189 women) with a mean age of 48 years accepted a second evaluative visit including detailed case history, exercise testing, laboratory tests for metabolic disturbances and for the stress hormones adrenalin (A), noradrenalin (NA), dopamine (D) and cortisol. They were also asked to answer questions on mental stress. Of the 484 patients 318 (66%) agreed to undergo venous and arterial blood sampling. In 87 cases, the arterial blood sampling failed due to technical difficulties.

In January 2007, all 413 patients still alive, except for 16 who had moved abroad and four who could not be traced, received information on this follow-up study including an informed consent to sign and return together with questions on all hospital admissions since 1992 with as many details as they could remember. In the patients´ medical records, all stated admissions were then checked by discharge diagnoses. All discharge notes were read. The

patient was classified as an event case if, during the follow-up period, there was a diagnosis of IHD or cerebrovascular disease. International classification of diseases (ICD-10) codes I20.0 to I25.9 and ICD-9 codes 410-414 were used to define the IHD group. For the cerebrovascular diagnoses ICD-10 codes from I61.2 to I69.4 plus codes G45.9 and G46.3 and ICD-9 codes 434X-436X were used. For patients with unspecified chest pain diagnosis (ICD-10 code R07.4) the discharge notes were again scrutinized in search of indications of ischemic heart disease.
For patients who had died during the follow-up period, causes of death were collected from the Cause of Death Registry from the Swedish Centre for Epidemiology at the National Board of Health and Welfare. These data were checked against the diagnoses in the medical records of each deceased patient.

The IHD and cerebrovascular groups were then analysed together, making up the event group (n = 74 or 26%). All other patients (n = 216 or 74%) made up the non-event group regardless of hospital admissions for other diagnoses or no further hospital admission during follow-up.

5.2 The Questionnaires

5.2.1 The Medical Outcomes Study short form 36 (SF-36)

SF-36 is a validated, generic health status questionnaire developed by Ware [116] and translated into several languages. Swedish data exist for the general Swedish population, for geographical subgroups, age groups, sex, educational grade and marital status [117, 118]. The Swedish norm database contains 8930 subjects. Data was gathered by seven postal surveys covering different parts of the country (total county, rural area and small to larger towns) with a response rate of 68%. The target population was 13152, age range was 15-93 years, mean age was 42.7 years and 48.6 % were men. The surveys were conducted during 1991-92. A second edition of the manual was published in 2002 [119].
SF- 36 consists of 36 questions grouped in eight dimensions: Physical Function (PF), Role Physical (RP), Bodily Pain (BP), General Health (GH), Vitality (VT), Social Function (SF), Role Emotional (RE) and Mental Health (MH). Two summary measures have been constructed on the basis of factor analysis and added to SF-36, the Physical Component Summary (PCS) and the Mental Component Summary (MCS) [120]. The scores were coded, summed and transformed according to the instructions produced by the questionnaire designers. The SF-36 results can be presented as a profile or by the summary measures. Numerically higher scores indicate better health.

5.2.2 Cardiac Health Profile (CHP)

The CHP is a disease specific health related quality of life questionnaire, tested for reliability and validity in a Swedish population with ischemic heart disease [121]. This questionnaire consists of three parts. Part I assesses the degree of angina pectoris (CCS-score) according to Canadian Cardiovascular Society classification. CCS I = ordinary physical activity does not cause angina, CCS II = slight limitation of ordinary activity, CCS III = marked limitation of

ordinary activity and CCS IV = inability to carry out any physical activity without discomfort [122]. Part II assesses HRQoL (16 items). Initially five factors were extracted. However, only key components are reported here i.e. Emotional (items 1, 2, 5, 6 and 7), Social (items 10, 11 and 12), Somatic functioning (items 14, 15 and 16) and Emotional Control (items 8 and 9) [123]. Part III consists of the subjective scoring of psychosocial "cost-benefit" of treatment interventions (two items). The Cardiac Health Profile uses a visual analogue (VAS) scale with verbal "anchors" at each side expressing extremes e.g. yes, very much - no, not at all. The scores are added and divided by the number of answered items. Low values are indicative of better health. This is the reverse of SF-36. In 2004, a reanalysis of CHP identified cognitive function as a principal component [124].

5.2.3 Zung Depression Inventory (ZDI)

The ZDI is a simple questionnaire for assessing depression. In its original version the questionnaire contains 20 items [125]. The response choices are "none or little of the time", "some of the time", "a good part of the time" or "most of the time". The scale items are added (1 - 4). Half of the items are worded positively and half negatively and thus a reversed scoring is utilized on those items. As originally described by Zung raw scores were transformed into an index by dividing the raw score by the maximum score and multiplying by 100. Index scores > 69 indicate severe depression, 60-69 indicate moderate depression, 50-59 indicate minimal to mild depression and a score < 50 is normal i.e. no depression present. The Zung questionnaire was somewhat altered as item number 19 was removed. Two years after the event it was thought to be unsuitable. Therefore, the maximum score possible in the present study was 76.

5.3 Measurements

5.3.1 Laboratory measurements

The salivary cortisol, the plasma cortisol, the routine laboratory testing in Paper IV and the metabolic measurements in Paper III of P-glucose (enzymatic hexakinase method with 4% CV at 5 and 15 mmol.L^{-1}), S-HDL-cholesterol (homogeneous enzymatic method with 5% CV at 1 and 2 mmol.L^{-1}) and S-triglycerides (enzymatic method with 4% CV at 1 and 2 mmol.L^{-1}) were performed according to standard laboratory procedures at the Department of Clinical Chemistry and Transfusion Medicine, Sahlgrenska University Hospital, Gothenburg, Sweden. Analyses reported in Papers I and II were made at the Department of Laboratory Medicine, Kungälvs Hospital. The analyses of the catecholamines were performed at Department of Clinical Pharmacology, Sahlgrenska University Hospital, Gothenburg, Sweden.

5.3.1.1 Salivary Cortisol

In Paper III, salivary cortisol was sampled twice in the morning. The subjects were instructed, orally and in writing, to collect as much saliva in their mouth as possible and then “chew” on a cotton swab (Salivette®, Sarstedt AB, Landskrona, Sweden) for 30 to 60 seconds. The first measurement was to take place immediately after awakening irrespective of clock time and

the second measurement was made after 15 minutes [126-128]. The participants were instructed to perform the test on a weekday and not to brush their teeth, smoke, have breakfast or put anything in their mouths before or during the sampling period. Marked with time of day and date, the swabs were replaced in their containers and returned by post to the laboratory. Salivary cortisol was determined by radioimmunoassay technique (Orion Diagnostica Oy, Espoo, Finland). Laboratory intra- and inter-assay coefficients of variation (CV) were < 10%.

5.3.1.2 Plasma Cortisol

In Paper IV, samples for plasma cortisol had been drawn from the brachial vein and analysed using radioimmunoassay technique, RIA Cortisol I 125, from Farmos Diagnostica, with CV 1.4 and 2.9%. The samples were collected before lunchtime but were not otherwise time-standardized.

5.3.1.3 Catecholamines

In Paper IV, the blood samples for catecholamines had been drawn from the radial artery after 15 minutes of supine rest and were collected in chilled glass tubes containing Na2-EDTA and glutathione on iced water. The samples were cold centrifuged (3000 rpm) at +4º C and frozen at -70ºC until analysis. High performance liquid chromatography (HPLC) with electrochemical detection was used for analysis [129]. For low and high values the CV was for noradrenalin 8.8% and 9.8%, for adrenalin 10.1% and 9.5% and for dopamine 17.9% and 22.6%.

5.4 Statistics

5.4.1 General considerations

Although parametric statistics are fairly robust, small samples and non-normal distribution samples may need to be analysed non-parametrically. This is also the requirement for qualitative data (nominal and ordinal). Yet, it has been argued that for transformed questionnaire data or data measured on a visual analogue scale parametric statistics might be used. However, statistical experts differ in views, as to the appropriateness of such a procedure.

Another area where opinions differ is the use of imputated values. The rational for this practise is that it may be better to use all acquired data and combine those with some imputated values instead of discarding all non-complete datasets. However, in both instances the result will be less reliable than with complete data. Inevitably in follow-up studies, there will be some data loss. Importantly, the data loss must not be systematic. Different methods of imputation are at hand. The EM-imputation (Expectation-Maximization) iterative procedure was used in Papers II and III [130].

The follow-up over time procedure used in this thesis highlights another potential statistical problem i.e. that of mass significance. The frequently chosen significance level of $\alpha = 0.05$ means that one out of 20 analyses may be statistically significant by chance alone. Thus, with

many analyses performed the risk of type I errors (finding associations where they do not exist) increase. By restricting the number of performed analyses or including for example the Bonferroni correction where significance levels are adjusted, the risk of type I errors are somewhat lessened.

Type II errors are the opposite of type I i.e. when no association or difference is found but where in fact there is one. In order to ascertain minimal risk of type II errors power analyses are performed. Power is equal to $1 - \beta$ where β is the false negative rate or the probability of a Type II error. Power is usually set at 80%. The power analysis is performed to calculate the minimal sample size or effects size needed in the study. To do so requires some estimate of expected effects and its variation in the studied population. These data are not always at hand, thus a "qualified guess" may be necessary. However, the analysis can also be made post hoc.
In the first parts of the thesis no power calculations were made at the planning stage. In later studies the ethical committee required power analyses. In Paper III sample size was estimated to be 250 based on an assumption of 10% pathological cortisol response in the study population. In Paper IV ideally a sample size of 200 in each group would have been required for power of 80% and a significance level of 0.05. The calculations were based on the assumption that there would be twice as many deaths/events in the CHD group as in the control group. However the study was a follow-up study and despite attempts to recruit all previous participant 60% took part in this follow-up. The event group had but 74 patients. Post hoc tests of stress markers in Paper IV show insufficient power to detect differences between event group and controls.

5.4.2 Statistical test used

In this thesis standard statistical tests were used for descriptive statistics; t-test for quantitative data and χ^2 - test for categorical data. Non-parametric statistics (Mann-Whitney U) were used analyzing the Cardiac Health Profile and the Zung questionnaires. For change over time i.e. for variables in dependent groups the Wilcoxsons Matched pair test was used (Paper I).

For transformed SF-36 scores (MCS and PCS) that were approximately normally distributed, parametric analyses have been performed (Paper I). To analyse changes over time for MCS and PCS scores repeated measures analysis of variance were used (Paper II) with age group as the grouping variable and time as the repeated-measure factor. As multiple comparisons were made the Bonferroni correction was used in the respective age group, adjusting observed significance levels. Repeated measures analysis of variance was also used in the post hoc analysis. One sample t-test was used analyzing MCS and PCS scores compared with the age and sex adjusted normative population.

Due to the incomplete dataset imputation using the EM-algorithm was performed, analyzing SF-36 scores (Paper II). As predictor variables, age of respondents and SF-36 scores at baseline were chosen. In Paper III, to make up a complete data set for the MetS variables, EM imputation was also performed. In the same Paper paired-samples t-test was used on logarithmically transformed data for the cortisol at awakening to 15 minutes later calculations. Initially Pitman´s nonparametric test [131] was used in the evaluation of continuous variables

and Fisher´s exact test was used to evaluate proportions (Paper IV). The Fisher´s exact test is a special form of Pitman´s test. A stepwise logistic procedure was used in the multivariate analyses. OR was calculated for the odds of dying of an IHD/cerebrovascular event in the study population, divided by the odds of dying of equal events in the control population.

Two-tailed tests were applied throughout. Generally, $p < 0.05$ was considered significant. Due to the large number of p-values created in Paper IV, no formal p-level was stated. Data have been analysed using the following statistical packages: STATISTICA®, Release 5, 3rd edition (Paper I), SPSS for Windows version 10.05 (Paper II) and version 15.0 (Paper III) and SAS version 9.1 (Paper IV).

5.5 Ethical considerations

All participants gave written informed consent after having been informed of the respective study orally and in writing except for participants in Paper IV who received a letter of invitation only. To answer these often used questionnaires repeatedly, were not seen as an ethical dilemma except for one item in the Zung questionnaire which was removed. All blood and cortisol samples except for the arterial sample in study IV can be regarded as standard procedures in health care and were not judged to be unduly harmful. For the arterial sample additional consent was sought. The study subjects were free to contact the author at all times.
All studies were approved by the local ethics committee (Papers I and II 264-94, S45-95, S81-96 and L185-97, Paper III Ö 044-03 and Paper IV 459-05, T226-06, T661-06).

6. Results

6.1 Paper I and II

The outcomes presented in Papers I and II cover the same patient groups and they were followed for two years i.e. at 3 and 6 months (Paper I) and 12 and 24 months (Paper II) post index infarction. Of the initial 72 there was a gradual reduction in study subjects. At two years a total of 16 or 22% of the patients had left the study for different reasons (moving out of catchment area, non renewal of consent and death), predominantly from the older age group.

6.1.1 CHP

At three months follow-up, there were statistically significant differences in Cardiac Health Profile; factors Emotional and Social functioning and Control between the younger and older age groups (Figure 6). Angina pectoris was reported by 44% of the patients at 6 months and there were statistical significant differences between patients with and without angina for the CHP items Physical Capacity (item14), ($\overline{x}$ ± SD) 60.4 ± 29.7 vs. 34.2 ± 19.7, p = 0.003 and General Health (item 15), ($\overline{x}$ ± SD) 51.4 ± 20.1 vs. 27.6 ± 21.5, p = 0.001. At 12 and 24 months, reported angina did not differ between age groups and was found in roughly 50% in both age groups at both times (50% versus 45% at 12 and 52% versus 44% at 24 months in younger compared with older patients).

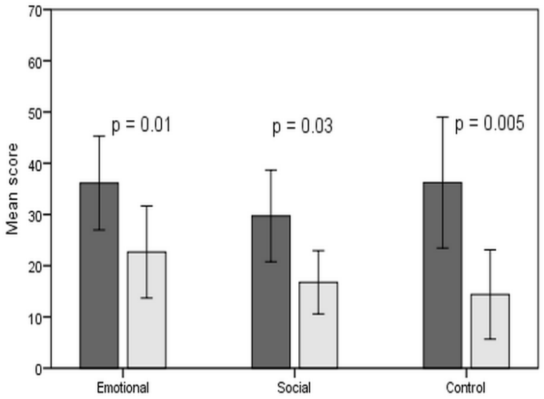

Figure 6. Cardiac Health Profile factors Emotional and Social functioning and Control three months after a first myocardial infarction by age group (mean ± 95% CI). Dark grey bars = patients < 59 years. Light grey bars = patients ≥ 59 years. Due to missing data n = 25 in age group < 59 and n = 22 in age group ≥ 59 years. Lower scores indicate better HRQoL.

Results from the CHP at two years, point in the same direction as at six months i.e. factors Emotional and Social Functioning showed statistically significant differences between groups (p = 0.03 and p = 0.05, respectively) demonstrating poorer quality of life in the age group < 59 years (Figure 7).

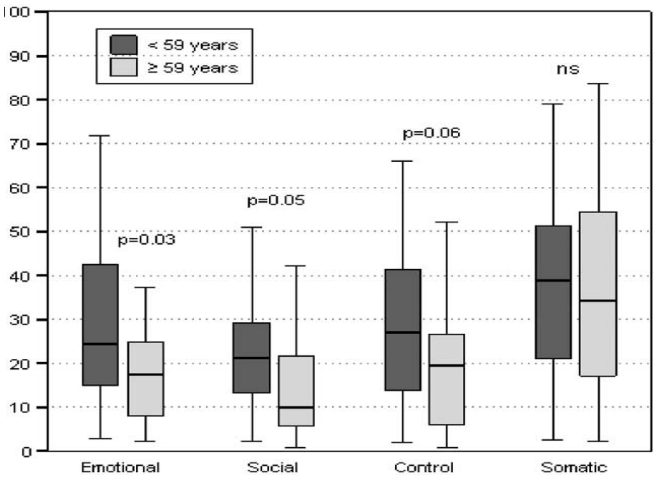

Figure 7. Box plot of Cardiac Health Profile factors Emotional, Social, Control and Somatic functioning two years after a first myocardial infarction by age group. Dark grey boxes = patients < 59 years. Light grey boxes = patients ≥ 59 years. Due to missing data n = 29 in age group < 59 and n = 23 in age group ≥ 59 years. Lower scores indicate better HRQoL.

6.1.2 SF-36

Predictors for MCS were age (p = 0.025) and Vitality (p = 0.020) both positively related to quality of life. Predictors for PCS were Physical Function (p = 0.003) and CCS score (p < 0.001) where angina grade was negatively related to QoL (Figure 8). Further, SF-36 factor General Health (GH) was found to predict readmission to hospital. A 10-unit increase in GH reduced the risk of readmission by 35% (RR = 0.65%, CI 0.46-0.92). From SF-36 it was shown that patients ≥ 59 years improved in Physical (PCS) and Mental Component Summary (MCS) scores, scoring comparable to community norms at 6 months (Figure 9). However, patients < 59 years improved in PCS but not in MCS, and scored significantly below age and sex adjusted community norms in both PCS ($\overline{x}$ = 44.7, CI 40.6–48.7 vs. $\overline{x}$ = 50.3, CI 49.3–51.4) and MCS ($\overline{x}$ = 45.9, CI 41.8–49.9 vs. $\overline{x}$ = 51.3, CI 50.3–52.4) at 6 months.

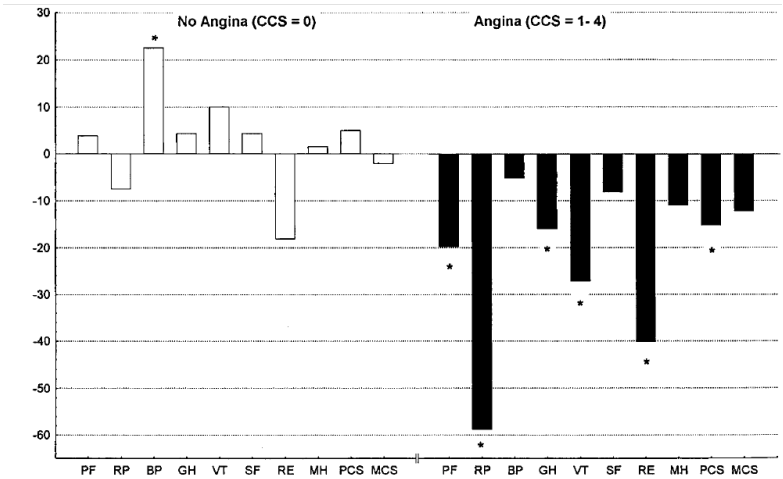

Figure 8. SF-36 scores in 6-month MI survivors by angina grade, deviation (%) from age- and sex-adjusted community norms. Open bars = no angina. Filled bars = angina (CCS grade = 1–4). * Denotes statistically significant differences (95% CI) from community norms. PF = Physical Function, RP = Role Physical, BP = Bodily Pain, GH = General Health, VT = Vitality, SF = Social Function, RE = Role Emotional, MH = Mental Health, PCS = Physical Component Summary and MCS = Mental Component Summary.

There were no statistically significant changes in SF-36 MCS scores at 12 and 24 months post infarction for the age group < 59 years (Figure 9). However, there were improvements in PCS scores, from baseline to 12 and to 24 months (p < 0.01 and p < 0.001, respectively) and from 6 to 24 months (p = 0.04). This patient group reached community norms in PCS scores after 2 years but scored significantly below norms in MCS scores throughout. In patients ≥ 59 years, no further statistically significant changes in the SF-36 summary scores took place after 6 months.

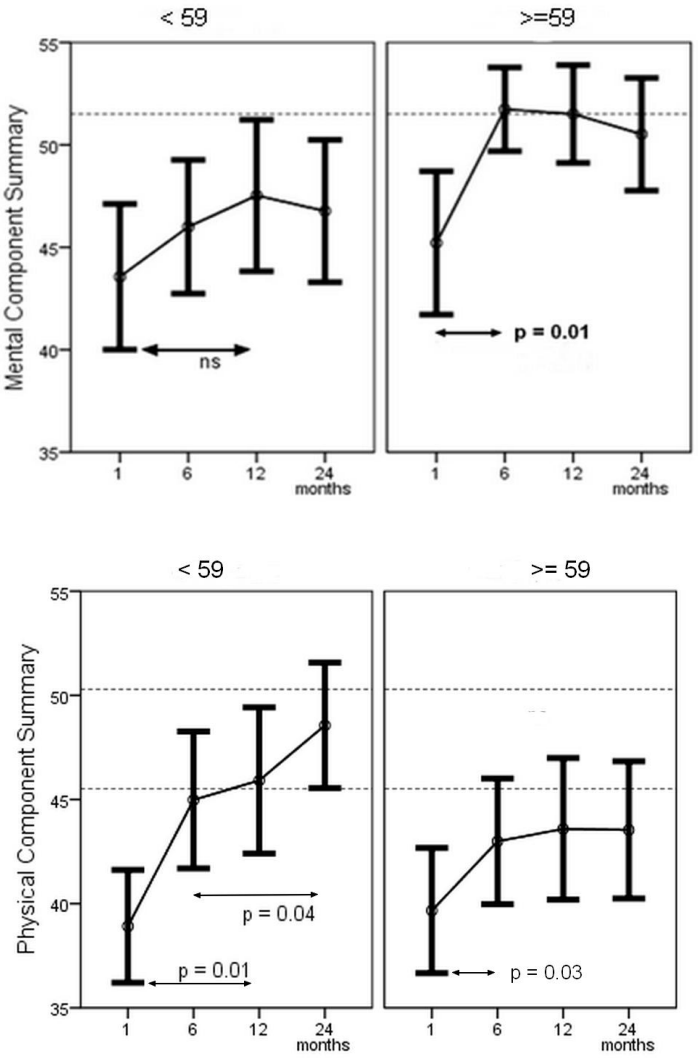

Figure 9. Mental and Physical Component Summary scores (mean and 95% Confidence Interval) at 1, 6, 12 and 24 months post myocardial infarction by age group. Left panels, patients < 59 and right panels, patients ≥ 59 years. Reference lines have been added to display the age and sex adjusted normative controls; mean score 51.5 for MCS and for PCS 50.3 and 45.5 for the younger and older age groups respectively. Higher scores indicate better HRQoL.

An effect size of -0.5 (CI -0.88 to -0.14) was found comparing MCS in the younger age group with population norms. This represents a medium sized effect. In PCS in the younger and in PCS and MCS in the older age group, the effect sizes were 0.1-0.2 indicating only small or trivial effects. Effect size calculations over time are found in Table 2.

Table 2. Effect size from 1 to 6 and 1 to 24 months post myocardial infarction by age group

		Age groups (years)					
		< 59	≥ 59			< 59	≥ 59
MCS	T1-T2	0.26	0.78	PCS	T1-T2	0.73	0.35
	T1-T4	0.33	0.55		T1-T4	1.21	0.38

MCS = SF-36 Mental Component Summary. PCS = SF-36 Physical Component Summary. T1-T2 = 1 to 6 months. T1-T4 = 1 to 24 months.

A post hoc analysis of MCS scores showed that the 19 patients with invasive cardiac procedure/s (percutaneous coronary intervention/coronary artery bypass grafting) did not improve in the overall mental health score (MCS) compared with patients without such procedures. Thus improvement in MCS from one to 12 and 24 months was only seen among patients without intervention, $p = 0.002$ and $p = 0.003$ respectively. The dichotomous measure emotional limitations or "reduced well-being" has been defined as ≤ 52 on the SF-36 mental health (MH) scale. At 2-years post AMI this measure was found to be 10% which is equal to that found in the general population.

6.1.3 ZDI

From the Zung Depression Inventory, used at 24 months post index event, a median score of 44.7 was found. However, it was shown that 25% of the patients could be classified as having mild depressive symptoms (scores ≥ 50 range 50-61), eight patients in the younger and five in the older age groups. There was no significant difference between age groups. Five patients in the older age group had incomplete data and no scores were calculated.

6.2 Paper III

The relative cortisol awakening response (CAR %) was explored in a population of randomly selected middle aged subjects in western Sweden. The choice of percentage change was due to differences in awakening cortisol values. The metabolic syndrome, a cluster of IHD risk factors, were identified using NCEP criteria and the percentage change or CAR% defined as (cortisol sample at 15 minutes minus at awakening) divided by the sample at awakening and multiplied by 100. CAR% was compared with that of the healthy controls. The MetS prevalence was 17.9% for men and 15.4% for women.

There were no statistical differences in the MetS components between the study participants and the population based INTERGENE cohort except for systolic blood pressure in men which was somewhat lower in the INTERGENE cohort compared with male study subjects (139 mmHg versus 144 mmHg, $p = 0.03$). All MetS components except systolic and diastolic blood pressure in men differed between MetS and non-MetS subjects. Men awoke significantly earlier than women, $p = 0.05$ and 14 men and 5 women performed the cortisol testing on a weekend contrary to instructions. There were also 22% non-responders defined as

subjects with no increase in cortisol between awakening and 15 minutes later. Three fourths of these had high awakening levels (mean 21.4 nmol.L^{-1}) and one fourth showed levels equal to or below the mean awakening level for responders (mean 10.7 nmol.L^{-1}).

The MetS women were significantly older and reported more depressive symptoms than non-MetS women but there were no differences in menopausal status or hormonal replacement therapy. Both men and women with MetS were also less formally educated and reported less alcohol consumption than their non-MetS counterparts. Cortisol values are shown in Figure 10.

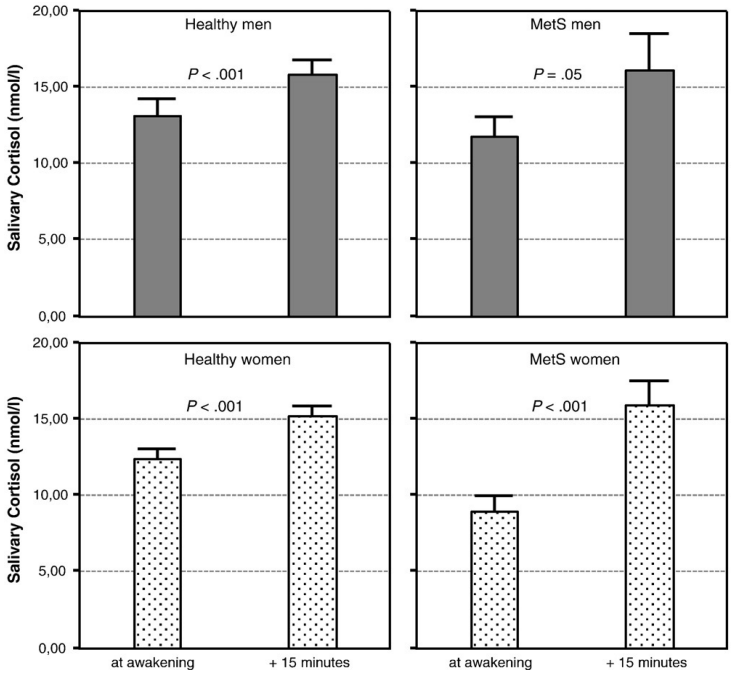

Figure 10. Salivary cortisol (nmol.L^{-1}) at awakening and 15 minutes later by sex and the MetS in men and women aged 45 to 70 years. Data are mean and SE. Solid bars = men; dotted bars = women. Statistical testing was performed on logarithmically transformed data.

A significant difference in CAR% was found between men and women with MetS, CAR% ($\overline{x}$ ± SE) 38.5 (13.1) % and 91.4 (17.0) %, respectively, p = 0.02. Women with the MetS awoke with a significantly lower cortisol level ($\overline{x}$ ± SE) 8.92 (0.96) nmol.L^{-1} than women without the syndrome 12.33 (0.69) nmol.L^{-1}, p = 0.05. They reached the same salivary cortisol level after 15 minutes ($\overline{x}$ ± SE) 15.87 (1.6) nmol.L^{-1} and 15.17 (0.63) nmol.L^{-1} respectively. Women with MetS had a CAR% of ($\overline{x}$ ± SE) 91.4 (17.0) %, and women without MetS had a CAR% of 36.5 (5.7) %, p < 0.001. The corresponding values for men were 38.5 (13.1) % and 36.0% (6.1) % and cortisol at awakening were ($\overline{x}$ ± SE) 11.77 (1.27) nmol.L^{-1} and 13.11 (1.03) nmol.L^{-1} for

MetS men compared to non-MetS men. The corresponding values after 15 minutes were ($\overline{x}$ ± SE) 16.04 (2.42) nmol.L^{-1} and 15.79 (0.89) nmol.L^{-1}. Thus, healthy men and women showed an increase in cortisol of about 40% from awakening to 15 minutes later as did men with MetS while the increase in CAR was 90% in women with MetS.

In univariate analysis, associations were found for CAR% and MetS ($F_{1,89}$ = 13.19, P < 0.001) and for CAR% and depressive symptoms ($F_{1,80}$ = 8.12, P = 0.01) in women, and also for CAR% and type of day the test was performed, i.e. weekday/weekend, in men ($F_{1,82}$ = 4.63, P = 0.03). There were no significant associations between CAR% and age, awakening time, alcohol, smoking status, marital status, education, work status, or physical activity for either sex. Furthermore, there were no significant associations between CAR% and the factors of the individual MetS components.

Thus, CAR% was associated with the MetS, depressive symptoms and type of day the cortisol sampling took place i.e. weekday/weekend. These significant variables were entered in a regression model. This model was significant only for women (R^2 = 18%, $F_{3,78}$ = 5.50, p = 0.002) but not for men ($F_{3,73}$ = 1.94 n.s.) The coefficients for women are shown in Table 3. The study indicates a sex difference in awakening cortisol. The result was adjusted for depressive symptoms a known factor related to the awakening response.

Table 3. Regression of relative change in the CAR on MetS, depressive symptoms, and weekday or weekend cortisol sampling for women aged 45 to 70 years.

	Coefficient b	Standard error (b)	t	p
constant	32.3	7.04	4.61	<0.001
MetS	49.8	17.9	2.78	0.01
Depressive symptoms	23.9	14.1	1.70	0.09
Weekday/weekend	-30.8	25.7	-1.20	0.24

6.3 Paper IV

In this 14-year follow-up study 60% or 290 out of the original 484 patients took part. During the follow-up period 24 patients had died with a diagnosis of ischemic heart or cerebrovascular disease, and 50 patients had been given such a diagnosis at hospital discharge. These 74 patients made up the event-group. The non-event group consisted of the other 216 participants. Consequently, there were 194 patients that could not be followed, the non-participants. The patients in the event group were older, had more pathological ECGs at ED, had more often a previous cardiovascular disease diagnosis or risk factors for such disease, and used more medication than the non-event group. All blood lipids except LDL-Cholesterol differed between the groups (Table 4). Patients in the non-event group had better exercise capacity at re-evaluation, mean (SD) of 154.8 (46.4) Watt (W) versus 132.5 (36.2) W for the event group, p < 0.001. The non-participants were younger, had less often a CVD

history, better blood lipids, lower body mass index (BMI) and were more often smokers (43% versus 32%) than participants.

Of all variables entered in univariate analyses only significant variables were then entered into two regression models. One model had NA included and the other had NA excluded as dependent variable. The reason for the choice of two models was the number of missing NA samples data. In the non-noradrenalin model age (OR 1.12, CI 1.06–1.19), previous history of angina pectoris (OR 9.69, CI 2.06–71.61), pathological ECG at emergency department visit (OR 3.27, CI 1.23–8.67), hypertension (OR 5.03, CI 1.90–13.76), smoking (OR 3.04, CI 1.26–7.63) and lipid lowering medication (OR 14.9, CI 1.60–152.77) were all associated with future ischemic heart or cerebrovascular events. When noradrenalin was included in the regression model high maximal exercise capacity was protective of an event (OR 0.986, CI 0.975–0.997). Previous history of angina pectoris (OR 3.91, CI 1.35–11.53) and pathological ECG at ED (OR 17.64, CI 2.79–346.95) were again associated with future ischemic heart or cerebrovascular events.

Table 4. Blood chemistry, cortisol and catecholamines in event group (ischemic heart disease or stroke), non-event group and non-participants.

	Event group	Non-event group	p-value	Event + non-event groups	Non-participants	p-value
Subjects	74	216		290	194	
Tot. Cholesterol *	6.3 (1.1)	5.8 (1.3)	0.01	5.9 (1.3)	5.6 (1.1)	0.01
LDL-C ***	0.3 (0.6)	0.4 (0.7)	ns	0.4 (0.6)	0.2 (0.5)	0.01
HDL-C **	1.3 (0.5)	1.4 (0.5)	0.01	1.4 (0.5)	1.3 (0.5)	0.01
Triglycerides *	2.1 (1.2)	1.5 (1.0)	0.001	1.6 (1.1)	1.8 (1.6)	ns
Blood Glucose *	4.8 (1.3)	4.3 (0.8)	0.002	4.4 (1.0)	4.6 (1.6)	ns
Cortisol †	377 (133)	390 (135)	ns	387 (134)	420 (172)	0.05
P-Adrenalin ‡	0.51 (0.37)	0.52 (0.34)	ns	0.52 (0.36)	0.54 (0.39)	ns
P-Noradrenalin ‡	2.44 (1.02)	1.90 (0.75)	0.001	2.06 (0.87)	1.80 (0.61)	0.01
P-Dopamine ‡	0.22 (0.28)	0.28 (0.77)	ns	0.27 (0.67)	0.20 (0.36)	ns

Data are mean (SD). * indicate < 5%, ** 5 to < 10%, *** 10 to < 15%, † 25 to < 35% and ‡ = 50% missing values. P-values denoted if $p \leq 0.05$. Metabolic values in $mmol.L^{-1}$, cortisol and catecholamines in $nmol.L^{-1}$.

Noradrenalin levels were highest in the event group mean (SD) 2.44 (1.02) $nmol.L^{-1}$, intermediate in the non-event group 1.90 (0.75) $nmol.L^{-1}$ and lowest among the non-participants 1.80 (0.61) $nmol.L^{-1}$. The reverse was found for cortisol i.e. cortisol values mean (SD) were for the event group 377 (133) $nmol.L^{-1}$, for the non-event group 390 (135) $nmol.L^{-1}$ and for the non-participants 420 (172) $nmol.L^{-1}$ (Table 4).

A post hoc comparison was made using death statistics from the Västra Götaland region. Regional data showed an expected IHD/cerebrovascular mortality of 2.8% per 14 years. In the present study, however, there were 24 or 8.3% such deaths during this period. This gives an Odds Ratio of 3.2 (CI 1.4 - 7.2). An all cause mortality of 10% or 30 subjects were expected

based on the above mentioned official statistics, but we found that 48 (17%) had died during follow-up, p = 0.04.
There were statistical differences between participants and nonparticipants regarding six of the stress questions but no statistical difference between event and non-event groups. For example, the non-participants affirmed significantly more noise exposure than the participants but were less likely to recently have lost a close relative. But, they did experience being under pressure or to "get stuck" in emotional relationships more than the participants did.

6.4 Results summary

- Improvements in HRQoL over time were found but with different quality of life patterns for younger compared with older first AMI patients. Younger patients had a more protracted recovery.

- Also, compared with an age and sex adjusted reference population the younger AMI patients had not recovered within the overall mental health domain two years post index event.

- Angina pectoris was associated with worse quality of life in the physical domain of HRQoL, but age and Vitality were positively related to HRQoL.

- A 10 unit increase in SF-36 General Health domain reduced readmission risk by 35%.

- Women with the metabolic syndrome had a cortisol awakening response twice over that of men with the metabolic syndrome and also of healthy men and women from a reference group of a randomly selected adult population.

- The women with the metabolic syndrome also had the lowest awakening cortisol levels.

- Traditional risk factors predicted future diagnosis of ischemic or cerebro-vascular events in a chest pain patient population followed for 14 years.

- The stress biomarkers cortisol and noradrenalin showed a graded response with the lowest cortisol and highest noradrenalin values in the event group compared with the non-participants and the non-event group showed intermediate values.

- Post hoc analysis in the mixed group of chest pain patient having visited the ED 14 years previously, demonstrated increased odds ratio for future IHD or cerebrovascular death compared with a reference population from the region.

7. Discussion

This thesis has touched upon three separate aspects of disease; risk factors foregoing disease or relapse, biochemical markers of disease states and disease outcome. More specifically, the main findings were that traditional risk factors, i.e. previous diagnosis of angina pectoris, hypertension, pathological ECG at ED, smoking and age did predict future hospitalization or death with a cerebrovascular/IHD diagnosis in a cohort of chest pain patients followed for 14 years and that there was 3-fold greater odds to die from IHD for these patients than for controls. In the cross-sectional study a biochemical marker of the HPA-axis function, i.e. the cortisol awakening response, was investigated and found to differ between men and women with the metabolic syndrome. In men there was no association with the MetS when adjustments had been made for depressive symptoms and for type of day the cortisol testing was performed. For women, CAR% was still associated with the MetS after adjustments. Further, outcome in terms of the overall mental health (SF-36 MCS score) after a first AMI was delayed in younger compared with older patients and also more profound compared with an age and sex adjusted control population. Age and vitality predicted quality of life in the mental dimension and physical function and angina predicted the outcome in the physical dimension of HRQoL after six months, where angina grade was inversely related to QoL.

7.1 Risk factors, IHD and HRQoL

The following risk factors were recognized in this thesis; previous diagnosis of angina pectoris, hypertension, pathological ECG at ED, smoking, age and also exercise capacity. Further, early in the disease process the SF-36 domain general health (GH) predicted rehospitalisation and SF-36 domains physical function (PF) and vitality (VT) were found to predict HRQoL at six months together with angina pectoris and age.

The results from the follow-up of chest pain patients (Paper IV) are in line with previous published results confirming classical risk factors to be associated with future IHD. It also supports previous findings from Gothenburg, showing unfavourable prognosis comparing men with and without chest pain [132]. However, diverse results have been published and low-risk patients with chest pain have been reported to be unlikely to sustain an adverse coronary outcome [133]. Contrary to this, Bodegard et al. [134] have reported a follow-up study after 26 years showing an increased risk of adverse cardiac events in patients with "possible angina" according to a WHO questionnaire. These authors point out that unless the follow-up time is sufficiently long the worsened outcome in the possible angina group would have been missed. Our results also support findings on beneficial effects of higher exercise capacity [135], and pathological ECGs at ED as a risk [136]. Outcome studies on chest pain may not be easily comparable as the respective patient mix and follow-up times differ. Moreover, diagnostic work-up particularly in chest pain cases of suspected non-cardiac or unknown aetiology are likely to vary considerably [137-139]. When interpreting the result in this thesis it must be remembered that the follow-up was not conducted on a low-risk group but on a mixed group of chest pain patients. This is likely to represent more of a clinical reality.

Misclassification of diagnoses is a recognised phenomenon in research. R07.4 was a frequent diagnosis but patients that had been given this diagnosis were not included in the event-group. Some unrecognised early stage IHD patients may well be hidden among these cases with unspecified chest pain [140]. However, if this would be the case, it would indicate underestimation in the strength of associations rather than overestimation.
Associations between some stress variables and the risk of future IHD events could not be established fully. However, the stress hormones of the non-participants provided some indications of such a possibility, see below. The items from the stress questions however are harder to interpret. Loss of a close relative was more frequent in the event group and is known to be related to stress. But the results between groups for some of the other items are contraintuitive. A lack of power may be an explanation.

After considering the differences in baseline data the non-participants were judged to be "healthier" than the participants. A loss of the "healthiest" in the follow-up process will make the non-event group more ill laden and its function as control group less suitable. This was the rationale performing a post hoc test on deaths. The odds ratio was shown to be increased in the event group compared with a regional control group strengthening the conclusion of increased risk of unfavourable outcomes in chest pain patients.

7.2 Biochemical markers, HPA-axis and SNS function

The non-participants (Paper IV), showed the lowest NA values compared with non-event and event groups. The non-participants also had the highest cortisol values compared with these groups. The cortisol values in the non-participants were in line with reported normal values [141] and importantly the prevalence of hypertension was equal across groups. The graded levels of the stress hormones suggest that a stress state might be present in the event group possibly via a perturbed HPA-axis (lowest cortisol) in combination with a more stress reactive sympathetic nervous system (highest NA) than in the other groups.

Despite many years measuring the cortisol awakening response, which is thought to express the HPA-axis activity, the complete function of this response has not been solved as yet. Anticipation of demands in the day to come following awakening has been proposed [80]. The MetS is a cluster of IHD risk factor shown to be associated with AMI [31, 142]. The prevalence of MetS in this study was comparable to Swedish data [32].

The result of the awakening response presented in this thesis is an example of sex-specific differences in CAR, in this case in the presence of the MetS. It is comparable with results from a study where chronically stressed women showed an awakening response greater than that of men [143]. The exact mechanisms underlying these sex differences are still to be revealed. Suggested mechanisms are the HPA-axis interaction with the gonadal axis [144, 145] and/or psychological or psychosocial factors; for instance, some stressors have been shown to have a dissimilar effect on men and women [146, 147]. A heightened cortisol response has been associated with IHD [96] and CAR has been shown to be elevated in patients with ACS in the acute phase [148].

As in previously reported studies, the awakening response was associated with depressive symptoms and weekday/weekend testing also in this study [149, 150]. However, these associations were sex dependent, with depressive symptoms significantly associated with CAR% in women and weekday/weekend significantly associated with CAR% in men only. Hyperactivity of the HPA-axis has been seen in major depression, although there may be different responses in subtypes of depression as have been suggested [151]. The participants in this study came from a randomly sampled population-based cohort. Therefore, it seems unlikely that finding should be due to subtypes of depressive disorders among the study participants. When adjusting for depressive symptoms, the main finding was still significant, indicating MetS to contribute independently to the awakening response in women.

The blunted CAR on weekends has been attributed to less anticipatory stress on weekends compared with weekdays [149]. Non-compliance with the cortisol sampling protocol has also been proposed as a cause of a flatter response [152]. In this study the expected lower response on weekends was found to be present in men. However, women showed a response on weekends similar to that found on weekdays, indicating the presence of more anticipated demands in this group. Yet, work status did not differ significantly between men and women.

The non-response pattern in studies of awakening cortisol is intriguing and a number of explanations have been put forward. Also described by Dockray [153], there were non-responders in the study showing high awakening levels with no further increase and participants with low awakening cortisol and no further increase indicating different mechanisms behind the non-response. There seems to be a small number of "true" non-responders but whether this is a normal or pathological phenomenon is not known at the present time [154].

This is also so for the low cortisol values at awakening which was found in women with MetS only. Low cortisol levels have been attributed to disease states such as stress sensitivity, pain, and fatigue. Further it has been reported in abdominal obesity, cancer patients and insomnia [155, 127, 156] but also been found in healthy individuals under stress. Thus, whether a low value is an indication of HPA-axis dysfunction centrally or peripherally or just a sign of normal adaptation to stress is not altogether evident [157-159]. Studies have reported associations between abdominal obesity and cortisol [160-162] but results are not consistent [126, 163, 164]. A low cortisol exposure has been found in men and women with abdominal obesity, in men it was related to waist circumference and in women to WHR [165]. Methodologically these studies differ making comparisons difficult.

7.3 Outcome in terms of HRQoL after a first AMI

Health related quality of life could be regarded as an outcome measure and/or as a risk factor (see 7.1). In this thesis HRQoL was primarily regarded as an outcome measure and the summary measures (physical and mental component summary scores) of the SF-36 questionnaire made up the main results supported by results from the CHP questionnaire. There were two key findings; the effects found in the mental sphere of quality of life were

long lasting and these effects struck younger patients worse than older AMI patients. The effect size was moderate but judged to be clinically relevant [166]. This comparison was made with the age and sex adjusted normative population at 2 years after the AMI.

The risks of impact on HRQoL were the expected for angina pectoris and SF-36 domain physical function (PF). The presence of angina was essentially equally distributed in both groups and is known to mostly influence the physical domain and is a major determinant of HRQoL [167, 168]. Patients leave hospital with physical restriction and when these are lifted an improvement in PF is likely to occur. However, the SF-36 domain mental health (MH) did not predict quality of life but vitality (VT) did. Tiredness is a common complaint after an AMI and may at least partly mask depressive disorders [169]. Loss of vitality or exhaustion has been linked to lower CAR [170]. The perception of self-rated health has been shown to predict mortality, morbidity and illness behaviour [171]. Thus, the finding of a protective effect of general health (GH) on rehospitalisation was therefore reasonable.

Signs of depressive symptoms were in line with previously published results. There seems to be fair agreement that depressive symptoms can be found in up to a quarter of the patients post infarction and represent an increased risk of adverse events [172-175]. However, emotional limitations, a SF-36 construct, and the Zung inventory at 2 years gave dissimilar results. The emotional limitation was roughly equal to the prevalence in the reference population. A possible reason for the different findings of psychological well-being is the manner in which psychological well-being is measured. It has been suggested that different instruments may be measuring different aspects of the same construct [176]. This may be illustrated by the phenomenon that Brink [177] has reported in an interview study, where patients did not label their symptoms as depression instead fatigue was a prominent complaint. Further, clinically diagnosed depression and self reported depressive symptoms do not necessarily match. Emotional distress has also been described as an overlap of depressed mood, anxiety, irritability and diminished energy. Importantly, tiredness is also a major symptom in cardiac failure, a source of generally low HRQoL.

In addition, there has been concern about older ages holding a more positive health outlook than younger subjects and that the wording in the quality of life questionnaire might be of importance. The SF-36 does not include specific age comparative items and would not have favoured the older age group in this respect [178]. That age might be associated with the patients' perception of HRQoL was a clinical impression that was verified. At that time, the connection between age and MCS had not been previously reported. However, indirectly there had been reports of results that could support such a finding [179, 104, 180, 57, 181]. For instance, Denollet et al. found younger distressed patients to constitute a high risk group for adverse events and lower quality of life. Ho et al. in 2008 [182] concluded that older AMI patients had fewer symptoms and better quality of life than younger patients and Schweikert et al. [183] reported lower quality of life compared with the general population in younger ages in AMI survivors. However, when comparing HRQoL outcomes it is important to keep in mind that specific instruments usually are more responsive to change while the generic instruments have advantages when comparisons are made between groups.

As has been previously reported, there are gender differences in perception of HRQoL [184]. But due to too few women in the outcomes studies (Papers I and II) no such analysis was undertaken.

7.4 Strengths and limitations

All studies included in this thesis were small and none of the studies were experimental. Thus, known drawbacks of small observational studies apply to them all. However, efforts were made to find control groups to compare results with and the selection of patients/study subjects have been based on random samples or consecutive patients. Yet, the control group in the risk factor study was not ideal and some suggestions have been put forward based on basic data of non-participants. Also, a post hoc analysis was performed. The control group in the outcome study was age and sex adjusted and based on general population data and the controls in the cross-sectional study came from a large random sampled population. One study is cross-sectional but the other two have followed a group of patients over time inevitably with some missing data some of which were imputated. There was also a sizeable loss of catecholamine data due to technical reasons. The participants lost to follow-up have been relatively small in the outcome and cross-sectional studies but substantially larger in the risk factor study and misclassification was a distinct possibility in that study. Yet, if misclassification had occurred it would have rather under than overestimated results. There have also been doubts about adherence to protocol especially in the cross-sectional study measuring the cortisol awakening response. But the main result did not change when these non-responders were excluded. For methodological reasons there have been challenges in interpreting single stress hormone results in the risk factor study. The lack of consistent results of the stress items in the risk factor study have been puzzling but may be due to too low a power. All results must thus be interpreted with some caution and further studies are clearly needed as more depth, larger studies and improvements in methodology are desirable.

8. Conclusion

This thesis has looked into different aspects of IHD and results indicate that the classical risk factors predict future ischemic or cerebrovascular events in a group of mixed chest pain patients and also that these patients may be at a higher risk of death than a reference population. Further, that there may be a sex dependent link between the metabolic syndrome and HPA-function as judged by the cortisol awakening response in women with the metabolic syndrome. And also, that the outcome after an AMI in terms of HRQoL specifically in overall mental health show long-lasting effects and lack of recovery in younger compared with both older AMI patients and with the general population.

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