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Manifestations and Survival in Coronary Heart Disease

Kerstin Dudas

Göteborg 2009

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ISBN 978-91-628-7593-0

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Printed by Geson Hylte Tryck AB, Göteborg, Sweden, 2009

To my family

Manifestations and Survival in Coronary Heart Disease

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ABSTRACT

Aim: To investigate how risk factors predict manifestations in coronary heart disease (CHD), and trends in short-term and long-term survival including trends in out-of-hospital mortality.

Populations and methods: In the first study 7388 men aged 47 to 55 and free of previous acute myocardial infarction (AMI) or stroke were investigated during 28 years' follow-up. In the second and third study we created a record linked database from the Swedish hospital discharge and death registries documenting all cases aged 35 to 84 years who had either been hospitalized for a first AMI or who had died from CHD outside hospital without a prior hospitalization for AMI. In the last study data were derived from 143, 457 consecutive patients aged 25 to 105 years from the Swedish Register of Cardiac Intensive Care (RIKS-HIA) with a first episode of either AMI or unstable angina (UAP).

Results: Serum cholesterol was a stronger predictor (OR 5.21) for future coronary artery bypass grafting (CABG) than for AMI. Smoking was a weaker risk factor for CABG than for AMI with no discernible increase in risk except in very heavy smokers (OR 2.19). Both short- and long-term case fatality after hospitalization for AMI decreased from 1987 to 1998, more in younger than in older patients. 28-day case fatality was reduced by half in male and female patients <55 years. This reduction was maintained throughout the first five years. The reduction in 28-day case fatality decreased with age to about one third among men and women aged 75 to 84 years. Hospital mortality decreased roughly by half over the period, whereas the reduction in out-of-hospital deaths was about one fourth. The great majority of all fatal first events in CHD occur outside hospital, and this proportion is increasing, particularly in younger CHD victims. Among patients with a first acute coronary syndrome event, male sex, slightly older age, as well as smoking, diabetes, and peripheral arterial disease are major determinants for presenting with AMI, rather than UAP. Differences with respect to smoking, diabetes, and peripheral arterial disease were more pronounced for women than for men.

Conclusions: There are decreasing trends in case fatality among patients in all ages with coronary heart disease admitted to hospital. Still, the absolute majority of deaths occur out-of-hospital. Different manifestations of coronary disease have different risk factor patterns, suggesting that secular changes in risk factor pattern could potentially influence the clinical expression of the disease.

Keywords: coronary heart disease, acute coronary syndrome, coronary-bypass grafting, mortality, case fatality, survival, manifestation, predictors, risk factors, trends, cholesterol

ISBN 978-91-628-7593-0 Göteborg 2009

LIST OF ORIGINAL PAPERS

This thesis is based on the following papers, identified in the text by their Roman numerals:

I. Dudas KA, Wilhelmsen L, Rosengren A. Predictors of coronary by-pass grafting in a population of middle aged men.
Eur J Cardiovasc Prev Rehabil. 2007 Feb;14(1):122-7

II. Dudas K, Lappas G, Rosengren A. Trends in short- and long-term prognosis after hospital admission for acute myocardial infarction 1987 to 2003 in 264 575 Swedish patients.
Submitted

III. Dudas K, Lappas G, Rosengren A.Trends in in-hospital and out-of-hospital deaths in coronary heart disease 1987 to 2003 in Sweden.
In manuscript

IV. Dudas K, Björck L, Stenestrand U, Wallentin L, Rosengren A. Differences between acute myocardial infarction and unstable angina - findings from the Register of Information and Knowledge about Swedish Heart Intensive Care Admissions (RIKS-HIA).
In manuscript

CONTENTS

ABBREVIATIONS

ACE	angiotensin-converting enzyme
ACS	acute coronary syndrome
AMI	acute myocardial infarction
BMI	body mass index
CABG	coronary artery bypass grafting
CCU	coronary care unit
CHD	coronary heart disease
CI	confidence interval
CVD	cardiovascular disease
ECG	electrocardiogram
ICD	International Classification of Disease
HR	hazard ratio
LDL-cholestrol	low-density lipoprotein cholesterol
MI	myocardial infarction
MONICA	the MONICA (Multinational MONItoring trends and determinants in Cardiovascular Disease) project
Non STEMI	non ST-elevation myocardial infarction
OR	odd ratio
PAD	peripheral arterial disease
PCI	percutaneous coronary intervention
PIN	personal identification number
RIKS-HIA	Register of Information and Knowledge about Swedish Heart Intensive care Admissions
SCD	sudden coronary death
SD	standard deviation
STEMI	ST-elevation myocardial infarction
UAP	unstable angina pectoris

INTRODUCTION

Despite decreasing trends in cardiovascular mortality, more than 40% of all deaths in Sweden are still due to cardiovascular diseases.[1] Coronary heart disease (CHD) is the single most common cause of death in Sweden, as well as in most other high-income countries. More than one in five women and men currently die from CHD in Europe.[2] In 2003 31% of all incident acute myocardial infarction (AMI) cases in Sweden died within 28 days.[3]

The atherosclerosis disease process

Occlusive vascular disease usually occurs as a result of arterial thrombus caused by a disrupted plaque and is responsible for most of the acute and lethal CHDs.[4] In the 19th century coronary thrombosis was regarded as a medical curiosity and the clinical-pathological processes did not begin to be elucidated until the beginning of the 20th century.[5,6] Previous research has shown that atherosclerosis is a systemic disease, beginning with fatty streaks and subsequently developing into intermediate and advanced lesions. A vulnerable plaque may rupture or progress into an advanced obstructive lesion (Figure 1).[4,7-9] Thrombosis over a plaque occurs by two different processes, erosion and rupture.[10] The risk of a future thrombotic event in a plaque is facilitated by a large lipid core, inflammatory reaction, low density of smooth muscle cells in the capsule, and a thin capsule.[7]

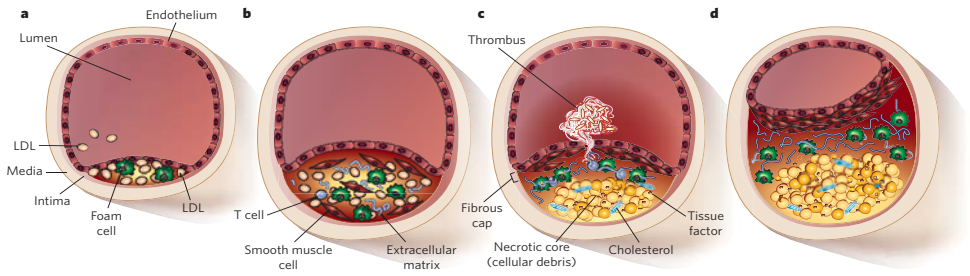

Figure 1. Initiation and progression of atherosclerosis. Atherosclerosis occurs at sites in the arterial tree where laminar flow is disrupted. A lesion begins as a fatty streak (**a**) and can develop into an intermediate lesion (**b**), and then into a lesion that is vulnerable to rupture (**c**) and, finally, into an advanced obstructive lesion (**d**).

Translating molecular discoveries into new therapies for atherosclerosis. Daniel J. Rader & Alan Daugherty. Nature 451, 904-913 (21 February 2008) doi:10.1038/nature06796. Reprinted with permission from Nature.

Classification of acute coronary syndrome

The acute coronary syndromes (ACS) represent a spectrum of events resulting from the interaction between the rupture, or erosion of the vulnerable atherosclerotic plaque and the subsequent thrombus formation. The clinical presentation is determined by the location of the culprit lesion, and by the severity, duration and extent of the resultant myocardial ischemia. Acute coronary syndromes can manifest as unstable an-

gina, non-ST elevation myocardial infarction (non STEMI), ST-elevation myocardial infarction (STEMI) or sudden death (Figure 2).[9,11] Acute myocardial infarction can be classified by clinical, electrocardiogram, biochemical and pathological characteristics.[12]

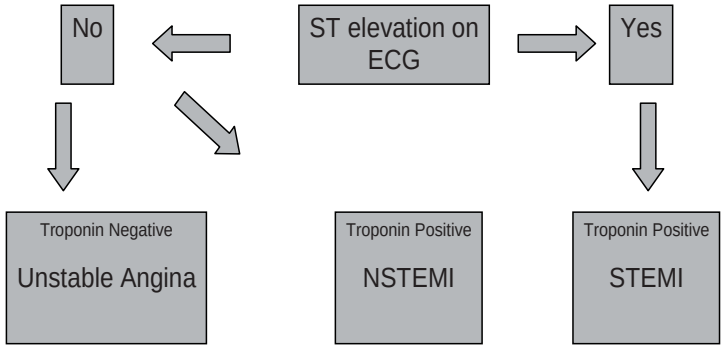

Figure 2. Acute Coronary Syndromes Classification.

Angina pectoris

Stable angina pectoris is characterized by discomfort or pain in the chest induced by effort, and relieved by rest.[13] Chronic angina pectoris is induced by ischemia, usually due to atherosclerotic narrowing of the coronary arteries. The resulting ischemia is reversible, there is no necrosis, and, accordingly, no markers of myocardial damage.[14, 15]

Acute coronary syndromes, unstable angina and acute myocardial infarction

In contrast to stable effort-induced angina pectoris, unstable angina (UAP) shares clinical and pathophysiological properties with myocardial infarction. Both in AMI and in unstable angina, ischemia results from a sudden occlusion or near-occlusion of a coronary artery by a thrombus induced by erosion or rupture of a plaque. Unstable angina pectoris comprises a broad spectrum of patients, however, the most common form includes the large majority of patients with established diagnosed or undiagnosed coronary atherosclerosis and an unstable plaque that has caused subtotal coronary occlusion.[16]

Myocardial infarction

The pathological definition of myocardial infarction (MI) is myocardial cell death caused by prolonged ischemia. In clinical settings MI is diagnosed when cardiac biomarkers are raised in patients with symptoms of ischemia and/or electrocardiogram (ECG) changes of indicating new ischemia or development of pathological Q-waves or imaging evidence of a new loss of viable myocardium.[17] The difference between

STEMI and non-STEMI is that STEMI often is caused by a total occlusion of a major coronary artery which is complete and sustained with persistent ST-segment elevation >20 minutes. In contrast, non-STEMI is characterized by no persistent ST-segment elevation, the occlusion is usually less than total, and distal perfusion may partly be maintained.[18,19]

Sudden death

Sudden coronary death (SCD) in coronary heart disease occurs early with many victims dying outside hospital[20-22] and can be the first and only symptom.[23] There are some difficulties in interpreting epidemiological data on sudden death because of the variability in the definition of sudden death.[24] One is that sudden death is a "*natural, unexpected fatal event occurring within one hour from the onset of symptoms in an apparently healthy subject or whose disease was not so severe as to predict an abrupt outcome*".[25] Results from the MONICA study (Multinational MONItoring trends and determinants in Cardiovascular Disease project) indicate that two out of three fatal cases below the age of 65 years occurred before reaching hospital.[26] In a UK study, dating from the mid90s, 74% of 1589 deaths from acute coronary heart attacks in people aged under 75 years occurred outside hospital and they found that the proportion of out-of-hospital to total deaths varied inversely with age from 91% at age <55 years to 67% at age 70-74 years.[27]

Risk factors and epidemiology

The overall and worldwide most important risk factors for both women and men are tobacco smoking and abnormal lipids, which together are responsible for two thirds of AMIs.[28,29] The history of epidemiology in cardiovascular disease (CVD) started in the late 1940s[30] and in the late 1960s the evidence for causal associations between risk factors that had been identified and disease became so strong that preventive trials were initiated. One early study by Ancel Keys 1953[31] was to become a cornerstone in the literature on epidemiology and prevention. Keys described the relationship between serum cholesterol levels and geographical variation in CHD mortality.[31] Twenty years later the Seven Countries Study added to the previous findings, showing that CHD risk was strongly related both to serum cholesterol levels and to diet high in saturated fat.[32-38] In countries where CHD rates have declined with Finland[39] the most striking example, public campaigns have sought to implement changes in lifestyle and risk factors. Later research has shown that the decline in CHD was explained by changes in serum cholesterol, blood pressure and smoking both in women and men.[40] The INTERHEART study concluded that lifestyle modification is of substantial importance at all ages and in both men and women to prevent CHD,[28] identifying, in addition to smoking and lipids, abdominal obesity, diabetes, hypertension, lack of regular physical activity, no daily vegetable and fruit consumption, and psychosocial factors as important modifiable risk factors.[28]

Register studies

The history of cause specific mortality statistics in Sweden dates back to the middle of the eighteenth century. With the person-based national hospital discharge registry

added to the possibility of linking registers through personal identification codes the potential for determing outcomes are exceptionally good in Sweden.[41,42] In addition, in contrast to registers only covering hospital discharges, out-of-hospital deaths can also be investigated. Because patients in clinical trials are selected, register data may better reflect the fate of patients in clinical practice.

Management of coronary heart disease/acute coronary syndrome

The management of acute myocardial infarction has evolved from the understanding that coronary thrombosis does not always cause sudden death and the therapy of absolute rest in bed for several days to today's modern treatment of CHD.[5,6] Coronary care units (CCUs) were first established in the 1960s in an effort to reduce the high early mortality in AMI of 30-40%.[6,43] The CCU arguably constitutes the most important single advance in AMI treatment. The control of death from arrhythmia, with external defibrillation and the combination of mouth-to-mouth breathing and sternal compression, cut the early mortality in half.[6,43,44] In 1970 online monitoring was developed. The introduction of thrombolytic therapy in the 1980s for treatment of STEMI, along with aspirin and β-blockers for all infarctions reduced mortality further.[6,45] Modern management of ACS consists of a battery of early risk stratification, alleviation of pain, breathlessness and anxiety,[18] and of pre-hospital or early in-hospital restoration of coronary blood flow and myocardial tissue reperfusion with primary percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG)) or fibrinolytic therapy.[18,46]

Compared to AMI, UAP has considerably better short-term prognosis,[47] although, ultimately, long-term prognosis may not differ greatly between patients with AMI and UAP.[48] While the development of coronary disease broadly is dependent on well-known risk factors clinical presentation and severity might be influenced by variations in risk factor pattern.[28] Apart from the changes in coronary care, risk factor pattern in the population has also changed considerably over the last decades.[49-51] Changes in risk factors in the population might also influence clinical presentation. Given the variation over time in treatment modalities, and in risk factors, the overall purpose of the present investigation was to describe and quantify some of these influences.

AIMS

General aim

To investigate how risk factors predict manifestations in coronary heart disease, and trends in short-term and long-term survival including trends in out-of-hospital mortality.

Specific aims

The aims of the thesis were:

- To assess risk factors for future coronary by-pass grafting as a first coronary event, and to compare them with risk factors for a first acute myocardial infarction. (Paper I)
- To examine age and gender-specific trends in long-term prognosis after admission for acute myocardial infarction. (Paper II)
- To investigate trends in the proportion who died in in-hospital and out-of-hospital in a first CHD event in Sweden. (Paper III)
- To compare patients with a first episode of either acute myocardial infarction or unstable angina pectoris, with respect to a range of risk factors and comorbidities. (Paper IV)

METHODS

Study populations and methods

Paper I

There were 7,388 participating (Figure 3) men free from prior AMI or stroke from the intervention group in the multifactor Primary Prevention Study that began in Göteborg, Sweden in 1970[52]. All men in the city who were born between 1915 and 1925 (n=30,000), except those born in 1923, were randomised into 3 groups of 10,000 men each.

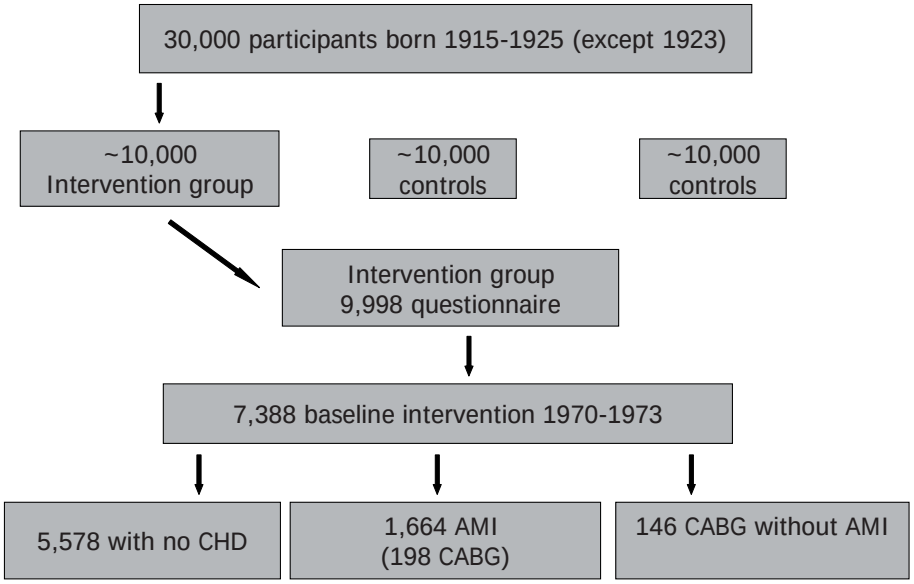

Figure 3. Participants in the multifactor Primary Prevention Study.

The men in the intervention group (intervention group; n=9 998; participants 7,388), gave their informed consent to participate in the study and were offered a screening examination to identify and treat risk factors. A second examination was done in 1974 to 1977, and a third in a 20% subsample in 1980. The intervention was essentially a high-risk strategy directed towards men with pronounced hypercholesterolemia, severe hypertension, or heavy smoking habits, according to predefined criteria with treatment for hypertension, hyperlipidemia or smoking offered at specialist clinics.[52] After 12 years outcome and risk factor pattern were found to be similar in the intervention and control groups[52] and hence we consider the intervention group to be representative of the background population in the city. The study was approved by the Ethics Committee for Medical Research at Göteborg University.

Information on smoking habits, physical activity during leisure time, treatment for hypertension, diabetes, psychological stress, myocardial infarction and stroke, and

family history of AMI were collected via a postal questionnaire sent to all men in the investigated group. Men who returned the questionnaire were invited to a clinical examination. Men who did not return the questionnaire were sent one reminder but after this no further action was taken. The screening examinations were performed in the afternoon. Blood pressure was measured after 5 minutes' rest with the subject seated. Body mass index (BMI) was calculated as weight/m^2. BMI was classified into six categories <20, 20-22.5, 22.5-25.0, 25.0-27.5, 27.5-30.0 and >30.0 kg/$height^2$. Smoking habits was coded as never smoked, former smoker of more than one month's duration, smoking 1-14 g of tobacco per day, smoking 15-24 g and smoking 25 g or more per day. One cigarette was considered to contain 1 g of tobacco, a cigarillo 2 g and a cigar 5 g of tobacco. Serum cholesterol concentrations were determined in blood samples taken after fasting for at least 2 hours according to standard laboratory procedures.[53] Physical activity during leisure time was categorized into four levels with 1 representing sedentary activity, 2 moderate activity such as walking or light gardening during at least four hours per week, and 3 regular, strenuous, or 4 very strenuous activities. Because there were few men in category 4, the two highest categories were combined. Psychological stress was assessed by way of one single question in the postal questionnaire and rated from 1 to 6, with 5 and 6 defined as permanent stress during the last year, or the last 5 years, before the examination, respectively.[54]

In the multifactor Primary Prevention study all participants were followed from the date of their baseline examination until 31 December, 1998, by running the data file of the men in the study against the Swedish national register on cause of death and the Swedish Hospital Discharge Register. All discharges from Sahlgrenska Hospital, which was the single major hospital in the city until 1977, and also the only hospital in the region with thoracic surgery, have been entered in the national register since 1970 (except 1976 due to a legislative change for that single year), and all discharges from Östra Hospital, the other major hospital of the city, that opened in 1978, were entered from the start.[55] In addition, until March 1983, all fatal and nonfatal myocardial infarctions fulfilling predefined criteria occurring in the study population were recorded in the Göteborg AMI Register.[56]

For the purpose of these analyses, cases of AMI and of men undergoing CABG without prior AMI were identified. AMI was defined as a discharge, or death with an International Classification of Diseases code of 410 (ICD 8 until 1986, ICD 9 until 1996) or I21 (ICD 10) as a principal diagnosis. Fatal cases were defined as AMI if the underlying cause of death was 410-414 (ICD 8 and 9) or I21-I25 (ICD10). To identify cases of aorto-coronary by-pass operations classification codes 3066, 3067 and 3091 were used prior to 1997 and FNA and FNC during 1997 and 1998. Codes for coronary angioplasty were not registered for the purpose of the present study. Forty-six men undergoing CABG in connection with an operation for aortic stenosis were excluded, leaving 146 men who had undergone CABG, 1664 men with AMI and 5578 men without evidence of CHD during follow-up; altogether 7388 men, for analysis. Of the men with AMI, 198 subsequently underwent CABG; they were categorized among the AMI group.

Papers II and III

In Papers II and III the personal identification number (PIN) was utilised to link data from the National Hospital Discharge register and the Cause of Death register. In the subsequent analyses all personal identifiers were removed and substituted with code numbers. The Swedish National Hospital Discharge register started to operate on a small scale in the 1960s. In 1980, hospitalizations from 16 counties were registered. By 1984, 19 counties, including the 3 largest cities (Stockholm, Goteborg and Malmo), or 85% of the Swedish population, were included in the register, and from 1987, it has been operating on a nationwide basis.

In Sweden, patients with AMI are almost exclusively hospitalized in public hospitals. Patients with coronary heart disease dying out of hospital are reported to the National Cause of Death Register. For Papers II and III registrations from 1980 to 1986 were used to exclude patients with a diagnosis of AMI before 1987. The International Classification of diseases (ICD) version 9 (ICD-9) was used from 1987 to 1996 and version 10 (ICD-10) from 1997 onwards.

In Paper II AMI was defined as being admitted to hospital and discharged with a first principal diagnosis of 410 (ICD-9) or I21 (ICD-10). From 1987 to 2003, 264 575 persons aged 35 to 84 years were admitted alive with a first AMI. The patients were followed through a linkage to the death registry until December 31, 2003. Cardiovascular death was defined as a death certificate diagnosis of 390-459 (ICD-9) or I00-I99 (ICD-10).

In Paper III a first event was defined as either admission with a first AMI (ICD 9 410, ICD 10 I21) or CHD death (ICD 9 410-414, ICD 10 I20-I25) without admission to hospital during the period January 1, 1987 to December 31, 2003. From 1987 to 2003, 377 030 persons aged 35 to 84 years were registered for a first AMI or death from CHD in one or both registries (Figure 4). In this paper persons with any prior CHD diagnosis were excluded.

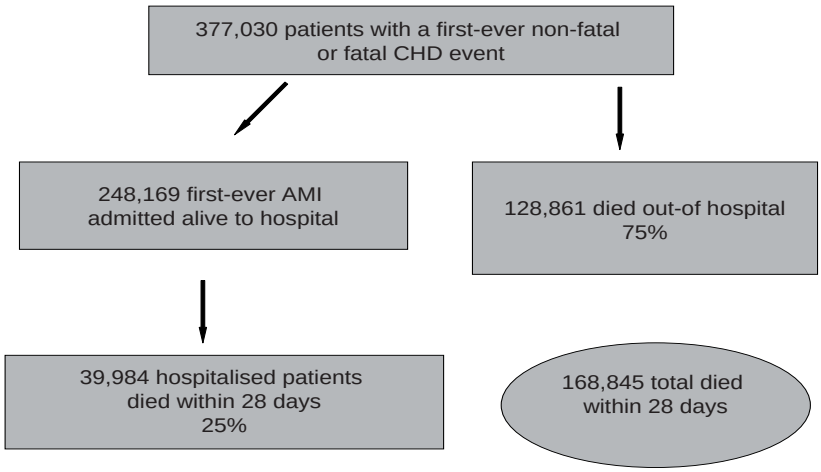

Figure 4. Study subjects in Paper III.

In both Papers II and III changes over time were studied relative to the first period 1987 to 1989. Analyses were done separately for the age groups <55 years, 55 to 64 years, 65 to 74 years, 75 to 84 years.

Paper IV

The Swedish Register of Cardiac Intensive Care (RIKS-HIA) started in 1995 with 19 participant hospitals, increasing gradually thereafter, and in 2005 72 out of 77 Swedish hospitals with CCUs were participating. All patients admitted to hospitals with coronary care units (CCUs) are continuously registered in the RIKS-HIA. The full protocol has been published previously.[57] (Detailed information and complete protocol are also available at http://www.riks-hia.se). On admission, patients receive written information about RIKS-HIA and other quality registries and have the right to deny participation, but few of the patients exercise this right. According to Swedish law, written consent is not needed, because quality control is an inherent part of hospital and other care. The register is approved by an ethics committee and the National Board of Health and Welfare. All personal identifiers are removed from the RIKS-HIA data file when used for research purposes.[58]

Paper IV is based on all consecutive patients who were admitted between January 1, 1995 and June 30, 2005. The patients were aged 25 to 105 years without a history of prior AMI or UAP. Of 143,478 patients, we excluded 21 patients with missing data on gender, leaving 143,457 patients, 98,479 diagnosed with a first AMI and 44,978 diagnosed with a first UAP.

Information on about 100 variables is reported on case records during the hospitalization and is filled in by nurses. In the present study we used information at admission on smoking status (never smoking, ex-smoker [defined as no smoking for more than 1 month before admission to hospital] and current smoker), known hypertension, diabetes mellitus (history or medication), previous heart failure, previous known symptomatic peripheral arterial disease (PAD), electrocardiography and other pharmacological treatment.

Definitions of acute myocardial infarction and unstable angina pectoris

Papers II, III and IV

The criteria for a diagnosis of AMI and unstable angina were known and identical for all participating hospitals using the World Health Organization and Joint European Society of Cardiology and American College of Cardiology Committee criteria.[59,60] However, ultimately, diagnoses were coded at the treating physician's discretion. The International Classification of diseases (ICD) version 9 (ICD-9) was used from 1987 to 1996 and version 10 (ICD-10) from 1997 onwards. AMI was defined as a discharge diagnosis with a principal diagnosis of 410 (ICD-9), or I21 (ICD-10). During the study period the biochemical criteria were revised in accordance with the ESC/ACC consensus document,[60] implying more sensitive criteria, and, accordingly, that more patients were diagnosed with AMI, rather than angina during the last years of the data collection. Diagnostic codes for angina were 411B and 413 (ICD 9), I20 (ICD 10). We operationally defined any acute admission to CCU with a diagnosis of angina

as unstable angina, because the broad diagnostic category of angina, without further specification was used for a significant number of patients. Planned admissions for diagnostic or therapeutic procedures were not included. Only first events were included, with a first event defined as no history of AMI, and no prior hospitalization in the register for any CHD (ICD9 410-414 and ICD 10 I20-I25).

Validation of registers

Papers II and III

A validation study of the register showed that, of all admissions to Swedish departments of internal medicine, including cardiology, a primary discharge diagnosis was lacking in 0.8% and 0.5% of the cases discharged with the diagnosis AMI had no valid PIN.[55] In a study using data from 1987 to 1995 a random sample of records from patients discharged with a diagnosis of either AMI or other coronary disease was validated by the national AMI register, the National Hospital Discharge Register and the National Cause of Death Register.[55] The predefined criteria for a definite myocardial infarction were met in 86%, with possible myocardial infarction diagnosed in an additional 9%. In records with a diagnosis of ischemic heart disease other than AMI (ICD-9 411-414) 3% met the criteria for myocardial infarction.[61] More recent validation data are missing but since then more sensitive and exact methods for diagnosing MI have been introduced, but also a lower threshold for diagnosing MI.[62]

Paper IV

The validity of source data has continuously been validated by comparison of the register information with the hospital patient records by an external monitor. There was a 94% agreement between the registered information and the source data in patients' records comprising 161 280 data point from 38 hospitals.[63]

Statistical methods

Paper I

Means were calculated with standard methods. To evaluate risk over time Cox proportional hazard ratios, with 95% confidence interval were calculated. The risk over time was adjusted for all variables significantly associated with AMI in univariate analysis. Age, serum cholesterol, body mass index, and systolic blood pressure were entered as continuous variables, whereas smoking was entered with five levels, physical activity with three, and stress as permanent versus all other, and family history, treatment for hypertension and diabetes as yes/no variables. To estimate the differences in association between the risk factors for AMI and CABG a multiple logistic regression analysis for the two diagnoses, AMI and CABG, was used in a generalized logit model. According to this we modelled the logits of three categories response variables (no risk, AMI and CABG) against the risk factors. In this model, age-adjusted odds ratios are obtained for the two separate outcomes, and then compared to see whether they are significantly different. SAS software statistical package (version 8e) were used for all analyses.

Paper II

Case fatality from all causes and cardiovascular causes of deaths (mortality) was calculated for 0-28 days, 28 days to 1 year, 1 year to 5 years and a total of 5 years for patients with a first-ever admission for AMI until 1998. Percentage changes are presented relative to the first period (1987 to 1989) with 95% confidence intervals (CIs). The 95% CIs for the changes were estimated using Poisson regression with age and period serving as covariates. Mean annual case fatality was calculated for 366 days to 5 years for patients admitted until 1998. The calculations were done for men and women separately for the age groups <55 years, 55 to 64 years, 65 to 74 years and 75 to 84 years. Cumulative cardiovascular and non-cardiovascular mortality was estimated for the periods 1987 to 1989, 1990 to 1992, 1993 to 1995, 1996 to 1998, 1999 to 2001 and 2002 to 2003 for patients hospitalized until 2003. Hospitalization rates for AMI were age-adjusted.

Men and women were analysed separately with logistic regression models. In order to assess the changing association of incidence year on case fatality we added a variable that was equal to YEAR x YEAR in order to assess the changes that did not follow a linear regression (a quadratic term of the time variable (YEAR)). The coefficient for this term gave a statistically significant odds ratio below 1, which indicates a time-decreasing effect. The same procedure was applied for the changing association of age on case fatality. The quadratic term for the age gave a statistically significant odds ratio above 1 which indicates an age-increasing effect on the change in case fatality.

Paper III

Descriptive statistics were calculated in form of counts and percentages and presented across different age-groups combinations and periods of incidence. The log-odds of mortality within 28 days was modelled as a linear function of age and period of incidence as odd ratio (OR) calculated through logistic regression. Percentage changes are presented relative to the first period (1987 to 1989). All analyses in Papers II and III were done with SAS version 9.1 and R version 2.6.

Paper IV

To describe baseline characteristics and differences we used means and percentages in patients with AMI and UAP. The independent associations between baseline characteristics (history of tobacco smoking (never smoking, former smoking and current smoking), history of hypertension, history of heart failure, history of diabetes and history of peripheral arterial disease, medication treatment before admission (eg. aspirin, β-blockers, angiotensin-converting enzyme (ACE) inhibitors, long-acting nitrate and lipid-lowering drugs) and AMI) were assessed by means of logistic regression, where AMI was entered as the dependent variable, with all variables in addition to age and sex used as covariates (possible confounders). To assess differences between men and women in each factor effect we included an interaction term in the model (gender x factor). Odds ratios were calculated from the logistic regression model. Because of the large size of the population, 99% confidence intervals were used. All statistical analyses were performed using the SPSS version 15.0 (SPSS Inc, Chicago, IL, USA).

RESULTS

Paper I

Of the groups that we investigated, men who underwent CABG without previous AMI had the highest mean total serum cholesterol 7.04 (standard deviation (SD) 1.21) mmol/l, followed by men with AMI or who died from CHD, 6.72 (SD 1.23), whereas men with no CHD had a mean baseline level of 6.36 (SD 1.12) (Table 1).

Table 1. Baseline characteristics by diagnosis during follow-up

	No CHD **Mean (SD) N= 5578**	**All MI** **Mean (SD) N= 1664**	**CABG cases without previous MI Mean (SD) N=146**
Age, mean (SD), year	51.4 (2.3)	52.1 (2.2)	51.0 (2.2)
BMI,mean (SD), kg/m²	25.4 (3.2)	26.0 (3.4)	25.8 (3.2)
Total serum cholesterol, mean (SD), mmol/L	6.36 (1.12)	6.72 (1.23)	7.04 (1.21)
Systolic blood pressure, mean (SD), mmHg	147 (21)	154 (23)	153 (22)
Diastolic blood pressure, mean (SD), mmHg	94 (13)	98 (14)	97 (14)
Family history, n (%)	1013 (18)	401 (24)	48 (33)
Diabetes, n (%)	73 (1)	68 (4)	6 (4)
Current smoker, n (%)	2653 (47)	969 (58)	60 (41)
Permanent stress, n (%)	1112 (20)	375 (23)	33 (23)

BMI differed only marginally between the groups. Men with coronary disease had higher mean systolic and diastolic blood pressure than men who remained free of CHD but there were no differences between the AMI and the CABG groups.

Even within the comparatively narrow age span of the men in the study, the risk of AMI increased sharply with age (Table 2). In contrast, older men were less likely to undergo CABG. Family history of CHD, serum cholesterol, hypertension and diabetes predicted both AMI and CABG, whereas high BMI, low physical activity and psychological stress were significantly associated only with AMI. Even light to moderate smoking (1-14 g/day) was associated with increased risk of AMI; hazard ratio (HR) 1.70 (1.50-1.94), whereas only very heavy smokers were more likely to undergo CABG, HR for 25 g/day or more 2.19 (1.02-4.66). Serum cholesterol was a stronger predictor for CABG than for AMI. Compared to men with serum cholesterol ≤5.0 mmol/l, men with serum cholesterol 5.1-6.4, 6.5-7.4 and >7.4 mmol/l had adjusted hazard ratios (HR) of 1.22 (1.00-1.49), 1.66 (1.35-2.03) and 2.04 (1.65-2.51) for AMI. Corresponding HRs for CABG were 1.57 (0.66-3.70), 3.44 (1.47-8.03) and 5.21 (2.20-12.31) after adjustment for age and other factors.

Table 2. Hazard ratios associated with cardiovascular risk factors for AMI and for ACB without prior AMI during follow up

	All AMI					ACB without prior AMI			
	Number in category	Observation years	Cases per 100 000 (n)	Hazard ratio (95% CI) age adjusted	Hazard ratio (95% CI) adjusted[1]	Observation years	Cases per 100 000 (n)	Hazard ratio (95% CI) age adjusted	Hazard ratio (95% CI) adjusted[1]
Age									
<50 years	1593	34790	715 (249)	1.00	1.00	32032	140 (45)	1.00	1.00
50-51	2402	52342	950 (497)	1.31 (1.12-1.52)	1.28 (1.10-1.50)	45806	105 (48)	0.75 (0.50-1.12)	0.81 (0.54-1.22)
52-53	1960	41623	1180 (491)	1.60 (1.38-1.87)	1.65 (1.41-1.93)	35038	103 (36)	0.73 (0.47-1.14)	0.86 (0.54-1.35)
>=54	1433	30284	1409 (427)	1.78 (1.52-2.09)	1.63 (1.38-1.91)	23689	72 (17)	0.52 (0.30-0.92)	0.51 (0.29-0.90)
Family history of AMI									
No	5926	128614	982 (1263)	1.00	1.00	111366	88 (98)	1.00	1.00
Yes	1462	30424	1318 (401)	1.36 (1.22-1.53)	1.36 (1.22-1.53)	25199	190 (48)	2.19 (1.55-3.10)	2.16 (1.53-3.06)
Body mass index									
<20.0	214	4226	970 (41)	1.10 (1.07-1.12)	1.08 (0.76-1.52)	3661	82 (3)	0.81 (0.24-2.72)	0.86 (0.25-2.90)
20.0-22.5	946	20553	886 (182)	1.00	1.00	18155	110 (20)	1.00	1.00
22.6-25.0	2236	49330	906 (447)	1.01 (0.85-1.20)	1.94 (0.88-1.24)	43110	88 (38)	0.80 (0.46-1.37)	0.79 (0.46-1.37)
25.1-27.5	2180	46972	1081 (508)	1.20 (1.02-1.43)	1.20 (1.01-1.42)	40192	117 (47)	1.07 (0.63-1.80)	0.97 (0.57-1.66)
27.6-30.0	1186	25284	1222 (309)	1.36 (1.13-1.64)	1.22 (1.01-1.47)	21057	119 (25)	1.08 (0.60-1.95)	0.86 (0.47-1.58)
>30.0	606	12297	1415 (174)	1.62 (2.32-2.00)	1.32 (1.06-1.64)	10049	129 (13)	1.21 (0.60-2.43)	0.86 (0.42-1.78)
Cholesterol									
≤5mmol/l	725	16120	726 (117)	1.00	1.00	14341	42 (6)	1.00	1.00
5.1-6.4	3292	73356	867 (636)	1.22 (1.00-1.48)	1.22 (1.00-1.49)	63759	64 (41)	1.52 (0.64-3.58)	1.57 (0.66-3.70)
6.5-7.4	2054	43259	1177 (509)	1.72 (1.41-2.11)	1.66 (1.35-2.03)	36919	149 (55)	3.50 (1.50-8.13)	3.44 (1.47-8.03)
≥7.4	1246	24914	1541 (384)	2.20 (1.79-2.71)	2.04 (1.65-2.51)	20395	216 (44)	5.21 (2.22-12.24)	5.21 (2.20-12.31)

Systolic blood pressure									
<130	1589	36425	662 (241)	1.00	1.00	32677	52 (17)	1.00	1.00
130-139	1380	30185	924 (279)	1.40 (1.18-1.66)	1.37 (1.15-1.63)	26475	102 (27)	2.02 (1.10-3.70)	1.90 (1.03-3.49)
140-152	1649	35846	993 (356)	1.48 (1.25-1.74)	1.42 (1.20-1.67)	31031	110 (34)	2.22 (1.24-3.97)	2.03 (1.13-3.64)
153-165	1356	28256	1239 (350)	1.86 (1.58-2.19)	1.73 (1.46-2.04)	23672	148 (35)	3.08 (1.72-5.50)	2.62 (1.46-4.72)
>165	1404	28133	1550 (436)	2.30 (1.97-2.70)	1.98 (1.68-2.34)	22545	146 (33)	3.16 (1.75-5.68)	2.43 (1.32-4.50)
Treatment for hypertension									
No	6981	151360	1007 (1524)	1.00	1.00	130526	102 (133)	1.00	1.00
Yes	407	7678	1823 (140)	1.84 (1.55-2.19)	1.30 (0.97-1.56)	6038	215 (13)	2.32 (1.31-4.11)	1.51 (1.82-2.79)
Diabetes									
No	7421	156690	1019 (1596)	1.00	1.00	135015	104 (140)	1.00	1.00
Yes	147	2348	2896 (68)	3.14 (2.46-4.01)	3.12 (2.46-4.01)	1550	387 (6)	4.70 (2.08-10.66)	5.19 (2.28-11.80)
Smoking									
Never smoking	2181	50284	778 (391)	1.00	1.00	44655	105 (47)	1.00	1.00
Former smoker	1497	33462	896 (300)	1.18 (1.02-1.38)	1.19 (1.02-1.38)	29415	132 (39)	1.28 (0.84-1.96)	1.29 (0.84-1.98)
1-14g/day	2231	46268	1249 (578)	1.64 (1.44-1.86)	1.70 (1.50-1.94)	38360	86 (33)	0.90 (0.57-1.40)	0.96 (0.62-1.51)
15-24g/day	1183	23463	1381 (324)	1.90 (1.64-2.20)	1.90 (1.64-2.21)	19444	98 (19)	1.02 (0.60-1.74)	1.11 (0.65-1.90)
25g/day or more	268	4968	1349 (67)	1.90 (1.46-2.46)	1.89 (1.45-2.46)	4162	192 (8)	2.13 (1.01-4.51)	2.19 (1.02-4.66)
Physical activity									
1	1894	39066	1247 (487)	1.00	1.00	32451	86 (28)	1.00	1.00
2	4340	93952	1022 (960)	0.80 (0.72-0.89)	0.86 (0.76-0.96)	80930	109 (88)	1.23 (0.80-1.88)	1.23 (0.80-1.89)
3	1154	26020	834 (217)	0.66 (0.56-0.77)	0.80 (0.68-0.95)	23184	129 (30)	1.42 (0.85-2.38)	1.66 (0.98-2.81)
Stress									
No	5868	110237	1169 (1289)	1.00	1.00	110237	102 (113)	1.00	1.00
Yes	1520	26328	1424 (375)	1.23 (1.10-1.38)	1.16 (1.04-1.31)	26328	125 (33)	1.27 (0.86-1.87)	1.28 (0.86-1.89)

[1]All HRs adjusted for age and for the other variables in the table. Serum cholesterol measurements missing in 71 subjects, data on smoking missing in 28, for BMI in 20 and SBP in 10.

An increase in serum cholesterol of 1 mmol/l was associated with an OR of 1.56 for CABG but only 1.30 for AMI (Table 3).

These odds ratios were statistically different (p=0.004). Likewise, there were significant differences in the effect of age (p<0.001) smoking (p<0.0001) and of a family history of AMI, with the latter being more strongly related to CABG than to AMI (p=0.04). There were no differences in the odds ratios for systolic or diastolic blood pressure, or diabetes. BMI, stress and physical activity were significant predictors for AMI, but not for CABG.

Table 3. Analysis of OR and differences between the subjects with AMI and subjects who underwent CABG without a previous AMI

	All AMI		**ACB cases without previous AMI**		**Differences between the coefficients**
	Odds ratio age-adjusted n=1664	**95% CI**	**Odds ratio** age-adjusted n=146	**95% CI**	**P-value**
Age (years)	1.31	1.24-1.39	0.85	0.72-1.00	<0.0001
BMI, (kg/m²)	1.14	1.09-1.20	1.09	0.95-1.25	0.25
Cholesterol (mmol/l)	1.30	1.24-1.36	1.56	1.38-1.76	0.004
Systolic blood pressure (mmHg)	1.01	1.01-1.01	1.01	1.01-1.02	0.40
Diastolic blood pressure (mmHg)	1.02	1.02-1.03	1.02	1.00-1.03	0.45
Treatment for hypertension (yes/no)	1.89	1.52-2.34	2.09	1.16-3.74	0.38
Family history of AMI (yes/no)	1.43	1.25-1.63	2.20	1.55-3.13	0.04
Diabetes (yes/no)	3.06	2.19-4.30	3.37	1.44-7.89	0.42
Smoking (1-5)	1.51	1.43-1.60	0.78	0.66-0.92	<0.0001
Physical activity (1-3)	0.83	0.76-0.90	1.27	0.98-1.64	*
Stress (yes/no)	1.16	0.99-1.35	1.03	0.64-1.65	*

* Not significant for CABG and therefore not tested

Paper II

During the period 1987 to 2003, 264 575 (64% men) persons aged 35 to 84 years were admitted alive with a first AMI. The mean age for men and women was 68 and 72 years, respectively.

Hospitalization rates

The age-adjusted hospitalization rates for a first AMI in men decreased from about 500 to 400 cases per 100 000 per year during the period 1987 to 2003. A flattening of the decrease was noticeable after 2001, when new diagnostic criteria were introduced. During the same period there were a barely discernible decrease from about 280 to 250 cases pr 100 000 in women (Figure 5).

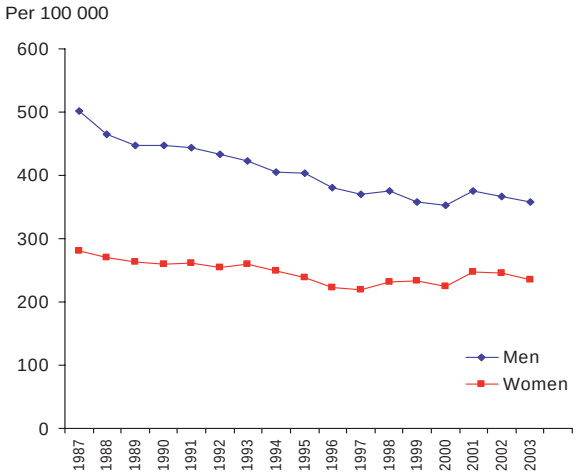

Figure 5. Age-standardised hospitalization rates for AMI per 100 000 per year in Sweden 1987 to 2003.

All cause mortality

Case fatality, defined as mortality from any cause, decreased in all age groups during the period 1987 to 1998 (Table 4). The decrease was more marked for younger than for older patients. In patients aged <55 years the decrease in 28-day case fatality was roughly maintained over the whole 5-year period. With older age, there was an increasing difference between the reduction in 28-day and in 5-year case fatality, such that in patients aged 75 to 84 only half of the reduction in 28-day case-fatality was maintained after 5 years. The reduction in short-term case fatality in men <65 years was slightly greater for men than for women of the same age, but with increasing age and length of follow-up the gender differences in reduction in case fatality decreased. In the two oldest age groups 5-year case fatality and changes in case fatality were similar in men and women.

Cardiovascular mortality

The pattern of case fatality from cardiovascular causes was consistent with that from all-cause mortality for men and women and in all age-groups (Table 5). The decrease in 28-day mortality was maintained in all age groups, with the exception of the oldest men and women, i.e. those aged 75 to 84 years. The decrease in mortality was more marked for younger men and women, with 5-year mortality in 1996 to 1998 being only half of that in 1987 to 1989.

Annual case fatality after the first year and up to the fifth follow up year was strongly associated with age, with a nearly tenfold difference between those aged <55 years compared with patients aged 75 to 84 years (Table 6). Final estimates of annual mortality after the first year post-MI among patients admitted in 1996 to 1998 was <1% in patients below 55 years, 2% for those aged 55 to 64 years, 4% for patients aged 65 to 74 years and 10% among those aged 75 to 84 years, with only minor differences between men and women.

Table 4. Case fatality from all causes in 264 575 Swedish patients admitted to hospital after 28 days, 1 year and 5 years by age, sex and period

	Men			28 days	1 year	5 year	Women			28 days	1 year	5 years
	Number with AMI admitted to hospital	Number who died within 5 years (≥28 days-5 years)	%	% * Decrease (95% CI)	% * Decrease (95% CI)	% * Decrease (95% CI)	Number with AMI admitted to hospital	Number who died within 5 years (≥28 days-5 years)	% *	% * Decrease (95% CI)	% * Decrease (95% CI)	% * Decrease (95% CI)
Age <55												
1987-1989	3995	615	15				830	135	16			
1990-1992	4116	469	11	26 (17-34)	32 (25-39)	26 (20-32)	866	133	15	19 (+2- 37)	22 (7-36)	7 (+9-22)
1993-1995	4182	392	9	41 (33-48)	44 (37-50)	38 (34-44)	915	98	11	32 (13-48)	42 (29-54)	39 (26-51)
1996-1998	4019	310	8	50 (43-57)	49 (43-56)	51 (46-55)	949	78	8	55 (39-69)	51 (38-62)	50 (38-60)
55-64												
1987-1989	7014	1887	27				2007	537	27			
1990-1992	6011	1286	21	25 (17-33)	25 (19-31)	20 (15-25)	1877	472	25	12 (+1-24)	6 (+4-16)	5 (+4-13)
1993-1995	5588	1023	18	33 (24-41)	32 (25-38)	30 (25-35)	1776	354	20	27 (14-39)	26 (17-35)	24 (16-31)
1996-1998	5427	855	16	44 (35-52)	42 (35-48)	38 (33-44)	1745	287	16	51 (39-63)	47 (38-56)	37 (29-44)
65-74												
1987-1989	11272	5232	46				5768	2671	46			
1990-1992	10589	4306	41	17 (13-20)	16 (14-19)	12 (10-14)	5373	2092	39	17 (10-24)	14 (8-20)	15 (11-18)
1993-1995	9474	3484	37	30 (26-33)	28 (26-31)	21 (19-23)	5099	1780	35	27 (21-33)	26 (20-31)	24 (21-28)
1996-1998	8115	2573	32	41 (37-45)	37 (34-40)	32 (29-34)	4395	1376	31	35 (28-42)	33 (27-39)	31 (27-35)
75-84												
1987-1989	9394	6547	70				8346	5601	67			
1990-1992	9373	6154	66	11 (8-14)	10 (7-12)	7 (4-9)	8292	5310	64	7 (3-10)	8 (4-12)	5 (1-8)
1993-1995	8961	5564	62	21 (18-25)	19 (16-21)	12 (10-14)	8131	4898	60	17 (13-21)	16 (12-19)	10 (7-14)
1996-1998	8414	4901	58	29 (26-33)	25 (23-28)	17 (15-20)	7357	4094	56	29 (25-33)	26 (22-30)	17 (14-21)

* Decrease in per cent compared with period 1987-1989

Table 5. Case fatality from cardiovascular causes in 264 575 Swedish patients admitted to hospital after 28 days, 1 year and 5 years by age, sex and period

	Men			28 days	1 year	5 year	Women			28 days	1 year	5 years
	Number with AMI admitted to hospital	Number who died within 5 years (≥28 days-5 years)	%	% * Decrease (95% CI)	% * Decrease (95% CI)	% * Decrease (95% CI)	Number with AMI admitted to hospital	Number who died within 5 years (≥28 days-5 years)	%	% * Decrease (95% CI)	% * Decrease (95% CI)	% * Decrease (95% CI)
Age <55												
1987-1989	3995	555	14				830	106	13			
1990-1992	4116	396	10	28 (19-36)	36 (29-43)	29 (23-35)	866	102	12	24 (3-41)	29 (14-42)	10 (+5-24)
1993-1995	4182	338	8	41 (33-49)	46 (39-52)	42 (36-47)	915	62	7	40 (22-57)	51 (40-63)	49 (37-60)
1996-1998	4019	239	6	51 (44-59)	55 (48-61)	58 (53-63)	949	55	6	53 (37-67)	55 (43-65)	52 (40-62)
55-64												
1987-1989	7014	1677	24				2007	456	23			
1990-1992	6011	1133	19	26 (17-33)	26 (19-32)	21 (15-26)	1877	398	21	8 (+7-20)	4 (+5-13)	5 (+3-12)
1993-1995	5588	861	15	35 (26-43)	36 (29-42)	34 (29-39)	1776	284	16	29 (16-42)	26 (17-34)	25 (17-32)
1996-1998	5427	684	13	46 (37-54)	46 (39-52)	44 (39-50)	1745	207	12	51 (38-63)	52 (44-60)	47 (40-54)
65-74												
1987-1989	11272	4692	42				5768	2378	41			
1990-1992	10589	3757	36	18 (14-22)	17 (14-20)	15 (12-17)	5373	1858	35	16 (9-22)	14 (8-19)	15 (11-18)
1993-1995	9474	2939	31	30 (26-34)	29 (26-32)	26 (23-28)	5099	1501	29	29 (22-35)	29 (23-34)	29 (25-32)
1996-1998	8115	2075	26	42 (38-47)	40 (37-43)	38 (36-41)	4395	1132	26	37 (29-44)	36 (30-42)	36 (32-40)
75-84												
1987-1989	9394	5845	62				8346	5107	61			
1990-1992	9373	5419	58	12 (8-15)	11 (8-14)	8 (5-10)	8292	4813	58	6 (2-10)	8 (4-12)	5 (2-9)
1993-1995	8961	4767	53	22 (18-26)	21 (18-23)	16 (13-18)	8131	4310	53	17 (13-21)	17 (13-21)	14 (10-17)
1996-1998	8414	4065	48	30 (27-34)	29 (26-31)	23 (21-26)	7357	3541	48	30 (26-34)	28 (24-32)	22 (18-25)

* Decrease in per cent compared with period 1987-1989

Table 6. Mean annual case fatality from all causes during 1 to 5 years in 264 575 Swedish patients admitted to hospital with a first ever AMI

	Men			Women		
	Number with AMI admitted to hospital	Number who died within 5 years (1 to 5 years)	Mean annual case fatality	Number with AMI admitted to hospital	Number who died within 5 years (1 to 5 years)	Mean annual case fatality
Age <55						
1987-1989	3995	615	1.5	830	135	1.3
1990-1992	4116	469	1.2	866	133	1.5
1993-1995	4182	392	1.0	915	98	1.0
1996-1998	4019	310	0.7	949	78	0.7
55-64						
1987-1989	7014	1887	3.2	2007	537	3.0
1990-1992	6011	1286	2.6	1877	472	2.8
1993-1995	5588	1023	2.1	1776	354	2.2
1996-1998	5427	855	1.8	1745	287	2.1
65-74						
1987-1989	11272	5232	6.7	5768	2671	6.5
1990-1992	10589	4306	5.9	5373	2092	4.9
1993-1995	9474	3484	5.4	5099	1780	4.4
1996-1998	8115	2573	4.4	4395	1376	3.9
75-84						
1987-1989	9394	6547	13.4	8346	5601	12.0
1990-1992	9373	6154	12.3	8292	5310	11.4
1993-1995	8961	5564	11.6	8131	4898	10.4
1996-1998	8414	4901	10.5	7357	4094	9.6

Short- and long-term survival

Among younger patients (<65 years), most of the improvement in short- and long-term prognosis was achieved during the first part of the study period, with little decrease in those hospitalized with AMI after the mid-1990s (Figure 6). Case fatality continued to decrease throughout the study period in older patients. The interaction between age and time on the effect of changes in case-fatality was significant ($p<0.0001$).

Paper III

During the period 1987 to 2003, 377,030 persons aged 35 to 84 years had a first CHD event, either a first AMI or death from CHD outside hospital. Of these, 128,861 (34.2%) died outside hospital, 39,984 (10.6%) died during hospitalization or within 28 days, leaving 55.2% surviving their first event (Table 7). In men and women below 55 years, more than one in five, or 22.5%, did not survive their first attack. The proportion dying within 28 days increased with age, such that more than half of victims 75 to 84 years, or 56.4% died. The overall proportion of all deaths occurring in people who were not hospitalized ranged from 82.7% among those aged <55 years, to 75.3% in those aged 75 to 84 years. The mean age for persons who died from a first CHD event outside hospital was 71 years, whereas the mean age for those who died after being admitted to hospital was 68 years.

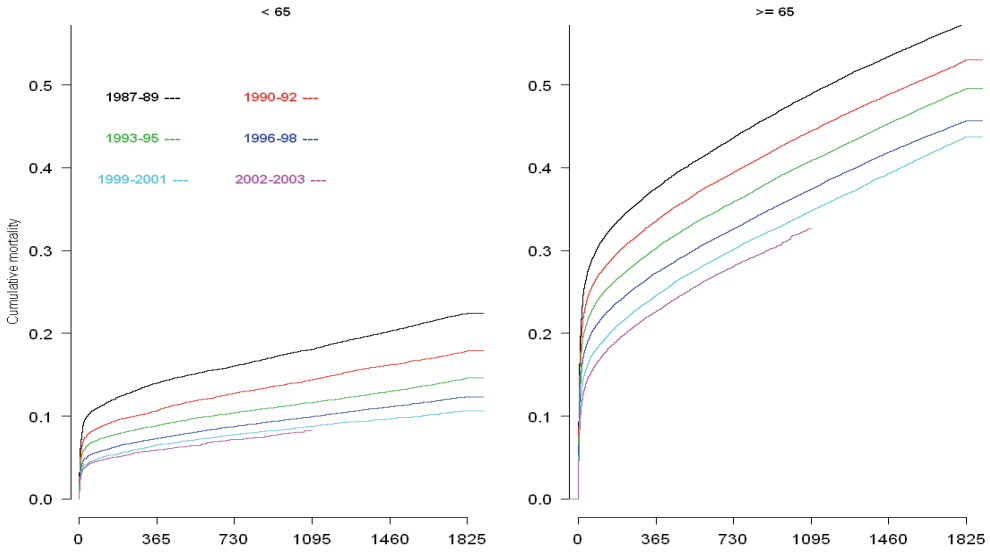

Figure 6. Cumulative mortality following a first AMI 1987 to 2003 by age and period.

Table 7. Case fatality in a first ever AMI or CHD 1987 to 2003, total 0 to 28 days, out of hospital, and in-hospital, up to 28 days

	Any first ever AMI or CHD, n	Cases (n) dying within 28 days	Total 28-day case fatality (%)	Cases (n) dying out-of-hospital	Proportion (%) who died out of hospital	Cases (n) dying in hospital or within 28 days	Proportion (%) who died in hospital or within 28 days	Proportion (%) of all deaths within 28 days occurring outside hospital
<55	33975	7519	22.1	6216	18.3	1303	3.8	82.7
55-64	58537	17556	30.0	14074	24.0	3482	5.9	80.2
65-74	116633	49032	42.0	37256	31.9	11776	10.1	76.0
75-84	167885	94738	56.4	71315	42.5	23423	14.0	75.3
Total	377030	168845	44.8	128861	34.2	39984	10.6	76.3

Both the proportion of those who died without being admitted to hospital and who died in-hospital or during the first 28 days declined between 1987 and 2003 (Table 8). Among persons aged below 55, the proportion of those who died in hospital, or during the first 28 days declined by more than half, from 5.8% to 2.5%, age-adjusted odds ratio (OR) 0.41 (95% confidence interval (CI) 0.33-0.52). The corresponding proportions for out-of-hospital death was 20.8% and 15.6%, OR 0.70 (95% CI 0.63-0.78). Similar decreases were observed for persons aged 55 to 64, and 65 to 74 years, both for those who were not hospitalized and those who died in the first 28 days after being admitted, with approximately 60% reduction, and 30% reduction, respectively. Even if substantially lower, compared with 1987 to 1989, total 28-day mortality in these age groups remained high, however, 23.8%, and 32.5%, respectively, in 2002 to 2003. In the oldest age group, 75 to 84 years, the total 28-day mortality in 1987 to 1989 was 63.5%, decreasing to 44.6% in 2002 to 2003, with a similar reduction of about 40% in those admitted to hospital and in those dying outside hospital.

Table 8. Case fatality in a first ever AMI or CHD, total 0 to 28 days, out of hospital, and in-hospital, up to 28 days, by age and period

	Any first ever event * n	Proportion (%) who died within 28 days	OR (99% CI)	Proportion (%) of total who died out of hospital	OR (99% CI)	Proportion (%) of total who died in hospital or in 0-28 days	OR (99% CI)
<55							
1987-1989	6089	26.6	1.00	20.8	1.00	5.8	1.00
1990-1992	6124	23.2	0.83 (0.77-0.90)	18.6	0.88 (0.80-0.96)	4.5	0.76 (0.65-0.90)
1993-1995	6244	22.1	0.78 (0.72-0.85)	18.4	0.86 (0.79-0.94)	3.7	0.62 (0.53-0.74)
1996-1998	6056	22.8	0.73 (0.67-0.79)	18.0	0.84 (0.76-0.92)	2.9	0.47 (0.40-0.57)
1999-2001	5847	20.3	0.70 (0.65-0.77)	17.3	0.80 (0.73-0.88)	3.0	0.50 (0.42-0.61)
2002-2003	3615	18.1	0.61 (0.55-0.67)	15.6	0.70 (0.63-0.78)	2.5	0.41 (0.33-0.52)
55-64							
1987-1989	12326	35.5	1.00	26.8	1.00	8.7	1.00
1990-1992	10713	33.4	0.91 (0.86-0.96)	26.3	0.98 (0.92-1.04)	7.0	0.80 (0.72-0.88)
1993-1995	9718	30.4	0.79 (0.75-0.84)	24.2	0.87 (0.82-0.93)	6.1	0.69 (0.62-0.76)
1996-1998	9279	27.6	0.69 (0.65-0.73)	22.7	0.80 (0.75-0.85)	4.9	0.54 (0.48-0.61)
1999-2001	9608	25.5	0.62 (0.58-0.66)	21.8	0.76 (0.71-0.81)	3.7	0.40 (0.36-0.46)
2002-2003	6893	23.8	0.57 (0.53-0.61)	20.2	0.69 (0.64-0.74)	3.6	0.39 (0.34-0.45)
65-74							
1987-1989	26050	48.0	1.00	34.6	1.00	13.3	1.00
1990-1992	24090	45.0	0.89 (0.86-0.92)	33.7	0.96 (0.93-1.00)	11.2	0.82 (0.78-0.86)
1993-1995	21374	42.0	0.78 (0.76-0.81)	31.8	0.88 (0.85-0.92)	10.2	0.73 (0.69-0.77)
1996-1998	18411	40.5	0.74 (0.71-0.77)	32.0	0.89 (0.86-0.93)	8.5	0.60 (0.56-0.64)
1999-2001	16354	36.1	0.61 (0.59-0.64)	28.8	0.76 (0.73-0.80)	7.3	0.51 (0.48-0.55)
2002-2003	10354	32.5	0.52 (0.50-0.55)	26.2	0.67 (0.64-0.71)	6.3	0.44 (0.40-0.47)
75-84							
1987-1989	33487	63.5	1.00	47.0	1.00	16.5	1.00
1990-1992	31984	60.5	0.88 (0.85-0.91)	42.0	0.91 (0.89-0.94)	15.7	0.94 (0.91-0.98)
1993-1995	30276	57.8	0.79 (0.76-0.81)	43.5	0.87 (0.84-0.90)	14.3	0.84 (0.81-0.88)
1996-1998	27558	55.5	0.72 (0.69-0.74)	42.8	0.84 (0.82-0.87)	12.7	0.74 (0.71-0.77)
1999-2001	26883	49.2	0.56 (0.54-0.58)	37.6	0.68 (0.66-0.70)	11.6	0.66 (0.63-0.70)
2002-2003	17697	44.6	0.48 (0.46-0.50)	34.8	0.60 (0.58-0.62)	10.8	0.61 (0.58-0.65)

* First ever-event= first ever hospitalized patients with AMI or patients who died in a first-ever AMI or CHD within 28 days

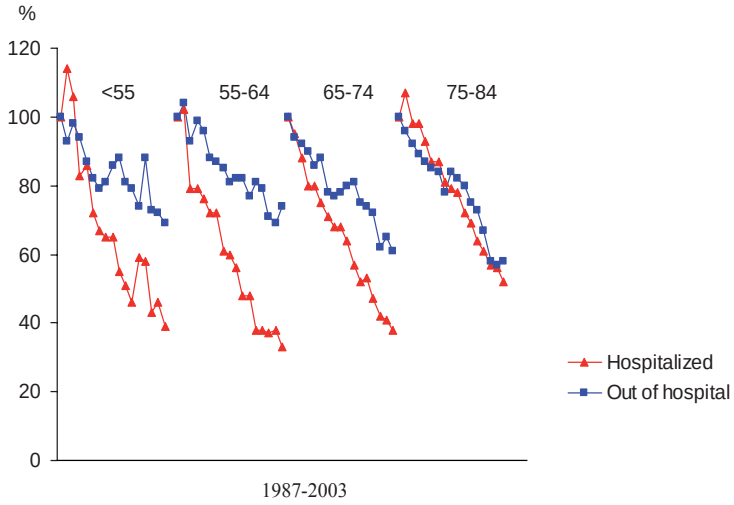

Figure 7. Relative change in out-of-hospital CHD deaths and 28-day mortality among hospitalized patients by age in 1987-2003.

Figure 7 shows the reduction over time in hospitalized and non-hospitalized persons.

Figure 8 illustrates the proportion of persons who died from a first CHD event without being admitted to hospital as a function of age and period. The proportion who died in hospital is shown for comparison. In persons aged <75 at least 4 out of 5 victims dying of CHD within 28 days were not admitted to hospital, with a steady increase over the period, such that, among persons aged <55 years, 86.2% of all deaths occurred in persons not admitted in the period 2002 to 2003.

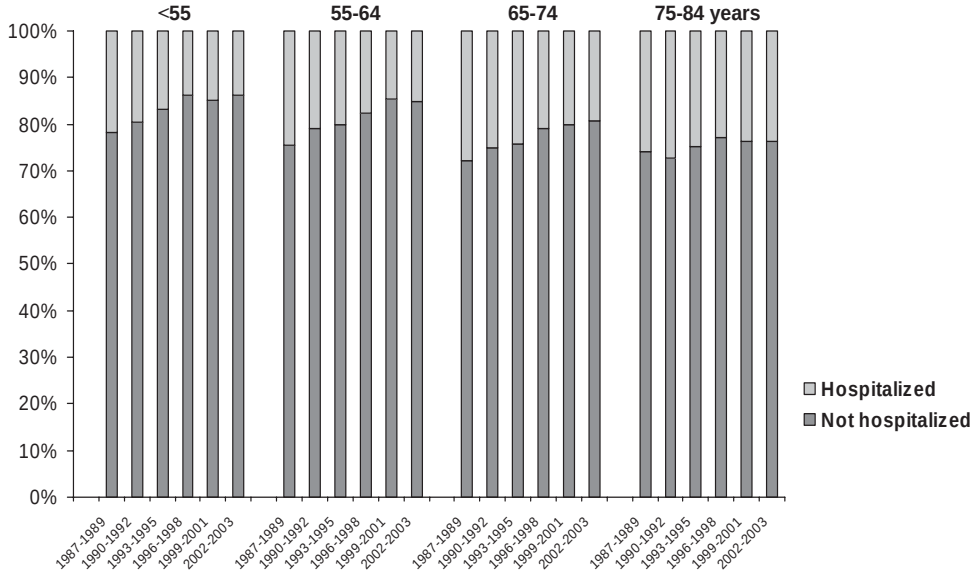

Figure 8. Out-of-hospital deaths as a proportion of all CHD deaths in 28 days in men and women by age and period in all MI 1987 to 2003.

Men generally had slightly higher out-of-hospital mortality but trends over time were similar for men and women (Figure 9).

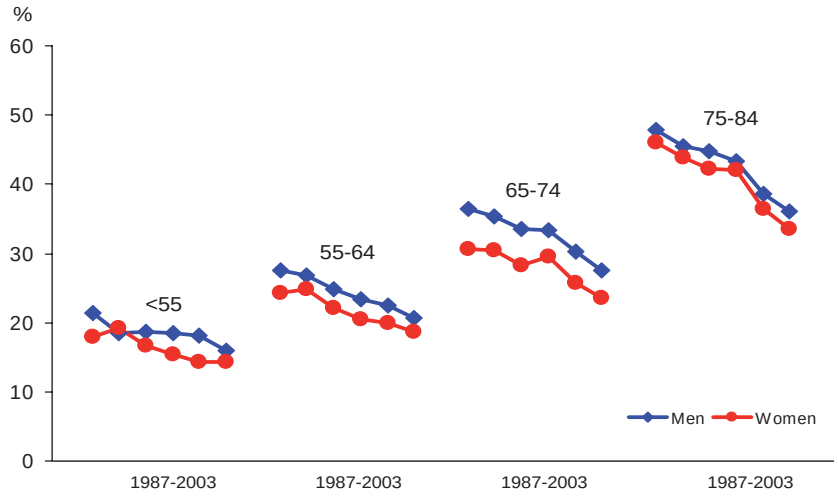

Figure 9. Out-of-hospital CHD death in men and women by age as a percentage of all first events 1987 to 2003.

Paper IV

Of 98,479 patients with AMI registered in the RIKS-HIA 38% were women, compared to 44% among 44,978 patients with UAP (Table 9). Patients with AMI were slightly older than patients with UAP (mean age 69.9 and 67.6 years, respectively). Smoking was more common in patients with AMI, 24.7% compared to 18.1% in patients with UAP. After adjustment for age, gender, and other concomitant conditions and medications, the OR associated with current smoking was 1.67 (99% CI 1.59 to 1.75). Hypertension was less common among AMI patients than among patients with angina, but after multiple adjustment the OR associated with this condition was instead slightly elevated at 1.09 (1.05 to 1.14). Diabetes was more prevalent among AMI patients, multiple-adjusted OR 1.42 (1.36 to 1.49), as was PAD OR 1.28 (1.17 to 1.41). Heart failure, and all medications were less prevalent among patients with AMI, particularly aspirin, nitrates, and statins.

Figures 10 and 11 show that the effect of smoking was more marked among women, compared to men. In younger men and women (<65 years) the prevalence of smoking among AMI patients was 43.0% and 49.4%, respectively, compared to 31.5% and 30.5% in men and women with UAP multiple-adjusted ORs 1.49 (1.38 to 1.61) in men, and 2.21 (1.98 to 2.48) in women. In older men and women, smoking was overall less common, but still associated with a higher risk of presenting with AMI, particularly among women, multiple-adjusted OR 2.06 (1.85 to 2.30). The OR associated with diabetes for presenting with AMI was 1.65 (1.43 to 1.90) and 1.70 (1.57 to 1.85) in younger and older women, with corresponding odds 1.29 (1.17 to 1.42) and

Table 9. Baseline characteristics in 143,457 patients with a first event of acute myocardial infarction or unstable angina pectoris, and odds ratios for presenting with AMI

	MI 61 (98479)	**UAP 39 (44978)**	**Age and gender adjusted OR**	**Multiple adjusted OR (99% CI)***
Age, mean, years	69.9	67.6	1.02 (1.02-1.02)	1.03 (1-03-1.04)
Women, % (n)	38 ((37527)	44 (19804)		
Never smoking, % (n)	51.2 (46813)	54.8 (21966)	1.00	1.00
Former smoking,% (n)	24.2 (22089)	27.1 (10849)	0.96 (0.93-1.00)	0.96 (0.92-1.00)
Current smoking, % (n)	24.6 (22543)	18.1 (7264)	1.83 (1.75-1.91)	1.67 (1.59-1.75)
Hypertension, % (n)	33.6 (32228)	36.5 (15228)	0.86 (0.84-0.89)	1.09 (1.05-1.14)
Heart failure, % (n)	6.4 (6258)	8.6 (3829)	0.62 (0.58-0.65)	0.77 (0.72-0.82)
Diabetes, % (n)	18.6 (18361)	15.8 (7116)	1.20 (1.16-1.25)	1.42 (1.36-1.49)
Peripheral arterial disease, % (n)	4.0 (3902)	3.5 (1558)	1.05 (0.97-1.14)	1.28 (1.17-1.41)
Aspirin, % (n)	25.3 (24501)	40.3 (17154)	0.44 (0.43-0.46)	0.62 (0.59-0.64)
β-blockers, % (n)	25.1 (24230)	38.1 (16213)	0.53 (0.51-0.55)	0.74 (0.71-0.77)
ACE-inhibitors, % (n)	12.4 (11951)	14.7 (6253)	0.79 (0.76-0.83)	0.95 (0.90-1.00)
Long-acting nitrates, % (n)	9.7 (9351)	24.4 (10372)	0.28 (0.27-0.30)	0.42 (0.40-0.44)
Statins, % (n)	7.0 (6746)	14.7 (6256)	0.46 (0.44-0.48)	0.61 (0.57-0.64)

*Adjusted for age, smoking, hypertension, heart failure, diabetes, peripheral arterial disease, aspirin, β-blocker, ACE-inhibitors, long-acting nitrates, statins and year of admission.

1.26 (1.17 to 1.36) in younger and older men. PAD was associated with higher risk of presenting with AMI only among women; OR 1.82 (1.26 to 2.63) and 1.58 (1.35 to 1.85) among younger and older women, respectively. Figures 10 and 11 illustrate differences separately for younger and older women and men. Strong interaction effects ($p<0.0001$) were seen for both young and older patients between smoking and gender, and between diabetes and gender.

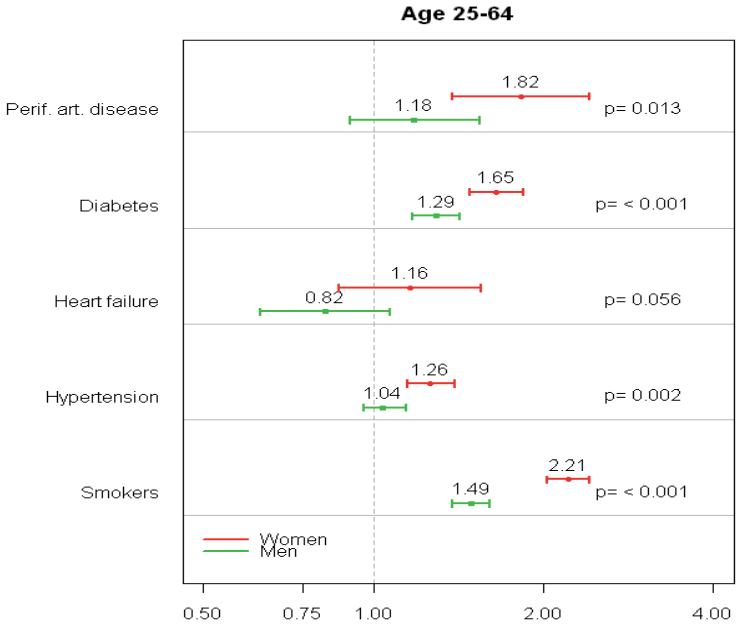

Figure 10. Odds ratios (99% CI) for presenting with AMI among patients aged 25-64 years admitted to Swedish CCUs with either AMI or angina. P-value refers to the difference between men and women (gender interaction effect).

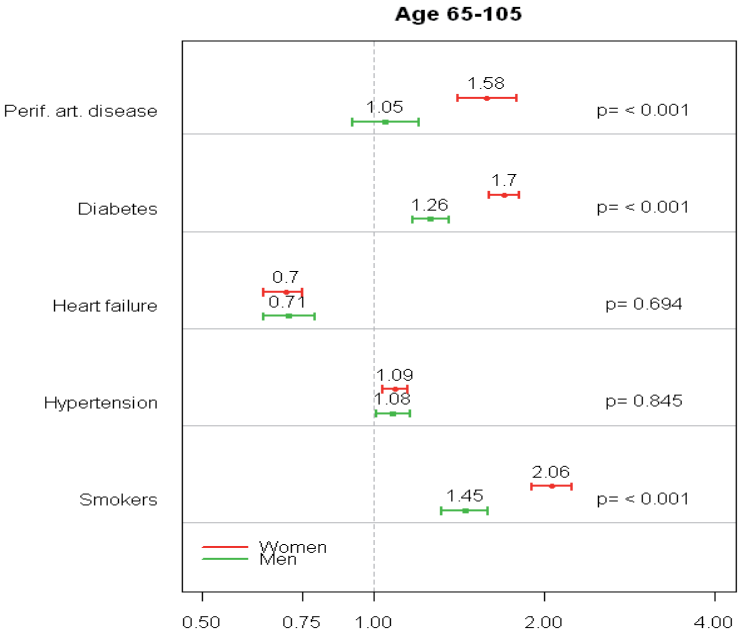

Figure 11. Odds ratios (99% CI) for presenting with AMI among patients aged 65-105 years admitted to Swedish CCUs with either AMI or angina. P-value refers to the difference between men and women (gender interaction effect).

DISCUSSION

Manifestations

Paper I

The findings in this study shown that whereas most coronary risk factors, by and large predicted both AMI and CABG, serum cholesterol was a stronger predictor of CABG than of AMI. Smoking was a weaker risk factor for CABG than for AMI, with no discernible increase in risk except in very heavy smokers. In addition, family history of AMI was a stronger predictor of CABG than of AMI.

Patients with angina pectoris who undergo CABG generally have extensisve and symptomatic CHD, and potentially a large atherosclerotic burden.[64-66] The results from the study could be relevant with respect both to differences in pathophysiology, and to potential changes in the clinical expression of the coronary disease over time. We know that life time risk of coronary heart disease and elevated serum cholesterol are strongly linked[56] and that low density lipoprotein (LDL) accumulates over time in the artery wall.[66] Patients with chronic stable angina have been demonstrated to have more stenotic lesions than patients with AMI.[67-70] Possibly, our finding of a stronger correlation between CABG and elevated levels of serum cholesterol than between AMI and cholesterol could be due to more extensive coronary lesions in the former, secondary to more widespread lipid deposits, but not necessarily a more pronounced tendency to plaque rupture. Conversely, the stronger relation between AMI and smoking may be due to a stronger link between smoking and coagulation factors, because the precipitating event in AMI is usually a plaque rupture, with ensuing thrombosis.

The finding that family history of AMI was more strongly linked to CABG than to AMI is unexpected but could be mediated through familial influences on serum cholesterol level.[71,72] The fact that the CABG patients were more physically active than the AMI patients is probably because physical activity will have provoked more symptoms. Hypertension and diabetes were equally strongly associated with both AMI and CABG.

Papers II and III

A need for more knowledge about CHD deaths occurring out-of-hospital has been identified.[73] The linking of the National Hospital Discharge Register and the National Cause of Death register[55] through personal identifiers made it possible to identify all first fatal, as well as non-fatal cases in a well defined large population, whereas most other studies have had to rely on smaller samples.[27,74] Reports, however, seem consistent, that, in spite of the improvement in CHD mortality and advances in CHD medical treatment, prevention and emergency transport systems, most of the fatal events still occur out-of hospital.[20-22,73,75-77] Our results are consistent with other studies that also report a modest improvement in out-of-hospital death during the last decades.[78,79] The American Heart Association Council on Clinical Cardiology Committee on Electrocardiography and Arrhythmias and the Council on Epidemiology and Prevention have underlined that we do not yet have the tools to identify patients at high risk for

most of the victims who died out-of hospital and that there is a need to evaluate, test and implement risk stratification strategies for this group.[80] Modelling studies have consistently shown that changes in risk factors are quantitatively much more important for reductions in coronary mortality than in-hospital treatment in acute coronary syndromes.[81-83] However, risk factor levels in the Swedish population are still far from optimal,[49] indicating that more prevention efforts are needed, particularly with a view to the increasing obesity levels.

Paper IV

We found that, among patients presenting with either AMI or angina as a first ACS episode, smoking, diabetes, and PAD were associated with increased risk for presenting with AMI, while prior heart failure, as well as prior use of aspirin, beta-blockers, long-acting nitrates, and statins were associated with lower risk. AMI patients were also slightly older, and with a higher proportion of men. The differences with respect to smoking, diabetes and PAD were more pronounced for women than for men. Cigarette smoking is a well-known risk factor for AMI and sudden cardiac death.[84] Moreover, cigarette smoking causes endothelial dysfunction and can increase the risk of atherotrombosis, influencing fibrinolytic and antitrombotic factors.[85,86] The mechanisms involved in tobacco smoking-related cardiovascular disease are not entirely clear; however, there is evidence for an increased propensity toward thrombosis in smokers.[87] Why this should affect men and women differently is not clear.

Survival

Paper II

Results from other studies, which also used administrative data, showed a similar improvement in case fatality in AMI.[61,88-91] In a study from Spain 28-day case fatality decreased from 18.3% to 11.4% in both men and women aged 25-74 years during the period 1978-1993.[88] Similar decreases were noted in Sweden and Denmark during the period 1987-1999.[90] In Scotland, 28-day in-hospital case fatality decreased from 25% in 1986 to 19% in 1995.[92]

Up until 1995, our data show that survival improved markedly in men and women below 65 years, but further changes were comparatively minor after this period. This could potentially mean that the gains of modern treatment in this age group have now been almost fully implemented and realised. Whereas changes in cardiovascular risk factors in the population explain a great proportion of the overall reduction in CHD mortality in the community,[81,93] further improvement in the prognosis of hospitalized patients will obviously depend on other factors, including better public knowledge, transportation, implementation of existing proven therapies but potentially also new modalities for treatment.[57,94] The findings in the present study are consistent with other large population-based studies regarding decreased case fatality,[92,93,95,96] even if our findings on the decline in case fatality are more pronounced.

Paper III

In persons with a first ever major CHD event 45% died within 28 days, with 3 of 4

fatal cases occurring in non-hospitalized persons. Even though case fatality decreased both in- and outside hospital, the decline in in-hospital mortality was steeper, which resulted in an increasing proportion of cases dying outside hospital, such that, in persons aged below 65, almost 8 out of 9 deaths occurred in non-hospitalized cases in 2002 to 2003.

The most plausible explanation for the higher proportion of out-of-hospital deaths in the present study, compared to some other studies[20-22,73,75-77] is that we included not only deaths from myocardial infarction, but also deaths from ischemic heart disease. In a study from the Massachusetts Department of Public Health[77] in which all types of cardiovascular deaths were included, there was a decline in the out-of hospital death of 18% over the 11 years between 1990 to 2001, consistent with the decline in our study of about 25% over 16 years. Even if an autopsy is performed a myocardial infarction may not be detected in the early stages of development, and accordingly, grouping deaths from AMI with death from any first ischemic event may more accurately capture out-of-hospital deaths caused by coronary heart disease.

Age and gender

Paper I

Even within the comparatively narrow age span of the men in the study, the risk of AMI increased sharply with age. In contrast, older men were less likely to undergo CABG. It is likely partly an effect of thoracic surgeons being less disposed to let older patients undergo CABG, with the assumption of more post-operative complications and multiple diseases in elderly[97,98]. During the almost 30-year follow-up of the study, coronary surgery expanded rapidly, but this will mainly have benefited the younger men of the study. By the mid-90s, the older men of the study were approaching 80 years. The study was limited to men and hence, results may not be generalisable to women.

Paper II

The most obvious decline was observed for 28-day case fatality rates among men and women below 65 years though the decline occurred earlier for men than for women. However, after this initial delay, survival improved in women as well, such that there were no gender differences in overall prognosis or in mortality from cardiovascular causes during the later years of the study period. Among patients aged 65 years and over, survival improved to the same extent for men and women, and, with the exception of slightly better overall survival among the oldest women, there were no substantial differences in the 5-year prognosis. Young female patients have been reported to have a poorer survival after AMI than men of the same age,[99,100] a finding largely explained, however, by higher out-of-hospital death rates among men.[101,102] During the early periods of the current study, survival improved more for younger men than for younger women, probably reflecting an earlier and more widespread use of thrombolytics in men.[103] However, this gender difference was reported to have decreased in Sweden after the early 1990s.[104] In a report from the Swedish Heart Intensive care Admissions register,[63] which included hospitalizations between 1998 and 2002, revascularisation was performed more often in men but there was no significant differ-

ence in in-hospital or 30-day mortality after adjustment for age. Older men had poorer 1-year survival, a finding not reproduced in the present study of more unselected AMI patients.

In the present study we could confirm a pronounced decrease in short-term case-fatality in AMI from 1987 to 2002, adding that this effect was sustained long-term, and more so regarding cardiovascular mortality. The decrease was more marked in younger patients, and was, among those aged below 65 years, initially steeper in men, with women, however, catching up in the last period 1996 to 1998. Little further improvement was seen in younger patients after 1999 to 2001, whereas long-term prognosis in patients 65 and over continued to improve. Final estimates for annual mortality after the first year post-MI for patients admitted in 1996 to 1998 varied from <1% in patients below 55 years to 10% among those aged 75 to 84 years, with little difference between men and women.

Paper III

Our study is consistent with other epidemiological studies, which show that most CHD deaths occur out-of hospital.[20-22,73-75,77] The proportion of patients in our study, who died out-of hospital was 76%, ranging from 83% among the youngest patients to 75% in those aged 75 to 84 years. This is higher compared to studies in the United States where the out-of hospital deaths from CHD were 66%[77] and 61%.[74] The results from the 3494 events in the FINAMI study,[20] which examined trends in out-of hospital CHD deaths in Finland during 1983 to 1997 among men and women aged 35 to 64 years, found that the proportion of out-of hospital death was 73% among men and 60% among women. These proportions did not change during the study period.[20] The results in the present study showing that the proportion of out-of-hospital deaths decreased with increasing age are consistent with the results from studies in Finland, Scotland and in the United States.[20,21,75] Men generally had slightly higher out-of-hospital mortality but trends over time were similar for men and women.

Paper IV

Gender differences in the clinical presentation of CHD have long been recognized,[105-107] with men more likely than women to have an initial presentation with AMI, whereas presenting with angina is more common among women. In more recent studies in patients with ACS, women were found to present more often with UAP,[108] however, in the Euroheart Survey,[47] this difference was found to be restricted to younger patients (<65 years). Our data are in line with these prior observations.

Smoking was the factor that was most strongly associated with a first-time presentation with AMI, but only moderately so among men, whereas the difference in smoking prevalence between patients presenting with AMI or UAP was much more pronounced in women. Half of all women <65 years with AMI in the present study were current smokers, a slightly higher proportion than among men with AMI (43%). Even though, in the present study, smoking was associated with more severe coronary disease in the shape of AMI, rather than angina, patients with AMI who are smokers have been demonstrated to have better prognosis, sometimes termed the "smoker's paradox".[109-111] These findings can, however, be explained by the fact that that smokers with AMI are

generally younger with less extensive coronary disease and also have less risk factors like diabetes and hypertension.[110] Even so, the findings of the present study underline that, not only is smoking, overall, a risk factor for CHD, it is also significantly associated with a more severe clinical presentation.

Among AMI patients, virtually all studies have shown diabetes to be more common among women than men, but the influence of diabetes on clinical presentation has only rarely been assessed. In the Euroheart Diabetes survey the influence of diabetes on presenting symptoms and clinical course was similar in men and women,[112] but this population represented a mixture of patients with both chronic and acute forms of CHD. In contrast, in the Euroheart ACS survey,[113] diabetes was associated with more severe forms of ACS. Women, but not men with diabetes, had higher risk of presenting with ST-elevation ACS, and developing Q-wave MI, suggesting a differential effect of diabetes on the pathophysiology of ACS based on the patient's gender. Although we did not specifically study outcome in the present study, diabetes in both men and women with AMI is known to affect both short-term and long-term outcome adversely.

Limitations

Paper I

Only men of a comparatively limited age span were studied which means that the findings may not be generalisable to younger men, to women and to the present era where indications for surgery will have changed and percutaneous interventions have emerged as a major procedure in coronary disease. Second, we did not have angiographic data in any patient group so the assumption that the men undergoing CABG had more extensive disease is not firmly underbuilt. Possibly, they were only more symptomatic, and there was probably a major overlap between the groups with respect to the extensiveness of their lesions. This, however, would probably have decreased the chances of detecting differences in the effect of the risk factors. Third, patients with mild angina who did not undergo CABG were not studied. CABG as an outcome may also be related to other factors than atherosclerosis such as availability of resources, local practices and severity of symptoms. In a prior analysis of this study population 128 men developed symptoms of angina with no prior AMI over the first 4 years of follow-up.[114] In multivariate analysis neither serum cholesterol nor smoking predicted angina but these findings may not be strictly relevant to the present analysis, where the men were much older. Coronary bypass surgery is only performed in five centres in Sweden, all of which were linked to the national Hospital Discharge register for practically all years of follow-up. Thus, only very few cases, if any, will have been missed.

Paper II

The introduction of new and more sensitive criteria in diagnostic markers in the year 2001 may explain some of the decline in the in-hospital mortality, suggesting that the improvement in prognosis is probably over-estimated.[115-117] However, this further emphasizes the lack of improval in prognosis after AMI in patients <65 years in the most recent period. The strengths of the study is the large number of cases and that we

were able to identify the patients through official registers. The hospital discharge diagnosis of AMI forms the basis of the Swedish AMI register which has been validated and examination of medical records for a national sample of ischemic heart disease patients suggested a high sensitivity (94%) and a high positive predictive value (86%) for ICD-9 code 410 in hospital discharge data with regard to definite AMI.[55]

Paper III

Another limitation in our study is the reliance on administrative registers. The quality of the statistics in mortality is therefore of fundamental importance,[55] with autopsies the most methodical examination to establish cause of death.[1,118-120] In Sweden the autopsy rates have decreased substantially during the last decades. Between 1970 and 2001 the autopsy rates in Sweden decreased from 50% to 15%, due to changes in legislation and financing. The autopsy rates vary by age group, decreasing less among younger patients.[115,120] Still, in 1998 to 2003 60% of all fatal AMI cases <65 years underwent an autopsy. In contrast, the proportion of victims 65 years old or more who underwent an autopsy decreased from 22% to 17% 1998 and 2003.[115] Accordingly, misdiagnosis in the younger CHD victims is less likely than among older patients. By Swedish law, an autopsy is required when the cause of death cannot be established. In the Framingham Heart Study death certificates due to out-of-hospital CHD were compared with physician-adjudicated sudden cardiac deaths, showing that SCD were overestimated by 47%.[121] However, because the autopsy rates were not stated, and they used a strict limit of symptoms lasting less than one hour to define a sudden death, and in addition defined 75% of the out-of-hospital deaths to be either non-sudden or of unknown cause, their results are not strictly comparable to our results. Other validation studies have shown much higher validity for a death certificate diagnosis of CHD in out-of-hospital deaths. In the study by Norris et al.[27] where the results bear a striking resemblance to our findings, with 91% of fatalities below 55 years occurring out-of-hospital, 86% of the 1589 cases identified dying out of hospital underwent an autopsy, with the rest carefully clinically validated. Accordingly, although the reliance in our study on administrative registers precluded detailed analysis, misclassification of non-coronary deaths as CHD deaths is probably relatively minor.

Paper IV

The definitions of unstable angina and angina are based on the physicians' judgment and were not strictly validated. Whereas there are strict and objective criteria for a diagnosis of AMI, there is in routine clinical practice no optimal way of validating unstable angina. With the reclassification of AMI criteria in 2001, a proportion of UAP episodes before that year would now be reclassified as small infarcts. However, reclassifying these episodes as AMI, using available laboratory markers, did not appreciably influence our findings. In addition, a proportion of patients with ACS may have had chest pain of non-cardiac origin. While the absolute majority of angina patients had either ECG changes on admission, or slight elevations of markers, some patients will have been diagnosed on the basis of typical symptoms only, or by a pathological stress test. These data were not systematically collected in our study. On the other hand, given the overall high prevalence of CHD in a Western population[65,122] it is more likely that CHD is underdiagnosed, and, accordingly, to exclude all patients with no objective signs of ischemia would provide a distorted view of patients with UAP.

CONCLUSIONS

- Serum cholesterol appears to be a stronger predictor for future CABG than for AMI, whereas smoking is not associated with future CABG, except in very heavy smokers, indicating that different risk factors are not related in the same way to different expressions of the disease. Both smoking rates and mean levels of cholesterol have declined in the Swedish population but other populations display other patterns. When risk factor patterns change the clinical expression of the disease may also change.

- Improvement of early survival in AMI was sustained long-term in patients up to 75 years of age though this trend was more pronounced in the younger than in the older patients. However, after the mid-1990s, there was little evidence of a further decrease in case-fatality in the younger patients. Still, mortality rates for the youngest patients are now very low, and further improvement in overall coronary mortality for this group will probably depend on early diagnosis, improved logistics of care and primary prevention. Although improvement in survival was maintained in the older patients, there seems to be considerably more scope for better treatment modalities.

- Of all deaths in a first CHD event, almost 80% currently occur outside hospital. Whereas the hospital case fatality decreased roughly by half, the reduction in out-of-hospital death was about one fourth, and accordingly, with an increasing proportion occurring out-of-hospital. At least in younger persons, hospital death rates are now very low, with currently only one in nine deaths in hospitalized patients. In order to achieve further reduction in case fatality, primary prevention will become increasingly more important.

- Among patients presenting for the first time with an ACS episode, male sex, slightly older age, as well as smoking, diabetes, and peripheral arterial disease are major determinants for presenting with AMI, rather than UAP. Differences with respect to smoking, diabetes, and peripheral arterial disease were more pronounced for women than for men.

POPULÄRVETENSKAPLIG SAMMANFATTNING

Bakgrund: Antalet individer som insjuknar och dör i hjärt- och kärlsjukdomar har minskat under de senaste årtiondena. Ungefär 42 procent av både kvinnor och män har hjärt- och kärlsjukdom som dödsorsak och bland personer 75 år och över dominerar sjukdomen som dödorsak. Gemensamt för kranskärlssjukdomar är atherosklerosen (åderförfettning) vars kliniska yttringar kan variera från kärlkramp till akut hjärtinfarkt eller plötslig död. Hur sjukdomen utvecklas och yttrar sig beror på en mängd olika faktorer. Utvecklingen av vård och behandling vid hjärt- och kärlsjukdom och förbättrade levnadsvanor tycks ha förändrat riskfaktormönstret och påverkat överlevnaden gynnsamt i befolkningen, framförallt har sjukhusdödligheten efter hjärtinfarkt minskat. Trots detta är hjärt- och kärlsjukdom fortfarande den vanligaste dödsorsaken i Sverige och västvärlden.

Syfte: Syftet med avhandlingen var att studera hur kranskärlssjukdom yttrar sig bland patienter som vårdats för kranskärlssjukdom på sjukhus eller insjuknat utanför sjukhus och hur överlevnaden har förändrats över såväl ett kort som ett längre tidsperspektiv.

Metoder: Delarbete I är resultat från Primärpreventiva studien, Göteborg med 28 års uppföljning via Sjukhusregistret och Dödsorsaksregistret. I studiegruppen ingick var tredje man i staden född mellan 1915 och 1925 (ej 1923) 7388 män ingick i studiegruppen. Männen var mellan 47-55 år när studien startade. Vi identifierade alla med hjärtinfarkt och de som genomgått kranskärlsoperation. Delarbete II och III bestod av data från Patientregistret och Dödsorsaksregistret under perioden 1987 till 2003 från 19 svenska län. Patienterna/de avlidna var i åldern 35-84 år. I delarbete II studerades dödligheten bland 264 575 män och kvinnor i olika åldersgrupper och tidsperioder som insjuknat i hjärtinfarkt för första gången. I delarbete III granskades dödligheten på och utanför sjukhus bland patienter som inte varit sjukhusvårdade för akut hjärtinfarkt tidigare, totalt 377 030 patienter. Det sista delarbetet IV, baseras på data från ett nationellt kvalitetsregister (RIKS-HIA), som registrerar patienter vårdade på hjärtintensivvårdsavdelningar. Vi identifierade riskfaktorer bland de patienter som insjuknat för första gången med hjärtinfarkt eller ett första insjuknande i sjukhusvårdskrävande kärlkramp mellan 1996 och 2005, patienterna var i åldern 25 år och uppåt.

Resultat: I delarbete I var högt kolesterol betydligt starkare förknippat med kranskärlsoperation än med hjärtinfarkt. Delarbete II visade att dödligheten efter infarkt minskade i alla åldersgrupper under perioden 1987-2003. Bland unga personer under 55 år halverades dödligheten jämfört med äldre 75-84 år, som minskade sin dödlighet med en tredjedel. Med stigande ålder och uppföljningstid minskade skillnaderna mellan män och kvinnor. Den årliga dödligheten bland patienter som insjuknade 1996 till 1998 var <1% bland patienter under 55 år och bland de äldsta 75-84 år var den årliga dödligheten 10%. I delarbete III påvisades att var 5:e patient under 55 år inte överlevde sin första hjärtinfarkt eller allvarlig hjärthändelse. Av dem som inte överlevde sin första hjärtinfarkt, (44% i samtliga åldrar), så avled de flesta utanför sjukhus, eller ca 80%. Vi kunde även visa att dödligheten i kranskärlssjukdom har minskat med 50% på sjukhus men endast med 25% bland patienter som avlider utanför sjukhus. Delarbete IV visar att bland patienter som vårdas för första gången för akut koronar-

syndrom, dvs antingen hjärtinfarkt eller sjukhusvårdskrävande kärlkramp är risken för att insjukna i hjärtinfarkt 1,5 gånger större bland patienter som röker än bland dem som insjuknar med sjukhusvårdskrävande kärlkramp. Detta kan uttryckas som att rökare har högre risk att insjukna i hjärtinfarkt, dvs. en allvarligare manifestation av sjukdomen. Bland unga kvinnor under 65 år som röker var risken två gånger högre. Diabetes och perifer kärlsjukdom var också förenat med minst 1,5 gånger högre risk för hjärtinfarkt, framförallt bland kvinnor.

Slutsats: Bland patienter med kranskärlssjukdom har dödligheten minskat i alla åldrar, främst bland sjukhusvårdade patienter med kranskärlssjukdom. För att minska antalet bland dem som avlider utanför sjukhus måste såväl riskgrupper som riskfaktorer identifieras. Kranskärlssjukdom utvecklas och yttrar sig på olika sätt beroende på ålder, kön och riskfaktorer.

ACKNOWLEDGEMENTS

Many people have meant a lot to me during the progress of this thesis. I wish to express my gratitude and appreciation to all people who have, in one way or another helped me and supported me during all these years. In particular I would like to acknowledge:

Professor *Annika Rosengren*, my supervisor and tutor, for always being there with support, interest, scientific guidance, research ideas and for all patience in guiding me through the epidemiology, statistics and language proficiency. Thanks for never giving up, for your infinite criticism and for your optimism in a thirty-six! year old epidemiology novice. Thanks also for friendship during these years.

Lena Björck, my dearest colleague and co-author for friendship and sharing all successes, adversities in writing, and co-working in PhD courses. Thanks for all the laughs.

Georg Lappas, my co-author and statistician for always supporting me and infinite patience in all the statistics.

Professor *Lars Wilhelmsen*, co-author for valuable co-operation.

My co-authors, Professor *Lars Wallentin* and Associate Professor *Ulf Stenestrand* in the work with RIKS-HIA database.

Professor *Karl Swedberg*, Head of the Department of Emergency and Cardiovascular Medicine, Sahlgrenska University Hospital/Östra, for supporting me and introducing me in cardiology.

Ann-Britt Johansson, our secretary, for friendship, always being there with a friendly word and my tutor in behaviour.

Catharina Welin, for friendship and the one who inspired me to begin with the PhD studies.

Docent *Henry Eriksson*, who inspired and introduced me to epidemiology.

Professor *Mikael Dellborg*, who thought me cardiology and introduced me to my tutor.

Barbro Westberg, Head of the Department of Medicine, for being a supportive chief.

Professor *Inger Ekman*, for support and pushing me towards for the PhD-studies in medicine and for the Master of Science in Health Care Science in Nursing.

Eva Thydén for invaluable help with administrative assistance and the layout of this thesis.

All colleagues and staff at the department of medicine at Östra sjuhuset.

Marie Andreasson, my dearest friend and colleague always reminding me of the real life in nursing.

Bertil and *Birgit*, my parents, for great support and love.

Björn, my brother, try to outdo me now!

Janos, my beloved husband for all support, love and patience during this process.

My children *Malin, Jonas* and *Johan* for love and for always reminding me of what is important in life, you are always in my heart.

Financial support was provided by: The Swedish Heart and Lung Foundation and and FoU-rådet in Göteborg and Södra Bohuslän, Västra Götalandsregionen.

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