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Impact of Risk Factors and Treatment in Coronary Heart Disease

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ABSTRACT

Aims: The aim of the present study was to explore how risk factors and medication influence clinical presentation and mortality in coronary heart disease (CHD) and to explain how much of the decrease in CHD mortality in Sweden that could be attributed to medical and surgical treatments, and how much to changes in cardiovascular risk factors.

Subjects and methods: We included 781 consecutive patients with a first acute myocardial infarction (AMI) during the period 1994 to 2002, to investigate trends in the use of lipid-lowering treatment, and changes in serum lipids. The second part of the study is based on 93,416 consecutive patients aged 25 to 84 years from RIKS-HIA, a national quality of care register that includes all patients admitted to CCUs in Sweden and admitted to hospital between 1996 and 2004 with a first AMI. The IMPACT mortality model was used to combine and analyze data on uptake and effectiveness of cardiological treatments and risk factor trends in Sweden, to investigate the relative contributions of these factors on the decline in CHD mortality in Sweden. The main data sources were official statistics, national quality of care registers, published trials and meta-analyses and national population surveys.

Results: In the single-centre study almost all patients under 65 years of age with a first AMI were treated with lipid-lowering drugs in 2002. Still, target levels for serum cholesterol were not met in a substantial number of patients. In the RIKS-HIA population, more than 50% of younger patients presenting with STEMI were smokers at the time of hospitalization. After adjustments, smoking was found to be an independent determinant for presenting with STEMI compared to non-STEMI. In addition, use of aspirin, β -blocker, ACE-inhibitor and statin prior to hospitalization were all associated with lower odds of presenting with STEMI compared to non-STEMI in both men and women. Between 1986 and 2002, CHD mortality rates in Sweden decreased by 53.4% in men and 52.0% in women aged 25 to 84 years. This resulted in 13,180 fewer deaths in 2002. By using the IMPACT model approximately 36% of this decrease could be attributed to treatments in individuals and 55% to population risk factor reductions. Adverse trends were seen for diabetes and overweight.

Conclusions: Despite a marked increase in lipid-lowering drug treatment, current target levels of <4.5 mmol/l for serum cholesterol are not met in a significant proportion of post-AMI patients. Tobacco smoking is a major determinant for presenting with STEMI, indicating that smoking is one of the major risk factors for presenting with more severe AMIs. Previous medication with aspirin, β -blocker, ACE inhibitor or statin is associated with substantially lower risk of presenting with STEMI. More than half of the CHD mortality decrease between 1986 and 2002 was attributable to reductions in major risk factors, mainly a large decrease in serum cholesterol, emphasizing the value of a comprehensive strategy that promotes primary prevention and evidence-based medical treatments, especially secondary prevention.

Key words: coronary disease, myocardial infarction, risk factors, smoking, lipid levels.

LIST OF ORIGINAL PAPERS

This thesis is based on the following studies, which will be referred to in the text by Roman numerals.

- I Björck L, Welin C, Rosengren A. Secular trends in lipid-lowering treatment and lipid levels after a first acute myocardial infarction.
J Vasc Health Risk Manag 2007;3:1045-51
- II Björck L, Rosengren A, Wallentin L, Stenestrand U. Smoking in relation to ST-segment elevation acute myocardial infarction: Findings from the Register of Information and Knowledge about Swedish Heart Intensive Care Admissions.
Submitted
- III Björck L, Wallentin L, Stenestrand U, Rosengren A. Medication in relation to ST-segment elevation myocardial infarction - findings from the Register of Information and Knowledge about Swedish Heart Intensive Care Admissions (RIKS-HIA).
In manuscript
- IV Björck L, Rosengren A, Bennett K, Lappas G, Capewell S. Modelling the Decreasing Coronary Heart Disease Mortality in Sweden between 1996 and 2002.
Accepted in the European Heart Journal, 2008

CONTENTS

ABSTRACT	3
LIST OF ORIGINAL PAPERS	4
ABBREVIATIONS	8
INTRODUCTION	9
What do we know about the development of atherosclerosis?	9
Cholesterol in relation to diet and weight	9
“Early era of epidemiology”	10
The Framingham Study and other early cardiovascular surveys	10
Modifiable risk factors	11
Dyslipidemia	11
Diet	11
Smoking	12
Physical activity	12
Overweight, diabetes and hypertension	12
Medical interventions and procedures	12
Aspirin	12
Beta-blockers	13
ACE-inhibitors	13
Statin - interventions against hyperlipidemia - early clinical trials	13
Fibrinolytic therapy, CABG andPCI	13
Other medical advances: hypertension, heart failure, cardiopulmonary resuscitation	13
Recent trends in coronary heart disease mortality	14
AIMS	15
SUBJECTS AND METHODS	16
Study I	16
Single-center study of patients <65 years discharged after a first MI	16
Follow-up visit	16
Definitions	16

Studies II and III	16
Patients with a first myocardial infarction, STEMI or non-STEMI	16
Definitions	17
Study IV	17
Mortality model	17
Deaths Prevented or Postponed in 2002	19
Mortality reductions attributable to treatments	19
Methods for calculating 95% confidence interval for weighted mean	21
Mortality reductions attributable to changes in risk factors	21
Comparison of estimated with observed mortality changes	22
Sensitivity analyses	22
STATISTICAL PROCEDURES	23
Study I	23
Studies II and III	23
Study IV	23
RESULTS	24
Study I	24
Lipid-lowering drugs and lipid levels	25
Study II and Study III	26
Study II	27
Study III	30
Medication use and clinical presentation	30
Study IV	33
Major cardiovascular risk factors	34
Medical and surgical treatments	34
Proportional contributions to the decrease in deaths	38
DISCUSSION	39
Study I	39
4S Study and implementing of lipid-lowering treatment	39
Lipid-lowering treatment, cholesterol levels and target levels	39
Lipid-lowering treatment, triglycerides levels and target levels	39
Study II	40
Study III	41
Study IV	42

LIMITATIONS	44
Study I	44
Studies II and III	44
Study II	44
Study III	44
Study IV	45
CONCLUSIONS	46
POPULÄRVETENSKAPLIG SAMMANFATTNING	47
ACKNOWLEDGEMENTS	49
REFERENCES	50
PAPER I-IV	
IMPACT Model Appendix	

ABBREVIATIONS

ACE	angiotensin-converting enzyme
ACS	acute coronary syndrome
AMI	acute myocardial infarction
AMORIS	AMORIS (apolipoprotein-related mortality risk) Study
AP	angina pectoris
ApoA1	apolipoprotein A1
ApoB	apolipoprotein B
ASA	acetylic salicylic acid (aspirin)
BMI	body mass index
BP	blood pressure
CABG	coronary artery bypass grafting
CAD	coronary artery disease
CCU	coronary care unit
CHD	coronary heart disease
CI	confidence interval
CK-MB	MB fraction of creatine kinase
CPR	cardiopulmonary resuscitation
CVD	cardiovascular disease
DM	diabetes mellitus
DPP	deaths prevented or postponed
ECG	electrocardiogram
ESC	European Society of Cardiology
HDL-cholesterol	high-density lipoprotein cholesterol
HF	heart failure
ICD	the International Classification of Diseases
LBBB	left bundle-branch block
LDL-cholesterol	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
NSTEMI	non ST-elevation myocardial infarction
OR	odds ratio
PCI	percutaneous coronary intervention
RCT	randomised clinical trial
RIKS-HIA	Register of Information and Knowledge about Swedish Heart Intensive Care Admissions
SCAAR	Svenska Coronar Angiografi- och Angioplastik Registret
SD	standard deviation
STEMI	ST-elevation myocardial infarction
UAP	unstable angina pectoris
4S-Study	the 4S-Study (Scandinavian Simvastatin Survival Study)

INTRODUCTION

During the last two decades rapid changes in coronary heart disease (CHD), with decreasing incidence and mortality, have been observed in Sweden as in most other Western countries.¹⁻³ In parallel, changes in clinical presentation with less severe myocardial infarctions and more unstable angina have also been documented.⁴⁻⁶ At the same time, there have also been marked changes in treatment in acute coronary syndromes, as well as advances in the treatment of heart failure, hypertension, hyperlipidemia, and secondary prevention.⁷⁻¹² Additionally, there have been changes, with respect to smoking, diet and physical activity. The net effects of these changes on CHD in Sweden are not known. The present work deals with different aspect, and potential consequences of these changes.

What do we know about the development of atherosclerosis?

In the early twentieth century Russian pathologists hypothesized that a diet rich in fat and protein accelerated the atherosclerotic process. As early as in 1908-1912, Anitschkow and colleagues, by feeding rabbits with dietary animal protein (eggs, dairy products and meat), established the relationship between cholesterol and atherosclerosis in the aorta.¹³ They also found that, if diet changed, the lipoid deposits in aorta decreased or disappeared, and that the lipoid deposits in rabbits closely simulate early human lesions. Anitschkow stated that even though the atherosclerotic process in man not is identical to the atherosclerotic process in experimental rabbits there is a remarkable similarity. Later research has confirmed Anitschkow's hypothesis.

Cholesterol in relation to diet and weight

A further step was taken when Vartiainen and Kanerva¹⁴ compared post mortem cases in Finland from 1940-1945, when Finland was at war, with controls from 1933-1938. They found that atherosclerosis increased with age in both cases and controls. In post mortem cases, who had died during peacetime there were more positive findings of atherosclerosis among people younger than 70, but less among older people. In wartime there was a decrease in the more severe forms of atherosclerosis, potentially explained by a different diet, with less cholesterol and animal protein, along with lower total calorie intake, accompanied by weight loss. The conclusion was that even though atherosclerosis is strongly connected with old age, it is a disease that possibly could be treated and prevented with diet. These findings were confirmed by the official statistics in Finland showing a significant lower rate of deaths reported from atherosclerosis during the war compared with that in the pre-war period.

These early findings were confirmed and reinforced by a later studies which were to become classic. In 1953 Enos, Holmes and Beyer published data from 300 young American soldiers (average age 22 years) who were killed in the Korean War.¹⁵ In 77% of the young men coronary artery changes were present, from fatty streaks to plaques narrowing the coronary artery lumen. These findings were confirmed by an autopsy study on patients aged 1 to 69 years, in which Strong found that coronary atherosclerotic lesions develop very early in life and at least 20 years before overt disease.¹⁶

More recently, McGill et al., in a series of papers based on autopsy data, described the development of atherosclerosis from childhood to adolescence, and its association with risk factors for coronary heart disease. These studies confirmed that atherosclerotic changes in the coronary arteries start early in life, long before symptoms occur.^{17,18,19} By halting this process by risk factor modification in the young McGill claims that 90% of the heart attacks could be prevented.²⁰

“Early Era of Epidemiology”

After World War II an increasing number of fatal heart attacks began to be reported, and there were speculations on why middle-aged men, seemingly healthy, were dropping dead.²¹ In the late 1940s the “era of epidemiology” started with several studies, which were later to become famous, chiefly of men with well-defined occupations, such as the London Transport Workers Study,²² the San Francisco Longshoremen²³ and the Minnesota Business and Professional Men Study²⁴, among others. This research developed into the inception of a multitude of later studies, which collectively have led to our present understanding of the causes of atherosclerosis.²⁵

In the early 1950s, US nutritionist Anselm Keys²¹ noted the low incidence of CHD in southern Europe, hypothesizing that this was the result of the traditional Mediterranean diet. In 1950 Keys published a paper showing a strong relation between diet and cholesterol levels in blood in clinically healthy men.²⁶ These observations together with his investigations in Naples, where the general population had low cholesterol levels and little CHD, were the start of the Seven Countries Study in 1957. In this landmark study, cardiovascular disease (CVD), frequency and risks were compared in different male populations from Italy, Spain, England, Scandinavia, South Africa and Japan. A strong relation was found between saturated fatty acid intake in the various locations, their mean cholesterol levels and CHD mortality.²⁷ Moreover, it gave the idea to start another investigation, the Framingham Study.

The Framingham Study and other early cardiovascular surveys

The Framingham Study started in 1949 and initially included 5 209 men and women, aged 30 to 60 years, living in the small town of Framingham, Massachusetts. The study still retains its initial focus on identifying major risk factors for cardiovascular heart diseases. A large number of cardiovascular cohort studies have followed after the Framingham Study. In Sweden the Goteborg Study of Men Born in 1913 started in 1963, followed by several others, for example Goteborg Multifactorial Primary Prevention Trial, and the MONICA Study conducted in Göteborg and in Northern Sweden.

Most studies have investigated Western populations. An exception to this is the fairly recent INTERHEART study, which, in addition to being conducted in 52 countries in all inhabited regions of the world, also elegantly summarized and quantified the risk factors for myocardial infarction. Abnormal lipids, smoking, hypertension, diabetes, abdominal obesity, psychosocial factors, low consumption of fruit and vegetables, and alcohol and regular physical activity together explained about 90% of all myocardial infarctions.²⁸

Modifiable risk factors

Cholesterol was the first known risk factor for atherosclerosis. However, other risk factors were additionally being recognized, such as smoking, hypertension, low physical activity, and diabetes. With time, it has increasingly become clear that most risk factors are preventable, and depends both on societal factors and on individual choices.^{20,28,29}

Dyslipidemia

In individuals, elevated total cholesterol is firmly associated with increased risk for coronary artery disease.^{29,30} However, although widely used, total cholesterol is a composite of several lipid components, including LDL, HDL and triglycerides. LDL, particularly small dense LDL, is a crucial element in plaque formation, whereas HDL has a protective function, being involved in 'reverse transport' of cholesterol, along with antioxidant and anti-inflammatory properties.

In recent years, apolipoproteins, such as apolipoprotein B (ApoB) which is the major protein component of LDL, apolipoprotein A1 (ApoA1), the major apoprotein of HDL, and particularly the ratio between these two apoproteins have received much attention.³¹ Even though the ApoB/ApoA1 ratio promises to be a very useful and accurate tool in prediction of CHD, its role as a treatment goal is not yet firmly established.

Lowering serum cholesterol, whether by dietary intervention or by evidence-based medications lowers the risk of CHD. The decrease in risk is age dependent. A relatively small decrease of 0.6 mmol (about 10%) in serum cholesterol, which may be achieved by moderate changes in diet, lowers the risk of CHD by about 50% at the age of 40 and by 20% at the age of 70.³²

Diet

The relation between diet and cholesterol levels has been shown in several studies but there are also examples in single countries. During the 1970s to 1990s coronary heart disease incidence and mortality in Finland decreased dramatically, which was explained by decreasing levels of cholesterol due to less intake of saturated fat.³³ These data are supported by a study performed in middle-aged Finnish male mental patients, where the effect on serum cholesterol of the traditional Finnish diet was compared with a more healthy diet with less saturated fat and less cholesterol, with the healthy diet served in one hospital and the traditional hospital diet in the other.

After six years the diets were reversed and the study continued for another six years. When on the healthy diet, patients had lower serum cholesterol levels and lower rates of CHD compared to the traditional hospital diet.³⁴ This study was repeated among female mental patients with the same result.³⁵ These findings are supported by a wealth of evidence showing that a healthy diet with unsaturated fat, as the main source of dietary fat, whole grains, fruit and vegetables rich in omega-3-fatty acids protects against coronary heart disease.³⁶

Smoking

Smoking is one of the most important risk factors for CHD, with the effect of smoking related to the amount of tobacco smoked daily. Both active and passive smoking increase the risk of CHD and are related to progression of atherosclerosis. Smoking cessation is the most effective of all preventive measures, particularly in patients with CHD, reducing mortality by about 50%.^{37,38} Moreover, worldwide, smoking causes a substantial proportion of all CHD cases and is the single most important preventable cause of disease and early death.²⁸

Physical activity

Lack of physical activity is one of the most important preventable causes of cardiovascular disease since physical activity influences several other risk factors such as cholesterol (e.g. HDL), insulin resistance, body weight and blood pressure. Early studies have shown an association between physical activity and CHD and mortality,^{23,24,39} with later studies verifying this relationship.⁴⁰

Overweight, diabetes and hypertension

The relationship between overweight and cardiovascular death is known, with recent studies showing that the regional distribution of adiposity could be more important than body weight in itself. Earlier studies used BMI as a marker for overweight and obesity, while recent studies have focused on waist-hip circumference or just waist circumference.^{41,42} Body weight also influences other risk factors such as blood pressure, glucose levels and lipid levels.

Diabetes and hypertension are both major risk factors for developing CVD. The relationship between increasing glucose levels and the risk of developing CVD is linear and continues down to the normal range.⁴³ Elevated blood pressure is a major risk factor not only for CHD, but also for heart failure and particularly for stroke. Similar to blood glucose and serum cholesterol, even a small increase in blood pressure levels is associated with increased risk of CVD. With every 10 mmHg increase in diastolic blood pressure or every 20 mmHg increase in systolic blood pressure the risk of CVD increases twofold.²⁹ Since hypertension is common in the Swedish population, both life-style changes and treatment of hypertension are important.⁴⁴

Medical interventions and procedures

In parallel with the evolving knowledge of the causes of CHD, there has been a revolution in medical treatment and interventions. Evidence-based therapies such as fibrinolysis, coronary revascularization (CABG, PCI) and medications such as aspirin, statin, ACE-inhibitor and β -blocker have achieved marked reductions in mortality in CHD patients.

Aspirin

Aspirin exerts an antithrombotic action through inhibition of platelet cyclooxygenase, and inhibits thrombin formation, leading to an antithrombotic effect.⁴⁵ The benefit of aspirin has been shown in the *Antithrombotic Trialists' Collaboration Study*. This large

systematic overview showed that aspirin (75-150 mg daily) significantly reduced cardiovascular events in high-risk patients as well as in patients with established CVD. Among patients with an acute MI the mortality reduction was estimated to 15%.⁴⁶

Beta-blockers

In MI patients, β -blockers reduce the cardiac rate and the myocardial metabolic demand, resulting in lower oxygen demand, and less widespread infarction. A large number of randomized controlled trials have demonstrated the benefits of β -blockers on survival in patients with acute MI as well as in long-term secondary prevention. The reduction in the odds of death in long-term trials is 23% but in short-term trials there was only a 4% reduction. However, β -blockers are underused in secondary prevention after myocardial infarction and, potentially, a larger number of patients would benefit by the treatment.⁴⁷

ACE-inhibitors

ACE-inhibitor exerts a cardioprotective effect by reducing myocardial hypertrophy and vascular hypertrophy with an additional effect on long-term remodeling. There are favorable effects of early treatment in patients with a large AMI and/or current or previous left ventricular dysfunction, but an early benefit has also been shown in unselected AMI patients. In addition, ACE-inhibitors may have a vascular protective effect on atherosclerosis progression and risk of plaque rupture. Moreover, ACE-inhibitors reduce cardiovascular mortality in high-risk patients, but the mechanisms are not entirely clear.^{48,49,50}

Statin - interventions against hyperlipidemia - early clinical trials

To investigate whether it was possible to prevent CHD with pharmaceutical drugs and /or interventions, a number of primary prevention trials were initiated with less encouraging results and with some deleterious side effects.⁵¹⁻⁵⁴ The failure to achieve a reduction in cardiac end-points with cholesterol lowering strategies was disappointing but, eventually, with the development of statins, an effective and safe way of reducing serum cholesterol, significant effects on CHD mortality could be shown. The first trial to unequivocally demonstrate this effect was the Scandinavian Simvastatin Survival Study (4S), with several later studies showing the same positive effects.⁵⁵⁻⁵⁷

Fibrinolytic therapy, CABG and PCI

The unequivocal benefit of fibrinolytic therapy in patients with ST-elevation MI was demonstrated in a number of trials in the 1980s with an overall reduction in mortality estimated to be 25%.⁵⁸ Later research has compared the effectiveness of fibrinolytic therapy vs. primary PCI in patients with ST-elevation myocardial infarction, showing a better outcome in patients with PCI intervention.⁵⁹

Other medical advances: hypertension, heart failure, cardiopulmonary resuscitation

Heart failure treatment has developed rapidly during the latest decades with important breakthrough of the benefits of β -blockers and the discovery of ACE-inhibitors along

with older medications in combination. Mortality due to heart failure is high, with more effective treatments demonstrated to improve the outcome. Antihypertensive treatment is evidence-based and lowers the risk of cardiovascular mortality.⁴⁴ Recent guidelines have introduced lower thresholds for treatment. Cardiopulmonary resuscitation (CPR) education in medical workers has also been implemented largely during the latest decades, but also in the general population. Higher survival rates after CPR has been demonstrated.⁶⁰

Recent trends in coronary heart disease mortality

During the last few decades both mortality rates and incidence have been falling in Sweden, in some European countries and in the US. Still, CHD remains the most common cause of death in Sweden and other Western regions.¹⁻³ Additionally, there is data showing that the decrease in mortality is now flattening in young people.⁶¹ Simultaneously there has been an increase in mortality in low and middle-income countries. Accordingly coronary heart disease will continue to be a major health problem in the foreseeable future, with an increasing number of deaths worldwide.

AIMS

General aim

The broad aim of the present thesis is to explore how risk factors and medication influence clinical presentation and mortality in coronary heart disease.

Specific aims

- To describe changes in the use of lipid-lowering drugs in young (< 65 years) male and female survivors of a first AMI after the publication of the first landmark trials on the effect of statins in CHD, and to quantify the ensuing changes in mean serum cholesterol and triglycerides. (Paper I)
- To explore the effect of smoking as a potential determinant of presenting with ST-elevation myocardial infarction (STEMI), the most severe form of myocardial infarction, among a large population of patients with a first AMI. (Paper II)
- To explore whether previous medication with aspirin, β -blocker, ACE-inhibitor or statin influence clinical presentation in a first AMI. (Paper III)
- To examine, by using the previously validated IMPACT CHD Mortality Model to explain the causes of the CHD mortality decrease in Sweden between 1986 and 2002, or, more specifically, how much of the decrease that could be attributed to medical and surgical treatments, and how much to changes in cardiovascular risk factors. (Paper IV)

SUBJECT AND METHODS

Study I

Single-center study of patients < 65 years discharged after a first MI

Subjects for this study were consecutively included among patients with a first MI discharged during the period 1994 to 2002 from the Coronary Care Unit (CCU) or step-down unit at the Sahlgrenska University Hospital/Östra. MI was defined as typical symptoms and either typical ECG changes and/or increased levels of creatine-kinase_{MB} subunit mass concentration (1994-2000 >10µg/l, from 2001 >5µg/l). All patients, with the exception of those not living in the catchment area, were routinely offered dietary counselling by nurses and dieticians in group sessions using essentially the same methods throughout the study period. The present study is based on those patients who attended a routine follow-up visit with a nurse three months post-discharge. After the exclusion of patients who died (n=30) before they could be investigated, and patients who lived outside the catchment area, or who did not attend the 3-month follow-up, 781 patients (607 men, 174 women) were available for the present investigation.

Follow-up visit

At the 3-month follow-up use, of any lipid-lowering drug and dosage was recorded, as were data on smoking, diabetes and hypertension. Body weight was measured on a lever balance to the nearest 0.1 kg while the patient was wearing indoor clothing. Height was recorded to the nearest centimetre. Body mass index (BMI, weight in kg/height in m²) was used as an index of relative weight and overweight/obesity. Blood samples were drawn from an antecubital vein at the visit or at a later visit (maximum 6 months after the AMI) after an overnight fast. Serum cholesterol and triglyceride measurements were determined according to standard laboratory procedures. Since 1993, serum cholesterol has been analysed according to Boehringer Mannheim (cat. no. 701912). This method is the standard method of the Laboratory of Clinical Chemistry (certified laboratory) at Göteborg University and remained constant through the study period.

Definitions

Hypertension was defined as diagnosed by a physician before hospitalization. Diabetes was defined as diagnosed by a physician before or during hospitalization. Target levels for total serum cholesterol were defined as <4.5 mmol/l according to the current European Society of Cardiology (ESC) guidelines.⁶²

Studies II and III

Patients with a first myocardial infarction, STEMI or non-STEMI

In Sweden, the Register of Information and Knowledge about Swedish Heart Intensive Care Admissions (RIKS-HIA) continuously registers all patients admitted to hospitals with coronary care units. RIKS-HIA started in 1995 with 19 participating hospitals,

increasing gradually to 72 of 77 Swedish hospitals in 2004. The register currently includes more than 95% of all CCU admissions in Sweden. All personal identifiers are removed from the RIKS-HIA data file when used for research purposes.^{63,64} The present study is based on all consecutive patients aged 25-84 years without a history of prior AMI who were admitted to any of the participating hospitals between 1 January 1996 and 31 December 2004 and discharged with a diagnosis of STEMI or non-STEMI. Of 105,365 patients, we excluded 5989 with missing data on smoking (6%), 5325 (5.4%) with left bundle-branch block (LBBB) and 635 (0.6%) with a pacemaker ECG. After these exclusions, the final sample included 93,416 patients admitted to hospital with their first AMI.

Case report forms filled in by nurses are used to record information on age, gender, tobacco smoking status (never smoking, ex-smoker [defined as not smoking for more than 1 month before admission to hospital] and current smoker), known hypertension, diabetes mellitus (history or medication), known hyperlipidemia, previous heart failure, previous angina pectoris, previous MI, previous coronary revascularization, previous medication (ACE-inhibitors, β -blockers, aspirin and lipid-lowering drugs), presenting symptoms, ECG, reperfusion treatment, other pharmacological treatment, intervention procedures, major complications and outcomes during hospital stay. Prior angina was defined as either known angina or prior medication with long-acting nitrates (Study III).

Definitions

The ST segment was recorded as the first choice of which of the following alternatives accurately described the ST segment on the electrocardiogram at entry:

1 = normal, 2 = left bundle-branch block or pacemaker, 3 = ST segment elevation, 4 = ST segment depression, 5 = T-wave inversion and 6 = other changes.

The criteria for a diagnosis of acute MI were standardized and identical for all participating hospitals using the World Health Organization and Joint European Society of Cardiology and American College of Cardiology Committee criteria.^{65,66}

Study IV

In this study, data from Sweden on population deaths and coronary heart disease were combined with data on risk factors and data of cardiological treatments in men and women 25-84 years old.

Mortality model

The cell-based IMPACT mortality coronary heart disease model^{6,9-11,67} was used to combine and analyse data on uptake and effectiveness of cardiological treatments and risk factor trends in Sweden. The model includes the major population risk factors: smoking, total cholesterol, systolic blood pressure, BMI, diabetes and physical inactivity. It also includes a comprehensive coverage of all standard evidence-based medical and surgical treatments used for CHD. The main data sources were official

statistics, national quality of care registers, published trials and meta-analyses and national population surveys.

Main data sources for the parameters used in the Swedish IMPACT Model are shown in Table 1. Aggregated data were used from registers kept by the Official Statistics of Sweden and the National Board of Health and Welfare, Swedish Quality of Care Registers, cardiovascular and other population studies (MONICA, INTERGENE, the Prospective Population Study of Women in Goteborg, the AMORIS Study). Effects of interventions were estimated from multicentre studies of cardiovascular interven-

Table 1. Main data sources for the parameters used in the Swedish IMPACT Model 1986 and 2002

	1986	2002
Population, deaths, CHD Mortality	The National Board of Health and Welfare	The National Board of Health and Welfare
Number of patients admitted yearly: MI, AP, HF	The Hospital Discharge Register	The Hospital Discharge Register
Number of patients treated with CABG	The Hospital Discharge Register	Swedish Quality Registry for General Thoracic Surgery, the Hospital Discharge Register
PCI	The Hospital Discharge Register	The Hospital Discharge Register, SCAAR.
Cardiopulmonary resuscitation in the community	Assume zero	Swedish Cardiac Arrest Registry
AMI, UAP	Assume zero	RIKS-HIA
Secondary prevention following AMI		EUROASPIRE ⁶⁸ , RIKS-HIA
Secondary prevention following CABG or PCI		EUROASPIRE ⁶⁸
Congestive Heart Failure		IMPROVEMENT (2002) ⁶⁹ OBS-CHF (2007) ⁷⁰
Treatment for chronic angina		EUROASPIRE ⁶⁸
Community angina pectoris: total	MONICA GOT & Northern Sweden	INTERGENE 2001-2004
Community chronic heart failure Prevalence	Assume same 1986 as 2002 ⁷¹	The Hospital Discharge Register 2003
Medication (ACE-inhibitors, β-blockers, spironolactone)	Assume zero	IMPROVEMENT (2002) ⁶⁹
Medication (aspirin, statins)	Assume zero	OBS-CHF ⁷⁰
Hypertension prevalence	MONICA GOT & Northern Sweden	INTERGENE
treated (%)	MONICA GOT & Northern Sweden	INTERGENE & MONICA Northern Sweden
Statins for primary prevention		INTERGENE
Population risk factor prevalence		
Current smoking, physical activity, obesity (BMI), diabetes	ULF, the Official Statistics of Sweden	ULF, the Official Statistics of Sweden
Systolic blood pressure	MONICA GOT & Northern Sweden	MONICA Northern Sweden & INTERGENE, the Prospective Population Study of Women in Goteborg.
Cholesterol	The AMORIS Study ⁷²	MONICA GOT & Northern Sweden, INTERGENE

Deaths Prevented or Postponed in 2002

Total population and age distribution data for Sweden in 1986 and 2002 were obtained from the National Board of Health and Welfare. We calculated the number of CHD deaths expected in 2002 if the CHD mortality rates in 1986 had persisted, by multiplying the age-specific mortality rates for 1986 by the population for each 10-year age stratum in the year 2002 (thus accounting for the increasing life expectancy of the population). Subtracting the number of deaths observed in 2002 from the number expected, then yielded the fall in the number of CHD deaths (prevented or postponed) in 2002, which the model needed to explain (Table 2).

Table 2. Number of CHD deaths and CHD mortality rate per 100,000 1986 and 2002 and DPP:s in 2002 in men and women in Sweden.

	1986		2002		DPP
	Number	Rate per 100,000	Number	Rate per 100,000	
Men	14780	544.1	7560	253.4	7220
Women	8280	291.5	4290	140.0	3990
Total	23,060		11,850		11,210

Mortality reductions attributable to treatments

The prevalence of CHD by diagnosis (AMI and UAP) was obtained from the Swedish Hospital Discharge Register. Case fatality rates and the risk reduction due to treatment, all stratified by age, sex, and diagnosis, were calculated by linking to the Swedish Death Register. The number of deaths prevented or postponed by each intervention in each group of CHD patients in the year 2002 was calculated by multiplying the number of people in each diagnostic group by the proportion of those patients who received a particular treatment, by the case-fatality rate over 1 year, and by the relative reduction in 1-year case-fatality by the administered treatment.^{9,11}

For example, in Sweden 2002, approximately 2755 men aged 55-64 were hospitalized with acute myocardial infarction (Table 3). Some 87% were prescribed aspirin, with an expected mortality reduction of 15%.⁴⁶ The expected age-specific 1-year case-fatality rate was approximately 4.9%. The number of deaths prevented or postponed for at least a year by the use of aspirin among men aged 55 to 64 were then calculated as:

$$2755 \times 0.87 \times 0.15 \times 0.049 = 18$$

Table 3. Example of a multi-way sensitivity analysis for men*

	Patient Numbers [†]	Treatment Uptake [‡]	Relative Mortality reduction [§]	One-year case fatality ^x	Deaths prevented or postponed
	a	b	c	d	(a x b x c x d)
Best estimate	2755	0.87	15%	4.9%	18
Minimum estimate	2205	0.70	11%	3.9%	7
Maximum estimate	3305	0.99	19%	5.9%	37

* In Sweden in 2002, about 2755 men aged 55-64 was hospitalized with AMI, of whom approximately 87% were given aspirin. Aspirin use reduces case-fatality rate by approximately 15%. The underlying 1-year case-fatality rate in these men was approximately 4.9%. The calculated number of deaths prevented or postponed was approximately 18. A multi-way sensitivity analysis was then performed. Lower and upper bounds for each parameter were estimated using either 95% confidence intervals where available or, failing that, using calculated bounds of plus or minus 20% (treatment uptake however was capped at 99%). Multiplying all lower-bound estimates together yielded the lower-bound estimate of deaths prevented or postponed, and multiplying all upper-bound estimates together yielded the upper-bound estimate of deaths prevented or postponed.

[†] Hospital Discharge Register Centre for Epidemiology (the EPC), the National Board of Health and Welfare

[‡] The Register of Information and Knowledge about Swedish Heart Intensive Care Admissions (RIKS-HIA), 2002.

[§] Antithrombotic Trialists' Coalition (2002). Lower and upper 95% CI from Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002;324:71-86.

Several adjustments were made to these basic analyses. While most of the therapeutic measures studied were not in use in 1986, this was not true for all treatments (e.g. CABG surgery for stable angina pectoris). In such cases, the number of deaths prevented or postponed as a result of the therapy as used in 1986 was calculated and subtracted from the figure for 2002, to calculate the net benefit. Recent results from the large COURAGE Trial⁷³ and the newly published meta-analysis by Cecil et al.⁷⁴ implied that there was no or small difference in relative risk reduction between PCI and optimal medical therapy in patients with stable coronary artery disease. Accordingly, we estimated the effectiveness of PCI in patients with stable angina to zero in the Swedish IMPACT Model.

We assumed that compliance, the proportion of treated patients actually taking therapeutically effective levels of medication, was 100% among hospital patients, 70% among symptomatic community patients, and 50% among asymptomatic community patients.^{75,76} To avoid double counting of patients treated, we identified potential overlaps between different groups of patients and made appropriate adjustments. To address the potential effect on relative reduction in case-fatality rate for individual patients receiving multiple treatments, we used the Mant and Hicks cumulative relative benefit approach.⁷⁷⁻⁷⁹

Relative Benefit = 1 - [(1 - relative reduction in case-fatality rate for treatment A) X (1 - relative reduction in case-fatality rate for treatment B) X ... X (1 - relative reduction in case-fatality rate for treatment N)]

Methods for calculating 95% confidence interval for weighted mean

The confidence interval (CI) estimation is based on the standard deviation of the samples and their size, which gives us the standard error (or variance) of the sample mean. Multiplying the standard error of the mean with the 1.96 provides an estimate of half of the 95% CI interval. When a weighted mean was used to give the mean for the whole population based on subsamples, the corresponding standard error was estimated accordingly as a weighted summation based on the standard errors of the subsamples. This procedure was used for data from the AMORIS Study⁷² and MONICA Study. Data from the ULF, the Official Statistics of Sweden, had the half 95% CI already estimated.

Mortality reductions attributable to changes in risk factors

Two approaches were used to calculate the numbers of deaths prevented or postponed as a result of changes in risk factors.

a) We used a *regression approach* for systolic blood pressure, cholesterol, and BMI. The number of deaths prevented or postponed as a result of the change in the prevalence or mean value for each of these risk factors was estimated as the product of three variables: the number of CHD deaths observed in 1986 (the base year), the subsequent reduction in that risk factor and the regression coefficient quantifying the change in mortality from coronary heart disease per unit of absolute change in the risk factor. For example, in 1986, there were 570 CHD deaths among 471 039 women aged 55-64 years. Between 1986 and 2002 the mean systolic blood pressure in this group decreased by 2.4 mmHg. The largest meta-analysis showed an estimated age- and sex-specific reduction in mortality of 50% for every 20 mmHg reduction in systolic blood pressure, generating a logarithmic coefficient of -0.035 .⁸⁰ The number of deaths prevented or postponed as a result of this change was then estimated as:

$$\begin{aligned}\text{Number of deaths} &= (1 - e^{(\text{coefficient} \times \text{change})}) \times \text{deaths in 1986} \\ &= (1 - e^{(-0.035 \times 2.4)}) \times 570 = 46.\end{aligned}$$

b) A *population-attributable risk fraction approach* was used to determine the impact of changing prevalence of smoking, diabetes and physical inactivity. The population-attributable risk fraction was calculated conventionally as $P \times (RR - 1) / 1 + P \times (RR - 1)$ where P is the prevalence of the risk factor and RR is the relative risk for CHD mortality associated with that risk factor. The number of deaths prevented or postponed was then estimated as the number of deaths from coronary heart disease in 1986 (the base year) multiplied by the difference between the population-attributable risk fraction in 1986 and that in 2002 (Table 12).

For example, the prevalence of diabetes in men aged 65-74 years increased from 6.1% in 1986 to 9.5% in 2002. Given a relative risk of 1.93,²⁸ the population-attributable risk fraction increased from 0.054 to 0.081. Additional deaths in 2002 attributable to an increased prevalence of diabetes were therefore calculated as follows:

$$\text{Deaths from coronary heart disease in 1986} = (4790) \times (0.081 - 0.054) = 129^{11,12,67,81}$$

Because independent regression coefficients and relative risks for each risk factor were taken from multivariate analyses, we assumed that there was no further synergy between the treatment and risk factor sections of the model or among the major risk factors.

The numbers of deaths prevented or postponed as a result of risk factor changes were systematically quantified for each specific patient group to account for potential differences in effect. Lag times between the change in the risk factor rate and event rate change were not modelled; it was assumed that these lag times would be relatively unimportant over a period of almost two decades.^{9,81,82}

Comparison of estimated with observed mortality changes

The model estimates for the total number of deaths prevented or postponed by each treatment and for each risk factor change were rounded to the nearest multiple of 5 deaths (e.g. 696 became 695). All of these figures were then summed and compared with the observed changes in mortality for men and women in each age group. Any shortfall in the overall model estimate was then presumed to be attributable either to inaccuracies in our model estimates or to other, unmeasured risk factors.^{9,11,80,83}

Sensitivity analyses

All the above assumptions and variables were tested in a multi-way sensitivity analysis using the analysis of extremes method.^{7,11,80} For each variable in the model, we assigned a lower value and a upper value, using 95% CIs when available and otherwise using $\pm 20\%$ (for the number of patients, use of treatment and compliance). For example, for aspirin treatment in men aged 55-64 years hospitalized with acute myocardial infarction, the best estimate was 18 deaths prevented or postponed. The minimum estimate from the multi-way sensitivity analysis was 7 and maximum estimate was 37 (Table 3).

STATISTICAL PROCEDURES

Study I

The SPSS statistical package (version 11.0) was used for all statistical analyses. Background data were divided into three 3-year periods: 1994-1996, 1997-1999 and 2000-2002. The results are shown as means and standard deviations (SD) for serum cholesterol, serum triglycerides and percentage treated with lipid-lowering drugs each 3-year period from 1994-2002. EpiInfo was used for statistical analysis of linear trends over the years 1994-2002. P-values <0.05 were considered significant.

Studies II and III

All statistical analyses were performed using SPSS version 15.0 (SPSS Inc, Chicago, IL, USA). Odds ratios (OR) were calculated from the logistic regression model. Because of the large size of the population, 99% CI, were used.

To describe differences between STEMI and non-STEMI, baseline characteristics were summarized as means or percentages (smoking [never smoking, current smoking and former smoking]), hypertension, diabetes, prior medication (e.g. ASA, β -blocker, ACE-inhibitor, statin), prior CABG or PCI). The independent association between smoking status and STEMI was assessed by means of logistic regression, where STEMI was entered as the dependent variable and the following variables were used as covariates (possible confounders): age, gender, history of smoking (never smoking, current smoking and former smoking), history of CABG, history of PCI, history of diabetes mellitus, history of hypertension, medications used before entry into the study (e.g. ACE-inhibitors, β -blockers, aspirin and lipid-lowering drugs) and year of admission. In Study III, history of heart failure and angina (defined as prior diagnose of angina or prior medication with long-acting nitrates) was entered into the model. To investigate potential interactions between gender and smoking, as well as between age and smoking, interaction terms (gender*current smoking and age*current smoking) were defined and introduced into the models in Study II. Finally we analyzed the proportion of patients with medication and how the use of any prior medication affected the risk of presenting with STEMI compared to non-STEMI irrespective of type of drug and created a variable as follows: no medication, one medication, two medications or three medications or more (Study III).

Study IV

All information is contained in the methodological section.

RESULTS

Study I

Baseline data on age, BMI, diabetes, hypertension, and smoking, as well as data at follow-up on smoking, serum cholesterol, serum triglycerides and lipid-lowering medication in the participants of Study I are shown in Table 4. From 1994 to 2002 718 men and women hospitalized at Östra with a first MI were included. Mean age for men was 54.0 years and for women 55.7 years. Smoking was common, 56% of the men and 59% of the women were active smokers at the time of the MI. About 20% of the patients had diabetes, with no difference between men and women, while hypertension was more common in women (43% and 25% in women and men, respectively). About two thirds of the women and three quarters of the men were overweight or obese.

Table 4. Baseline characteristics for 781 patients, 607 (78%) men and 174 (22%) women, with a first myocardial infarction

		1994-1996 ¹	1997-1999 ²	2000-2002 ³	Total
Age, n, mean, (SD)	Men	54.1 (8.32)	53.3 (6.98)	54.4 (7.43)	54.0 (7.65)
	Women	55.9 (7.07)	54.9 (7.80)	56.1 (7.09)	55.7 (7.29)
	Total	54.5 (8.11)	53.7 (7.20)	54.8 (7.40)	54.3 (7.60)
BMI, mean (SD)	Men	27.7 (3.70)	28.3 (3.56)	27.5 (3.96)	27.8 (3.76)
	Women	27.5 (4.20)	29.0 (6.45)	27.8 (4.34)	28.1 (5.09)
	Total	27.6 (3.80)	28.4 (4.41)	27.6 (4.05)	27.9 (4.09)
BMI 25-29.99, % (n)	Men	55 (120)	52 (92)	53 (104)	53 (316)
	Women	38 (20)	40 (22)	35 (22)	37 (64)
	Total	51 (140)	49 (114)	48 (126)	50 (380)
BMI 30, % (n)	Men	24 (52)	27 (47)	22 (43)	24 (142)
	Women	30 (16)	33 (18)	33 (21)	32 (55)
	Total	25 (68)	28 (65)	25 (64)	26 (197)
Diabetes, % (n)	Men	21 (48)	12 (21)	21 (42)	18 (111)
	Women	19 (10)	18 (10)	23 (15)	20 (35)
	Total	21 (58)	13 (31)	21 (57)	19 (146)
Hypertension, % (n)	Men	24 (55)	26 (46)	25 (52)	25 (153)
	Women	44 (24)	42 (23)	42 (27)	43 (74)
	Total	29 (79)	30 (69)	29 (79)	29 (227)
Smoking, % (n)	Men	60 (134)	57 (100)	53 (108)	56 (342)
	Women	59(32)	62(34)	55(36)	59 (102)
	Total	60 (166)	58 (134)	53 (144)	57 (444)
At follow-up					
Smoking % (n)	Men	29 (66)	22 (39)	21 (43)	24 (148)
	Women	30 (16)	33 (18)	20 (13)	27 (47)
	Total	29 (82)	25 (57)	21 (56)	25 (195)
Serum cholesterol mmol/l, mean, (SD)	Men	6.18 (1.29)	5.52 (1.12)	4.58 (1.14)	5.46 (1.36)
	Women	6.11 (1.26)	5.56 (1.24)	4.97 (1.28)	5.51 (1.34)
	Total	6.16 (1.28)	5.53 (1.15)	4.68 (1.18)	5.47 (1.36)
Serum triglycerides mmol/l, mean, (SD)	Men	2.61 (1.91)	2.34 (1.40)	1.82 (0.97)	2.27 (1.53)
	Women	2.24 (1.75)	1.97 (1.04)	1.82 (1.02)	2.00 (1.30)
	Total	2.54 (1.88)	2.25 (1.32)	1.82 (1.00)	2.20 (1.49)
Lipid-lowering medication, % (n)	Men	18 (41)	46 (81)	73 (151)	45 (273)
	Women	24 (13)	40 (22)	86 (56)	52 (91)
	Total	19 (54)	44 (103)	77 (207)	47 (364)

¹1994-1996 225 men and 54 women, ²1997-1999 177 men and 55 women, ³2000-2002 205 men and 65 women

Lipid-lowering drugs and lipid levels

The proportion of patients treated with lipid-lowering drugs increased substantially during the study period in both men and women (Figure 1). In 1994 10% of all men and 23% of all women were treated with lipid-lowering drugs. This increased continuously over the period, and in 2002, the last year of the study, about 90% of all men and women were treated with lipid-lowering drugs (p for linear trend <0.0001).

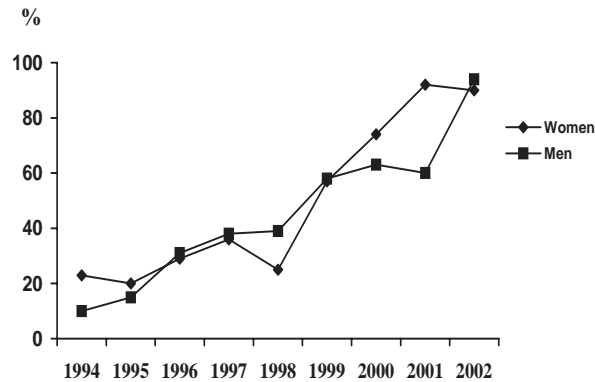


Figure 1. Percent of men and women with lipid lowering medication at 3-month follow-up after hospitalization for first myocardial infarction during 1994-2002.

In 1994 mean serum total cholesterol concentrations were 6.53 mmol/l (SD 1.27) and 6.32 mmol/l (SD 1.34) in men and women, respectively. During the study period, mean cholesterol decreased steadily and, in 2002 the mean serum cholesterol in men and women, respectively, was 4.31 mmol/l (SD 1.16) and 5.13 mmol/l (SD 1.47). (Figure 2), p for linear trend <0.0001 for both men and women.

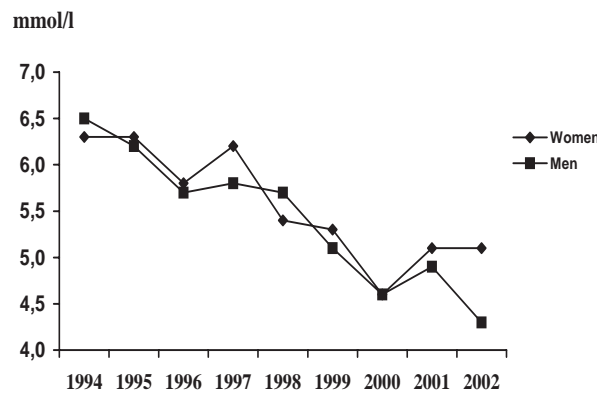


Figure 2. Mean serum cholesterol in men and women at 3-month follow-up after hospitalization for first myocardial infarction during 1994-2002.

Mean serum triglycerides also decreased during the years 1994 to 2002. In 1994 mean serum triglycerides were 2.55 mmol/l (SD 1.58) in men and 2.16 mmol/l (SD 1.11) in women. In 2002 mean serum triglycerides had decreased to 1.72 mmol/l (SD 0.81) and 1.77 mmol/l (SD 1.13) in men and women respectively (Figure 3) (p for linear trend over time <0.0001 in men and <0.005 in women).

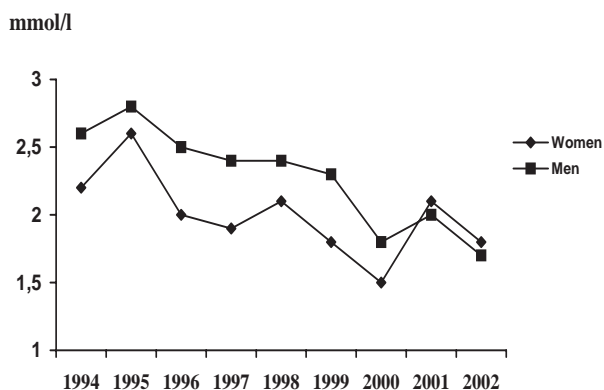


Figure 3. Mean serum triglycerides in men and women at 3-month follow-up after hospitalization for first myocardial infarction during 1994-2002.

In 2002, 65% of the men and 50% of the women had total cholesterol levels <5.0 mmol/l. If target levels for serum total cholesterol instead were defined as <4.5 mmol/l, these levels were achieved in 56% of the cases in men and 35% in women.

Study II and Study III

In total, we included 93,416 patients (35.6% women and 64.4% men) during 1994 to 2004 hospitalized with a first admission for AMI, out of which 38.2% presented with STEMI and 61.8% with non-STEMI. The proportion of patients with STEMI decreased from about 43% in 1996 to 35% in 2004 (Table 5).

Table 5. Clinical presentation (STEMI or non-STEMI) by year of registration in 93 416 patients with a first myocardial infarction in the RIKS-HIA registry

Year of admission	STEMI % (n)	Non-STEMI % (n)
1996	42.9 (2474)	57.1 (3299)
1997	40.7 (3122)	59.3 (4553)
1998	39.5 (4243)	60.5 (6502)
1999	40.3 (4377)	59.7 (6484)
2000	39.3 (4400)	60.7 (6801)
2001	38.6 (4472)	61.4 (7101)
2002	36.1 (4211)	63.9 (7468)
2003	35.2 (4184)	64.8 (7699)
2004	35.0 (4208)	65.0 (7818)

Table 6 shows baseline characteristics for patients in Study II and Study III. Of the 93,416 patients, 38.2% presented with STEMI and 61.8% with non-STEMI. Patients with STEMI more often were men and also slightly younger, compared to patients with non-STEMI. Moreover, smoking was more common in STEMI, with 31% of patients with STEMI current smokers, compared to 22.9% in non-STEMI patients. Patients with non-STEMI had significantly more hypertension, diabetes, heart failure, prior angina pectoris and known cardiovascular disease with prior PCI or CABG. All differences were statistically significant ($p < 0.0001$).

Table 6. Baseline characteristics in 93 416 patients presenting with a first myocardial infarction, STEMI (38.2%) or non-STEMI (61.8%). Studies II and III

	STEMI (n=35 691) %	Non-STEMI (n=57 725) %	P-value
Age, mean, year	66.4	67.4	<0.0001
< 65	40.9	37.4	<0.0001
Women	33.7	36.7	<0.0001
Smoking			
Current smokers	31.0	22.9	<0.0001
Never	45.5	48.6	
Past	23.5	28.5	
Hypertension	30.0	36.1	<0.0001
Diabetes	16.2	18.9	<0.0001
Heart failure	2.5	5.8	<0.0001
Prior angina pectoris*	20.5	26.9	<0.0001
Prior PCI or CABG	1.7	5.9	<0.0001

*defined as prior diagnose of angina or prior use of long-acting nitrates

Study II

Smoking was more common in patients with STEMI, 31.0% compared to 22.9% in non-STEMI were current smokers (age- and sex-adjusted OR 1.40 (99% CI: 1.34 to 1.47)). After multiple adjustments (hypertension, diabetes, prior CABG or PCI, medication on admission (aspirin, β -blocker, ACE-inhibitor or statin), smoking was still significantly associated with higher risk of presenting with STEMI, OR 1.33 (99% CI: 1.26 to 1.39) (Table 7).

Table 7. Demographic and clinical characteristics by presentation in patients with a first myocardial infarction (STEMI or non-STEMI) and odds ratios for presenting with STEMI

	STEMI % (n) 38 (35 691)	Non-STEMI % (n) 62 (57 725)	Age-adjusted OR (99% CI)	Multiple-adjusted OR (99% CI)*
Age, mean, year	66.4	67.4		
< 65 (%)	40.9	37.4	1.16 (1.12 to 1.20)**	
Women (%)	33.7	36.7	0.90 (0.87 to 0.94)	
Smoking (%)				
Never	45.5	48.6	1.0	1.0
Former	23.5	28.5	0.87 (0.83 to 0.91)	0.92 (0.88 to 0.96)
Current	31.0	22.9	1.40 (1.34 to 1.47)	1.33 (1.26 to 1.39)
Hypertension, %	30.0	36.1	0.77 (0.75 to 0.80)	1.08 (1.03 to 1.14)
Diabetes, %	16.2	18.9	0.84 (0.80 to 0.88)	1.00 (0.95 to 1.05)
Prior revascularization, %	1.7	5.9	0.28 (0.25 to 0.31)	0.49 (0.43 to 0.56)

*adjusted for hypertension, diabetes, prior revascularization, sex, age, year of admission and medication.

**Crude

The prevalence of smoking decreased by age and in the oldest age group about 10% were current smokers (Figures 4 and 5). The highest proportions of smokers were found in men and women with STEMI below the age of 50, 58% and 67%, respectively. The difference between patients with STEMI and non-STEMI decreased with age in both men and women.

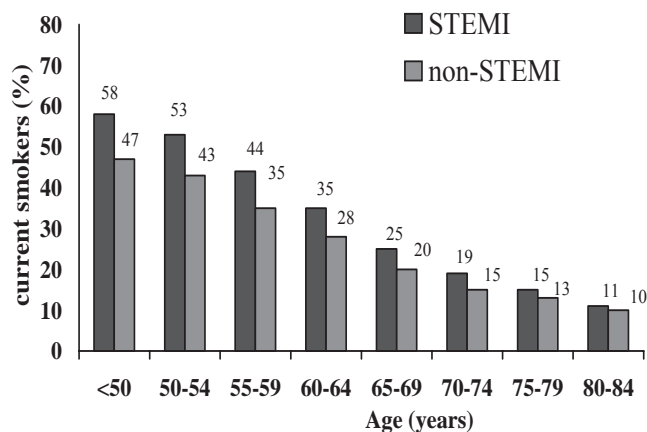


Figure 4. Smoking by age among men admitted to hospital with a first AMI, STEMI or non-STEMI.

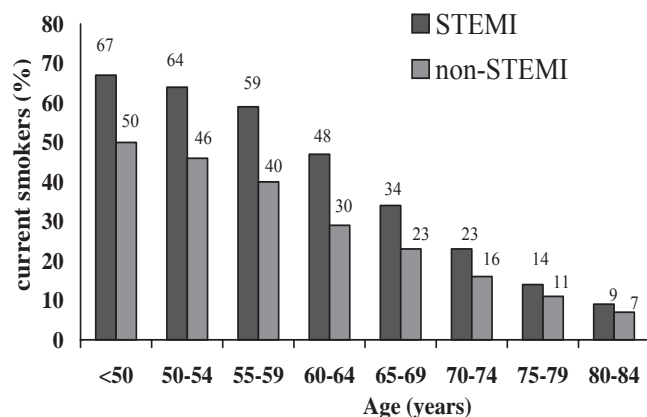


Figure 5. Smoking by age among women admitted to hospital with a first AMI, STEMI or non-STEMI.

Patients <65 years

Current smoking was more prevalent among men and women <65 years with STEMI, with a more pronounced difference among the women: multiple-adjusted OR in men 1.33 (99% CI: 1.22 to 1.43) and in women 2.01 (99% CI: 1.75 to 2.30) (test for interaction $p < 0.0001$). Prior CABG or PCI was associated with lower risk of presenting with STEMI in both men and women. Hypertension and diabetes was associated with increased risk of presenting with STEMI but only in women (Table 8).

Table 8. Demographic and clinical characteristics by age, gender and presentation (STEMI or non-STEMI) and odds ratios for presenting with STEMI

	Men				Women			
	STEMI (11 355) (99% CI)	Non-STEMI (15 741) (99% CI)	Age-adjusted OR (99% CI)	Multiple-adjusted OR (99% CI)*	STEMI (3243) (99% CI)	Non-STEMI (5900) (99% CI)	Age-adjusted OR (99% CI)	Multiple-adjusted OR (99% CI)*
< 65	54.5	55.2			55.7	55.6		
Age, mean, year								
Smoking								
Never smoked	29.9	33.0	1.0	1.0	27.5	38.2	1.0	1.0
Ex-smoker	23.8	30.6	0.86 (0.79 to 0.94)	0.92 (0.85 to 1.01)	15.7	22.7	0.97 (0.82 to 1.16)	1.01 (0.85 to 1.21)
Current smoker	46.4	36.4	1.38 (1.27 to 1.49)	1.33 (1.22 to 1.43)	56.8	39.1	2.07 (1.81 to 2.37)	2.01 (1.75 to 2.30)
Hypertension, %	22.3	28.8	0.73 (0.68 to 0.79)	1.06 (0.96 to 1.16)	30.1	33.4	0.86 (0.76 to 0.97)	1.19 (1.01 to 1.39)
Diabetes, %	13.2	15.0	0.88 (0.80 to 0.96)	1.05 (0.94 to 1.16)	17.2	17.2	1.00 (0.86 to 1.16)	1.26 (1.07 to 1.49)
Prior revascularization	1.6	6.0	0.26 (0.21 to 0.32)	0.53 (0.42 to 0.67)	1.1	4.2	0.26 (0.17 to 0.42)	0.60 (0.37 to 0.97)
> 65	73.8	74.1			68.0	69.1		
Age, mean, year								
Smoking								
Never smoked	49.4	48.7	1.0	1.0	68.0	69.1	1.0	1.0
Ex-smoker	32.3	36.8	0.86 (0.80 to 0.92)	0.92 (0.85 to 0.98)	13.9	17.3	0.84 (0.75 to 0.93)	0.87 (0.78 to 0.96)
Current smoker	18.4	14.5	1.23 (1.13 to 1.34)	1.14 (1.04 to 1.25)	18.1	13.5	1.42 (1.28 to 1.57)	1.33 (1.20 to 1.48)
Hypertension, %	30.7	36.3	0.77 (0.72 to 0.83)	1.08 (1.00 to 1.16)	39.2	44.5	0.80 (0.75 to 0.86)	1.09 (1.00 to 1.18)
Diabetes, %	16.2	20.1	0.77 (0.72 to 0.84)	0.90 (0.82 to 0.98)	19.7	22.1	0.87 (0.80 to 0.95)	1.04 (0.95 to 1.14)
Prior revascularization	2.4	7.4	0.30 (0.25 to 0.36)	0.48 (0.40 to 0.58)	1.1	4.3	0.25 (0.19 to 0.33)	0.41 (0.31 to 0.56)

*adjusted for hypertension, diabetes, prior revascularization, age, year of admission and medication.

Patients ≥ 65 years

In older men and women (≥ 65 years) with STEMI, tobacco smoking was overall less common, with about 18% of both men and women current smokers, compared to 14.5% and 13.5%, respectively, in men and women with non-STEMI (Table 8). Smoking was related to a higher risk of STEMI also in older patients: multiple-adjusted OR in men 1.14 (99% CI: 1.04 to 1.25) and in women 1.33 (99% CI: 1.20 to 1.48). Diabetes (multiple-adjusted OR 0.90, 99% CI: 0.82 to 0.98) carried less risk of presenting with STEMI in men aged ≥ 65 years, but not in women. Prior PCI or CABG was associated with less risk of presenting with STEMI in both men (multiple-adjusted OR 0.48, 99% CI: 0.40 to 0.58) and women (multiple-adjusted OR 0.41, 99% CI: 0.31 to 0.56).

Study III

Medication use and clinical presentation

In subsequent analyses we compared the use of aspirin, β -blocker, ACE-inhibitor and statin prior to the AMI in STEMI compared to non-STEMI. Patients with STEMI less often had any of the four medications investigated; aspirin (18.3% vs. 34.0%), β -blocker (20.4% vs. 33.2%), ACE-inhibitor (9.6% vs. 14.4%) and lipid-lowering therapy (e.g. statin) (6.1% vs. 13.5%) prior to the AMI compared to non-STEMI patients (Table 9). We used logistic regression in a multivariable model to investigate separately how the use of medication with aspirin, β -blocker, ACE-inhibitor and statin prior to the AMI affected the risk of presenting with STEMI. All models were adjusted for age, sex, hypertension, diabetes, heart failure, angina, prior use of aspirin, β -blocker, ACE-inhibitor, statin, prior revascularization, smoking and year of admission. Overall, prior use of aspirin (multiple adjusted OR 0.60 [99% CI 0.57 to 0.63]), β -blocker (multiple adjusted OR 0.71 [99% CI 0.67 to 0.75]), ACE-inhibitor (multiple adjusted OR 0.84 [99% CI 0.79 to 0.90]), and statin (multiple adjusted OR 0.67 [99% CI 0.63 to 0.73]), were all independently and substantially associated with lower risk of presenting with STEMI (Table 9).

Table 9. Proportion of patients with prior medication of aspirin, β -blockers, ACE-inhibitor and statin in patients with STEMI or NSTEMI and odds ratios (OR) for presenting with STEMI

Medication	STEMI (n=35 691)	NSTEMI (n=57 725)	Age-adjusted OR (99% CI)	Multiple-adjusted OR (99%CI)
Aspirin	18.3% (6544)	34.0% (9 615)	0.44 (0.42 to 0.46)	0.60 (0.57 to 0.63)
β -blockers	20.4% (7278)	33.2% (19 186)	0.52 (0.50 to 0.54)	0.71 (0.67 to 0.75)
ACE-inhibitor	9.6 % (3426)	14.4% (8331)	0.64 (0.60 to 0.67)	0.84 (0.79 to 0.90)
Statins	6.1% (2187)	13.5% (7776)	0.41 (0.39 to 0.44)	0.67 (0.63 to 0.73)

*Adjusted for sex, age, hypertension, diabetes, heart failure, prior angina, prior revascularization, all four medications, smoking and year of admission

Next, we investigated the association of each medication separately in men and women, and for women aged 25 to 64 and 25 to 84. Effects were consistent for all four types of medication, with no suggestion of any interaction effects by either age or sex, Figures 6-9.

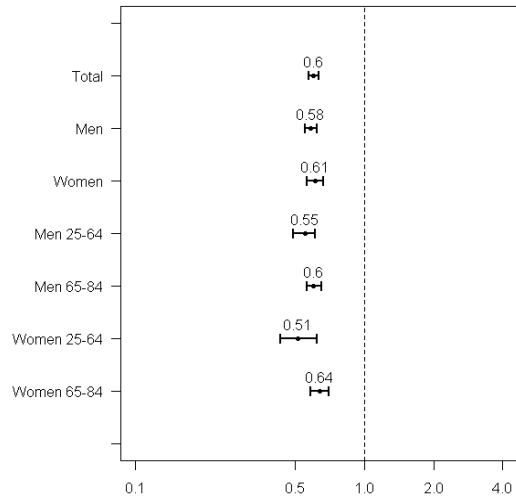


Figure 6. Multiple adjusted odds ratios (99% CI) for presenting with STEMI compared to non-STEMI by age and sex for aspirin use.

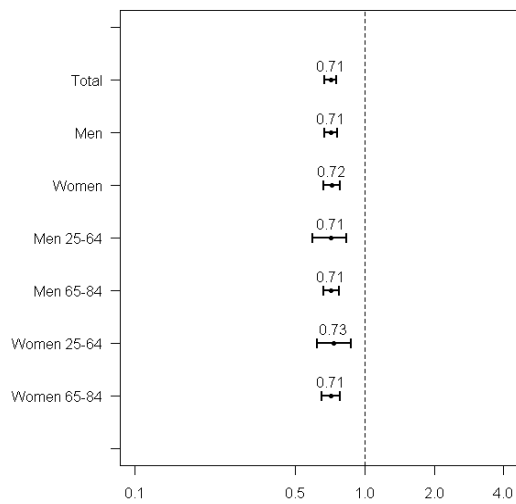


Figure 7. Multiple adjusted odds ratios (99% CI) for presenting with STEMI compared to non-STEMI by age and sex for β -blocker use.

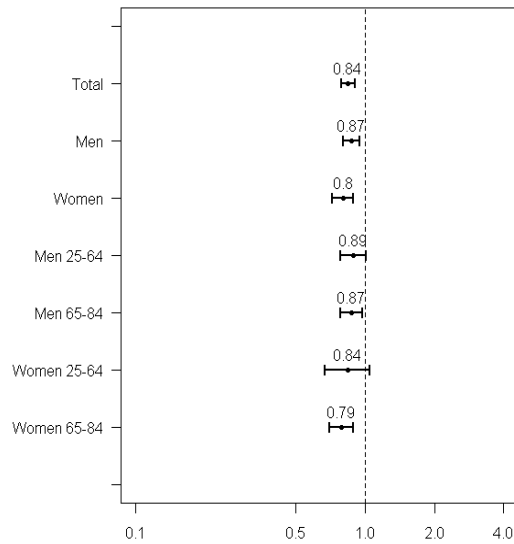


Figure 8. Multiple adjusted odds ratios (99% CI) for presenting with STEMI compared to non-STEMI by age and sex for ACE-inhibitor use.

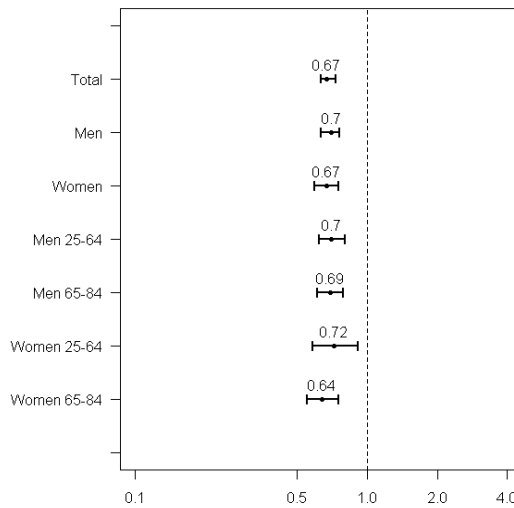


Figure 9. Multiple adjusted odds ratios (99% CI) for presenting with STEMI compared to non-STEMI by age and sex for statin use.

Finally, we analyzed the proportion of patients with medication and how the use of any prior medication affected the risk of presenting with STEMI compared to non-STEMI, irrespective of type of drug (Table 10). A higher proportion of patients with STEMI had no medication at all prior to the AMI, compared to patients with non-STEMI (63.7% vs. 46.1%), whereas a lower proportion of patients with STEMI had three or four medications, 3.6% and 10.3%, respectively. One medication, irrespective of type, was associated with lower risk of presenting with STEMI compared to

non-STEMI, multiple-adjusted OR 0.71 (99% CI 0.68 to 0.75). Adding one more drug further decreased the risk of presenting with STEMI compared to non-STEMI to approximately half (OR 0.51, 99% CI 0.48 to 0.54). Treatment with three or four drugs decreased the risk of presenting with STEMI even more; multiple-adjusted OR 0.37 (99% CI 0.33 to 0.40) although this group only included a small proportion of the patients.

Table 10. Proportion of patients treated with aspirin, β -blocker, ACE-inhibitor and statin prior to the AMI (STEMI or non-STEMI) and OR for the risk of presenting with STEMI compared to non-STEMI

Medication prior to AMI	STEMI n (%)	Non-STEMI n (%)	Age-adjusted OR (99% CI)	Multiple-adjusted OR (99% CI)
No medication	22723 (63.7)	26585 (46.1)	1.00	1.00
One medication	7934 (22.2)	14281 (24.7)	0.66 (0.63 to 0.68)	0.71 (0.68 to 0.75)
Two medications	3761 (10.5)	10903 (18.9)	0.41 (0.39 to 0.43)	0.51 (0.48 to 0.54)
Three or four medications	1273 (3.6)	5956 (10.3)	0.25 (0.23 to 0.27)	0.37 (0.33 to 0.40)
Total	35691 (100)	57725 (100)		

Study IV

Between 1986 and 2002, CHD mortality rates in Sweden decreased by 53.4% in men and 52.0% in women aged 25 to 84 years. The age-adjusted CHD rates per 100,000 population fell from 544.1 to 253.4 among men 25 to 84 years and from 291.5 to 140.0 among women aged 25-84 years. In 1986 there were 23,060 deaths among this age group recorded as due to coronary heart diseases, according to the International Classification of Diseases, 9th Revision (codes 410-414). In 2002, a total of 11,850 such deaths were recorded, according to the International Classification of Diseases, 10th Revision (codes I20-I25). However, had the death rates from 1986 persisted in 2002 another 11,215 deaths would have occurred, which translates to a total of 13,180 CHD deaths postponed or prevented, when taking the increasing numbers in the population into account. During the same period all-cause mortality per 100,000 declined from 1482.6 in 1986 to 1082.5 in 2002 in men and from 1018.6 to 832.4 in women. The proportion of deaths due to CHD decreased from 36.7% and 28.6% in 1986 to 23.4% and 16.8% 2002 in men and women respectively.

Approximately 11,985 of the 13,180 decrease in number of deaths could be explained using the Swedish IMPACT model. Overall, the model accounted for 90.9% of the total mortality decrease in Sweden between 1986 and 2002. The remaining 9.1% was presumed to be attributable either to inaccuracies in our model estimates or to other, unmeasured factors.

Figure 10 shows comparison of model estimated and observed reductions in deaths from CHD in Sweden between 1986 and 2002, stratified by age and sex. The bars show the observed deaths in each age group, with diamonds being the best-model estimate, and vertical lines the extreme minimum and maximum estimates in the sensitivity analysis.

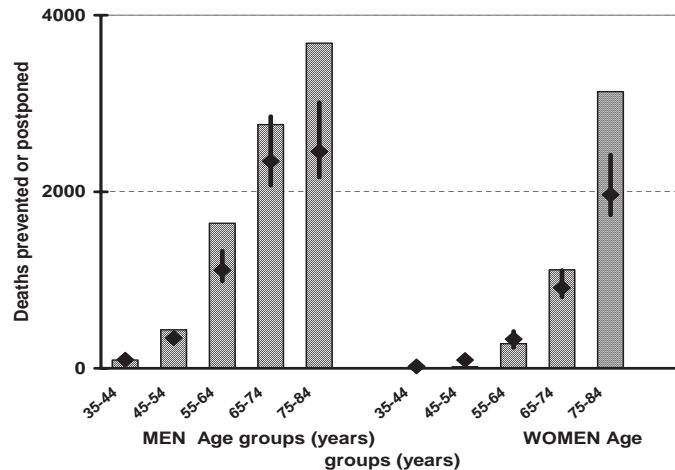


Figure 10. Comparison of model estimated and observed reductions in deaths from CHD in Sweden between 1986 and 2002, stratified by age and sex.

Major cardiovascular risk factors

Changes in the major cardiovascular risk factors together explained some 55% of the total mortality decrease between 1986 and 2002. The largest reduction in deaths was explained by substantial reductions in total cholesterol levels, from 6.15 mmol per liter in 1986 to 5.51 mmol per liter in 2002, explaining approximately 39 percent of the mortality reduction. The reduced smoking prevalence, from 28.9% in 1986 to 18.6 % in 2002, explained about 9% of the mortality reduction. The remaining mortality decrease was explained by decreased levels of systolic blood pressure (2.6 mm Hg) but also by a decrease in physical inactivity with trends towards more organized exercise and higher activity level especially in older people. However, adverse trends were seen with respect to the proportion of population who were overweight or obese, with increasing mean BMI from 24.3 to 25.4. The prevalence of diabetes increased from 2.7% to 3.8% from 1986 to 2002 (Table 11).

Medical and surgical treatments

Changes in medical and surgical treatments together explained some 36% of the total mortality decrease between 1986 and 2002. The largest reduction came from the use of secondary-prevention medications or rehabilitation after acute myocardial infarction (8.9%). The mortality decreases attributable to hospital and community treatments for heart failure and initial treatment for AMI and UAP accounted for 6.9% and 7.4% respectively. For AMI, the largest contributions came from aspirin, cardiopulmonary resuscitation, ACE-inhibitors, β -blockers and thrombolysis. Smaller proportions were explained by treatment for hypertension (4.4%) and chronic angina (4.0%). Revascularization for chronic angina and statins for primary prevention contributed relatively small reductions, 2.6% and 1.5% respectively. Coronary artery bypass surgery and angioplasty in connection with AMI or UAP accounted for less than 1% of deaths prevented or postponed (Table 12).

Table 11. Deaths from Coronary Heart Disease Prevented or Postponed as a Result of Changes in Population Risk Factors in Sweden 1986 – 2002

Risk factor**	Absolute Level of Risk Factor [†]		Changes in Risk factor		Beta Regression Coefficient for Change in Mortality Rates	Relative Risk	Deaths Prevented or Postponed					
	1986	2002	Absolute change	Relative change (%)			Best Estimate [‡]	Minimum Estimate [‡]	Maximum Estimate [‡]	Best estimate [‡]	Minimum Estimate [‡]	Maximum estimate [‡]
Total cholesterol, mmol/l	6.15 (6.14-6.16)†	5.51 (5.47-5.55)†	-0.64	-10.4			5210	4400	6390	39.5	33.4	48.5
Men					-0.633							
Women					-0.517							
Smoking prevalence, %	28.9 (27.5-30.3)†	18.6 (17.1-20.1) †	-10.3	-55.4			1195	955	2575	9.1	7.2	19.5
Men					2.52							
Women					2.14							
Systolic blood pressure, mmHg	133.8 (133.2-134.4)†	131.2 (130.6-131.9)†	-2.6	-1.9			900	740	1145	6.8	5.6	8.7
Men					-0.032							
Women					-0.040							
Physical inactivity, %	16.0 (14.8-16.8)†	11.5 (10.5-12.7)†	4.3	-27.3			790	75	1800	6.0	0.6	13.6
Men					1.27							
Women					1.33							
BMI, kg/m ²	24.3 (23.1-25.4)†	25.4 (23.8-27.0)†	+1.1	4.7			-265	-150	-415	-2.0	-1.1	-3.1
Men					0.065							
Women					0.062							
Diabetes prevalence, %	2.7 (2.2-3.2)†	3.8 (3.1-4.5)†	+1.1	40.7			-630	-325	-1005	-4.8	-2.5	-7.6
Men					2.66							
Women					3.53							
Total risk factors							7200	5695	10490	54.6	43.2	79.6

Notes: numbers of DPPs were rounded to nearest 0 or 5*. Total adult (age 25-84) population in 1986 was 5,565,255. † Sourced from Official Statistics of Sweden (smoking prevalence, Physical inactivity, BMI and diabetes), the AMORIS Study (cholesterol 1986) and the WHO MONICA Project (GOT and Northern Sweden), the Study of men born 1913, the Population Study of Women in Gothenburg, INTERGENE (blood pressure and cholesterol). Units are percent change in mortality rate per unit of risk factor as shown in column one. Additional details of data sources are described in the Supplementary Appendix. ‡ Minimum estimate 0.8 of best estimate, maximum estimate 1.2 of best estimate. †† Figures in parentheses denote 95% CI

Table 12. Estimated Deaths Prevented or Postponed by Medical or Surgical Treatments in Sweden in 2002

Treatments	No of Eligible Patients	Patients Receiving Treatment (%)	Relative Risk Reduction (%)	Mean Case Fatality	Absolute Risk Reduction	Deaths Prevented or Postponed					
						Best Estimate*	Minimum Estimate†	Maximum Estimate‡	Best Estimate*	Minimum Estimate†	Maximum Estimate‡
Acute myocardial infarction				percent		no. of deaths					
Resuscitation in the community	20955	—	—	0.117	—	745	470	1495	5.7*	3.5*	11.3*
Resuscitation in the hospital	3965	39	0.05	0.117	0.019	70	15	50	0.5	0.1	0.4
Thrombolysis	800	100	0.32	0.117	0.320	230	165	615	1.8	1.2	4.7
Aspirin	20955	18	0.22	0.117	0.022	70	45	140	0.5	0.3	1.1
Beta blocker	20955	81	0.15	0.117	0.018	260	155	475	2.0	1.2	3.6
ACE inhibitor	20955	85	0.04	0.117	0.005	75	45	145	0.6	0.3	1.1
Primary angioplasty	20955	51	0.07	0.117	0.008	80	65	100	0.6	0.5	0.8
Primary CABG	20955	8	0.31	0.117	0.029	40	25	90	0.3	0.2	0.7
Treatments in 1986 subtracted	20955	0	0.20	0.117	0.023	0	0	5	0.0†	0.0†	0.1
Unstable angina						-80	-45	-125	-0.6	-0.3	-1.0
Aspirin & heparin	17290	56	0.33	0.067	0.021	225	155	500	1.7*	1.2*	3.8*
Aspirin alone	35	35	0.15	0.067	0.010	45	20	140	0.4	0.2	1.2
Glycoprotein IIb/IIIa antagonists	10	10	0.09	0.067	0.006	5	5	10	0.1	0.1	0.1
CABG	1	1	0.43	0.067	0.027	0	0	5	0.0†	0.0†	0.0†
Angioplasty	4	4	0.32	0.067	0.020	10	10	20	0.1	0.1	0.2
Secondary prevention after myocardial infarction											
Aspirin	99815	77	0.15	0.079	0.009	1175	640	3010	8.9*	4.9	22.8
Beta blocker	56	56	0.23	0.079	0.018	330	195	680	2.1	1.0	5.2
Ace inhibitor	37	37	0.20	0.079	0.018	220	105	545	2.5	1.5	6.4
Statin	49	49	0.22	0.079	0.017	245	135	585	1.7	0.8	4.1
Warfarin	7	7	0.22	0.079	0.017	40	25	110	1.9	1.0	4.4
Rehabilitation	18	18	0.26	0.079	0.018	70	50	250	0.3	0.2	0.8
Secondary prevention after CABG or PCI	41950			0.034		430	260	1065	3.3	2.0	8.1*

Aspirin	78	0.15	0.034	0.005	110	50	240	0.8	0.4	1.8
Beta blocker	66	0.23	0.034	0.007	90	40	295	0.7	0.3	2.2
ACE inhibitor	43	0.20	0.034	0.007	60	60	90	0.5	0.4	0.7
Statin	58	0.22	0.034	0.009	105	60	260	0.8	0.5	2.0
Warfarin	8	0.22	0.034	0.005	10	5	30	0.1	0.0	0.2
Rehabilitation	37	0.26	0.034	0.008	55	45	150	0.4	0.4	1.1
Treatments in secondary-prevention 1986 subtracted					-10	-5	-20			
Chronic angina	132215				535	435	1045	4.0	3.3	7.9
CABG 1994 to 2002	76790	0.22	0.036	0.007	390	365	775	2.9	2.8	5.9
with CABG in 1986 subtracted					-35	-25	-55	-0.3	-0.2	-0.4
Angioplasty, 1994-2002	23740	0	0.060	0	0	0	0	0	0	0
Aspirin in the community	158550	0.15	0.012	0.002	40	30	60	0.3	0.2	0.4
Statins in the community	158550	0.22	0.012	0.003	140	65	265	1.1	0.5	2.0
Heart failure with hospital admission	7030				365	190	805	2.8	1.5	6.1
ACE inhibitor	48	0.20	0.209	0.049	100	50	240	0.8	0.4	1.8
β-blocker	39	0.35	0.209	0.073	115	55	290	0.9	0.4	2.2
Spironolactone	10	0.30	0.209	0.063	25	15	65	0.2	0.1	0.5
Aspirin	51	0.15	0.209	0.029	70	30	125	0.5	0.3	1.0
Statins	35	0.22	0.209	0.016	55	40	85	0.4	0.3	0.6
Heart failure in the community	46095				550	390	885	4.1*	2.9	6.7*
ACE inhibitor	48	0.20	0.061	0.009	120	95	145	0.9	0.7	1.1
β-blocker	49	0.35	0.061	0.021	210	175	265	1.6	1.3	2.0
Spironolactone	10	0.30	0.061	0.019	25	20	40	0.2	0.2	0.3
Aspirin	51	0.15	0.061	0.009	130	70	350	1.0	0.5	2.6
Statin	35	0.22	0.061	0.014	65	30	85	0.5	0.2	0.6
Hypertension treatments	1 488900	0.13	0.010	0.001	575	245	955	4.4	1.8	7.3
Statins for lipid reduction (primary prevention)	3 922480	0.30	0.007	0.001	200	70	550	1.5	0.5	4.2
Total Treatments					4790	2850	10290	36.3*	21.6	78.2*

Note: numbers of eligible patients and category totals of deaths prevented or postponed were rounded to nearest 0 or 5, totals may therefore not always sum exactly. *Subject to rounding error. †CABG less than 0. ACE denotes angiotensin-converting enzyme, AMI acute myocardial infarction, CABG coronary artery bypass graft surgery, CPR cardiopulmonary resuscitation, GP glycoprotein, PCI percutaneous coronary intervention (with or without stent), and UAP unstable angina. Additional details of data sources are described in the Supplementary Appendix. ‡Minimum estimate 0.8 of best estimate, maximum estimate 1.2 of best estimate.

Proportional contributions to the decrease in deaths

Figure 11 demonstrates the results of the sensitivity analysis. The proportional contributions of specific treatments and risk factor changes to the overall decrease in CHD mortality in Sweden between 1986 and 2002 remained relatively consistent. Thus, all initial treatments for AMI and UAP together accounted for approximately 970 fewer deaths, representing 7.4% of the total decrease of 11,985 deaths. The minimum estimated contribution was 625 fewer deaths (4.7%), and the maximum was 1995 (15.1%) (Table 12). The contribution of treatment for AMI and unstable UAP was consistently smaller than that for secondary prevention treatments, irrespective of whether best, minimum or maximum estimates were compared.

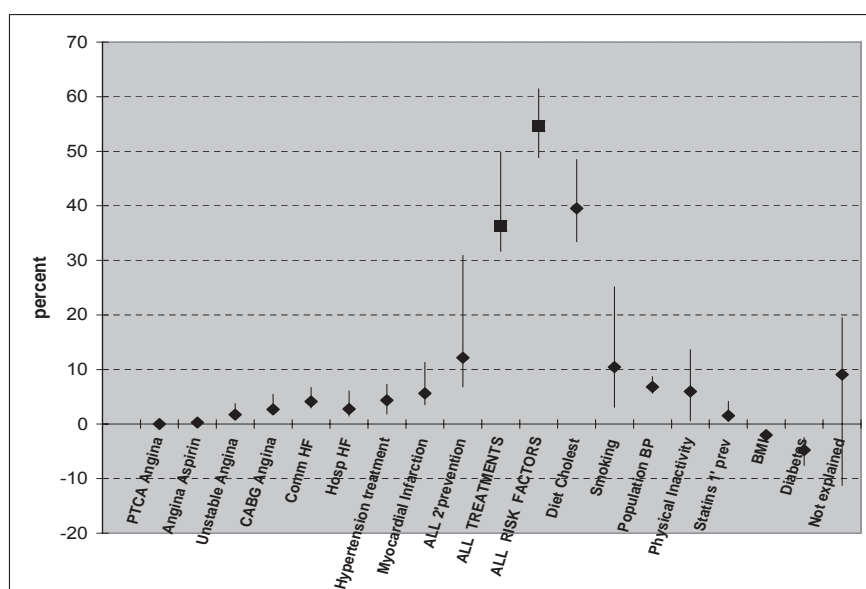


Figure 11. The proportional contributions of specific treatments and risk factor changes to the overall decrease in CHD mortality in Sweden between 1986 and 2002. The bars show the observed deaths in each age group, with diamonds being the best-model estimate, and vertical lines the extreme minimum and maximum estimates in the sensitivity analyses.

DISCUSSION

Study I

4S Study and implementing of lipid-lowering treatment

The results from the 4S study,⁵⁵ the first study to demonstrate unequivocally the benefits of statin therapy in CHD patients, were presented in 1994 and confirmed in subsequent investigations (CARE⁵⁶, HPS⁵⁷). The present study provided an opportunity to investigate the implementation of this landmark study. From 1994 to 2002 the use of lipid-lowering medication (eg. statins) in our single-centre study increased from about 10% to 90%. The results from the study correspond with those from the Swedish centre (Malmö) in the Euroaspire II study⁶⁸ except for the higher percentage treated with a statin in our study (90% compared with 74% in CHD patients in Euroaspire II). In the Euroaspire II survey 65% of the patients reached target levels (≤ 5 mmol/l) for serum total cholesterol; in our study 62% reached these target levels.

Lipid-lowering treatment, cholesterol levels and target levels

In 2002, the Heart Protection Study (HPS)⁵⁷ established that lowering cholesterol with 40 mg simvastatin daily substantially reduced the incidence of major vascular events in high-risk individuals, irrespective of initial cholesterol level. Following the results in the trial, patients are now routinely treated with 40 mg simvastatin, regardless of initial cholesterol concentrations. Among the 98 patients discharged in 2002, 8.1% (n=8), however, had no lipid-lowering treatment due to side effects (n=2), liver disease (n=4) or unknown reasons (n=2). Among the patients in the present study mean serum cholesterol decreased from about 6 mmol/l in both men and women to 4.31 and 5.13 mmol/l in men and women, respectively, corresponding to what might have been expected in the men, but less than that in women. However, the decrease in total serum cholesterol may also partly be attributed to population trends, with decreasing total serum cholesterol in the Göteborg population,^{84,85} and elsewhere.⁸⁶ This decrease is probably partly attributable to diet changes in the population⁸⁷, with less saturated fat and more fruit and vegetables. Women with a first AMI had higher mean levels of total serum cholesterol at the end of the study compared to the men, probably because a higher proportion of women had less than 40 mg Simvastatin; 18% of all men but 30% of all women in the last year of the study.

Lipid-lowering treatment, triglycerides levels and target levels

A decrease in mean serum triglycerides was also observed (from 2.55 and 2.16 mmol/l in 1994 to 1.72 and 1.77 mmol/l in 2002 in men and women, respectively). Although there is no target level for serum triglycerides in the current European guidelines⁸⁸ increased triglyceride levels are known to be an important risk factor, particularly in women.⁸⁹ In the definition from the US National Cholesterol Education program serum triglycerides >1.7 mmol/l is one of the criteria for the metabolic syndrome. Even though the target for lipid-lowering treatment is serum LDL cholesterol concentrations, triglyceride levels are also affected by statin treatment. The increasing use of lipid-lowering drugs probably explains why serum triglycerides have decreased despite increasing BMI levels. In our population a large proportion were overweight,

but with no change over time. Despite widespread treatment with statins, a substantial proportion of the patients did not reach target levels for serum cholesterol or recommendations for triglycerides.

Study II

In this large survey that included more than 90,000 individuals with a first AMI we found that tobacco smoking was strongly associated with STEMI, particularly among younger patients (i.e. <65 years of age) and among women. The proportion of active smokers decreased with age, as did the difference in smoking prevalence between patients with STEMI and patients without STEMI. In the oldest age groups only a small number of the patients were regular smokers, with little or no difference in clinical presentation between smokers and non-smokers.

From the early 1980s, both incidence and mortality from CHD have decreased markedly in Sweden. The decline is partly due to risk factor improvement at the population level, with less tobacco smoking and decreasing levels of total cholesterol.⁸⁴ The percentage of regular smokers in the general population in Sweden is currently among the lowest in the world, or less than 20%.⁹⁰ Reduction in coronary mortality is likely due to improved treatment and changes in risk factor pattern.^{8,11,91} In addition to decreasing incidence and mortality, reduced case fatality has been observed, along with a change in clinical presentation with milder symptoms, smaller and less severe infarctions.^{4,5,91} Although this trend might be a consequence of increased awareness and admission of less severe cases, changes in risk factor levels might also contribute.

Potentially, lower smoking rates in the population could explain decreasing case severity and reduced coronary mortality. Some studies have, however, found that smokers with AMI have lower mortality rates compared to non-smokers, a phenomenon often referred as “smokers paradox”,⁹²⁻⁹⁴ but this reduced mortality could equally well be due to the fact that smokers with AMI are generally younger, with fewer other risk factors such as diabetes, or hypertension, and also have less extensive coronary disease.⁹⁴ In addition, in the present study we found that patients with STEMI had higher mortality than non-STEMI patients: 11.8% compared to 9.3%, despite the fact that patients with non-STEMI were older and had more diabetes. After adjusting for age and diabetes patients presenting with STEMI still had higher mortality, adjusted RR 1.58 (99% CI 1.52 to 1.63) for 30-day mortality and 1.22 (99% CI 1.19 to 1.26) for 1-year mortality. These findings are consistent with results from the CREATE Study in which Indian patients with STEMI more often were men, current smokers and had a higher 30-day mortality.⁹⁶

Only a few studies have examined the shift in case severity as a potential cause of the decreasing case fatality in AMI. Data from Finland indicate decreasing incidence and mortality, which were attributed to improved primary prevention and better acute coronary care.^{10,96} During the same period, the proportion of milder infarctions increased.⁹¹ The US-based ARIC Study⁴ (the Atherosclerosis Risk in Communities), however, provided mixed support for a decrease in the severity of myocardial infarction. The proportion of patients with STEMI increased with 10% per year from

1987 to 1994 while the mean peak creatine kinase level decreased with 5% per year during the same period. Moreover, there was an increase of hospitalized infarctions and a decline in case fatality. It should be noted that neither the ARIC Study nor the FINMONICA MI Register Study included information on smoking, which, according to our data, could be important when exploring factors determining severity of myocardial infarction.

In the present study a stronger association was observed between smoking and STEMI in women, with two thirds of the women <55 years with STEMI still active smokers on admission. Cigarette smoking is a well-known risk factor for AMI and sudden cardiac death.⁹⁷ Furthermore, cigarette smoking has been shown to cause endothelial dysfunction, coronary vasospasm and can increase the risk of atherothrombosis, influencing fibrinolytic and antithrombotic factors.^{98,99} Women with chest pain more often than men have normal angiograms¹⁰⁰ and a higher prevalence of plaque erosion.¹⁰¹ In addition, elevated levels of procoagulant factors have been shown to increase the risk of myocardial infarction in young women.^{97,102} The mechanisms involved in smoking-related cardiovascular disease are not entirely clear; however, there is evidence for an increased propensity toward thrombosis in smokers.⁹⁷ Why this should affect men and women differently is not clear, but because there was no increase in risk in former smokers, short-term effects on coagulation and fibrinolysis could form part of the explanation.

Study III

In the present analyses we found that among patients with a first AMI, previous medication with aspirin, β -blocker, ACE-inhibitor and/or statin was protective against presenting with ST-elevation, implying a shift towards smaller and less immediately damaging infarctions. This effect was present independent of a number of other factors. The risk of presenting with STEMI decreased with the number of medications used prior to AMI.

Risk factors for CHD have been investigated earlier in numerous studies.^{27,28} However, little is known about pharmacologic treatment and how it may influence the clinical presentation in ACS. The use of statin and β -blocker has shown to be associated with less risk of presenting with myocardial infarction compared to stable angina.¹⁰³ This was a comparatively small study, conducted in less than 1,400 patients, but similar to our study, the results implied that prior medication could result in less severe clinical presentation.

Of the medications that we studied, aspirin has a well-documented anti-platelet effect or “anti-clotting” effect. The benefit of aspirin has been shown in the Antithrombotic Trialists’ Collaboration Study. The trial showed that aspirin significantly reduced cardiovascular events in high-risk patients as well as the event or recurrent events among patient with established CHD.⁴⁶ Aspirin exerts an anti-thrombotic action through inhibition of platelet cyclooxygenase, and inhibits thrombin formation, leading to an antithrombotic effect. Accordingly, the protection from transmural ischemia through this antithrombotic effect is a probable mechanism.⁴⁵

Beta-blockers reduce heart rate and the myocardial metabolic demand, probably resulting in lower oxygen demand, resulting in less widespread infarction, when administered early in AMI. A large number of randomized controlled trials have demonstrated the benefits of β -blockers on survival in patients with acute MI as well as in long-term secondary prevention after MI.⁴⁷

ACE-inhibitors have been shown to have cardioprotective effects reducing myocardial hypertrophy and vascular hypertrophy. In addition, ACE-inhibitors probably have a vascular protective effect at atherosclerosis progression and plaque rupture. Moreover, ACE-inhibitors have been shown to reduce the cardiovascular mortality in high-risk patients, but the mechanisms are not entirely clear.^{48,49}

The relation between serum cholesterol and ischemic heart disease has been unequivocally demonstrated.^{29,81} This relation is supported by angiographic findings from clinical trials showing that lowering cholesterol levels slows the progression and promotes the regression of coronary atherosclerosis. The beneficial effect of statins on morbidity and mortality in patients with CHD has been shown in several randomized clinical trials. Moreover, the benefit of cholesterol-lowering therapy in patients with CHD and average cholesterol levels has been demonstrated.^{55,57} Anti-inflammatory and anti-thrombotic effects have been postulated, which could explain our findings.

Study IV

CHD mortality rates in Sweden declined by more than half between 1986 and 2002. The largest contributor to the decrease in mortality was the reduction in major risk factors. The results from the Swedish model are consistent with the majority of earlier models that consistently suggest that risk factor improvements explain more of the mortality decline than treatments, ranging from 44% in the USA to 72% in Finland.⁷⁻¹⁰

However, adverse trends were also seen. There were contradictory data for physical activity with trends towards more organised exercise and higher activity level in older people (approximately 27%) but less regular daily activity.⁹⁰ Furthermore, the increased BMI from 24.3 to 25.4 and increase in diabetes prevalence from 2.7% to 3.8% accounted for approximately 900 extra deaths in 2002.

Cardiology treatments developed rapidly during the period of study (1986-2002). Approximately 36% of the Swedish mortality decrease was attributable to the combined effects of modern cardiological treatments. Thrombolysis accounted for only a small proportion of the deaths prevented by initial treatments for acute myocardial infarction, compared to aspirin and cardiopulmonary resuscitation. Revascularization from CABG surgery and angioplasty for AMI and UAP together accounted for less than 1% of the reduction in mortality, vs. 5% in the US model.⁸ This comparatively low contribution could partly reflect the lower rates of angioplasty in acute coronary syndromes in Sweden, compared to other industrialized countries (www.Heartstats.org). Moreover, the meta-analysis used in the model relates to earlier studies of CABG before the efficacy of medical treatments was recognized. Therefore it is likely to be an overestimation of potential benefits even if allowing for better surgical techniques.

Irrespective of whether best minimum or maximum estimates were used, the largest contribution from medical treatment came from secondary prevention. The foremost medications were β -blockers and aspirin followed by statins and ACE-inhibitors.

Modelling studies have a number of potential strengths. The best models can transparently integrate and simultaneously consider huge amounts of data from many sources. However, models are dependent on the variable extent and quality of data available on CHD risk-factor trends and treatment uptakes. Even so, population data and hospital discharge registries in Sweden are particularly good and cover almost 100%. Data from RIKS-HIA cover more than 90% of Swedish hospitals. Since Sweden has almost no private hospitals and no private CCU, the data probably reflect the majority of the Swedish population. This, together with a long tradition of maintaining registries and national population surveys, should minimize the problem of making assumptions on less reliable data.

LIMITATIONS

Study I

This study is a single centre study and the data may not be representative for Swedish patients at large. Moreover, the data in this study are derived from a university (teaching) hospital, which may explain the slightly higher proportion of patients treated with statins in our hospital compared to data from the national quality care register RIKS-HIA. In addition, our study only included younger patients (i.e. less than 65 years of age). Furthermore, there was no systematic information regarding diet counselling and compliance. Finally, the study was limited to patients discharged from the CCU and step-down unit, and accordingly, we have no information for patients treated in other units. However, national data from RIKS-HIA show a similar increase in usage of lipid-lowering drugs in patients below the age of 80 years from 12% in 1995 to 82% in 2004. Since data in this register include both university (teaching) and regional hospitals, but also smaller hospitals, this could explain the slightly higher proportion of patients treated with statins in our hospital. Moreover, our study included only younger patients (<65 years).

Studies II and III

The diagnostic criteria for MI were changed in 2001, with a lower limit for MB fraction of creatine kinase (CK-MB) from > 10 to $> 5\mu\text{g/l}$.⁶⁵ This lower limit has probably led to the fact that patients previously diagnosed as UAP in later years received a non-STEMI diagnosis. Thus, this circumstance will have contributed to a larger proportion of patients with non-STEMI. Whether the difference in current smoking between different diagnostic categories also was affected is unknown.

Study II

Validation of the RIKS-HIA shows a misclassification of tobacco smoking in a small proportion (<5%) of the patients. To what extent this classification error influenced the difference between patients with or without STEMI is unknown but the effect is likely to have been minor. Missing data on smoking habits may underestimate the proportion of smokers, especially in older age groups. Moreover, in former smokers no data on when the patients gave up tobacco smoking are recorded, other than the fact that it was more than one month before the onset of the AMI. The extent to which this potential misclassification may have influenced our findings is unknown. However, because smoking is less common among older patients, this problem is mainly limited to the younger age groups.

Study III

A number of surveys have studied compliance with prescribed drugs in cardiac patients. Although there have been methodological problems comparing the studies, previous literature reviews have shown compliance problems associated with chronic diseases and estimates of the effect of long-term treatment. If there was an overestimation of compliance to medication in our study,⁷⁶ this would lead to an underestima-

tion of the effect of medication for presenting with STEMI compared to non-STEMI. Furthermore, patients with missing data on previous medication were considered as not being on that particular medication, which may lead to an underestimation of the effect of medication.

Study IV

The best models can transparently integrate and simultaneously consider huge amounts of data from many sources. Explicit assumptions can then be tested by sensitivity analyses.¹⁰ However, modelling studies also have limitations, about 10% of the decreased mortality remains unexplained, which could be due to factors not included in the model. For example, the IMPACT Model does not include data on socioeconomic status. Since low socioeconomic status is an independent risk factor for coronary heart disease in men and women, socioeconomic changes could be a contributory cause to the observed decrease in CHD mortality.^{104,105} Furthermore, shortfall in the model could also be attributable either to inaccuracies in our model estimates or to other, unmeasured risk factors.

The Model included only those aged 25 to 84 years because of very limited data in older groups. In addition the model fit was poorer in the youngest and oldest aged women, explaining less of the observed decrease in CHD mortality in these age groups compared to men. Elderly patients and women have been shown to be underrepresented in many clinical trials and surveys in cardiovascular heart disease.¹⁰⁶ We also assumed that effectiveness in the population equalled efficacy in randomized trials. Our treatment benefits may therefore be slightly overestimated. The lower agreement observed with expected deaths in women is partly due to less data but perhaps also because women develop coronary artery disease later than men.¹⁰⁷ This highlights the need for future work with respect to gender differences and differences between younger and older ages.

CONCLUSIONS

- After the results from the Scandinavian Simvastatin Survival Study (4S) were presented in 1994 there has been an increasing use of lipid-lowering medication in AMI patients. In the present study almost all patients under 65 years of age with a first AMI were treated with lipid-lowering drugs at the end of the study period. Still, target levels for serum cholesterol were not met in a substantial number of patients.
- Smoking is a major determinant for presenting with ST-elevation MI, the most severe and damaging form of AMI, particularly among younger patients and among women.
- In patients presenting with a first AMI, prior medication with aspirin, β -blocker, ACE-inhibitor and statin was significantly associated with less risk of presenting with STEMI, a more damaging and severe AMI, compared to non-STEMI, in both men and women regardless of age.
- The risk of presenting with STEMI decreased with the number of medications prior to the AMI, emphasizing the importance of using evidence-based medications in high-risk patients.
- Between 1986 and 2002 CHD mortality has decreased with more than 50% in both men and women.
- More than half of the substantial CHD mortality decrease in Sweden between 1986 and 2002 was attributable to reductions in major risk factors, mainly a large decrease in total serum cholesterol from 6.15 to 5.51 mmol/l, explaining approximately 40% of the mortality reduction.
- Medical and surgical treatment together explained 36% of the mortality reduction. The largest reduction came from the use of secondary prevention medications or rehabilitation after acute myocardial infarction. This accounts for 9% of the reduction.

POPULÄRVETENSKAPLIG SAMMANFATTNING

Bakgrund: Både antalet som insjuknar och andelen som dör i hjärtinfarkt har minskat. Samtidigt har hjärtinfarkterna blivit mildare och mindre allvarliga. Andelen som insjuknar i den allvarligaste och dödligaste formen av hjärtinfarkt (ST-höjningsinfarkt) har också minskat, samtidigt som fler insjuknar med instabil kärlkramp. Detta kan bero på förändringar i medicinsk behandling men också på förändrade riskfaktorer i befolkningen, främst minskad rökning men även lägre kolesterol. Trots detta är sjukdomar i hjärtats kranskärl den vanligaste dödsorsaken i Sverige och stora delar av världen.

Syfte: Syftet med avhandlingen var att belysa hur förändringar i riskfaktorer och i medicinsk behandling påverkar den kliniska presentationen vid hjärtinfarkt och dödligheten i hjärtinfarkt.

Metod: Vi undersökte 781 patienter under 65 års ålder med en första hjärtinfarkt. Tre månader efter infarkten registrerades hur många som hade blodfettsänkande läkemedelsbehandling, och deras lipidvärden (delarbete I).

Registret för RIKS-HIA är ett nationellt kvalitetsregister som registrerar patienter som vårdats på avdelningar för hjärtintensivvård. Alla patienter 25-84 år gamla, totalt 93 416, som insjuknat i hjärtinfarkt, utan tidigare hjärtinfarkt, och som vårdades mellan åren 1996 och 2004, ingick i undersökningen (delarbete II och III).

Svenska data från ett flertal olika källor användes i den statistiska modellen - IMPACT model- för att kombinera information om riskfaktorer med information om kardiologiska behandlingar hos män och kvinnor mellan 25 och 84 år (delarbete IV).

Resultat: Efter att resultaten från 4S-studien presenterades har användandet av blodfettsänkande medicin införts och ingår idag i rutinbehandlingen efter hjärtinfarkt. 1994 hade 10% av männen och 23% av kvinnorna i studien blodfettsänkande behandling. Denna andel ökade gradvis och år 2002 behandlades 90% av alla kvinnor och män vårdade för förstagångshjärtinfarkt med blodfettsänkande läkemedel.

I RIKS-HIA var rökning vanligt bland infarktpatienterna, och mer än hälften av de som insjuknade med ST-höjningsinfarkt rökte. Rökning var starkt associerat med att insjukna i ST-höjningsinfarkt, den allvarligare formen av hjärtinfarkt, speciellt bland yngre infarktpatienter (<65) och kvinnor. För yngre kvinnor (<65 år) med hjärtinfarkt som rökte var risken att insjukna i ST-höjningsinfarkt fördubblad jämfört med icke ST-höjningsinfarkt. För män under 65 år och kvinnor 65 år och äldre var risken ungefär 1,33 gånger så stor om man rökte.

Tidigare medicinering med aspirin, Betablockerare, ACE-hämmare och blodfetsänkande medicin (statin) minskade risken för att drabbas av en allvarligare hjärtinfarkt (ST-höjningsinfarkt) oavsett ålder och kön. Risken att insjukna i en allvarligare hjärtinfarkt minskade med antalet mediciner

Andelen som insjuknar och dör i kardiovaskulär sjukdom har halverats mellan 1986 och 2002.

Vi fann att mer än hälften, ca 55 procent, av den minskade dödligheten kan förklaras av förbättrade riskfaktorer i befolkningen, främst en kraftig minskning av kolesterol men även en lägre andel rökare. Den minskade dödligheten kan även förklaras av förbättrade medicinska behandlingsmetoder (cirka 36%). Behandling vid akut hjärtinfarkt och instabil kärlkramp förklarade 7.4% av den minskade dödligheten. Mindre än 1% av den minskade dödligheten förklarades av behandling med ballongvidgning och kranskärlsoperation vid akut hjärtinfarkt och instabil kärlkramp. Den behandlingsmetod som förklarade den största andelen av den minskade dödligheten var sekundärpreventiv behandling (ca 9%).

Slutsats: Resultaten från 4S studien har visat att behandling med blodfettsänkande läkemedel (simvastatin) är ofarlig och minskar risken för en ny hjärtinfarkt. Blodfettsänkande behandling ingår numera i den rutinmässiga behandlingen av yngre patienter med förstagångshjärtinfarkt och har som väntat lett till lägre kolesterolnivåer. Trots detta har fortfarande en ganska stor andel av patienterna för höga kolesterolvärden.

Rökning är vanligt hos yngre patienter med hjärtinfarkt. Rökning ökar risken för att insjukna med ST-höjningsinfarkt jämfört med icke ST-höjningsinfarkt, speciellt bland yngre och hos kvinnor.

Tidigare medicinering med aspirin, Betablockerare, ACE-hämmare och blodfettsänkande läkemedel (statin) minskar risken för att insjukna i ST-höjningsinfarkt jämfört med icke ST-höjningsinfarkt.

Dödligheten i hjärtinfarkt har halverats mellan 1986 och 2002. Detta kan till största delen förklaras av lägre kolesterol och en lägre andel rökare i befolkningen men även av förbättrad medicinsk behandling. Resultaten visar att det är viktigt att arbeta med förebyggande insatser och att uppmuntra och underlätta hälsosamma levnadsvanor i befolkningen. Samtidigt är det viktigt att behandla enligt erkända medicinska metoder, framför allt sekundärpreventiv behandling.

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