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From Stenting to Preventing

*Invasive and Long-term Treatment for Coronary
Artery Disease in Sweden*

KRISTINA HAMBRÆUS



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Abstract

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Coronary artery disease (CAD) is the leading cause of death worldwide. Treatment with coronary interventions, long-term treatment and life style changes can reduce symptoms and improve prognosis. The aim of this thesis was to investigate aspects of invasive treatment for multivessel coronary artery disease, and to investigate adherence to prevention guidelines one year after myocardial infarction.

We used the national quality registry SWEDEHEART to collect data on long term treatment one year after myocardial infarction for 51 620 patients < 75 years of age. For 17 236 of the patients, we collected LDL-cholesterol measurements from SWEDEHEART and defined use of lipid lowering drugs from the Prescribed Drug Register. We developed a questionnaire for post-PCI-patients to investigate patients' understanding of cause and treatment of coronary artery disease. For 23 342 PCI-patients with multivessel coronary artery disease, SWEDEHEART-data was linked to Swedish health data registries to determine one year outcome for patients undergoing incomplete vs. complete revascularization.

Lipid control (LDL-cholesterol < 1.8 mmol/L) was attained by one in four patients one year after myocardial infarction, whereas blood pressure control (< 140 mmHg) was attained by two thirds of patients. Lipid and blood pressure control was lower for women but there was no gender difference in smoking cessation rate: 56 %. Over 90 % of patients were treated with a statin after myocardial infarction but treatment was intensified for only one in five patients with LDL-cholesterol above target.

The questionnaire study revealed that non-modifiable factors such as age and heredity were more often seen as cause of coronary artery disease than modifiable life style factors. Only one in five patients perceived CAD as a chronic illness, requiring life style changes.

Two thirds of PCI-patients with multivessel disease underwent incomplete revascularisation, and this was associated with a twofold risk for the combination of death, myocardial infarction and repeat revascularization up to one year, compared to patients who underwent complete revascularization.

We conclude that long term treatment after myocardial infarction is suboptimal in relation to guideline recommendations. Assessment of patients' views on CAD and better health education post PCI may facilitate life style changes. Further studies need to investigate whether complete revascularization will improve outcome for PCI-patients with multivessel disease.

Keywords: Coronary artery disease, guideline adherence, prevention, cholesterol treatment, lifestyle, percutaneous coronary intervention

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List of Papers

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

- I Hambraeus K, Tydén P, Lindahl B. Time trends and gender differences in prevention guideline adherence and outcome after myocardial infarction. Data from the SWEDEHEART-registry. *Submitted manuscript*
- II Hambraeus K, Lindhagen L, Tydén P, Lindahl B, Lagerqvist B. (2014) Target-attainment rates of low-density lipoprotein cholesterol using lipid-lowering drugs one year after acute myocardial infarction in Sweden. *The American Journal of Cardiology*, 2014 113(1):17-22.
- III Perk J, Hambraeus K, Burell G, Carlsson R., Johansson P, Lisspers, J. (2014) Study of Patient Information after percutaneous Coronary Intervention (SPICI): should prevention programmes become more effective? *EuroIntervention* pii: 20130221-02. [Epub ahead of print]
- IV Hambraeus K, Jensevik K, Lagerqvist B, Lindahl B, Carlsson R, Farzaneh-Far R, Kellerth T, Omerovic E, Stone G, Varenhorst C, James, S. Long-term Outcome of Incomplete Revascularization after Percutaneous Coronary Intervention in the Swedish Coronary Angiography and Angioplasty Registry (SCAAR). *Submitted manuscript*

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Abbreviations

ACE	Angiotensin converting enzyme
ACS	Acute coronary syndrome
AMI	Acute myocardial infarction
ARB	Angiotensin receptor blocker
ASA	Acetyl salicylic acid
BMS	Bare metal stent
CABG	Coronary artery by-pass graft surgery
CAD	Coronary artery disease
CCS	Canadian Cardiovascular Society
CR	Complete revascularization
CVD	Cardiovascular disease
DES	Drug eluting stent
ECG	Electrocardiogram
FFR	Fractional flow reserve
HLR	Swedish Heart and Lung Patients Association
IR	Incomplete revascularization
LDL-C	Low density lipoprotein cholesterol
MI	Myocardial infarction
NSTEMI	Non-ST-segment elevation myocardial infarction
PCI	Percutaneous coronary intervention
RIKS-HIA	Register of information and knowledge about Swedish heart intensive care admissions
SCAAR	Swedish Coronary Angiography and Angioplasty Register
SEPHIA	Secondary prevention after heart intensive care admission
SPICI	Study of Patient Information after percutaneous Coronary Intervention
STEMI	ST-segment elevation myocardial infarction
SWEDEHEART	Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies

Preface

It is fascinating and maybe horrifying that a few millimeters of pathology in a coronary artery - or even just a few micrometers if you consider the rupture in the atherosclerotic plaque - can have such dramatic and life-threatening consequences. Pain, anxiety and sometimes collapse of the circulatory system can arise within minutes when a blood clot is forming and a myocardial infarction is evolving. Equally fascinating is the fact that these lesions can be treated with tiny wires, balloons and stents through a small puncture on the wrist. This intervention can often quickly relieve the symptoms and restore normal circulation.

But while treatment is done quickly and with small things, prevention of this deadly disease necessitates a life-long as well as a global perspective. Not only of the whole body but the whole context in which we live; what we eat and drink, how we move about, our work and our relationships, and how fortune is distributed around the world.

I have always been intrigued by this difference in perspective in coronary artery disease, from a small blood clot to world health, from a matter of minutes to life-long commitments. In this thesis I have tried to incorporate these different views on coronary artery disease.

Introduction

Coronary Artery Disease

Historical notes

Coronary artery disease is often regarded as a disease caused or aggravated by our modern life-style: cheap junk food available at all hours, exposure to tobacco and other toxins, modes of transportations that do not involve use of our skeletal muscles and a stressful environment with constant input to our sensory systems.

A recent study of ancient human remains have however revealed that atherosclerosis was common even long before fast food chains and flat screen TVs. In a recent study, whole body CT scans of 137 mummies from four different geographical regions or populations, representing varying diets and circumstances of life and spanning more than 4000 years, were obtained. Calcifications consistent with atherosclerosis were examined, either in the form of a plaque in the artery wall or as calcifications along the expected course of an artery within the carotid, coronary, aortic, iliac or peripheral vascular beds. Probable or definite atherosclerosis was found in one third of the mummies, suggesting that atherosclerosis could be an inherent component of human aging rather than just a product of contemporary life style ¹.

Incidence and mortality

Age standardized all-cause mortality decreased by more than half in Sweden from 1952 to 2010. This means that death occurs later in life, since everybody will die eventually, and has resulted in the calculated life expectancy for a child born in 2008 to be about 14 years longer than in 1945 ².

There is a clear gender difference in mortality and hence life expectancy: for a female it was 4 years longer than for a male in 2011. This gender difference reached its maximum in Sweden about 1980, when cardiovascular mortality began to decline for men, having increased in the 1950s, -60s and 70s. The most important contributor to this decrease was the decline in mortality from cardiovascular diseases (CVD), whereas for example death from cancer remained unchanged during this period ². Coronary artery disease (CAD) is the most important contributor to cardiovascular death.

There is also a large gender difference in incidence of myocardial infarction: in 2012 the incidence for women was 344/100 000 and for men it was 522/100 000 in Sweden.³

The decline in mortality from myocardial infarction is explained by a combination of reduction in incidence and better chances of surviving for those falling ill. The risk of dying of a myocardial infarction has been reduced by more than half in the last 20 years and the incidence has been reduced by about 40 %⁴. The incidence for a first time infarction has been reduced by 25 % for men and 31 % for women since 2001³.

For cases treated in hospital, the short-and medium term prognosis after myocardial infarction has improved greatly: age standardized case fatality within 28-days decreased from 21 % in 1998 to 13 % in 2012³. However, a large number of cases do not draw the benefits of this improvement. Out of the individuals who died in 2012 with myocardial infarction as underlying or contributing cause, 6000 died on the same day as the diagnosis³.

The fact that both incidence and mortality are strongly associated with age and gender suggests biological and genetic causes of the disease, but there are also indications of environmental influence. Level of education is one such important factor. In 2012 the incidence of myocardial infarction among Swedish men aged 45-74 with compulsory school only was 40 % higher compared to men with post-secondary education. Among women the difference was 60 %³.

In a global perspective, age-standardized death rate from CAD has declined steeply since 1980 in the Western, high-income regions, but has increased in Eastern Europe, Central Asia, South Asia, and East Asia. In 2010 it was the leading cause of death worldwide⁵.

The reasons for the observed decline in CVD mortality in many countries have been investigated, trying to model the impact of risk factor changes as well as use of medical treatment for cardiovascular disease. According to Björk et al, more than half of the substantial CVD mortality decrease in Sweden between 1986 and 2002 was attributable to reductions in major risk factors, mainly a large decrease in total serum cholesterol, but also in smoking and blood pressure. The greatest contribution from specific treatments came from secondary prevention treatments after acute myocardial infarction (AMI), such as aspirin, statins, beta-blockers and Angiotensin converting enzyme (ACE)-inhibitors. Treatments that were given for a short period of time, such as acute treatment for myocardial infarction, or were given to individuals at low risk, such as statins in primary prevention, had less impact on the CVD mortality in the population⁶. These findings are in line with other international studies^{7, 8}. Figure 1 shows this in comparison to other population studies.

As the short-term mortality rate decreases and more patients survive their first myocardial infarction, the need for effective strategies to prevent recurrent disease becomes increasingly important.

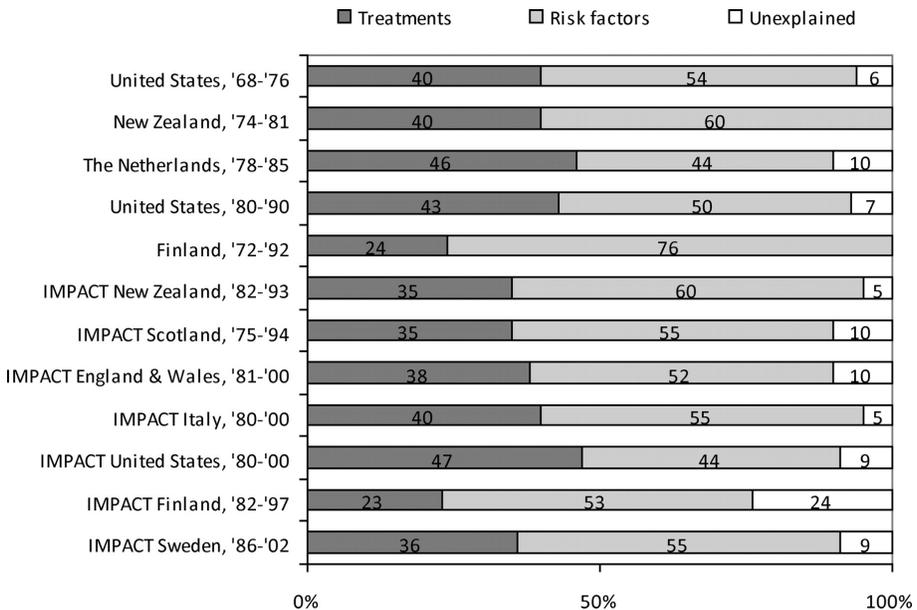


Figure 1. Percentage decrease in deaths from coronary heart disease attributed to treatments and risk factor changes in different population studies. Reprinted with permission from Oxford University Press⁹.

Risk factors

The term “risk factor” describes characteristics of individuals in a population that are particularly susceptible to a disease¹⁰. To determine whether associations between such factors and the occurrence of disease represents a cause-effect relationship, it has been suggested that a number of criteria should be considered. These include among others the strength of the association, consistency of findings from several studies and biological plausibility¹¹. When a causal relationship has been established, this may have implications for preventive measures.

As coronary artery disease reached epidemic proportions in the Western world in the mid-twentieth century, epidemiological studies such as the Framingham study and the Seven Countries Study were launched. They identified factors associated with CAD: age and gender, lifestyle, diet, elevated blood pressure, cholesterol and cigarette smoking^{12,13}. The Whitehall I and II studies also contributed knowledge about the association between low job control and risk of coronary heart disease¹⁴. A recent large case-control study, the INTERHEART-study, investigated risk factors for AMI in differ-

ent ethnical and geographical populations. It confirmed that the most important risk factors are abnormal lipids, smoking, hypertension, diabetes, abdominal obesity, psychosocial factors, dietary factors, and physical inactivity across different parts of the world. Together, these factors accounted for over 90 % of the risk of a myocardial infarction¹⁵.

Knowledge about the biological mechanisms linking the individual risk factors to the development of atherosclerosis is evolving, but many aspects are still not completely understood. Inflammation seems to be a key factor however, promoting all steps of the atherosclerotic process¹⁶.

Diabetes carries an increased risk for developing CAD compared to individuals without diabetes, and the risk is even more increased in individuals with obesity¹⁷. A recent meta-analysis has also demonstrated that the increased risk of CAD is 44 % greater in women with diabetes than in men with diabetes¹⁸. The two major metabolic disturbances in diabetes type II, insulin resistance and hyperglycemia are pro-atherogenic, likely having additive and perhaps synergistic effects¹⁹. The pathophysiological mechanisms are complex and also linked to obesity. Insulin resistance induces an atherogenic dyslipidemia via mechanisms linked to the accumulation of free fatty acids in the liver, seen in visceral obesity²⁰.

The biological effects of psychosocial risk factors, such as depression, on the development of coronary artery disease, might be mediated through several different mechanisms involving neuroendocrine dysfunction, immune activation, endothelial dysfunction and thrombotic predisposition²¹.

Smoking induces vascular dysfunction, increased adherence of platelets and macrophages and thus induces a pro-coagulant and inflammatory environment²². As with diabetes, it seems that women are more susceptible to the increased risk for CHD induced by smoking²³.

Blood pressure is strongly related to mortality from ischemic heart disease²⁴. Several pathophysiological mechanisms link hypertension to the development of atherosclerosis. These include pressure-driven convection of lipoproteins across the endothelium and increased inflammatory reactions in the arterial wall. Dyslipidemia and insulin resistance also influence blood pressure via several pathways, such as the renin-angiotensin system, the sympathetic nervous system and endothelium-dependent vasodilatation²⁰.

Total cholesterol is positively associated with mortality from ischemic heart disease in both middle and old age and at all blood pressure levels²⁵. In patients with familiar hypercholesterolemia, premature atherosclerosis is developed even in the absence of other risk factors²⁶, which supports the idea that elevation of LDL is required for atherogenesis. The subendothelial retention of lipoproteins is seen as the key initiating process in atherogenesis²⁷. Thus many of the risk factors interact in the development of atherosclerosis (Figure 2).

An important characteristic of these risk factors is the fact that they are potentially modifiable. According to a statement from The World Health

Organization (WHO), the vast majority of all CVD mortality could be prevented with adequate changes in lifestyle²⁸.

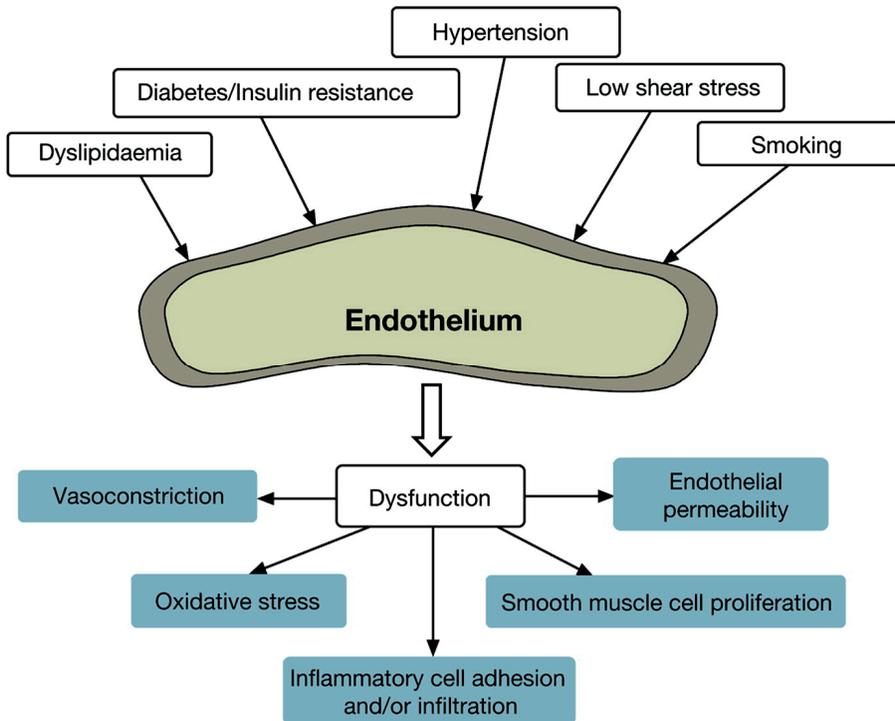


Figure 2. Induction of endothelial dysfunction by common cardiovascular risk factors. Reprinted with permission from Elsevier²⁰.

Atherosclerosis

Atherosclerosis is a lipoprotein-driven disease that leads to plaque formation at multiple sites of the arteries, typically in the abdominal aorta, coronary arteries, iliofemoral arteries and carotid bifurcations.

Biomechanical factors seem to play a role in the formation of plaques. Sites that are susceptible are characterized as having low endothelial shear stress; located near branch points and along inner curvatures²⁹. Plaque formation occurs at these sites through multifaceted mechanisms involving lipoprotein retention, inflammatory cell recruitment, apoptosis and necrosis, smooth muscle cell proliferation and matrix synthesis.

Low-density lipoproteins are essential in the development of atherosclerosis. These cholesterol-containing particles accumulate in the arterial wall, where the LDL-particles are modified by oxidation²⁷. Modified LDL activates the immune system and is a driver of inflammation³⁰. Leucocytes also adhere to susceptible sites on the innermost layer of the vessel and migrate into the arterial wall, where they mature into macrophage/foam cells that

take up lipids and grow in size until they become unstable and undergo apoptosis. Large accumulations of necrotic acellular, lipid-rich material are found in progressive atherosclerotic lesions and may eventually develop into confluent necrotic cores³¹. Smooth muscle cells migrate to the innermost layer of the vessel where they produce extracellular matrix molecules, such as collagen, and form a fibrous cap over the lesion³².

Inflammation also plays a part in gradual thinning of the fibrotic cap that covers the necrotic core, and pathological studies have identified thin cap fibroatheromas as the precursor lesions of ruptured plaques³³. Features of a rupture prone plaque are shown in figure 3. A gap or rupture in the fibrous cap of the atheroma exposes the highly thrombogenic core to the blood coagulation components, leading to a thrombosis. This may decrease or completely block blood flow in the artery thus causing ischemia in the myocardium supplied by the artery³⁴.

The plaques in the coronary arteries may remain asymptomatic, they may become obstructive causing stable angina, and/or they can rupture causing acute thrombosis and acute coronary syndromes, all in an unpredictable manner.

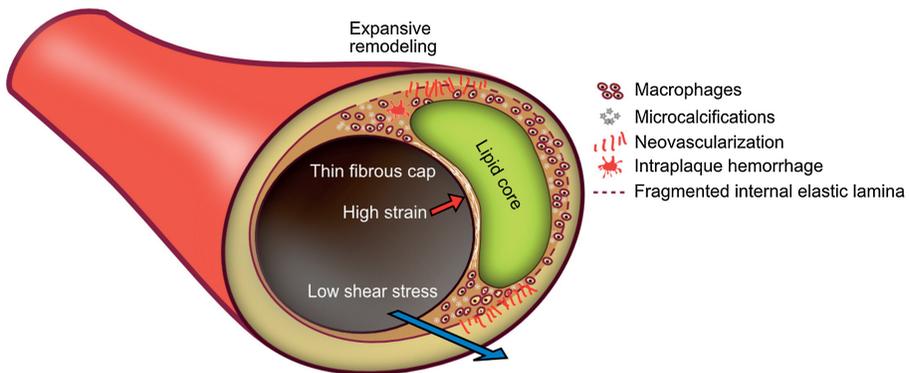


Figure 3. Pathobiologic and local hemodynamic features of high-risk (rupture prone) plaque. Reprinted with permission from Elsevier³⁵.

Clinical presentation

Chest pain is the most common symptom caused by myocardial ischemia. It is usually located near the sternum but may also be localized to the back, upper part of the abdomen, neck, jaws or arms. The pain may also radiate to these localizations. Atypical symptoms are nausea, fatigue, profuse sweating, palpitations, syncope, shortness of breath and anxiety. Atypical symptoms may arise in combination with chest pain or alone.

Stable coronary artery disease is characterized by episodes of reversible myocardial ischemia, which are usually inducible by exercise or stress and

typically caused by atherosclerotic and/or functional alterations of epicardial vessels and/or microcirculation. Stable angina might be the first symptom of coronary artery disease or follow an episode of unstable angina or myocardial infarction. Unstable angina by definition is not accompanied by a rise of cardiac biomarkers but includes chest pain at rest, new onset angina, destabilization of previously stable angina and post-MI angina³⁶.

Acute myocardial infarction (AMI) is defined as myocardial cell death due to prolonged myocardial ischemia. The most common cause of ischemia is a coronary event caused by plaque erosion or rupture. Diagnosis is based on measurement of cardiac biomarkers together with typical symptoms, electrocardiogram (ECG)-changes or imaging evidence of new loss of viable myocardium³⁷. Based on the ECG appearance, myocardial infarctions are classified as non-ST-segment elevation myocardial infarction (NSTEMI) or ST-segment elevation myocardial infarction (STEMI). In the latter case the artery is typically totally occluded by a sustained thrombus, whereas in NSTEMI the thrombus is usually incomplete and dynamic. The term acute coronary syndrome (ACS) includes acute cases of unstable angina without raised biomarkers.

Prevention

The first manifestation of coronary artery disease can be sudden cardiac death. Thus, preventing the disease from occurring is in many cases the only possible option to influence its' course. The most effective strategies for prevention have been discussed for several decades. The English epidemiologist Geoffrey Rose argued that a large number of people exposed to a low risk is likely to produce more cases than a small number of people exposed to a high risk. This has been an argument for the "population strategy" for prevention, i.e. aiming at reducing the level of a risk factor in the whole population, as opposed to the "high risk strategy" where instead the (few) people with the highest risk for developing disease would be targeted for risk-reducing interventions. These principles are illustrated in figure 4 .

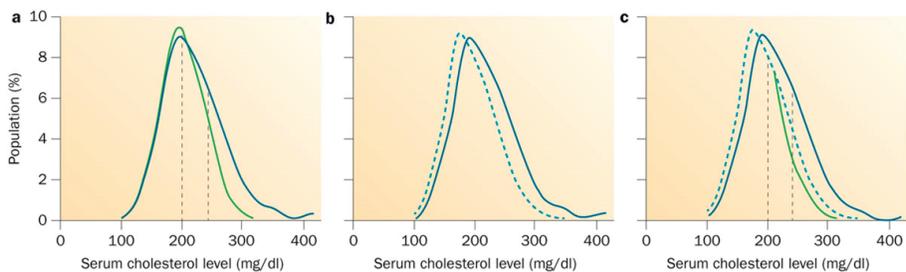


Figure 4. **a.**A “high risk” approach, treating individuals with high cholesterol (blue line) to reduce the number at risk (green line). **b.** A “population approach” reducing cholesterol levels in the whole population. **c.** Combined high-risk and population approaches. Reprinted with permission from Nature publishing group³⁸.

This theory has been investigated in a recent publication in which preventive interventions, that have had an impact on mortality and morbidity rates in the Netherlands, were identified and classified into population versus high-risk approaches. The gains achieved by the different approaches were compared, concluding that considerably larger health gains have been achieved with the population approach. (Figure 5)³⁹.

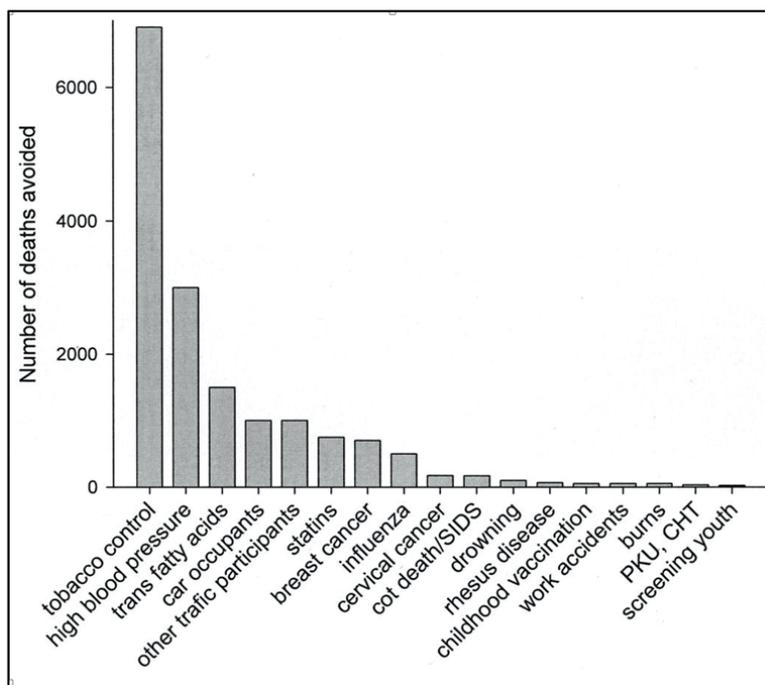


Figure 5. Successful preventive interventions in the Netherlands, ranked by absolute yearly number of deaths avoided (1970–2010). Reprinted with permission from Oxford University press³⁹.

The problem with the population strategy is the fact that "a measure that brings large benefits to the community offers little to each participating individual", which is called the prevention paradox⁴⁰. The small gain for each individual might reduce the willingness to accept such interventions in the population. If the intervention also carries a risk, for example for side effects of a drug, this calls for careful consideration of the balance between risk and benefit.

Prevention has traditionally been divided between primary prevention – before disease has occurred, and secondary prevention – aiming at avoiding recurrent events after a clinical manifestation of disease such as myocardial infarction or stroke. In modern treatment guidelines, this concept has been replaced by the recognition that atherosclerosis is a continuous process. Estimation of total risk for CVD has become an important tool to identify individuals with the highest risk for serious development of the disease, and to guide patient management⁴¹. This might be seen as a compromise between the population and the high-risk strategy. The risk scores used in the recent U.S. guidelines for cholesterol treatment for example place a very large proportion of the adult population in the at-risk-category and thus make them eligible for statin treatment^{42 43}. This has been controversial, cost-effectiveness for this has however been estimated to meet societal acceptable levels⁴⁴.

It is generally accepted in current treatment guidelines for prevention that clinical manifestation of disease, i.e. what would qualify as secondary prevention, puts the individual in the highest risk category for new cardiovascular events⁴⁵. Diabetes⁴⁶, smoking⁴⁷, cholesterol⁴⁸, diet⁴⁹, and psychosocial factors⁵⁰ are known to maintain their status as factors influencing prognosis after a cardiac event has occurred, whereas the significance of obesity is controversial⁵¹.

Invasive treatment

Symptomatic coronary artery disease can be treated invasively, either with coronary artery by-pass graft surgery (CABG) or percutaneous coronary interventions (PCI), both methods aiming at improving blood flow distal to flow limiting stenoses. The choice between these methods depends on angiographic findings, patient characteristics and clinical setting. Recent guidelines recommend that this decision is made by a multidisciplinary team. In general, CABG is recommended over PCI for patients with stable coronary artery disease, low predicted surgical mortality and involvement of the left main coronary artery together with complex coronary anatomy, or three-vessel disease with complex coronary anatomy⁵².

PCI is a technique that has evolved over the years, from plain balloon angioplasty to include the use of bare metal stents and later to drug-eluting stents, which has increased the durability of this treatment. A recent network

meta-analysis investigated whether revascularization improves prognosis compared to medical treatment among patients with stable coronary artery disease. CABG and new generation drug eluting stents, but not balloon angioplasty, bare metal stents, or early generation drug eluting stents, were associated with improved survival in this study, and CABG was also associated with a reduced risk of MI⁵³.

For patients with NSTEMI-ACS and a high risk of serious development of the disease, a strategy of early coronary intervention/revascularisation decreases the risk of death and/or re-infarction⁵⁴. This approach is recommended in the Swedish and European practice guidelines^{55,56}.

In the case of STEMI the first aim is to restore the blood flow in the occluded coronary artery as soon as possible, either with a thrombolytic ideally given within 30 minutes or with primary percutaneous coronary intervention (PCI) within 90 minutes after first presentation^{57,58}. The rate of primary PCI for STEMI has risen dramatically in Sweden from approximately 25 to 70 % in the last decade⁵⁹.

Multivessel disease, i.e. significant coronary artery stenosis in more than one main vessel, is frequently identified in patients with suspected or confirmed ischemic heart disease (figure 6). Around half of all patients presenting with ST-segment elevation myocardial infarction (STEMI)^{60,61} and up to two thirds of patients with non-ST-segment elevation acute coronary syndrome (NSTEMI-ACS) have more than one diseased vessel.^{62,63}

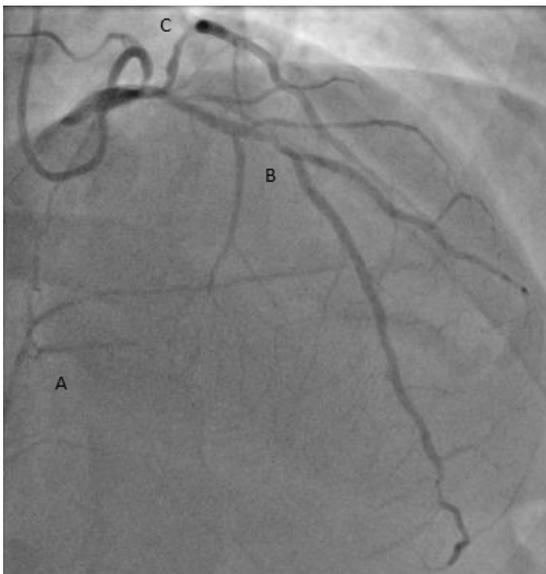


Figure 6. Coronary angiography of multivessel disease. **A.** Collateral filling of occluded right coronary artery. **B.** Stenosis in left anterior descending artery. **C.** Stenosis in marginal branch.

There is a concept of multiple unstable lesions occurring simultaneously in the coronary vessels, which might have a negative effect on the prognosis of the patient⁶⁴. This might be due to the diffuse underlying inflammation of the atherosclerotic process. Previous studies have demonstrated the angiographic occurrence of complex lesions in non-infarct related arteries^{65, 66}. A recent study using optical coherence tomography also demonstrated frequent occurrence of vulnerable plaque, or thin cap fibroatheromas, in addition to ruptured plaque in patients with myocardial infarction⁶⁷.

Incomplete revascularization (IR), i.e. performing percutaneous coronary interventions (PCI) of some but not all angiographically significant lesions has been associated with an increased risk for future cardiovascular events in observational studies and subgroup analyses of randomized trials⁶⁸⁻⁷¹. Complete revascularization (CR) of all significant stenoses however necessitates a more complex intervention with a potentially higher risk for complications, increases radiation exposure and use of contrast agent and has been associated with worse prognosis for patients with STEMI in some observational studies^{72, 73}, whereas others have suggested the opposite⁷⁴.

For patients presenting with stable angina or NSTEMI-ACS, practice guidelines do not formally address the issue of performing complete vs incomplete revascularization with PCI, however assessment of lesions with functional methods such as fractional flow reserve (FFR) is recommended to avoid unnecessary treatment of non-significant stenoses^{36, 56, 75}. For patients presenting with STEMI, PCI of non-culprit vessels in the acute setting is generally discouraged in guidelines, except for patients presenting with cardiogenic shock, persistent ischemia or in patients where ECG-localisation of the infarction is ambiguous and leads to difficulties in identifying the culprit lesion^{57, 58}.

The concept of multivessel PCI remains controversial.

After discharge

Coronary artery disease is a chronic illness, and treatment should aim at keeping it asymptomatic for long periods of time. After an acute event, the risk of new events and mortality is higher during the first year and declines in the following years, but over a period of 5 years, readmissions to hospital remain common^{76 77}.

Practice guidelines issue recommendations regarding pharmacological and lifestyle interventions to prevent new and recurrent cardiovascular disease^{45 43, 78-80}. Long-term treatment of coronary artery disease mainly target the following factors: blood pressure and lipid control, exercise training, tobacco use, dietary habits and stress management.

Programmes for smoking cessation are highly cost-effective for decreasing morbidity and mortality⁴⁷. Exercise based cardiac rehabilitation reduces

overall and cardiac mortality and reduces hospital readmissions⁸¹. A change in dietary habits can decrease the risk of re-infarction⁸². There is also some support for reduction of depression and anxiety and decrease in the risk of re-infarction and mortality with psychosocial support and behavioural therapy. The evidence for which patient category that is likely to benefit from specific types of treatment is however still lacking⁸³⁻⁸⁵. For individuals with manifest arteriosclerotic disease there are well-established recommendations of pharmacological treatment. Dual antiplatelet therapy with ASA⁸⁶ and clopidogrel⁸⁷, prasugrel⁸⁸ or ticagrelor⁸⁹, β -blockers^{90, 91}, ARBs⁹² and ACE-inhibitors^{93, 94} have been shown to decrease morbidity and mortality after myocardial infarction with or without impaired left ventricular function. Statins were introduced on a large scale after the Scandinavian Simvastatin Survival Study, comparing simvastatin to placebo in patients with coronary artery disease and demonstrating a survival benefit⁴⁸. Intensive statin therapy was demonstrated to further reduce non-fatal events in a meta-analysis⁹⁵.

Cross-sectional studies in Europe have indicated that there is substantial under-treatment according to prevention guidelines even in patients with manifest CAD^{96, 97}.

Patients' attributions of risks and causes

Misconceptions regarding the disease held by patients might contribute to low rates of risk factor control and life style changes after a coronary event. This may in part be based on "misfearing", the human tendency to fear instinctively rather than factually, i.e. to fear things that are not dangerous but not fear things that impose serious risk⁹⁸. Patients may regard the asymptomatic and invisible coronary artery disease as harmless, and procedures undertaken in the acute or symptomatic phase as having a greater impact on the course of the disease than they actually have⁹⁹. A meta-analysis concluded that illness perceptions predict attendance at cardiac rehabilitation, even though effect sizes were small: AMI patients who view their condition as controllable, as symptomatic, and with severe consequences, and who feel that they understand their condition are more likely to attend¹⁰⁰. This association was also found in a more recent questionnaire study, although the reply rate was below 50 %¹⁰¹.

A meta-analysis found that stressors, ill fate and bad luck were often seen as causes of heart disease when respondents were asked about their own heart disease, whereas overweight and hypertension were ranked higher when respondents were asked about other people's heart disease¹⁰². A qualitative study of women 3 months post AMI found that stress was considered to be the cause of myocardial infarction and the significance of lifestyle factors was considered uncertain by the women¹⁰³.

Quality of care

Measuring and improving quality

Measuring performance in health care has been proposed as a foundation of quality improvement, the idea behind it being that we cannot improve what we cannot measure. In a paper from 1998, Donald M Berwick stated that “measurement without change is waste, while change without measurement is foolhardy” and that “health care has developed a very long leg in measuring and a very short leg in managing change, and is therefore walking in circles”, indicating that measuring in itself is not enough to change practices.¹⁰⁴

The gap between guidelines and clinical practice that has been demonstrated⁹⁶ means that the potential benefits of evolving scientific evidence are not fully realized. Barriers and facilitators for bridging this gap by implementation of evidence based practices have been investigated and described in theoretical frameworks. They include the content of quality improvement efforts, the type of evidence that is to be implemented, the organizational processes that are used to implement the quality improvement effort, and features of the organizations that are involved in the process^{105 106}.

Quality registries

The use of disease specific quality registries has become increasingly common in Sweden and many other countries. The purpose is generally to assess quality, to monitor changes in quality and content of delivered care over time, to support continuous quality improvement and in many cases to form the basis for research, mainly observational¹⁰⁷. They also make it possible to evaluate inequalities in care delivery with respect to age, gender and geographical region¹⁰⁸, to monitor new treatments and interventions as they are applied in a real life setting¹⁰⁹, to gather information on rare events such as stroke after myocardial infarction¹¹⁰, and they may also be used for construction and validation of risk prediction models of important outcomes¹¹¹.

The Swedish quality registries receive logistic and economic support from the Swedish government and the Swedish Association of Local Authorities and Regions. They are annually monitored and approved for continued funding by an Executive Committee.

In a recent paper investigating elements that facilitate and hinder quality improvement based on a national quality registry on stroke, the authors concluded that the quality registry in itself was only one tool in the quality improvement process; other factors such as collaboration of local stakeholders and management systems for presenting and using the data are also necessary. The time spent on registering was seen as a hinder for quality improvement¹¹².

Health data registries

Population statistics have been registered in Sweden since 1749. The cause of death was originally determined by the priests, but from 1951 death certificates were issued by doctors and followed international classifications for cause of death ¹¹³. The Swedish National Inpatient Register was founded by the National Board of Health and Welfare 1964. It has complete coverage since 1987 and includes diagnoses coded according to the international classification of disease (ICD) system ¹¹⁴. All physicians, private and publicly funded, must deliver data to this register. The Prescribed Drug Register includes all prescribed drugs dispensed in Swedish pharmacies since 2005 ¹¹⁵. Since the government-administered Swedish Health data registries are mandatory they cover they have a high degree of coverage of the Swedish population. They are however less detailed regarding disease-specific data and important aspects of management other than diagnosis and dates for admission and discharge.

The Swedish quality registries can be linked to the mandatory health data registries via the personal identification number for each Swedish citizen which supplements the disease specific data in the quality registries with reliable outcome data with a high degree of completeness.

Overall purpose and specific aims

Overall purpose

The overall purpose of this thesis was to investigate different aspects of contemporary treatment for coronary artery disease in Sweden, covering the spectrum from percutaneous interventions to long-term prevention of recurrent events in the post-acute phase.

Specific aims

- I To report adherence to practice guidelines after AMI in Sweden and to investigate gender differences and time trends in risk factor control rate, symptoms and readmissions one year after AMI, using a national quality register.
- II To describe real life use of lipid lowering drugs and resulting LDL-C target attainment rates one year after AMI in a large unselected patient cohort.
- III To investigate PCI-patients' attribution of causes of coronary disease, perception of information provided by the care-giver and self-assessment of lifestyle changes.
- IV To determine current practice regarding completeness of revascularization in patients with multivessel disease undergoing PCI, and to investigate the association of incomplete revascularization with death, repeat revascularization and reinfarction.

Methods

Setting

Data was collected by hospital staff in the setting of routine health care in Swedish hospitals between 2005 and 2013. Blood samples and measurements of blood pressure were also collected via primary care centres for study I and II. In study III, questionnaires were distributed to PCI-patients by hospital staff, also in the setting of routine health care. An overview of the studies' design, populations, data sources and main outcome measures is shown in table 1.

Table 1. *Summary of the studies' design, populations, data sources and main outcome measures. SWEDEHEART, Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies*

Study	Study design	Study population	Data sources	Main outcome measures
Paper I	Observational registry study	51 620 AMI-patients	SWEDEHEART + National Cause of Death Registry	Risk factor control, symptoms readmissions one year post AMI
Paper II	Observational registry study	17 236 AMI-patients	SWEDEHEART + Prescribed Drug Registry	LDL-C target attainment one year post AMI
Paper III	Cross-sectional study	1 073 PCI-patients	Questionnaire	Patients' views on information after PCI
Paper IV	Observational registry study	23 342 PCI-patients	SWEDEHEART + National Patient Registry + National Cause of Death Registry + Prescribed Drug Registry	Death, myocardial infarction and repeat revascularization one year post PCI

Data sources

National Quality Registries

RIKS-HIA

The Register of Information and Knowledge about Swedish Heart Intensive care Admissions (RIKS-HIA) started in 1995 and includes background variables, diagnostic procedures, coronary interventions, complications, diagnosis and medication at discharge for patients with acute coronary syndromes. Data from this registry has been utilized in a large number of publications. An early publication from RIKS-HIA demonstrated that early initiation of statin-treatment at or before hospital discharge was associated with reduced one-year mortality in patients with AMI ¹¹⁶. Some of the main areas of research have since been describing treatment and outcome for AMI-patients with and without co-morbidities such as diabetes ^{117, 118} and chronic kidney disease ^{119, 120}, gender differences ^{121, 122} and guideline adherence ^{123 124}.

SCAAR

The Swedish Coronary and Angioplasty register (SCAAR) includes data on all consecutive patients from all centers that perform coronary angiography and PCI in Sweden since 1998. Detailed data regarding each procedure such as indication, angiographic finding, time of day for the procedure, vascular access, type of procedure, stent type and size, inflation pressure, amount of contrast, radiation dose and adjunctive pharmacological treatment are entered into the registry by the operator ¹²⁵. SCAAR has been utilized for example to investigate performance of different types of stents ^{126 127}, adjunctive drug treatment ^{128, 129} and subsets of coronary artery disease ^{130, 131}.

SEPHIA

In order to obtain data on long-term results of management in the acute and rehabilitation phase, we developed the registry for Secondary Prevention after Heart Intensive care Admissions (SEPHIA) in 2003-2004. The case report form and on-line registration technique were tested in 10 hospitals of various types and sizes before finalisation. 35 Swedish hospitals participated in 2005, when the registry started, increasing to 65 out of 73 Swedish hospitals in December 2013. Data is collected on two occasions post AMI; at 2 months and at one year after the event. The registered variables include cardiac symptoms, readmissions and events after discharge, tobacco use, level of physical activity, sick leave, participation in hospital based exercise training programmes, medication, measurements of cholesterol, blood pressure and waist circumference ^{132, 133}.

SWEDEHEART

In December 2009 the RIKS-HIA and SEPHIA-registries were merged with the registries for coronary angioplasty (SCAAR) and cardiac surgery to form the SWEDEHEART-registry¹³⁴. SWEDEHEART is co-funded by the Swedish government and the Swedish Association of Local Authorities and Regions. It is annually monitored and approved for continued funding by an Executive Committee. Results are reported publicly at hospital level.

According to Swedish law no informed consent is needed for registration of a patient in the registry. However, all patients must have information of their participation in the registry and have the right to withdraw their participation.

Registration technique

Data is entered into the registry database on-line using individual login and password. The on-line registration technique also gives each user access to feedback reports, with the results of the centre shown in comparison to target levels, and in comparison to the other participating centres in Sweden.

Data quality and degree of coverage

Validation is done for some variables by automated checks and warnings to prevent the input of incorrect data, and logistics control information such as personal identity number and site. Definitions are displayed on the screen as data are entered. A majority of the variables are mandatory in order to obtain complete data. Data reliability has been checked against source data for random samples of records, revealing 93-97 % agreement¹³⁴. The degree of coverage compared to the National Patient Registry (see below) at patient level was 100 % for angiography and PCI. For admissions of AMI-patients < 80 years of age it was 80-90 % and of these, follow up-registrations for secondary prevention after AMI for patients <75 years of age increased from 30 % in 2005 to 80 % in 2013.

The Swedish Health Data Registries

The Swedish Prescribed Drug Register started in July 2005 and includes all dispensed prescriptions in Swedish pharmacies for all Swedish citizens¹¹⁵. It contains prescription date and dispensing dates, dispensed amount of the drug, and personal identification number of each individual. Drugs are coded according to the World Health Organization Anatomical Therapeutic Chemical Classification (ATC)¹¹⁵.

The National Patient Registry includes all in-patient care in Sweden since 1987. All county councils in Sweden delivers information to NPR at the National Board of Health and Welfare regarding age and gender, geographical data, length of stay, main and secondary diagnosis of all patients, includ-

ing their personal identification number ¹¹⁴. The overall positive predictive value of diagnoses for in-patient care in the register is about 85-95% ¹¹⁴.

The National Cause of Death Registry includes all deaths, including date of death and cause of death, for Swedish residents regardless if the event occurred in Sweden or abroad. Cause of death is coded according to the tenth revision of the international classification of disease (ICD 10) ¹¹³.

Questionnaire Paper III

As there was no earlier validated questionnaire for Swedish patients post PCI with the specific items that were needed, we created the questionnaire *de novo*. It was compiled by the authors of the study together with two members of the patients' association (HLR) who acted as "patient research partners" in order to incorporate the patients' perspective.

The cardiologists in the team prepared a first set of questions which were then reviewed and adapted by the two psychologists of the author group who had extensive experience in the field of patient questionnaires. After revisions, the patient research partners from HLR contributed further comments, after which a third version was tested among a group of patients who had recently undergone an acute PCI. After final minor changes, the questionnaire was approved by all for use in the study. The questionnaire covered the following items: patients' beliefs regarding what caused their coronary artery disease, information given to the patient at discharge and at the first follow-up visit to the out-patients clinic, information on the need for lifestyle modification, invitation to and participation in a physical training program, level of physical activity (number of times a week the patient engaged in physical activity of low, intermediate or high intensity), availability of a smoking cessation program at the center and tobacco habits (number of cigarettes or packages of moist snuff per day, if any), availability of nutritional counseling and food habits (food frequency questionnaire regarding intake of vegetables, fruit/berries, fish and unhealthy snacks) after PCI, and availability of a stress management program.

Study population and design

Papers I, II and IV were observational registry-based studies. Paper III was a cross-sectional questionnaire study.

For Paper I, consecutive patients below the age of 75 and discharged alive after a myocardial infarction were invited to participate in the SWEDEHEART/SEPHIA-registry and be interviewed by a nurse or physician during

an outpatient visit or via telephone on two occasions. For each follow-up blood samples (total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, blood glucose and HbA1c) and measurements of blood pressure and waist circumference were obtained either at the follow-up centre, or provided via the primary health care centre upon request from the follow-up centre. The study included 51 620 patients enrolled in 2005-2013.

For Paper II, patients aged <75 years, participating in the 2-month and/or 1-year follow-up after an AMI in the SWEDEHEART/SEPHIA registry between 2005 and 2009 were identified. The prescribed Drug Registry was merged with SWEDEHEART/SEPHIA to identify patients from the cohort who had at least one purchase of any prescribed lipid-lowering drug during the study period and who had at least one measurement of LDL-cholesterol, either at the first and /or the second SWEDEHEART/SEPHIA-follow-up. This resulted in a study population of 17 236 patients.

For Paper III a questionnaire was handed out by a cardiac nurse to post-PCI patients at 29 centers in 2011, including centers with and without acute PCI service. The questionnaire was handed out at the standard follow up visit six to ten weeks after the PCI. The replies were sent anonymously to the Heart and Lung Patients' Association for analyses.

For Paper IV, consecutive patients with PCI performed from January 2006 to 2010 were identified in the SWEDEHEART/SCAAR-registry.

Patients with single-vessel disease or previous coronary by-pass surgery were excluded, as well as patients with missing data for revascularization status. Patients with missing data for time of day (on call versus within office hours) for the procedure were also excluded, resulting in a study population of 23 342 patients. Incomplete revascularization was defined as any non-treated significant stenosis in a coronary artery supplying > 10 % of the myocardium. Outcome up to one year post PCI was investigated for the IR and CR-groups.

Statistical methods

Parametric and non-parametric tests

Differences in proportions were examined through the use of Chi-square tests for categorical variables (paper I and III) and two-sided Fischer's exact test (paper II). Mann-Whitney U-test was used for continuous variables (paper I).

A p-value < 0.005 was considered significant.

Logistic regression

To examine factors associated with the occurrence of symptoms and readmissions in Paper I we calculated odds ratios (OR) with 95 % confidence intervals (CI) using logistic regression analyses, adjusting for patient level baseline factors known to influence symptoms and prognosis: age, gender, previous myocardial infarction, smoker at baseline, on sick-leave at admission, previous cardiac surgery, history of heart failure, diabetes, infarction classified as a ST- segment elevation myocardial infarction (STEMI), PCI during hospital stay, EF below 40 % at discharge and year of enrollment.

In paper II, the probability of reaching the treatment target of LDL-C 2.5 mmol/L was assessed, for patients with LDL-C above target at the previous visit, using a logistic regression model. As explanatory variables, the models included gender, age, diabetes, previous myocardial infarction, stroke, previous revascularization, hypertension, statin treatment before admission, smoking status, year of AMI, treated and untreated LDL-C (linear term), and statin treatment before follow-up visit.

Propensity score and Cox regression

In randomized trials comparing treatments, the allocation to treatment group will not be confounded by neither measured nor unmeasured confounders, whereas in observational studies, treatment selection is influenced by characteristics, measured or unmeasured, of the subjects. The propensity score is a balancing score that can be used in observational studies to try to compensate for the imbalance in observed baseline covariates. The propensity score is the probability of treatment assignment conditional on observed baseline characteristics¹³⁵. By including it in the analyses the distribution of observed baseline covariates is made more similar between treatment groups. The basic assumption for the method is that there are no unmeasured confounders that influence treatment assignment and outcome. Logistic regression is the most commonly used method for estimating the propensity score.

Cox regression compares the incidence (hazard) rate: number of new cases of disease, or mortality rate, per population at-risk per unit time. It has the basic assumption that the hazard ratio is constant over time. A propensity score was estimated and included in an adjusted Cox regression model in order to estimate the endpoints in the two treatment groups in Paper IV: patients with incomplete vs. patients with complete revascularization.

Ethical considerations

The fact that information is gathered in national quality registries might be perceived as a violation of personal integrity for participating patients. Ef-

forts have been made to reduce this risk. All patients are informed of their participation in the SWEDEHEART-registry and have the right to decline participation, in which case their information will be erased from the registry. As the database is compiled for research use, data is encoded and personal identification numbers are not used. The large number of participating patients makes it unlikely that any individual can be identified based on for example age or gender.

Studies I, II and IV were approved by the regional ethics committee in Uppsala and study III was approved by the regional ethics committee in Linköping.

Summary of Results

Paper I

Baseline characteristics for the study population are shown in table 2. Non-SEPHIA-patients are included in the table for comparison of baseline characteristics; revealing similar age- and gender distribution but more heart disease in their medical history compared to the study population.

There were some gender differences seen in this study regarding the use of pharmacological treatments post AMI. Women used less ACE-inhibitors but more ARB than men at 12 months post infarction (47.3 % vs 58.0 %, $p < 0.001$ for ACE-inhibitors, 28.6 % vs. 22.5 %, $p < 0.001$ for ARB, in women and men). There were also small but statistically significant gender differences in the use of ASA, other antiplatelet drugs (clopidogrel, ticagrelor or prasugrel), statins, and beta-blockers.

Gender differences were also seen in target achievement rates for important risk factors: LDL-cholesterol < 1.8 mmol/L or reduction by < 50 % was reached by 24.4 % (25.1 % vs 22.4 %, $p < 0.001$, for men and women). Blood pressure control (< 140 mmHg systolic) was reached by 66.4 % of men vs. 61.9 % of women, $p < 0.001$.

The overall long-term use of secondary prevention medication showed small increases during the study period. Blood pressure control increased over time (59.1% vs. 69.5 %, $p < 0.001$ in 2005 and 2012 cohorts) but there was no improvement in lipid control seen during the study period (26.9 % vs. 28.0 %, $p = 0.44$ in 2005 and 2012 cohorts).

Smoking cessation rate one year post AMI was 55.6 % without any difference between genders or over time. More women participated in exercise training programs within cardiac rehabilitation (42.8 % vs. 40.1 %, $p = 0.001$). An increase in participation rate was seen from 2005 to 2013. (Figure 7)

Readmissions due to heart disease occurred in 18.2 % of women and 15.5 % of men and decreased over the study period (20.8 % to 14.9 %). After adjustment for a number of covariates, OR was 1.22 (95 % CI 1.14-1.32) for women vs. men and 0.94 (95 % CI 0.92-0.96) for the 2012 vs. the 2005 cohort.

Fewer women than men reported absence of angina at both follow ups, 79.1 % of women compared to 84.9 % of men were in CCS-class 0 at the one year follow up (unadjusted OR 0.67, 95 % CI 0.64-0.71). After adjustment the OR for absence of angina remained significantly lower for women (0.63, 95 % CI 0.59-0.68).

Table 2. Baseline characteristics. *AMI-cases from the same time period and the same age range, surviving to discharge but not included in the SEPHIA-registry. §Only patients from the same hospitals as the 2005-cohort. †At admission. ‡LVEF, Left ventricular ejection fraction before discharge

	Non- SEPHIA *	SEPHIA- patients total	Men	Women	2005-cohort	2012- cohort §
Number of patients	37457	51620	38249	13371	2615	3387
Median age (IQR)	64(57-69)	63 (57-69)	63 (56-68)	65 (58-70)	63(57-69)	64(57-69)
Women (%)	27.6	25.9	-	-	26.8	26.3
Hypertension (%)	42.7	41.8	39.9	47.0	39.2	42.0
Mean syst BP (mmHg)†	147.1	149.4	149.2	149.7	149.0	150.0
Mean LDL (mmol/L)†	3.11	3.21	3.19	3.23	3.08	3.25
Smokers (%)	31.8	30.9	29.6	34.9	31.3	29.6
Diabetes (%)	23.9	20.1	19.6	21.5	19.8	20.3
History of MI (%)	17.7	14.7	15.6	11.9	16.7	16.7
History of PCI (%)	10.8	10.4	11.3	7.9	10.1	14.2
STEMI (%)	37.5	39.8	41.2	35.7	42.2	36.3
PCI during hospital stay (%)	63.4	76.2	79.5	66.8	67.0	78.4
LVEF‡ < 40% (%)	17.8	15.0	15.5	14.1	17.9	13.5
Discharge medication:						
Aspirin	93.4	95.9	96.9	95.3	94.4	96.6
ACE-inhibitor	59.8	61.4	66.9	60.0	55.3	67.4
ARB	13.4	12.3	13.3	16.1	10.4	16.3
Beta blocker	89.6	92.1	92.2	91.1	90.7	91.5
Clopidogrel/prasugrel/ ticagrelor	78.6	88.0	88.3	87.0	80.4	89.3
Statin	89.8	94.6	96.6	94.1	91.5	96.2

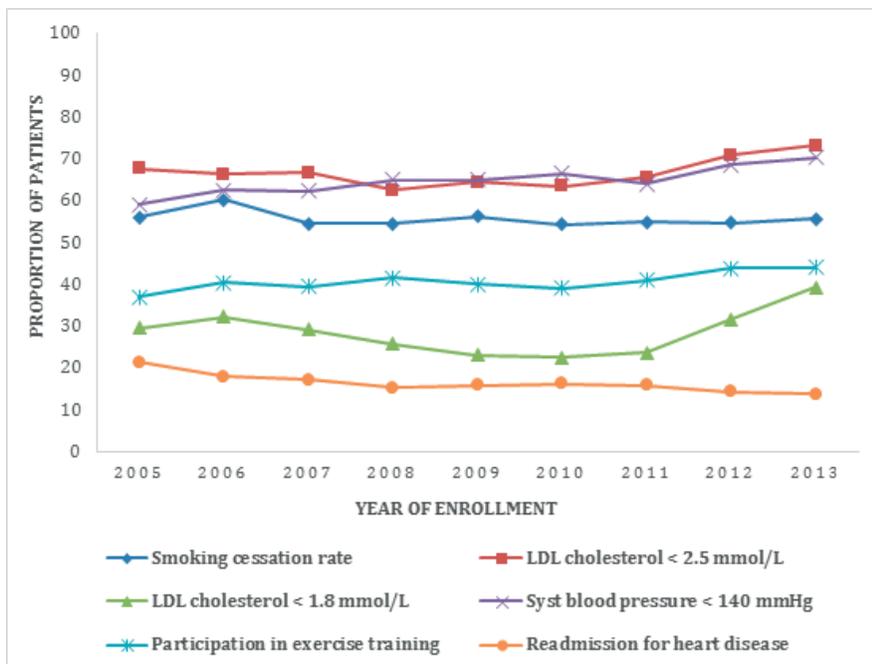


Figure 7. Target achievement one year post AMI per year of enrollment

Paper II

In paper II we demonstrated that statin treatment has become standard for all patients with AMI, with more than 90 % of patients receiving statins at discharge.

Simvastatin ≤ 40 mg was used by 80 % of patients at discharge and at two months post AMI, and 68 % at one year post AMI. Intensive statin therapy (LDL-C lowering capacity > 40 %) was prescribed for 8.4 %, 11.9 % and 12.2 % at these time points. Combinations of statin/ezetimibe were quite unusual; they were prescribed for 1.1 % at discharge, 2.8 % at two months and 5.0 % at one year post AMI. The most frequent drug in the intensive statin therapy group was 80 mg atorvastatin at discharge and after two months (3.9 % and 4.7 %) and atorvastatin 40 mg after one year (4.0 %).

Target LDL-C, defined as <2.5 mmol/L, was achieved in 74.5 % of all patients at two months post AMI and by 72.3 % at one year. Patients with diabetes had better lipid control rates: 79.1 % and 79.5 % vs. 73.4 % and 70.6 % at two and twelve months post AMI ($p < 0.001$ for both time points). Lipid control rates were lower in women at follow up. (Figures 8-9).

Treatment was intensified (i.e. increased dose or switch to a more potent drug) for 21.3 % of patients with LDL-C above recommended level at the first follow up, and for 12.0 % of such patients at the second follow up.

At the two month follow up, patients with diabetes were more likely to reach the target, whereas previous statin treatment, higher LDL-C at admission (both treated and untreated values), smoking at admission and history of MI were factors correlating to increased risk of not reaching treatment target. At the one year follow up, higher LDL-C at admission (both treated and untreated values) and higher LDL-C at two months post AMI were associated with increased risk of not reaching treatment target.

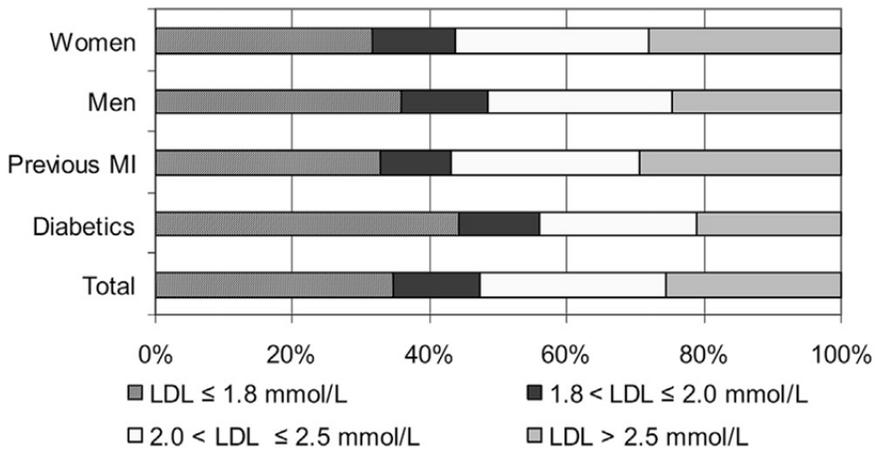


Figure 8. Frequency of LDL-C-levels 2 months after AMI in different groups. MI, myocardial infarction.

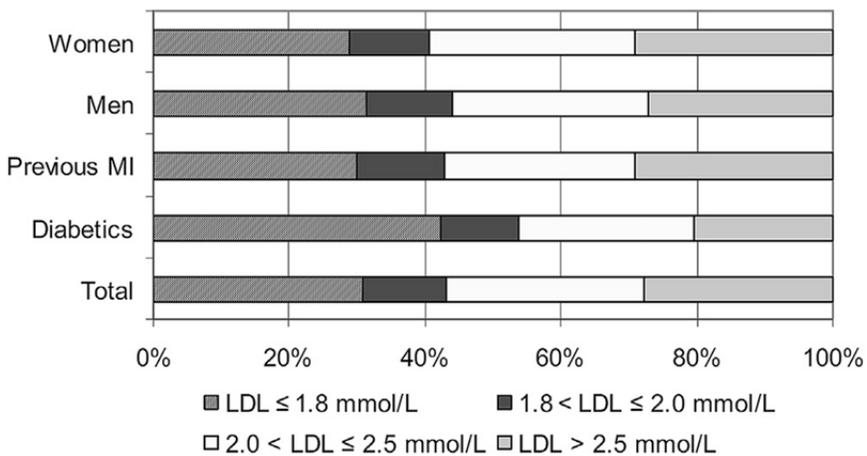


Figure 9. Frequency of LDL-C-levels 1 year after AMI in different groups.

Paper III

In total, 1,800 questionnaires, representing 10 % of the annual Swedish PCI-population, were sent to the participating hospitals. 1598 were handed out by nurses within the time frame of the study and 1073 replies were received (67 %) One quarter of the respondents were women, mean age was 66 (34-89 years). 55 % of patients were in the age group 60-74 years.

Most patients (83%) had undergone PCI due to an acute coronary syndrome. After PCI, 28% still had chest pain complaints and in one in ten patients this resulted in limitations in their activities of daily living.

When asked what might have caused their cardiac condition, patients chose non-modifiable risk factors (heredity and age) more frequently than the modifiable factors smoking, lack of physical activity and inappropriate food habits (Table 3). Among the younger patients (<60) stress, fatigue and depression rated high as a possible cause.

Barely one in five patients believed that they still had a cardiovascular disorder and that they should consider lifestyle modification.

The use of tobacco (mainly cigarette smoking) before undergoing PCI was three times more common than in the general Swedish population (39%). After PCI, this diminished to 16%, still above the national level. The majority of smokers failed to be referred to a smoking cessation program. When comparing patients who believed that they had been cured with those who understood that CAD is a chronic illness, there was a tendency to greater tobacco cessation in the latter group (61 vs. 49%, $p=0.05$).

The majority were invited to participate in exercise training programs. Participation was more common among younger patients: 58% among patients up to 60 years of age, 60% among patients in the age group 60-74 years, respectively, and 39% among the elderly participated. However, fewer than 50% attained the recommended levels (150 minutes per week) of daily physical activity

Three-quarters of the patients received nutritional counseling, commonly through an educational meeting with a dietician. After that, 40% decided to change and improve food habits (Table 4). Almost half (45%) did not consume fruit and vegetables daily as recommended in the prevention guidelines. There was a highly significant difference (53 vs. 25%, $p<0,001$) in adopting healthier food habits among those who were recommended to change diet as compared to those who perceived that no behavioral changes were needed.

Table 3. Patients' responses to causes of the disease

Causes of CVD	All	Female	Male	Age <60	Age 61-74	Age >75
Heredity	52	59	50*	64	52	33
Stress, fatigue, depression	45	46	45	65	43	19
Ageing	41	34	43**	15	44	69
Poor food habits	31	21	35***	43	33	15
Use of tobacco	25	29	24	34	28	8
Physical inactivity	22	21	23	39	20	8
Other	11	12	9	17	9	8

Difference between females and males: *p<0.05, **p<0.01, ***p<0.001

Table 4. Rates of participation in cardiac rehabilitation programs and lifestyle changes

Physical activity	All	Female	Male	<60 yr	61-74 yr	>75 yr
Invited to training program	78	77	79	84	83	63
Participation ongoing/planned	43	47	42	58	60	39
Physically active	47	43	48	49	49	45
Food Habits						
Received nutritional counselling	71	68	73	77	70	59
Changed food habits	40	35	42*	51	41	22
Tobacco						
Used tobacco before PCI	38	37	39	45	41	16
Still using tobacco	16	14	20*	20	20	10
Invited to cessation program	17	20	18	35	18	7
Stress						
Regularly stressed	21	26	20*	39	18	4
Invited to stress management program	5	7	5	12	4	0

*comparison of males vs. females: p<0.005

Paper IV

Out of the 23 342 patients included in the study, 15 165 (65 %) had incomplete revascularization (IR) at the index procedure. Patients in the IR group were older, more likely to be female, had more extensive coronary disease and more often ST-segment elevation myocardial infarction at presentation, than those with complete revascularization. IR patients were more often treated with DES. Prescription of long-acting nitroglycerin at discharge was also more common in the IR-group.

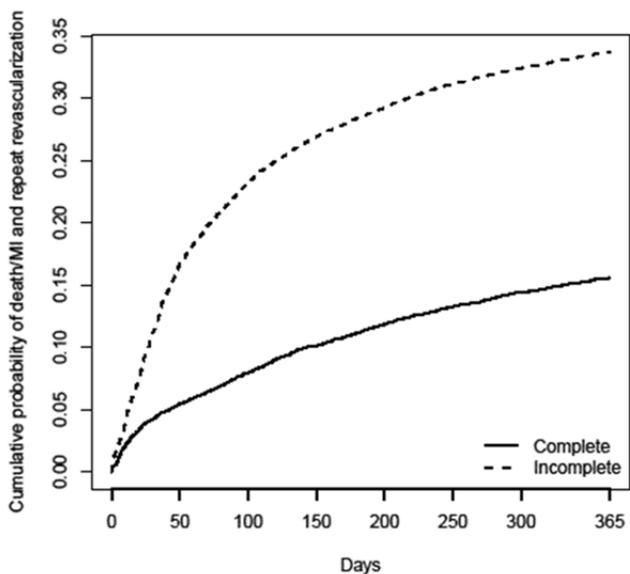
The probability of death, myocardial infarction and repeat revascularization up to one year post PCI is shown in figure 10.

Frequencies of the individual endpoints are shown in table 5. A total of 5,071 events of the primary composite endpoint (death, myocardial infarction or repeat revascularization) occurred up to one year in the IR group compared to 1,254 events in the CR group (unadjusted HR 2.48 (95 % CI [2.33-2.64], $p < 0.0001$). After multivariable adjustment including a propensity score, the difference in risk of death, myocardial infarction or repeat revascularization for the IR and CR groups remained significant; adjusted HR 2.12 (95 % CI [1.98 - 2.28], $p < 0.0001$).

When we analyzed death, with repeat revascularization as a time dependent covariate, the unadjusted HR for IR compared to CR was 2.05 (95 % CI [1.80-2.32], $p < 0.0001$). For the combined endpoint of death/myocardial infarction HR was 1.92 (95 % CI [1.77-2.09], $p < 0.0001$) for IR compared to CR. These differences remained statistically significant after adjustment, HR 1.29 (95 % CI [1.12 - 1.49], $p = 0.0005$) for death and HR 1.42 (95 % CI [1.30 - 1.56], $p < 0.0001$) for the combination of death/myocardial infarction.

A significantly higher hazard for IR compared to CR patients was consistent across all subgroups.

However, when we analyzed death up to one year only in patients surviving to discharge, the differences in HR between the IR and CR-groups did not remain in all subgroups. (Table 6).



Patients at risk								
Complete	8177	7734	7529	7349	7118	6752	6425	6003
Incomplete	15165	12670	11658	11093	10598	9941	9427	8797

Figure 10. Kaplan-Meier graph of the probability of death, myocardial infarction and repeat revascularization up to one year of follow up for patients with complete vs. incomplete revascularization

Table 5. Events during one year of follow up

	Incomplete revascularization	Complete revascularization	All
Events during 1 year of follow-up n (%)	N=15,165	N=8,177	N=23,342
Death	1,080 (7.1)	307 (3.8)	1,387 (5.9)
Revascularization PCI*	3,107 (20.5)	698 (8.5)	3,805 (16.3)
Revascularization CABG †	594 (3.9)	108 (1.3)	702 (3.0)
Revascularization total	3,580 (23.6)	763 (9.3)	4,343 (18.6)
Myocardial Infarction	1,570 (10.4)	492 (6.0)	2,062 (8.8)
Combined outcome of death/MI‡	2,470 (16.3)	754 (9.2)	3,224 (13.8)
Combined outcome of death/MI‡/revascularization	5,071 (33.4)	1,254 (15.3)	6,325 (27.1)

*percutaneous coronary intervention, †coronary artery by-pass grafting, ‡myocardial infarction

Table 6. Unadjusted and adjusted hazard ratio for death with one year of follow up. Repeat revascularization is analyzed as a time dependent covariate. Only patients surviving to discharge are included (N=22771).

	Hazard Ratio (95% CI)			
	Unadjusted	P-value	Adjusted	P-value
All patients	1.77 (1.52; 2.06)	<.0001	1.24 (1.05; 1.48)	0.0127
STEMI*	1.41 (1.08; 1.84)	0.0116	1.06 (0.80; 1.41)	0.6867
NSTE-ACS†	1.91 (1.54; 2.37)	<.0001	1.38 (1.08; 1.76)	0.0112
Stable CAD‡	1.63 (1.07; 2.48)	0.0217	1.27 (0.79; 2.03)	0.3296
Diabetes	1.68 (1.28; 2.19)	0.0002	1.40 (1.03; 1.90)	0.0331
Nitroglycerin treatment	1.66 (1.22; 2.27)	0.0013	1.04 (0.73; 1.49)	0.8297
Previous MI§ and/or PCI ¶	1.67 (1.28; 2.17)	0.0002	0.94 (0.70; 1.27)	0.6885
DES# (any)	1.49 (1.11; 1.98)	0.0070	1.03 (0.75; 1.43)	0.8463
BMS** (only)	1.74 (1.44; 2.10)	<.0001	1.30 (1.05; 1.60)	0.0152

*ST-elevation myocardial infarction, †non-ST-elevation acute coronary syndrome, ‡coronary artery disease, § myocardial infarction, ¶ percutaneous coronary intervention, #drug eluting stent, **bare metal stent

Discussion

Study design and methodological consideration

The papers I, II and IV are observational studies based on registries with prospectively collected data. They collected patients from within the SWEDEHEART-registry from overlapping time periods. Three quarters of the SWEDEHEART /SEPHIA-patients had undergone PCI for myocardial infarctions and conversely 80 % of SWEDEHEART/SCAAR patients in paper IV had acute coronary syndrome as qualifying event. The patients in paper III had also undergone PCI, 80 % of them for acute coronary syndromes. In many cases the study populations overlap, but there are also important differences regarding age and indication which is a reason for caution in making direct comparisons.

The SWEDEHEART/SEPHIA-registry is to our knowledge one of few registries to publish data on long term fulfilment rate of secondary prevention targets as well as patient reported outcome from such a large proportion of the AMI-population in one country. Nonetheless, an outpatient registry collecting data from follow-up visits will necessarily introduce some selection bias, since death or disabling disease such as stroke will prevent patients from participating.

Measurements of LDL-cholesterol and blood pressure was not mandatory in SWEDEHEART/SEPHIA until 2013, resulting in missing data for these variables, about 25 % for LDL-cholesterol and 15 % for blood pressure in Paper I. We cannot exclude the possibility that patients with complicated disease or risk of low adherence to medication were more likely to complete these measurements, which would perhaps underestimate the risk factor control rate. It might however also reflect routines at each center and not be due to patient characteristics. This missingness will prohibit the use of the registry for local quality assessment and one could argue that we should have regarded the missing data as “not at target”. We did not use any techniques for imputation of data, since the main objective was to describe current guideline adherence and risk factor control in paper I. In Paper IV there were 8 % missing data for the variable “time of day”, which was used as a covariate for the adjusted analyses, but a sensitivity analysis revealed that it did not influence the primary outcome. In paper III there was no log of included patients, therefore we could not perform analyses of non-respondents.

The reply rate of almost 70 % was however high, and the fact that the questionnaires were strictly anonymous may have contributed to this.

The accurateness of SWEDEHEART-data has previously been investigated for RIKS-HIA, revealing 93-97 % agreement with patient records. The system is also to some extent designed to avoid misclassifications, for example as definitions of the variables show on the screen as data is entered. It is however likely that there is some variability for example in how the significance of a coronary stenosis is classified. The use of FFR measurement as an additional method to evaluate which stenoses were functionally significant, as opposed to relying on anatomical estimation, was used in only a minority of patients. Increased use of FFR measurement in stable and non-STEMI ACS-patients has the potential to re-classify patients regarding number of diseased vessels and has been shown to improve outcome¹³⁶.

We encountered some inconsistencies when examining prescription and drug purchase patterns in the Swedish Prescribed Drug Register, for example varying time intervals between drug purchases. This may reflect varying patient level adherence, but might also be influenced by the 12 month time period for subsidization of prescribed drugs to patients in Sweden, which determines patients cost for the individual purchase. The 6 month run in period used to determine on-going treatment was chosen to allow for these variations.

Cholesterol was measured in Paper I and II at each center using various commercially available analysis tools, allowing for variations in reported cholesterol levels. This however also reflects real life practice.

Confounding by indication, i.e. treatments being chosen based on the characteristics of the patient, is an important problem in non-randomized studies comparing the effectiveness of different treatments as in Paper IV. We used propensity score methodology to try to reduce the effect of this. We also did propensity score matching as a sensitivity analysis, which gave similar results.

Findings

Pharmacological treatment

In Paper I we found that the use of drugs for secondary prevention one year after an AMI was high with over 90 % of the patients using ASA and statins and 85 % using beta blockers. This was higher compared to registry-data from Belgium and UK, in which 78-82 % used ASA and 61-64 % used statins 6 months after AMI⁷⁷. The use of ASA, statins and beta blockers in our study were comparable to those found in the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation trial (COURAGE)¹³⁷, in which optimal medical treatment was compared to a combination of optimal

medical treatment and PCI for stable coronary artery disease. Prescription at discharge of long term preventive treatment was similar in the SEPHIA-cohort in Paper I and the SCAAR cohort in Paper IV, in the latter with only small and non-consistent differences between the two studied treatment groups.

The majority of patients in Paper II were treated with moderate-dose simvastatin, which was well in accordance with the Swedish guidelines that were valid during the study period as a first line treatment. However, for the majority of patients, this was not followed by a "treat-to-target" strategy with titration of treatment in case LDL-C remained above the guideline-defined target of 2.5 mmol/L. The "treat-to-target", strategy has not been specifically evaluated in any major prospective randomized controlled trial for AMI-patients, compared to a strategy of a fixed dose of 20 or 40 mg of simvastatin, a fact which is reflected in the recent U.S. guidelines for cholesterol treatment⁴³. An observational study has suggested that adherence might be better with a "treat-to-target" strategy compared to a "fire-and-forget" strategy without repeated measuring of LDL-C¹³⁸. This study however could not discriminate between the effect of repeated measuring, which in itself might increase motivation for patients, and effect of the titration.

Intensive lipid lowering therapy, defined as statins with a LDL-C-lowering capacity of more than 40 %, or combination therapy with ezetimibe, was used in only 9.5 % of patients at discharge, which is considerably lower compared with data from the U.S. Get With The Guidelines database where 38.3 % of patients were discharged with intensive lipid lowering therapy¹³⁹, and not in accordance with the latest European or U.S. guidelines^{43, 45}.

Risk factors

Paper I revealed that risk factor control regarding blood pressure, cholesterol levels, and smoking habits during the first year after AMI was suboptimal in relation to what is recommended in practice guidelines. Improvements in target achievement rates over the study period were seen mainly for blood pressure control, whereas smoking cessation at one year remained at just over 50 %. The results still compared favorably to a European multi-centre -survey conducted in 2006-2007 in which blood pressure target (defined as < 140/90 mmHg or <130/85 mmHg for patients with diabetes) was reached by 44 %, cholesterol target (defined as total cholesterol < 4.5 mmol/L) was reached by 49 % and 17 % were smokers⁹⁶. The lipid control in our studies were in fact comparable to the aggressive treatment arm of a study, where patients managed at dedicated research centers focusing on treating hyperlipidemia with atorvastatin were compared to patients treated in usual care¹⁴⁰.

The patients' causal attributions of modifiable risk factors revealed in Paper III differed from the risk factor profiles, more pronounced than the findings in a previous smaller study¹⁴¹. Smoking, lack of physical activity and food habits were regarded as important causes of the disease by up to a third of the patients, in contrast to the fact that 38 % were tobacco users at the time of the PCI. At follow up around 2 months after PCI, less than half of patients were attaining targets for healthy food habits and physical activity.

This is in line with the findings of a large sub study of a randomized trial, where patients reported adherence to diet, physical activity and smoking cessation 30 days after a NSTEMI. One third of patients reported adherence to diet and exercise, and this was associated with a lower risk for recurrent cardiovascular events by 6 months¹⁴².

Participation in cardiac rehabilitation

Participation in exercise training programs remained below 50 % at one-year post AMI during the study period, despite robust recommendations for this in national and international guidelines. Other studies have reported referral rates similar to this¹⁴³, as well as participation rates in general cardiac rehabilitation programs after PCI¹⁴⁴ and MI¹⁴⁵ whereas current reports of overall uptake to exercise training post AMI are scarce.

A majority of the PCI-patients responding to the questionnaire in Paper III was invited to physical training, but only 43 % reported that participation was ongoing or planned. It was more common for younger patients to participate. We did not investigate reasons for non-participation in this study.

Gender differences

Paper I revealed small but statistically significant differences between men and women in the use of ASA and statins at one year. The reason for this is unclear since this treatment is recommended for all patients after a myocardial infarction. One possible explanation could be more drug side effects being experienced by women as has previously been described¹⁴⁶. The differences in the use of ACE-inhibitors and angiotensin receptor blockers might also be due to the higher frequency of hypertension at baseline seen in women in our study. We also found that women were readmitted to hospital more often than men in study I, for cardiac as well as for non-cardiac conditions. Female gender has previously been associated with higher risk for readmission after PCI¹⁴⁷. A study on elderly patients' 30 day readmissions post AMI however revealed no gender difference in comorbidity adjusted HR for readmission¹⁴⁸.

Outcomes: symptoms and readmissions

The majority of patients in Paper I reported no cardiac symptoms at follow up one year after a myocardial infarction. In earlier NSTEMI/ACS-studies comparing invasive and conservative strategies, patients in the invasive arms reported less angina. In the FRagmin and Fast Revascularisation during In-Stability in Coronary artery disease Investigators (FRISC) II-trial 78 % of invasively treated patients were free from angina at the 6 month visit ¹⁴⁹. In a sub study of the DANAMI-2-trial, 81.5 % of women and 84.5 % of men treated with primary PCI reported no angina at 12 months ¹⁵⁰.

Cardiac symptoms were not captured in paper IV. However, treatment with long-acting nitroglycerin likely reflects symptoms of angina pectoris, and we did observe that long-acting nitroglycerin use was more common in the IR group. It was still much less common than in the COURAGE-trial, where around 60 % of patients used nitrates at baseline, decreasing to around 55 % at one year in the PCI-group¹³⁷.

The consumption of health care was substantial in the SWEDHEART/SEPHIA-patients in Paper I, with one third of the patients requiring rehospitalisation for cardiac or non-cardiac conditions. In the FRISC II-trial ¹⁴⁹ 31 % of patients in the invasive arm were readmitted within 6 months compared with 49 % in the conservative arm. It has previously been calculated that by 2005 60 % of admissions for coronary heart disease were readmissions, reflecting a growing prevalent pool of AMI-survivors, due to the improvement in mortality rates in the last decade ¹⁵¹, but in our study unadjusted analyses showed a lower rate of cardiac readmissions in the later compared to earlier study period.

In Paper IV we observed a high event rate associated with incomplete revascularization after PCI: 33% in the group who had incomplete revascularization and 15 % in the group who had complete revascularization experienced adverse cardiac events. This difference in outcome is consistent with two recent meta-analyses. One study investigated STEMI-patients and it demonstrated an association of multivessel PCI with improved long-term survival and reduced repeat PCI. There was however an increase in in-hospital mortality when multivessel PCI was performed during the index primary PCI-procedure, not seen with a staged procedure¹⁵². The other excluded STEMI-studies but included studies where revascularization was performed with CABG or PCI, and the authors found an association between complete revascularization and lower risk for death, myocardial infarction and repeat revascularization¹⁵³. Only a few small randomized trials have been performed. One study included 219 patients without on-going myocardial infarction and randomized patients to culprit-only PCI vs. complete revascularization and showed similar in-hospital and 1-year MACE rates¹⁵⁴, and one recent study including 465 patients with STEMI demonstrated re-

duced risk of cardiovascular events with complete revascularization in the same setting¹⁵⁵.

Strengths and limitations

The main strengths in our studies are the sizes of the SWEDEHEART-cohorts used in Papers I, II and IV, and the fact that data is collected prospectively in the setting of routine health care, which contributes to the generalizability of the results. The SWEDEHEART/SCAAR-registry includes every patients treated with PCI in Sweden. The SWEDEHEART/SEPHIA-registry has a lower degree of coverage but is to our knowledge one of the largest cohorts of post AMI-patients that have been followed for one year with interviews and measurements.

The questionnaire developed for Paper III was developed in collaboration between several professions and members of the patients' association, ensuring that different perspectives were considered.

Linkage to the Swedish health data registries gave access to reliable and complete data on prescribed drugs, medical history and outcome in Papers II and IV.

There are some limitations: first, the issue of unmeasured confounders must always be considered when interpreting results of non-randomized studies comparing treatments, as in Paper IV. Since there are no clear guideline recommendations, the decision to perform complete rather than more limited revascularization was likely based on the patient's characteristics and preferences, together with the knowledge and experience of the operator, the appearance of the coronary vessels and the technical complexity of the lesions. All of these details cannot be completely captured in this registry despite taking many other potentially confounding variables into account. Second, the SWEDEHEART-registry does not capture data on socioeconomic circumstances, which are known to influence treatment and outcome¹⁵⁶. Third, Paper I and II only included data on long-term treatment for patients under the age of 75, despite the fact that the proportion of elderly is increasing in the community, which limits the generalizability. Fourth, data regarding medical history, drug treatment and readmissions were only captured in the SWEDEHEART-registry and not validated against the Swedish health data registries in papers I and II, which may have introduced some misclassifications.

Implications

Are quality registries useful for quality improvement and research?

Quality registries have been recognized as a potentially powerful tool for monitoring of delivered care at a national and local level, for quality improvement and for research. Regarding quality improvement, it has however been suggested that neither the registration in itself, feedback loops to users nor public reporting of results is sufficient to achieve change. The context in which it is used and the appreciation of registered data as being accurate and important by stakeholders are also necessary factors. Successful quality improvement effort using quality registries have been reported^{157 158}. In the SWEDEHEART/SEPHIA-registry we however demonstrated a very slow rate of improvement in Paper I from 2005 to 2013. There might be several possible reasons for this. One of them might be that the registered nurses who are responsible for registering data in the registry have too little influence on decision making regarding routines and standard practices that would need to change in order to achieve better results. Eldh et al found that quality improvement was initiated by people acting on the output data, which requires both knowledge about how to interpret the data and how to perform quality improvement, together with a context that allows and encourages this action.¹¹²

The issue of limited resources may also play a role for the use of expensive but efficient pharmacological treatment. The fact that the target achievement rate for lipids seems to be improving in 2012 and 2013¹⁵⁹ coincides with the availability of generic atorvastatin from 2011 in Sweden, might reflect this. No such tendency could be seen in lipid control in Paper II which included patients in the period from 2005 to 2009, before generic atorvastatin was available.

Is the optimal medical treatment still sub-optimal?

The COURAGE trial demonstrated that optimal medical therapy is a safe alternative to PCI in patients with stable coronary artery disease who do not have severe angina or severe ischemia on stress testing, or stenosis of the left main coronary artery. The participants received “optimal medical treatment” which was not much different compared to what we found in paper I. Still there was a residual risk, which was greater for patients with higher number of stenotic vessels and low ejection fraction¹⁶⁰. Paper II revealed potential for improvement regarding titration of lipid lowering treatment post AMI in Sweden. Further studies are needed to investigate whether this is true also for blood pressure control.

Should risk factor targets differ between men and women?

There are some fundamental differences between genders in incidence and mortality in coronary artery disease. Knowledge about the reasons for this is evolving but still many questions are unsolved. The early epidemiological studies investigated only men, but knowledge about the risk factors for coronary artery disease in women has grown. Some risk factors seem to be particularly grave for women, such as diabetes, hypertension and smoking¹⁵. Studies of risk factors and their association with disease must also take into account the cultural and political context in different populations, since for example the proportion of women who are smokers, varies greatly between different societies¹⁵.

Practice guidelines in most cases recommend the same treatment for men and women. A previous observational study investigating guideline adherence in in-hospital coronary care, concluded that women receive slightly less treatment than men regarding invasive procedures and prescription of drugs at discharge¹²². The authors found similar one year mortality rates for men and women, whereas age-standardized case fatality for all cases of myocardial infarction in Sweden is slightly lower for women³. This leads to the question whether prevention and/or treatment recommendations should in fact be different for men and women, and if intensified prevention and treatment for men could reduce the inequalities seen in incidence of CAD and overall mortality, which will require further studies.

What we know and what we see

Despite the fact that we know that coronary artery disease is a manifestation of a systemic predisposition for atherosclerosis, a knowledge that is based on genetic, molecular, microscopic, clinical and epidemiological research, the visualization of the disease on an ECG or a coronary angiography can be very powerful in convincing the mind that the problem lies within small segments of the coronary artery tree. In the short perspective, it does, but for long-term results and for prevention it is necessary to maintain the systemic perspective.

Paper III revealed important differences in the knowledge and attitudes that we as health care workers want to convey to the patients, and their views regarding the nature, causes and suitable preventive measures for coronary artery disease. A minority of the PCI-patients in paper III seemed to have perceived that CAD is a chronic disease that cannot be cured by a coronary intervention alone. An overconfidence in the curative role of PCI as has also been reported recently by Lee et al⁹⁹. In a review by Young et al containing 10 smaller studies a misalignment was found between the patients' and health professionals' perception of the information¹⁶¹.

In a recent study that found that illness perceptions and causal attributions were associated with attendance at cardiac rehabilitation, the authors suggested that early screening of perceived causal factors (both modifiable and non-modifiable) may help to identify appropriate individuals for targeted intervention ¹⁰¹.

The Health Belief Model ¹⁶², developed in the context of behavioral science, is aimed at explaining individuals' preparedness to change health behavior. According to this model, for behavioral change to occur, it is necessary that the patient understands and accepts that CAD is a severe disease to which he or she is particularly vulnerable, perceives that personal health benefits are possible through behavioral change, that the barriers can be overcome by his or her own efforts, that there is a "trigger" to start acting, and that the patient feels assured of his or her own competence ¹⁶³. Consideration of these factors may improve health education after coronary events.

How can treatment and long-term outcome of coronary artery disease be improved?

Maintaining life style changes, participating in cardiac rehabilitation programs and adhering to prescribed medication after a myocardial infarction is challenging for many patients and this can only in part be influenced by health care workers. This means that patients also have to view the elements of long term treatment and life style changes as accurate and important.

The very high rate of adverse cardiac events seen within the first year after PCI in multivessel disease in paper IV, together with the high readmission rate seen in Paper I, reveals that the problem requires a long-term approach and is in many cases not solved with invasive treatment.

Through more effective health education models, the patients could become more willing to adopt healthy life-style changes. Through effective quality improvement efforts, guideline adherence for secondary prevention could be improved. Whether a change in treatment strategy for patients with multivessel disease could potentially improve outcome will require further studies.

Conclusions

- The data from a national quality registry of long term treatment after myocardial infarction, SWEDEHEART/SEPHIA, compared favorably to previous studies of risk factor target attainment after myocardial infarction. However, a remaining preventive potential was revealed by shortcomings in uptake to cardiac rehabilitation programs, life style changes and effective pharmacological treatment. Improvements over the study period were only seen for some risk factors, and strategies should be developed to provide high quality of care for all aspects of the prevention of recurrent disease.
- Statin treatment after AMI in Sweden has become standard, but titration to reach recommended LDL-C levels is still suboptimal. Strategies to further improve implementation of guidelines are needed.
- The SPICI study showed that PCI-patients often regarded non-modifiable factors as causal for their coronary artery disease and PCI as a curative treatment. There is a need for an in-depth revision of cardiac rehabilitation in order to improve patients' understanding of the disease and to support lifestyle changes.
- For patients with multivessel disease undergoing PCI, incomplete revascularization achieved at the time of hospital discharge was associated with high risk of death, repeat revascularization or myocardial infarction in the first year. Further studies need to investigate whether complete revascularization will improve outcome for patients with multivessel disease treated with PCI.

Future research

There are some remaining questions regarding the studies included in this thesis: the high readmission rate found in Paper I should be further explored as to the precise diagnoses and timing of these events. The relationship between statin treatment and LDL-levels should be re-investigated in the light of patent releases for high intensity statins and new guidelines for treatment. Data in Paper IV should be supplemented with data regarding long term medical treatment, target achievements and patient reported outcomes for the subset of SCAAR-patients who are also enrolled in SEPHIA.

Invasive and pharmacological treatment for coronary artery disease is continuously evolving and improving. Further studies are needed to investigate the importance of the different elements of cardiac rehabilitation and post infarct care in the light of modern acute phase treatment. Examples are training programs, diet, level of physical activity, and their relative contributions to improved outcome. New methods for facilitation of behavioral change also need to be explored, such as electronic reminder and feed-back systems, on-body bio-feedback systems and more effective health education methods. The issue of complete vs. incomplete revascularization should be investigated in a randomized trial, preferably with adjunctive methods for determining the significance of the stenoses, such as FFR.

Svensk sammanfattning

Kateterburen behandling och långtidsbehandling av kranskärslssjukdom

Kranskärslssjukdom är den vanligaste dödsorsaken i Sverige, även om både antalet inträffade fall och dödligheten har minskat de senaste decennierna. I många delar av världen ökar dock kranskärslssjukdom och utgör också globalt den vanligaste dödsorsaken. Riskfaktorer är förhöjda blodfetter, rökning, högt blodtryck, diabetes, bukfetma, psykosociala faktorer, ohälsosamma matvanor och fysisk inaktivitet. Dessa riskfaktorer är möjliga att påverka och sjukdomen kan därför till stora delar förebyggas.

Kranskärslssjukdom orsakas av inlagringar i kärlväggen i hjärtats kranskärl. Kärlförändringarna kan leda till kärlkramp, som ger övergående symtom oftast vid fysisk ansträngning, eller hjärtinfarkt, som ger mer ihållande symtom och oftast orsakas av att det också har bildats en blodpropp i kärlet som hindrar blodflödet.

Om man har drabbats av kranskärslssjukdom finns det effektiv behandling både i akutskedet och på lång sikt, som minskar risken för allvarlig utveckling av sjukdomen. Behandlingen innefattar ofta ingrepp i kranskärlen med antingen by-passoperation eller, vilket är mer vanligt, med kateterburna ingrepp, så kallad ballongvidgning. Det är allvarligare att ha förträngningar i flera kärl samtidigt. Man kan i sådana fall antingen behandla alla förträngningar, eller välja ut de som man tror ger mest besvär. Tidigare forskning har inte entydigt visat vilken av dessa strategier som är bäst.

Efterbehandling innefattar läkemedel och livsstilsförändringar vilket påverkar riskfaktorerna och förebygger nya hjärthändelser. De rekommenderade behandlingarna är effektiva när det gäller att förebygga nya insjuknanden och död, men tidigare studier har visat en viss underbehandling.

Nationella kvalitetsregister används i Sverige för att kontrollera hur väl man följer de behandlingsriktlinjer som är utarbetade baserat på tidigare forskning. Kvalitetsregistren kan också användas för forskning. De svenska hälsodataregistren, som Socialstyrelsen ansvarar för, kan sammanlänkas med kvalitetsregistren för att få data avseende läkemedel, sjukhusinläggningar och dödsfall. Det har tidigare inte funnits något kvalitetsregister för långtidsbehandling och uppföljning efter hjärtinfarkt.

Syftet med den här avhandlingen var att undersöka olika aspekter av vård för kranskärlssjukdom i Sverige både när det gäller kateterburen behandling och långtidsbehandling för att förebygga nya hjärthändelser.

Avhandlingen innehåller fyra delarbeten.

För att kunna genomföra det första arbetet byggde vi upp ett nationellt kvalitetsregister (SWEDEHEART/SEPHIA). Där registrerades data om långtidsbehandling av blodtryck och blodfetter under första året efter en genomgången hjärtinfarkt. Vi samlade också in data avseende andra faktorer som kan bidra till att minska risken för att drabbas av en ny hjärthändelse, såsom rökstopp och fysisk träning. I registret samlades också information om man hade behövt läggas in på sjukhus under det första året efter hjärtinfarkten, och om man hade symtom i form av kärlkramp eller andnöd.

Vi fann att resultaten av långtidsbehandling var jämförbara med tidigare internationella studier, men att det fortfarande fanns utrymme för förbättring när det gäller att nå målvärden för blodtryck, kolesterol, rökfrihet och deltagande i träningsprogram efter hjärtinfarkt. De flesta patienterna hade inga symtom i form av kärlkramp eller andnöd vid återbesöken, men det var vanligt att man behövde läggas in på sjukhus igen under det första året efter hjärtinfarkten.

I det andra arbetet undersökte vi behandlingen med blodfettssänkande läkemedel genom att använda det svenska Läkemedelsregistret och sammanlänka data med SWEDEHEART/SEPHIA för att se vilket läkemedel som förskrevs och i vilken dos, vilka nivåer av kolesterolsänkning man lyckades uppnå och om man ändrade behandlingen om man inte nådde målen.

Resultaten visade att nästan alla patienter fick kolesterolsänkande behandling med läkemedelsgruppen statiner, men att man sällan intensifierade behandlingen även om man uppmätte kolesterolvärden över målnivån i samband med återbesök.

I det tredje arbetet skapade vi ett frågeformulär som delades ut till patienter som genomgått behandling med kranskärlsröntgen och ballongvidgning av förträngningar i kranskärlen. Vi frågade efter vad patienterna trodde var orsaken till att de hade drabbats av kranskärlssjukdom, vilken information om sjukdomen de fick i samband med ingreppet och vid återbesöket, vilken information de fick om vikten av livsstilsförändringar, vilka hjärtrehabiliteringsprogram som de erbjudits att delta i, hur det såg ut med deras livsstilsfaktorer - tobaksanvändning, motion, matvanor, stress - före och efter ingreppet. De ifyllda frågeformulären skickades in anonymt.

Enkätsvaren visade att patienter som genomgått ballongvidgning oftare ansåg att sjukdomen var orsakad av faktorer som inte går att påverka, såsom ålder eller ärftliga faktorer, än den var orsakad av påverkbara faktorer som

tobaksvanor, motionsvanor eller matvanor. Fyra av tio uppfattade informationen från vårdpersonal att de var botade och att livsstilsförändringar inte behövdes. Två tredjedelar erbjöds deltagande i träningsprogram och kostinformation, men färre än hälften hade förändrat sina vanor gällande mat och motion.

I det fjärde arbetet använde vi det nationella kvalitetsregistret för kranskärlsröntgen och ballongvidgning, SWEDEHEART/SCAAR, för att studera patienter som hade förträngningar i flera kärl samtidigt och som genomgick ballongvidgning. I en del fall behandlades alla förträngningarna och i en del fall bara en eller några. Vi jämförde patienter som genomgick komplett behandling med dem som genomgick inkomplett behandling avseende risk för hjärtinfarkt, död eller nytt kranskärlsingrepp under det första året.

Vi fann att patienter med flera förträngda kärl som genomgick inkomplett behandling med ballongvidgning hade en hög risk för att drabbas av död, hjärtinfarkt eller behöva ett nytt kranskärlsingrepp under det första året efter behandlingen. Risken var lägre för patienter som genomgått komplett behandling.

Sammanfattningsvis visar avhandlingen att långtidsbehandlingen efter en hjärtinfarkt kan förbättras avseende att nå målvärden för viktiga riskfaktorer. Det kan ske genom noggrannare uppföljning, ökat deltagande i efterbehandlingsprogram och justering av mediciner. Genom att ta reda på vad patienterna själva tror om sin sjukdom kan man också bli bättre på att bättre förmedla till patienterna hur viktigt det är med en hälsosam livsstil för att förebygga ny hjärthändelser. Ytterligare studier behövs för att ta reda på om komplett behandling skulle förbättra prognosen för patienter med förträngningar i flera kärl.

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