Coronary artery disease and prognosis
Dedication
Till Axel, Folke, Elis och Anna
Coronary artery disease and prognosis
in relation to cardiovascular risk factors, interventional techniques and systemic atherosclerosis.
Abstract

Aim: To evaluate the prognosis associated with location and severity of coronary and systemic atherosclerosis in patients with coronary artery disease (CAD) in relation to risk factors and interventional techniques.

Methods: The thesis comprised six longitudinal studies based on three patient cohorts: The Swedish Coronary Angiography and Angioplasty Registry, the Västmanland Myocardial Infarction Survey, and the Thrombus Aspiration in ST-Elevation myocardial infarction in Scandinavia study, to evaluate clinical outcome relative to coronary lesion location and severity, extracoronary artery disease (ECAD), intervention techniques, and leisure-time physical inactivity (LTPI).

Results: Stent placement in the proximal left anterior descending artery (LAD) was more often associated with restenosis than was stenting in the other coronary arteries. The use of drug-eluting stents in the LAD was associated with a lower risk of restenosis and death compared to bare-metal stents. Thrombus aspiration in in the LAD during acute ST elevation myocardial infarction (MI) did not improve clinical outcome, irrespective of adjunct intervention technique. Clinical, but not subclinical, ECAD was associated with poor prognosis in patients with MI. Longitudinal extent of CAD at the time of MI was a predictor of ECAD, and coexistence of extensive CAD and ECAD was associated with particularly poor prognosis following MI. Self-reported LTPI was associated with MI and all-cause mortality independent of ECAD.

Conclusions: Drug-eluting stents, but not thrombus aspiration, improved prognosis following percutaneous coronary intervention in the proximal LAD. Self-reported LTPI, clinical ECAD, and systemic atherosclerosis defined groups with poor prognosis after MI.

Keywords: Atherosclerosis, Myocardial infarction, Coronary artery disease, Extra-cardiac artery disease, Coronary stent, Thrombus aspiration, physical inactivity, Prognosis

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The indicated Roman numerals are used throughout the text to reference these studies. Reprints were made with permission of the publishers.
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<th>Description</th>
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<tr>
<td>AMI</td>
<td>Acute myocardial infarction</td>
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<tr>
<td>BMS</td>
<td>Bare metal stent</td>
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<tr>
<td>CAD</td>
<td>Coronary artery disease</td>
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<tr>
<td>CI</td>
<td>Confidence interval</td>
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<tr>
<td>CVD</td>
<td>Cardiovascular disease</td>
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<td>DES</td>
<td>Drug eluting stent</td>
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<tr>
<td>ECAD</td>
<td>Extracoronary artery disease</td>
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<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
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<tr>
<td>GRACE</td>
<td>Global Registry of Acute Coronary Events</td>
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<tr>
<td>HR</td>
<td>Hazard ratio</td>
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<tr>
<td>HF</td>
<td>Heart failure</td>
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<tr>
<td>ICD</td>
<td>International classification of diseases</td>
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<tr>
<td>LAD</td>
<td>Left ascending artery</td>
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<tr>
<td>LCX</td>
<td>Left circumflex artery</td>
</tr>
<tr>
<td>LM</td>
<td>Left main artery</td>
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<tr>
<td>LTPI</td>
<td>Leisure time physical inactivity</td>
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<td>MI</td>
<td>Myocardial infarction</td>
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<tr>
<td>PCI</td>
<td>Percutaneous coronary intervention</td>
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<tr>
<td>RCA</td>
<td>Right coronary artery</td>
</tr>
<tr>
<td>SCAAR</td>
<td>Swedish Coronary Angiography and Angioplasty Registry</td>
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<tr>
<td>SES</td>
<td>Sullivan extent score</td>
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<tr>
<td>ST</td>
<td>Stent thrombosis</td>
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<tr>
<td>STEMI</td>
<td>ST segment elevation myocardial infarction</td>
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<tr>
<td>Abbreviation</td>
<td>Description</td>
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<td>--------------</td>
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<td>SWEDHEART</td>
<td>Swedish Web-system for Enhancement and Development of Evidence-based care in Heart Disease Evaluated According to Recommended Therapies</td>
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<tr>
<td>TA</td>
<td>Thrombus aspiration</td>
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<td>TASTE</td>
<td>Thrombus Aspiration in ST-Elevation myocardial infarction in Scandinavia</td>
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<td>VaMIS</td>
<td>Västmanland Myocardial Infarction Survey</td>
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INTRODUCTION

Background

Atherosclerosis
Atherosclerosis is a pathological process affecting arteries throughout the body, and, when manifested as cardiovascular disease, has emerged as leading cause of death globally. The term ‘atherosclerosis’ is derived from the Greek words *athere* for gruel or porridge and *sklerosis* meaning induration or hardening, describing the properties of the necrotic core and the fibrous cap in advanced atherosclerotic plaque. Although much is known about the atherosclerotic process, gaps in the knowledge remain, and there is no agreed-upon comprehensive hypothesis regarding its pathogenesis.

Pathophysiology
The American Heart Association (AHA) classifies progression of atherosclerotic plaque in six grades of lesion.(1) Lesion grading, along with primary histological findings, approximate onset time, and clinical manifestations, is presented in Table 1. The initial phases (Stages I and II) of atherosclerosis are characterized by an accumulation of lipid-rich macrophages (foam cells), smooth muscle cells, and extracellular matrix in the intima, causing focal thickening and formation of lipid rich intimal xanthoma ‘fatty streaks’ containing both intracellular and extracellular lipids. The fatty streaks may also contain T-lymphocytes indicative of inflammation. These early signs of atherosclerosis have been reported in children and adolescents.(2) At the intermediate stage (III), pathological intimal thickening is apparent, along with small pools of extracellular lipids. Calcification may be present, probably secondary to smooth muscle cell necrosis. Subsequent stages (IV and V) are characterized by an extracellular lipid core with necrosis, infiltration by macrophages, and progressive encapsulation by fibrous tissue. As the atherosclerotic lesion advances, the plaque acquires a microvasculature network (*vasa vasorum*) and calcified areas. In late-stage complicated lesions (Stage VI), the necrotic core expands and is progressively infiltrated by macrophages and inflammatory cells, while the fibrous cap shrinks. Complicated lesions are prone to plaque rupture and haemorrhage, potentially leading to
thrombus formation, further plaque progression, and acute cardiovascular events.

<table>
<thead>
<tr>
<th>I</th>
<th>Initial</th>
<th>Isolated macrophage foam cells</th>
<th>From first decade</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>Fatty streak</td>
<td>Fatty streak lesion. Mainly intracellular lipid accumulation</td>
<td>Clinically silent</td>
</tr>
<tr>
<td>III</td>
<td>Intermediate</td>
<td>Type II changes with addition of small extracellular lipid pools</td>
<td>From third decade</td>
</tr>
<tr>
<td>IV</td>
<td>Atheroma</td>
<td>Type II changes with addition of extracellular lipid core</td>
<td>Clinically silent or overt</td>
</tr>
<tr>
<td>V</td>
<td>Fibroatheroma</td>
<td>Lipid core(s) and fibrotic layer(s)</td>
<td>From forth decade</td>
</tr>
<tr>
<td>VI</td>
<td>Complicated</td>
<td>Surface defect, hematoma-hemorrhage, thrombus</td>
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</table>

Table 1. Adapted from ‘A definition of advanced types of atherosclerotic lesions and a histological classification of atherosclerosis. A report from the Committee on Vascular Lesions of the Council on Arteriosclerosis, American Heart Association.’(1)

Risk factors for atherosclerotic cardiovascular disease

For clinical reasons, it is important to distinguish non-modifiable risk factors such as age, male sex, and family history of cardiovascular disease (CVD) from modifiable risk factors like smoking, hyperlipidemia, and hypertension. Modifiable risk factors for CVD are common in the general population. In a study of Swedish men 45-79 years old, only 1% did not exhibit at least one of five important modifiable risk factors.(3) In the global INTERHEART study it was estimated that the modifiable risk factors smoking, hypertension, diabetes, waist to hip ratio, fruit/vegetable consumption, physical activity, alcohol consumption, blood apolipoproteins, and psychosocial factors accounted for more than 90 percent of the risk for an initial cardiovascular event.(4) Multiple risk factors have an additive effect on cardiovascular risk.

Physical inactivity

Physical inactivity has reached pandemic proportions and is a major risk factor for non-communicable disease. It is associated with about 9% of premature deaths globally.(5) Physical inactivity is reported to carry risks
equal to those of smoking and obesity.\(5\) The population attributable fraction associated with physical inactivity has been reported to be in the range of 6 to 22% of premature morbidity related to myocardial infarction (MI).\(5\) It has been estimated that 31% of the world’s population is physically inactive \(6\), and trends in transport and occupational environments point toward a continuing decrease in activity levels.\(7\) Recently, with emerging evidence of the high health risks associated with a sedentary lifestyle, focus has been redirected from the benefits of physical exercise to the harm related to physical inactivity.\(8\)

**Location of atherosclerosis**

Although biological and pathophysiological mechanisms underlying atherosclerosis are likely to be uniform throughout the vascular system,\(9\) the disease affects segments of the arterial tree in a disproportionate manner, and the uneven distribution and progress of atherosclerosis is not fully understood. The local hemodynamic and rheological vascular environment is an important factor, with sites of turbulent flow, such as bifurcations, being prone to atherosclerosis progression, possibly driven by the impact of shear stress on endothelial function \(10\). Some arterial beds, such as the arteries of the upper limb, are for the most part spared from atherosclerosis, while lower limb atherosclerotic lesions are relatively common. The influence of risk factors seems to vary among arterial beds and in large vs. small arteries. Smoking is the most significant modifiable risk factor for lower limb disease, especially in proximal arteries \(11\), while diabetes has a stronger association with distal lower limb disease.\(12\) Hypertension is the dominant risk factor for cerebrovascular disease \(13\), but is more strongly associated with disease in distal rather than proximal segments of the cerebral arterial tree \(14\), while smoking and hyperlipidemia show stronger associations with extra-cranial lesions.\(15, 16\)

**Coronary artery disease**

In the coronary arteries, obstructive atherosclerotic disease can be present in any of the three major epicardial vessels, the left ascending artery (LAD), left circumflex artery (LCX), and right coronary artery (RCA), as well as in the left main stem artery. The most common location for significant coronary artery disease (CAD) in patients admitted for diagnostic coronary angiography is the LAD \(17\), which is typically the largest vessel of the three main branches, supporting roughly 50% of the
myocardial mass.(18) An obstructive coronary lesion will potentially cause ischemia in the myocardium distal to the stenosis. Thus, not only the supportive burden of the diseased vessel, but also the proximal-to-distal location of the lesion is a factor determining the extent of myocardial mass at risk of ischemic stress during stable coronary disease or in jeopardy during an acute coronary event. The clinical presentation of a patient with CAD is largely determined by the focal location and severity of the coronary culprit lesion. A coronary angiogram will reveal, in addition to information of the culprit lesion location and severity, any presence of disseminated, diffuse atherosclerotic coronary disease. This collateral information is often disregarded, since its clinical implications have not been established.

**Extracoronary artery disease**

In this thesis, extra-coronary artery disease (ECAD) is defined as atherosclerotic disease in arteries outside the coronary arteries. The principal clinical manifestations of ECAD are

- Cerebrovascular disease, possibly leading to ischemic stroke or intracranial bleeding;
- Aortic disease, possibly leading to aortic dissection or obstruction;
- Renovascular disease, possibly leading to kidney dysfunction;
- Lower limb artery disease, possibly leading to claudication and critical limb ischemia.

The prognosis in ECAD is generally poor and carries approximately the same level of risk for morbidity and mortality as a diagnosis of myocardial infarction.(19) Despite this, studies have shown that medical treatment and secondary prevention measures are not as rigorously pursued in ECAD patients as in those suffering from coronary artery disease. (20)

**Multifocal atherosclerosis**

Atherosclerosis has wide ranging effects on the vascular system, but treatment is often a response to the clinical manifestations and limited to a single stenosis. Patients with significant disease in an arterial bed have a high risk of associated disease in other regions. For example, patients with significant internal carotid artery stenosis showed concurrent CAD in up to 35% of cases, while patients with clinical lower limb disease showed co-incidence of CAD as high as 50% and cerebrovascular disease up to 20%.(21)
Coronary artery disease is one of the most important local manifestations of atherosclerosis, frequently clinically manifested as acute myocardial infarction (AMI). Despite the strict definition of AMI, the event exhibits substantial heterogeneity, and the severity of coronary angiographic findings can vary considerably among patients with AMI even when the clinical presentation is similar (Figure 1).(22) Research has established covariation of CAD and ECAD (peripheral, cerebrovascular, renal, and aortic) with important prognostic implications.(20)
Figure 1. Coronary angiograms showing the left coronary arteries of two patients with acute myocardial infarction and similar clinical appearance. Panel A shows normal coronary arteries and panel B shows severe diffuse atherosclerotic disease.
Treatment of atherosclerotic disease

General principles

Risk factor intervention
All major treatment guidelines recommend that patients with manifest atherosclerotic disease practice risk factor modification by adopting a non-atherogenic lifestyle. Patients are advised to quit smoking; adhere to a diet rich in fruits and vegetables, whole grains, low-fat dairy products, skinless poultry and fish, nuts, legumes, and vegetable oils; and engage in physical exercise. (23, 24) However, ensuring patient compliance with lifestyle changes is often a challenge, and large intervention studies have failed to demonstrate a beneficial effect of focused programs.(25)

Pharmaceutical treatment
For the vast majority of patients with established atherosclerosis, lifestyle changes alone are not sufficient to minimize the risk of future cardiovascular events. Several classes of drugs have demonstrated risk attenuation in different patient groups. The most frequently recommended and used medications for cardiovascular disease prevention are those addressing hypertension (beta blockers, calcium channel blockers, angiotensin converting enzyme inhibitors), hyperlipidemia (statins, PSK9 inhibitors), and platelet aggregation (acetylsalicylic acid, P2Y12 inhibitors). More recently a new class of drugs targeting inflammation has shown a beneficial effect on prognosis after a CVD event.(26)

Treatment of ischemia
The clinical manifestations of atherosclerosis are generally due to intraluminal narrowing, resulting in the inability of the affected vessel to conduct its main task that of delivering a sufficient quantity of oxygenated blood to an organ. The symptoms of ischemia differ depending on the vessel segments affected. Treatment often involves mechanical restoration of blood flow either by endovascular dilatation or by surgical implantation of a conduit bypassing the diseased vessel.

Coronary artery disease
In addition to the general treatment of atherosclerosis by risk factor intervention and preventive therapeutics, coronary ischemia is frequently
Coronary artery disease and prognosis

Coronary artery bypass surgery
The first method developed to mechanically restore blood flow in a coronary artery was surgical implant of a conduit between the aorta and healthy coronary arteries in order to bypass a diseased vessel section. The conduits are autologous transplanted veins (typically from the calf) or arteries (typically from the inner thoracic wall). This method remains first line treatment for complex and disseminated coronary disease, especially in the presence of diabetes.(27)

Percutaneous coronary intervention
The most common revascularisation treatment for coronary artery disease is PCI. The method rapidly gained popularity after its introduction in 1977 by German radiologist Andreas Grünzig, and is now one of the most frequent in-hospital invasive treatments conducted, with more than 21,000 registered procedures in Sweden in 2016 (www.socialstyrelsen.se). The basic principle is to insert a catheter into the arterial system through the arm or the groin and to intubate the coronary artery ostium under X-ray guidance. Through the catheter, the coronary artery can be filled with a contrast dye to make the artery visible by X-ray and allow identifying the location of a coronary artery lesion. The next step is to pass the diseased vessel segment with a soft coronary wire that is used to guide tools for intracoronary treatment or diagnostics.

Methods in PCI

Balloon dilatation
The crucial technological achievement that enabled coronary intervention was the development of a semi-compliant balloon that, in a deflated state, could be advanced through the artery to the position of a stenotic lesion and inflated to dilate the lesion. In contemporary PCI, balloon dilatation is rarely the sole intervention due to a 20-30% risk of restenosis and re-occlusion within the first year.(28, 29) However, balloon dilatation is still the backbone of any standard PCI procedure both for pre-dilatation before a stenting procedure and, frequently, for post-dilatation after stenting using a high pressure non-compliant balloon to optimize stent apposition.
Stenting
The dominant technique for treatment of coronary lesions in contemporary PCI is stent placement. A coronary stent is a small metal mesh tube mounted on a deflated coronary balloon. The balloon is inserted into the coronary artery and inflated at the position of the lesion, expanding the stent to support the vessel wall and optimize the vessel lumen opening. The balloon is then deflated and withdrawn, leaving the stent in position. The introduction of stents dramatically improved short- and long-term outcomes after PCI compared to balloon angioplasty alone. (28) Stenting is often performed after pre-dilatation with an angioplasty balloon. The term ‘direct stenting’ refers to stenting without prior dilatation.

Drug eluting stents
Ordinary bare metal stents (BMS) confer a risk for in-stent restenosis of about 10-15% within the first year (28, 29) and a risk of acute re-occlusion due to stent thrombosis (ST) of about 1.1% in the first year.(30) Drug eluting stents (DES) were developed to minimize the risk of long-term stent failure. Drug eluting stents typically contain a cytostatic or cytotoxic drug bound to the stent by a polymer. The design allows the drug to be slowly eluted to the vessel wall to inhibit cell proliferation, thereby reducing the risk of in-stent intima hyperplasia and restenosis. The risk for in-stent restenosis has been markedly reduced since the introduction of the DES (31) but, in the first generation DES there was concern about possible increased risk of ST, (32) and the optimal clinical and anatomical conditions for the use of DES has been under debate.

Thrombus aspiration (TA)
An ST-elevation myocardial infarction (STEMI) is a clinical emergency most often caused by a ruptured complicated plaque (AHA lesion class VI) in the coronary arteries, with thrombus formation leading to acute vessel occlusion. Hypothetically, evacuation of intracoronary thrombus should lead to prompt reperfusion, minimizing myocardial damage. Techniques have been developed to clear the coronary artery of the thrombus as an adjunct to balloon dilatation and stenting. The most frequently used thrombectomy devices consist of a soft plastic tube inserted into the coronary artery through which thrombus can be aspirated with a syringe or pump (Figure 2). Several early small- and medium-scale studies have
demonstrated a positive effect of routine TA STEMI on infarct size and mortality. (33, 34)

Figure 2. Thrombus aspirated from a coronary artery through a thrombectomy catheter in a patient with ST-elevation myocardial infarction.
AIMS

General

The primary aim of the research reported in this thesis was to evaluate the prognosis associated with location and severity of coronary and systemic atherosclerotic pathology in patients suffering from CAD in relation to cardiovascular risk factors and intervention techniques.

We hypothesized that, in patients with CAD, coronary and extracoronary dissemination and location of atherosclerosis would influence prognosis, and that this association could be altered by specific intervention techniques and consideration of risk factors.

Aims of Studies

I. To evaluate prognosis following PCI in proximal lesions relative to treated coronary artery (LAD/LCX/RCA) and intervention technique.

II. To assess the impact of physical inactivity on prognosis following AMI in relation to extracoronary atherosclerotic disease.

III. To investigate the prognosis following STEMI relative to intervention strategy.

IV. To evaluate the effect of manual thrombus aspiration in patients suffering from STEMI with culprit lesion in the proximal- or mid-LAD.

V. To compare the impact of subclinical versus symptomatic ECAD in patients with AMI.

VI. To explore the extent and severity of coronary atherosclerosis relative to systemic atherosclerosis and prognosis.
MATERIALS AND METHODS

ETHICS

Studies were approved by the Ethical Review Board in Uppsala, Sweden (2011:333, 2005:169, 2010:111) and conformed to the criteria of the Helsinki Declaration on ethical principles for medical research involving humans.

METHODS

Study I

Study design

Study I was a retrospective longitudinal cohort study based on information derived from the internet-based Swedish Coronary Angiography and Angioplasty Registry (SCAAR), which is a part of the national Swedish Web-system for Enhancement and Development of Evidence-based care in Heart Disease Evaluated According to Recommended Therapies (SWEDEHEART) registry. The SCAAR registry is a national clinical-quality registry containing detailed information of all interventions in the 29 centres that perform coronary angiography and PCI in Sweden. The SCAAR registry is independent of commercial funding, and registry data have been verified annually in every participating hospital since 2001 by comparing 50 variables in 20 randomly selected interventions to information in patient records. The overall correspondence of data is 95.2%. (35)

All patients in Sweden identified in SCAAR from May 1 2005, to May 1 2011 undergoing PCI for isolated proximal coronary artery stenosis in the LAD, RCA, or LCX (segment 6, 1, or 11) (36) were included in the study.

Follow-up

Follow-up time was a minimum of 3 months and a maximum 3 years. Information on restenosis and ST was collected from SCAAR. Long-term information of vital status and date of death was obtained by merging the comprehensive National Population Registry with the SCAAR database.
Studies II, V, and VI

Study design
Studies II, V, and VI were prospective longitudinal cohort studies based on The Västmanland Myocardial Infarction Survey (VaMIS) population (clinicaltrials.gov Identifier NCT 01452178). Study II was designed to evaluate the impact of leisure time physical inactivity on prognosis following MI. Study V evaluated the impact of clinical and subclinical ECAD on prognosis following MI, and Study VI investigated the relationship between extent of coronary atherosclerosis and ECAD in MI patients and the impact of systemic atherosclerosis on prognosis.

VaMIS
From November 2005 through May 2011, patients ≥18 years of age admitted to the coronary care unit of Västmanland County Hospital, Västerås, Sweden were screened for participation in VaMIS. The patients were referred from a well-defined geographic area comprising the municipalities of Sala, Surahammar, and Västerås, with a combined population of approximately 170,000. Inclusion criteria were a diagnosis of MI in accordance with the European Society of Cardiology and the American College of Cardiology guidelines (37) by electrocardiogram and a troponin I level ≥0.4 µg/L as biomarker criterion. Of 1459 patients screened, 1008 were included in the study. For every patient with acute MI ≤80 years of age, a gender-matched individual from the same geographic area having the nearest date of birth as listed in the population registry was contacted for screening and invited to take part as a control subject, unless this individual had been previously diagnosed with MI. The acceptance rate among the first individuals contacted was 61%. In 18% of cases, it was necessary to contact more than two individuals before identifying a control subject. Due to logistics, investigation of controls was delayed an average of 9.6 months compared to patients. All patients and control subjects gave written informed consent.

Patient reported data
Baseline data of medical history and lifestyle were assessed by questionnaire two to four days following diagnosis in MI patients and at the time of enrolment in control subjects. All subjects were asked about their leisure time physical activity during the past year according to a single-item question developed by Saltin and Grimby.(38) This tool has
been validated against biological measures (39) and has been used in previous epidemiological studies. (40-42) The subjects were asked to describe their activity level as low (mostly sedentary with activities such as walking, biking, gardening less than 2 h per week), mild (physical activity, usually without breaking a sweat, such as walking, biking, gardening more than 2 h per week), moderate (vigorous exercise with sweating, 1-2 times per week for at least 30 minutes), or strenuous (vigorous exercise with sweating for at least 30 minutes, three or more times per week). Subjects reporting low physical activity were considered leisure time physically inactive (LTPI), but all reported activity levels were used when calculating dose-response. Education level, smoking, and alcohol use were self-reported. Hypertension, hyperlipidemia, diabetes mellitus, angina pectoris, stroke, intermittent claudication, and pulmonary disease were defined as history of physician-diagnosed disease. We sought to avoid missing data in the questionnaire by a follow-up interview with subjects providing incomplete data.

**Laboratory data**

For patients with MI, acute clinical blood samples were drawn at admittance to the hospital. Troponin I was assessed on two additional occasions during the first 24 h of hospitalization. Additional blood samples required for the study were collected within three days of hospital admission. For controls, all blood tests were conducted at time of enrolment.

**Physiology**

Vascular ultrasound and echocardiography were performed within 25 days of study enrolment. When the image quality was adequate, left ventricular ejection fraction was assessed using Simpson’s biplane method (43), otherwise visually estimated. Vascular ultrasound included examination of the carotid, infra-renal aorta, and renal arteries. The examinations were performed by one of three experienced vascular technicians blinded to the clinical history of the participants. A combination of morphologic evaluation of lumen irregularities and Doppler flow measures was used to define significant disease in any of the examined vessel segments. For estimate of lower limb atherosclerotic disease, ankle brachial index was calculated, with disease defined as ankle brachial index <0.9 or ≥1.4 (44, 45) in either limb. Physiological examinations that were non-diagnostic or lacked data, were categorized as
no significant disease. ECAD was defined as significant disease in any of the examined extra-cardiac arterial beds.

**Interpretation of coronary angiograms**

Patients with an available coronary angiogram recorded during index hospitalization were included in an analysis of longitudinal coronary atherosclerotic extent. All coronary angiograms were examined by an experienced invasive cardiologist or an experienced and specially trained cardiac nurse, both blinded to patient clinical data. Five percent of the angiograms were examined by two investigators to calculate inter-observer variability. We used the Sullivan extent score (SES) method(46) based on visual estimation. In brief, the coronary arterial tree was divided into 15 segments according to AHA definition.(36) (Figure 3) Coronary atherosclerosis was defined as irregularities in the vessel lumen restricting >20% of total lumen diameter. For each segment, we visually estimated the longitudinal extent of atherosclerosis as a percentage, which was then multiplied by a factor representing the surface area of the studied segment relative to the entire coronary arterial tree. Ultimately each angiogram would thereby confer a SES value from 0 to 100.

Follow-up data on survival, emigration, and date of death were obtained by linking the database to the comprehensive Swedish National Population Registry based on Swedish citizens’ unique 10-digit personal identification number. Information on cardiovascular mortality and hospitalization for cardiovascular disease was obtained from the Swedish National Patient Register and the Cause of Death Register.
Studies III and IV

Study design

Studies III and IV were post-hoc subgroup analyses of the prospective, multicenter, registry-based, randomized, controlled Thrombus Aspiration in ST-Elevation myocardial infarction in Scandinavia (TASTE) study. The TASTE study was an open-label clinical trial designed to evaluate the effect of TA on mortality following PCI in patients with STEMI. Patients ≥18 years old with a diagnosis of STEMI within 24 h of symptom onset and planned PCI indicated by coronary angiography were eligible for inclusion and randomized in a 1:1 fashion to PCI + TA or PCI only. The SCAAR registry platform was used for randomization and for collection of baseline clinical and procedural data. In Study III, the possible interaction of device (aspiration device, stent type) and intervention technique (direct stenting, post-dilatation) on the main outcome was examined. Study IV was designed to evaluate the effect of TA in a subset of patients with potentially large anterior myocardial infarction (symptom-onset-to-intervention time ≤5 hours, infarct lesion located in the proximal or mid-
LAD, and a thrombolysis in myocardial infarction (TIMI) score < 3), i.e.,
the inclusion criteria for the INFUSE-AMI study).(48)

STATISTICAL ANALYSES
In all studies, continuous data were summarized as mean ± SD for
normally distributed variables, or median and interquartile range for
skewed data. Categorical variables were presented as frequency or
percentages as appropriate. Differences within patient groups were assessed
with an unpaired Student’s t-test for normally distributed continuous
variables, Mann–Whitney U test for non-normally distributed continuous
variables, and Pearson’s χ²-test test for categorical variables. All reported p
values are two-sided. A p-value of <0.05 was considered significant.

Study I
The primary endpoints were restenosis, definite ST, and all-cause
mortality. The patients were categorized according to treated proximal
vessel segment (LAD/ RCA/ LCX). The cumulative adjusted relative risk of
mortality and restenosis was calculated using the Cox proportional hazard
method. All adjustment variables were forced into the statistical model.
The low incidence of ST in the population did not allow for multivariate
adjustment.

Study II
To test for differences between patients and control subjects, we used the
paired-sample Student’s t-test for continuous variables and McNemar’s test
for categorical variables. A conditional logistic regression analysis was
conducted to examine the association between LTPI and MI. Kaplan-Meier
curves were used to evaluate differences in mortality of active and LTPI
groups. In both the patient and control groups, the hazard ratio (HR) for
LTPI was calculated using the Cox proportional hazard regression model.
A backward selection was conducted to exclude variables with no
significant impact on outcome.
Study III
Study endpoints were mortality, rehospitalization for MI, and ST. The Kaplan–Meier method was used to estimate cumulative event rates and a Cox proportional hazard regression model to calculate adjusted cumulative risk ratios of outcomes with respect to aspiration catheter type and different interventional methods. Multiple imputations of unknown or missing baseline and procedure information was performed. Background and procedural factors were forced into the Cox regression model for calculation of the adjusted mortalities. Due to few events, only covariates demonstrating significant differences were used in the model for myocardial infarction, and, for ST, the low number of events did not allow for adjusted analysis.

Study IV
The study outcome variables were all-cause mortality, rehospitalization for recurrent MI or heart failure (HF), ST, and the composite of all-cause mortality, MI, HF, and ST at one year. The Kaplan-Meier method was used to assess cumulative event rates. Hazard ratios for endpoints at one year were calculated using the Cox proportional hazard method with randomized treatment group as the only factor. The results were analyzed according to the intention-to-treat principle.

Study V
The primary composite endpoint was cardiovascular death [International Classification of Diseases 10th revision (ICD) code I00-I99] or hospital admission because of recurrent AMI (code I21), HF (code I11.0 or I50), or stroke (code I61 or I63). The secondary endpoint was all-cause mortality. The Wilcoxon rank-sum test was used to compare two groups, and the Kruskal-Wallis rank test was used for three groups for continuous variables with skewed distribution. Fisher's exact test was used to assess differences in categorical variables. Results of post-hoc tests are presented with Bonferroni-corrected p-values. The cumulative incidence of the endpoints was analyzed using the Kaplan-Meier method, and differences between groups were evaluated by the log-rank test. Cox regression models were used to evaluate the crude and adjusted associations between ECAD status and outcomes. Separate analyses including multiplicative interaction terms were performed. Post-hoc power analyses were conducted according to Latouche et al.(24)
Study VI

We calculated intraclass correlation (49) to estimate inter-observer agreement of SES assessment. Logistic regression analysis was used to calculate the odds ratio for ECAD relative to SES. The primary outcome variables were all-cause mortality and the composite of cardiovascular death and rehospitalization. The Kaplan-Meier method was used for analysis of cumulative event rates throughout the study period. Differences were assessed with the log rank test. Hazard ratio was calculated using the Cox proportional hazard method.
RESULTS

Study I
Baseline characteristics are listed in Table 2. The mean follow-up time was $792 \pm 368$ days. The distribution of stable CAD and acute coronary syndrome was roughly similar with respect to culprit vessel, but the clinical presentation of acute coronary syndrome differed.
<table>
<thead>
<tr>
<th></th>
<th>LAD</th>
<th>RCA</th>
<th>LCX</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>4476</td>
<td>2070</td>
<td>1294</td>
<td></td>
</tr>
<tr>
<td>Age, years, mean (SD)</td>
<td>64.0 (11.5)</td>
<td>65.3 (10.8)</td>
<td>64.5 (10.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female, %</td>
<td>28.1</td>
<td>37.2</td>
<td>28.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Previous PCI, %</td>
<td>15.9</td>
<td>19.9</td>
<td>22.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Previous myocardial infarction, %</td>
<td>14.2</td>
<td>18.3</td>
<td>20.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Diabetes mellitus</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.47</td>
</tr>
<tr>
<td>IDDM, %</td>
<td>5.8</td>
<td>5.9</td>
<td>6.4</td>
<td></td>
</tr>
<tr>
<td>NIDDM, %</td>
<td>8.4</td>
<td>9.4</td>
<td>7.9</td>
<td></td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>41.3</td>
<td>47.1</td>
<td>47.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hyperlipidemia, %</td>
<td>38.2</td>
<td>43.1</td>
<td>43.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Smoking status</strong></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Active smoking, %</td>
<td>19.7</td>
<td>29.2</td>
<td>25.4</td>
<td></td>
</tr>
<tr>
<td>Former smoker, %</td>
<td>29.4</td>
<td>33.7</td>
<td>36.4</td>
<td></td>
</tr>
<tr>
<td><strong>Indication for PCI</strong></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stable coronary artery disease, %</td>
<td>16.8</td>
<td>16.1</td>
<td>16.2</td>
<td></td>
</tr>
<tr>
<td>NSTE-ACS, %</td>
<td>44.2</td>
<td>39.1</td>
<td>56.7</td>
<td></td>
</tr>
<tr>
<td>STE-ACS, %</td>
<td>36.5</td>
<td>41.9</td>
<td>24.6</td>
<td></td>
</tr>
<tr>
<td>Other, %</td>
<td>2.5</td>
<td>2.9</td>
<td>2.5</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Baseline data at time of index procedure relative to treated vessel. PCI—percutaneous coronary intervention, IDDM—insulin dependent diabetes mellitus, NIDDM—non-insulin dependent diabetes mellitus, NSTE-ACS—non-ST-elevation acute coronary syndrome, STE-ACS—ST-elevation acute coronary syndrome Outcome according to treated vessel
The incidence of restenosis was significantly more frequent in the LAD than in the LCX [(adjusted HR 2.28, confidence interval (CI) 1.56-3.34, p > 0.001], but not compared with the RCA (adjusted HR 0.94, CI 0.73-1.22, p = 0.658) (Figure 4A).

Acute definite ST was present in 0.9% of stents at one year. The cumulative incidence rate was 1.3% during 792 days of follow-up. The rate of ST was significantly higher in the LAD than in the LCX (HR 2.32, CI 1.11-4.85, p = 0.024) (Figure 4B).

We observed no difference in mortality after PCI in the proximal LAD compared to the two other coronary arteries both unadjusted and after multiple adjustments for possible confounders. (Figure 4C and Figure 4D).

Figure 4. Estimated cumulative event rates after PCI in proximal major coronary arteries. Panel A shows the risk for restenosis adjusted for clinical and procedural factors. Panel B shows the unadjusted risk of acute definite stent thrombosis. Panel C shows the risk for all-cause mortality. Panel D shows the risk for all-cause mortality adjusted for clinical and procedural factors.
Drug eluting stents vs. bare metal stents

Combined data of the three arteries showed DES to be associated with a lower restenosis rate compared with BMS (adjusted HR 0.48, CI 0.36-0.64, p < 0.001). The difference was significant in the LAD (adjusted HR 0.39, CI 0.27-0.55 p < 0.001), but no significant difference was found in the RCA or the LCX. There was no significant impact of stent type on the risk for definite ST. When analysing all-cause mortality relative to stent type, results differed according to artery. Drug eluting stents in the proximal LAD were associated with significantly lower mortality compared to BMS (adjusted HR 0.58, CI 0.41-0.82, p = 0.002) (Figure 3A). In the proximal RCA and LCX there was no significant difference between DES and BMS with respect to mortality (Figure 5B and 5C).
Figure 5. Estimated cumulative event rates after PCI according to stent type. Panels show adjusted risk for all-cause mortality with respect to stent type in the proximal LAD (Panel A), the proximal RCA (Panel B), and the proximal LCX (Panel C).
Studies II, V, and VI

Leisure time physical inactivity
Leisure time physical inactivity (LTPI) was reported by 36.8% of MI patients and 14.6% of control subjects (p < 0.001). Screening-diagnosed ECAD was significantly more prevalent in MI patients than in controls. In the conditional regression analysis, LTPI showed significant association with MI (unadjusted OR 3.4 CI 2.59-4.45, p < 0.001; adjusted OR 2.14, CI 1.56-2.94, p < 0.001). Survival after enrolment in the study relative to LTPI is displayed in a Kaplan-Meier curve (Figure 6). At one year, the unadjusted risk of death was 9% for LTPI patients vs. 2% for active patients (p < 0.001). At 6 years, the values were 30% and 10%, respectively (p < 0.001). The corresponding mortality risk for the control subjects were 1% at one year for LTPI vs. 0% for active (p = 0.15), while at 6 years the values were 19% vs. 5% (p = 0.002).
Figure 6. Cumulative survival relative to self-reported leisure time physical activity in myocardial infarction patients and controls.
Dose-response was assessed using the four categories of collected activity data. For MI patients there was a clear dose-response association, and the unadjusted all-cause mortality was significantly reduced with each increment of activity level: inactive vs. mild exercise = HR 0.32 CI 0.19-0.53 \((p < 0.001)\), vs. moderate exercise = HR 0.23 CI 0.12-0.44 \((p < 0.001)\), vs. strenuous exercise = HR 0.067 CI 0.01-0.48 \((p < 0.001)\) (Figure 7). For controls showed a trend in the same direction, but differences were not significant.

![Cumulative survival relative to level of self-reported leisure time physical activity in myocardial infarction patients.](image)

To examine factors potentially linking LTPI to post-MI mortality, we investigated patient baseline data at admittance (Table 3). Age did not differ between active and inactive patients, but females were significantly over-represented in the inactive group. Most cardiovascular risk factors
and concomitant diseases were more common in the inactive group, but objective measures of ECAD did not differ significantly between groups. Maximum troponin I level did not differ significantly, but markers of inflammation and heart failure C-reactive protein and B-type natriuretic peptide were significantly higher in inactive patients, as were markers of impaired glucometabolic regulation.
Table 3. Characteristics of leisure time physically active vs. inactive patients with myocardial infarction

<table>
<thead>
<tr>
<th></th>
<th>Active patients</th>
<th>Inactive patients</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>464 (63.2)</td>
<td>270 (36.8)</td>
<td></td>
</tr>
<tr>
<td>Age, mean (SD)</td>
<td>63.38 (9.23)</td>
<td>66.23 (10.29)</td>
<td>0.25</td>
</tr>
<tr>
<td>Alcohol consumption, n (%)</td>
<td>346 (74.6)</td>
<td>150 (55.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of, or active, smoking, n (%)</td>
<td>299 (64.4)</td>
<td>204 (75.6)</td>
<td>0.002</td>
</tr>
<tr>
<td>Angina pectoris, n (%)</td>
<td>87 (18.8)</td>
<td>88 (32.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Intermittent claudication, n (%)</td>
<td>13 (2.8)</td>
<td>35 (13.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stroke, n (%)</td>
<td>29 (4.1)</td>
<td>29 (10.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pulmonary disease, n (%)</td>
<td>48 (10.3)</td>
<td>37 (13.7)</td>
<td>0.70</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>67 (14.4)</td>
<td>66 (24.4)</td>
<td>0.001</td>
</tr>
<tr>
<td>Hyperlipidemia, n (%)</td>
<td>148 (31.9)</td>
<td>99 (36.7)</td>
<td>0.11</td>
</tr>
<tr>
<td>Extra cardiac atherosclerotic disease, n (%)</td>
<td>155 (33.4)</td>
<td>95 (35.2)</td>
<td>0.62</td>
</tr>
<tr>
<td>Left ventricular ejection fraction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;55%, n (%)</td>
<td>280 (62.6)</td>
<td>123 (46.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>35-54%, n (%)</td>
<td>142 (31.8)</td>
<td>110 (41.6)</td>
<td></td>
</tr>
<tr>
<td>&lt;35%, n (%)</td>
<td>25 (5.6)</td>
<td>31 (11.8)</td>
<td></td>
</tr>
<tr>
<td>BMI ≥30, n (%)</td>
<td>86 (18.7)</td>
<td>82 (31.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CRP (mg/L), median (Q1-Q3)</td>
<td>3.00 (2.00-8.00)</td>
<td>6.00 (3.00-21.50)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Maximum troponin-I (pg/L), median (Q1-Q3)</td>
<td>6.54 (1.78-26.44)</td>
<td>6.46 (1.99-6.46)</td>
<td>0.96</td>
</tr>
<tr>
<td>proBNP (ng/L), median (Q1-Q3)</td>
<td>903 (346-1979)</td>
<td>1910 (748-5201)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HbA1c (Momo S %), mean (SD)</td>
<td>4.93 (1.01)</td>
<td>5.17 (1.26)</td>
<td>0.004</td>
</tr>
<tr>
<td>Creatinine (μmol/L), mean (SD)</td>
<td>89.9 (38.4)</td>
<td>100.5 (85.8)</td>
<td>0.036</td>
</tr>
<tr>
<td>Hb (g/L), mean (SD)</td>
<td>145.9 (15.5)</td>
<td>140.0 (17.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Albumin (g/L), mean (SD)</td>
<td>35.3 (3.8)</td>
<td>33.7 (4.3)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Abbreviations: MI, Myocardial infarction; BMI, Body mass index; CRP, C-reactive protein; BNP, B-type natriuretic peptide; Hb, Hemoglobin.
Prognostic impact of extracoronary artery disease

The prevalence of ECAD was 35.9% (n = 235), with 141 (60.0%) exhibiting subclinical and 94 (40.0%) showing clinical ECAD. Compared to patients without ECAD, those with ECAD were older, more frequently had hypertension, prior MI, impaired renal function, and lower hemoglobin count. Patients with ECAD, especially when clinically overt, were, at admission, more frequently receiving treatment with anti-atherogenic medication according to guidelines than were patients without ECAD. In the Kaplan-Meier analyses, ECAD was significantly associated with poorer long-term prognosis related to both the primary composite outcome of cardiovascular death/hospital admission for recurrent cardiovascular event and all-cause mortality (Figure 8).

In the unadjusted Cox regression analysis, both clinical and subclinical ECAD were significantly associated with the primary endpoint. In the adjusted model, clinical ECAD, but not subclinical ECAD, was significantly associated with cardiovascular events (HR 2.10, 95% CI, 1.34-3.27, p = 0.001 and HR 1.35, 95% CI 0.89-2.05, p = 0.164, respectively). Clinical, but not subclinical, ECAD was independently associated with all-cause mortality (HR 3.12, CI 1.98-4.92, p < 0.001 and HR 1.21, CI 0.75-1.93, p = 0.436, respectively).
Coronary and systemic atherosclerosis

Of the 1008 patients included in the VaMIS study, a coronary angiogram was available for 544. The intraclass correlation for inter-observer agreement in the SES calculations was 0.89 (95% CI 0.77-0.95). The median SES for all subjects was 17 (interquartile range 17). Compared to patients with limited CAD (SES <17), those with extensive CAD (SES ≥17) were significantly more likely to exhibit ECAD (single location 17.5% vs. 35.7%; polyvascular, 4.5% vs. 10.3%, respectively p < 0.001). Mean follow-up for all-cause mortality was 7.7 ± 2.9 years. Mortality throughout the study period was 35.5% (n = 94) in the group with extensive coronary disease and 22.2% (n = 62) in patients with limited coronary disease (p = 0.001). Mean follow-up time of all patients to the composite endpoint of cardiovascular death/hospitalization for cardiovascular disease was 6.7 ± 3.1 years. The proportion of subjects reaching the composite endpoint throughout the study period was 40.8%
(n = 108) of patients with extensive CAD and 22.9% (n = 64) of subjects with limited CAD (p < 0.001).

The presence of most established cardiovascular risk factors was associated with significantly higher SES at time of MI compared to patients not carrying the risk. Current smoking was associated with significantly lower SES than non-smoking (smoker mean SES 16.4±11.7; non-smoker mean SES 19.2±13.6, p = 0.023).

We combined data of extent of coronary atherosclerosis with that of ECAD to define groups with extensive, moderate, or limited systemic atherosclerosis. Extensive systemic atherosclerosis was defined as extensive CAD (SES ≥ median) and ECAD. Moderate systemic atherosclerosis was defined as either extensive CAD or ECAD. Limited systemic atherosclerosis was defined as limited CAD (SES < median) and no ECAD. The cumulative all-cause mortality risk stratified by group was examined in a Cox regression analysis, unadjusted and adjusted for the majority of parameters included in the Global Registry of Acute Coronary Events (GRACE) risk score 2.0 as proposed by National Institute for Health and Care Excellence guidelines.(50, 51) Extensive systemic atherosclerosis was associated with a particularly low survival rate compared to patients with limited systemic atherosclerosis (HR 2.9, 95% CI 1.9-4.5, p < 0.001; adjusted for GRACE parameters HR 1.8, 95% CI 1.1-3.0, p = 0.019), as well as compared to patients with moderate systemic atherosclerosis (HR 2.2, 95% CI 1.4-3.3, p < 0.001; adjusted for GRACE parameters HR 1.8, 95% CI 1.1-2.6, p = 0.024) (Figure 9).

The risk for the composite endpoint of cardiovascular death/hospitalization for cardiovascular disease was significantly higher in patients with extensive systemic atherosclerosis compared to patients with limited systemic atherosclerosis (HR 3.1, 95% CI 2.1-4.7, p < 0.001, adjusted for GRACE parameters HR 2.9, 95% CI 1.8-4.8, p < 0.001) and patients with moderate systemic atherosclerosis (unadjusted HR 2.1, 95% CI 1.4-3.0, p < 0.001, adjusted for GRACE parameters (HR 1.9, 95% CI 1.2-3.1, p < 0.004) (Figure 10).
Figure 9. Cumulative risk of death for myocardial infarction patients relative to systemic atherosclerotic disease burden.
Figure 10. Cumulative risk in myocardial infarction patients of the composite endpoint of cardiovascular death or hospitalization for cardiovascular disease relative to systemic atherosclerotic disease burden.
Studies III and IV

The TASTE study
Twenty-nine PCI centers in Sweden, along with one in Iceland and one in Denmark participated in the trial. During the study period, 11,956 patients with STEMI underwent PCI and were registered in Swedish angiography and angioplasty registry, and 7244 patients were randomized. No patient was lost to follow-up. Six patients withdrew consent and were excluded from analysis after the date of withdrawal. Following randomization, 93.9% of patients in the thrombus aspiration group underwent thrombus aspiration, and 4.9% of patients in the PCI-alone group underwent thrombus aspiration.

Aspiration Catheters
The three most commonly used aspiration catheters were the Eliminate catheter (n = 1748), the Export (n = 1291), and the Pronto (n = 380). Data of other catheter types (n = 97) and cases in which catheter type was not stated (n = 105) are not reported. There were no differences in outcome among the three catheters with respect to death, reinfarction, or ST (Table 4).
<table>
<thead>
<tr>
<th></th>
<th>N (%)</th>
<th>All-cause death (%)</th>
<th>Hospitalization for a new myocardial infarction (%)</th>
<th>Stent thrombosis (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Terumo Eliminate</strong></td>
<td>1748 (48.3)</td>
<td>5.4</td>
<td>2.5</td>
<td>0.9</td>
</tr>
<tr>
<td><strong>Medtronic Export</strong></td>
<td>1291 (35.7)</td>
<td>Unadjusted 5.0</td>
<td>HR 0.93 (0.68-1.28), P=0.67</td>
<td>HR 1.07 (0.68-1.68)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adjusted with missing imputation</td>
<td>HR 0.96 (0.69-1.34), P=0.83</td>
<td>HR 0.98 (0.62-1.56), P=0.94</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HR 0.72 (0.30-1.69), P=0.45</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Vascular Solutions Pronto</strong></td>
<td>380 (10.5)</td>
<td>Unadjusted 4.5</td>
<td>HR 0.87 (0.49-1.39), P=0.47</td>
<td>HR 1.27 (0.67-2.40), P=0.47</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adjusted with missing imputation</td>
<td>HR 1.04 (0.61-1.78), P=0.88</td>
<td>HR 1.29 (0.66-2.53), P=0.46</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HR 0.6 (0.14-2.63), P=0.50</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The Terumo Eliminate catheter was used as reference for hazard ratios (HR) and 95% confidence intervals. NA, not applicable.
Direct Stent and Pre-dilatation
Direct stenting was performed in 1388 of 3621 patients (38.3%) randomized to TA and in 843 of 3623 patients (23.3%) randomized to PCI only. The risk of all-cause death and reinfarction and ST did not differ between the two randomized treatment groups in direct-stented patients. Pre-dilatation before stenting was performed in 2064 (57.0%) of patients randomized to TA and in 2613 (72.1%) randomized to PCI only. No differences were observed in the risk of all-cause mortality, reinfarction, or ST between the two randomized treatment groups in patients in whom pre-dilatation was performed. No significant interaction between TA or PCI only and pre-dilatation or direct stenting was found for any of the three outcomes.

Drug-Eluting and Bare Metal Stent
A total of 1703 patients (47.0%) randomized to TA and 1742 (48.1%) randomized to PCI only received DES. All-cause mortality did not differ between the two randomized groups when analysing patients treated with DES and BMS separately. No differences were seen in rates of reinfarction or ST in patients randomized to TA or PCI only, receiving DES or BMS. No significant interaction between TA or PCI only and DES/BMS was found for any of the three assessed outcomes.

Post-dilatation
Post-dilatation was performed in 1183 patients (32.7%) randomized to TA and in 1153 patients (31.8%) randomized to PCI only. No differences were observed in the risk of all-cause mortality or ST between the two randomized groups. No post-dilatation was used in 2269 (62.7%) patients randomized to TA or in 2305 (63.6%) patients randomized to PCI only. The risk of all-cause mortality, reinfarction, and ST did not differ in the two randomized treatments. No interaction of TA or PCI only with post-dilatation/no post-dilatation was found for any of the three outcomes.
Subgroup with Potentially Large Anterior MI
A total of 1826 patients (25.2%), 897 randomized to TA and 929 randomized to PCI only, fulfilled the INFUSE-AMI-based criteria (treated within 5 h of symptom onset, culprit lesion in the proximal or mid-LAD, TIMI flow <3 before PCI). (48) In this sub-study, 95.7% (n = 858/897) of the patients randomized to TA underwent TA, while 96.9% (n = 900/929) of patients in the PCI-only group had PCI only. During the procedure, 78.3% (n = 1430) were treated with bivalirudin, and 18.9% (n = 346) received glycoprotein IIb/IIIa inhibitors.

Clinical Outcome
In the sub-study cohort, 64 (7.1%) patients randomly assigned to TA died within one year, compared to 63 (6.8%) patients randomized to PCI only (HR 1.05, CI 0.74–1.49, p = 0.77). Of patients randomized to TA, 26 (2.9%) were hospitalized for MI within the following year compared to 31 (3.3%) in the PCI-only group (HR 0.87, CI 0.51–1.46, p = 0.59). Sixty-one patients (7.0%) randomized to TA were hospitalized for HF during the first year compared to 58 patients (6.3%) in the PCI-only group (HR 1.10 CI 0.77–1.58, p = 0.58). Stent thrombosis did not differ significantly at one year and was reported in eight patients (0.9%) in the TA group and 11 patients (1.2%) in the PCI-only group (HR 0.75, CI 0.30-1.86, p = 0.53). The one-year combined endpoint of all-cause mortality/rehospitalization for MI, HF, or ST occurred in 137 (15.3%) patients in the TA group and in 141 (15.2%) patients in the PCI-only group (Figure 11, HR 1.00, CI 0.79–1.26, p = 0.99). There was no significant difference in the reported frequency of in-hospital neurological complications or rehospitalization for stroke at one year in the two treatment groups (14 patients [1.6 %] in the TA group and 12 [1.3 %] in the PCI-only group, p = 0.69).
Figure 11. Estimated cumulative probability of the combined endpoint of all-cause mortality, hospitalization due to reinfarction, heart failure, or stent thrombosis within one year of PCI only (PCI) or PCI with thrombus aspiration (PCI+TA).
DISCUSSION

In the growing and aging global population, cardiovascular mortality is increasing despite improved cardiovascular care.\(^{(52)}\) The 30-day post-MI prognosis has improved dramatically over the past two decades in Sweden, while the prognosis from 30 days to one year has not been correspondingly reduced.\(^{(53)}\) A key factor in optimal therapy for the individual with cardiovascular disease is adequate classification and risk assessment, enabling focused, individually-tailored treatment both in the acute setting and in primary and secondary prevention. Our research has confirmed that prognosis is associated with the specific location of coronary lesions as well as the extent and severity of coronary and systemic atherosclerosis. We have evaluated intervention methods and potential paths to more effective secondary prevention in relation to coronary and extracoronary lesion location and severity.

**Coronary lesion location and prognosis**

In Study I we demonstrated that clinically driven diagnosis of restenosis and definite ST were more frequent after PCI in the proximal LAD compared to the LCX, but not when compared with the RCA. We found no increased mortality risk associated with PCI in the proximal LAD compared to the other two major coronary arteries; however, Study IV revealed higher risk of all-cause mortality and hospitalization for HF in the subgroup with lesions in the proximal- or mid-LAD compared to the TASTE population not included in that subgroup. An important difference between the proximal LAD cohort of Study I and the selected subgroup in Study IV is that the latter included only STEMI patients with TIMI flow $<3$, while, in the proximal LAD cohort of Study I, 36.5% of treated patients had a STEMI diagnosis, and TIMI flow was not specified. This difference may explain disparities in the results and difference in prognosis according to indication for treatment is in accordance with previous findings.\(^{(54)}\)
Coronary lesion location and intervention methods

In Study I, we found the restenosis rate, as well as the mortality risk, related to lesions in the proximal LAD to be lower following implantation of DES compared to BMS. Rates of definite ST did not differ with stent type. Accordingly, DES, as opposed to BMS, use in the proximal LAD was associated with a reduced risk of death. Since the publication of Study I, the first generation DES evaluated in the study has been succeeded by a new generation DES that has shown superior clinical results (30), and in current clinical practice in Sweden, nearly all deployed coronary stents are the new generation DES. (55) In contrast, as demonstrated in Studies III and IV, TA as an adjunct to PCI did not show clinical benefit in patients with STEMI and infarct-related lesions in the proximal- or mid-LAD. Further, in the TASTE study cohort, DES use, post- and pre-dilatation and selection of aspiration device were in line with the neutral findings of the overall TASTE study. Accordingly, the use of routine TA in STEMI currently carries a lower grade of recommendation in guidelines (56), and the use of TA in Sweden has markedly declined since the publication of the studies. (55)

Coronary and extracardiac atherosclerosis

Although the severity of systemic atherosclerotic pathology can vary widely among MI patients (57), initial clinical presentation may be similar, and current guidelines stratify risk based on readily accessible clinical markers such as electrocardiogram changes and biochemical evidence of myocardial necrosis, as opposed to extent of atherosclerosis. (58) Systemic atherosclerosis is not a well-defined entity with predictable progression. Although the coronary vessels are the most common locations for single vessel arterial disease, timing and severity of concomitant atherosclerosis in other arterial beds varies. (20, 59) Therefore, and since not all patients with coronary disease suffer from acute coronary obstruction, MI may occur early, late, or not at all in patients with systemic atherosclerotic disease, probably reflecting the presence and predominance of a humoral thrombotic state vs. local atherothrombotic factors in the idiosyncratic pathophysiological process leading to MI.

For this reason, optimal secondary preventive therapy may differ depending on extent of systemic atherosclerosis. For example, the clinical cost/benefit calculation of dual antiplatelet therapy for more than one year post-MI appears altered by the presence of systemic atherosclerosis. (60)
and might therefore reinforce the indication for direct factor Xa inhibitors in secondary prevention. (61) In addition, the effects of novel, potentially plaque-reducing, lipid-lowering agents such as proprotein convertase subtilisin/kexin type 9 inhibitors might differ with the presence and location of extracardiac artery disease. (62) The recently published Canakinumab Anti-inflammatory Thrombosis Outcomes Study found that interleukin-1β inhibition with canakinumab improved cardiovascular prognosis after MI, confirming the inflammatory hypothesis of atherothrombosis. (26) However, directing the therapy to specific high risk groups might be prudent, given the side effects and cost of this novel treatment. Estimates of systemic atherosclerosis could play a part in the individual tailoring of therapy. In Study VI, we found the longitudinal extent of coronary atherosclerosis at time of MI to be associated with ECAD, and more than one-third of the patients in the study with extensive coronary disease also exhibited ECAD. The combination of extensive coronary disease and ECAD defined a group with particularly poor prognosis.

**Extracardiac atherosclerosis and screening**

Study V revealed that clinical ECAD was significantly and independently associated with the long-term risk of adverse cardiovascular events after hospitalization for AMI, while subclinical ECAD was not. Several previous studies have shown that patients with CAD and concomitant clinical ECAD are at increased risk of recurrent adverse cardiovascular events and mortality. (4, 5, 7, 9, 10) The reported incidence of ECAD among patients with AMI is has ranged from 13% to 43% depending on study population and definition. (63-66) An association has also been demonstrated between asymptomatic abnormal ankle brachial index and cardiovascular mortality following acute coronary syndrome. (64, 67) Although systemic atherosclerosis is associated with a poorer prognosis than single-location arterial disease, this increased risk has not been reflected in greater focus on management of risk factors in patients with polyvascular disease. (20) This may provide a rationale for screening patients with AMI for subclinical ECAD to obtain accurate prognostic information to guide therapies. However, results of Study V do not support routine screening for subclinical ECAD in patients with AMI, as the added prognostic information seems weak. In contrast, in Study VI, when combining information of coronary atherosclerotic longitudinal extent with that of ECAD (subclinical and clinical) we found evidence of
an incremental prognostic value independent of parameters included in conventional risk scoring. Furthermore, there was an association between the extent of coronary atherosclerosis and ECAD, offering a possibility and rationale to selectively screen for ECAD in patients with extensive coronary atherosclerosis, but this needs to be prospectively confirmed. Different concepts for an integrated non-invasive approach to estimate the systemic atherosclerotic burden has been proposed. (9, 68-70) Our study contains results partly from non-invasive examinations but also from invasive procedures. However, this is a practical approach extracting data from invasive procedures already performed as part of routine management of MI.

**Coronary and extracardiac atherosclerosis and cardiovascular disease prevention**

After identifying patients with elevated risk, the next question is how that risk might be attenuated. Studies V and VI did not reveal evidence of less rigorous medical management of ECAD patients compared to patients without ECAD. However, lifestyle factors may rival medication in importance. In Study II, we focused on LTPI and found that simple self-reporting showed inactivity to be strongly associated with risk of MI and of death for both MI patients and controls, independent of ECAD and other potential confounders. Our data indicated that this association could be at least equally important as other well-established cardiovascular risk factors, including smoking and obesity.

The cardio-protective role of physical activity has been recognized since the pioneering work of Morris (1953).(71) Recently, due to emerging evidence,(7) focus has shifted from the protective role of physical activity to the harm of sedentary behavior per se. In a study by our group, even a limited period of extreme inactivity like 60 days of bed rest for healthy volunteers was associated with an increase in cardiovascular risk markers.(72) Exercise-based cardiac rehabilitation after MI is effective in reducing all-cause and cardiovascular mortality. (73) The association of pre-MI LTPI with mortality following MI is less clear, and results from earlier studies are conflicting. (42, 74, 75) Animal studies suggest that physical training before MI helps to preserve post-MI myocardial systolic function.

A strength of Study II was that detailed information about patient characteristics allowed us to control for subclinical ECAD, which might be expected to discourage an active lifestyle and be a possible factor linking
LTPI to cardiovascular morbidity and mortality. However, our results do not support an association between ECAD and LTPI.

This study shows that identifying physical inactivity at the time of admission for MI, even based a simple questionnaire, provides essential prognostic information in a group of patients potentially in need of a high level of support to motivate exercise. Addressing this issue only in secondary prevention is an oversight. Our findings emphasize the detrimental role of physical inactivity in a primary preventive setting, since physical inactivity, in addition to increasing the risk for MI, also increases the risk for all-cause mortality irrespective of MI. When resources need to be prioritized, it seems logical to primarily focus on lifestyle intervention programs aiming at minimizing sedentary behavior in the most vulnerable groups, including patients with extensive coronary atherosclerosis and ECAD, as identified in Study VI.
CONCLUSIONS

1. When performing PCI in the proximal LAD, DES is warranted since it is associated with lower risk of restenosis and death than BMS.
2. Routine TA is not clinically beneficial in STEMI even in patients with a large extent of myocardium at risk.
3. The neutral results of routine TA in STEMI are not influenced by type of aspiration device, stent type, direct stenting, or post-dilatation.
4. The longitudinal extent of coronary atherosclerosis at the time of MI, as estimated visually, is a significant predictor of ECAD.
5. The combination of extensive coronary disease and significant ECAD is associated with a particularly poor prognosis following MI.
6. There may be a rationale for screening MI patients with extensive coronary atherosclerosis for ECAD to investigate the extent of systemic atherosclerosis and increase accuracy of prognostic information to aid in individualized treatment.
7. In unselected MI patients, the prognostic value of screening for ECAD is doubtful.
8. Self-reported LTPI can be used to predict MI and all-cause mortality independent of ECAD.
LIMITATIONS

General limitations
Several limitations of this thesis need to be acknowledged. The different study cohorts, the diverse questions addressed in the studies, and the varied statistical methods used could make it difficult for the reader to comprehend the overall message. However, all the studies, although conducted in different settings, address prognosis following clinical CAD and ways in which it may be altered by medical intervention and lifestyle. Despite statistical adjustments, in all non-randomized studies there is an intrinsic risk of unaccounted-for confounders. In particular, clinical decisions such as DES treatment, use of post-dilatation, or choice of aspiration catheter are likely to be influenced by unreported physician- and patient-related factors.

Specific limitations

Study I
Unreported patient-related factors may influence the choice of stent (DES/BMS). During the study period, use of DES ranged from 10.2% to 71.7%, depending on hospital. Thus, the choice of stent type was probably more influenced by hospital policy than by patient-based physician selection. Our definition of ST was not identical to that of the Academic Research Consortium (76) which in later studies has emerged as the standard definition. The reported incidence of restenosis and ST were clinically driven and did not necessarily reflect the underlying pathophysiological processes. The low incidence of ST in the population did not allow for the adjusted Cox regression model.

Study II
Physical activity level was retrospectively collected and based on a simple 4-level classification. However, this method has been used and validated in previous large epidemiological studies (40-42), and the consistency in the results between patients and controls, along with the finding of a dose-response relationship of activity level with outcome, strengthens the validity of the data. If a simple question regarding physical activity can provide important information, clinical applicability is likely confirmed.
All patient history data may be subject to recall bias, possibly influenced by the presence of acute disease. Data on left ventricular ejection fraction was available only for patients and not for controls.

**Study III**
With the exception of thrombus aspiration, the invasive procedures studied were not part of the randomization in the TASTE trial, and were therefore prone to bias. There were differences in use of anticoagulation and platelet inhibition agents at baseline and during procedures and in clinical classification of heart failure with respect to aspiration catheter type, most likely due to variation in operator and institutional preferences. Specifics of the thrombus aspiration procedure were not reported, but adherence to standards for the procedure was encouraged. (47)

**Study IV**
This was a post-hoc analysis of the TASTE material, and the TASTE study was not powered to demonstrate clinical differences in the studied subgroups. Nevertheless, our sub-study was the largest study in the field focusing on patients with extensive myocardium at risk, and we found no evidence of a more pronounced effect of TA in this subgroup compared to the findings in the main TASTE trial. The study was not blinded, and clinical endpoints were not adjudicated. However the national registries from which information of clinical events was obtained are comprehensive and reliable (77-80), and there is no reason to assume systematic reporting bias with respect to treatment group. Although we aimed to include high risk patients, some patients with high risk did not undergo randomization, primarily due to inability to provide consent.(47) One-year data on rehospitalization for HF and stroke was not complete for all patients, and these endpoints may be, to a minor extent, underreported in this study. The lack of clinical effect of TA was confirmed in a patient-level meta-analysis of the three largest studies (including TASTE) in patients with STEMI.(81)

**Study V**
One-third of the screened patients were excluded because of dementia, confusion, logistical problems, or declining to participate. For these patients, we have no baseline characteristics or follow-up data, but it is likely that they were more burdened with disease at baseline and had poorer prognosis compared with the study population. Our findings
cannot be generalized to all AMI patients, but we believe that our study population was an unbiased sample of daily practice AMI patients <80 years of age that are willing to undergo non-invasive vascular screening. Long-term adherence to medication was not monitored.

Study VI
Grading of coronary atherosclerosis was based on visual estimate of lumen irregularities rather than objective measures or direct intracoronary imaging of atherosclerotic plaques using techniques such as intravascular ultrasound or optical coherence tomography. However, coronary angiographic scoring has shown satisfactory agreement with intravascular visualization.(82) The method used in this study resulted in close inter-observer agreement (although intra-observer agreement is not assessed) and is easily adopted in routine clinical practice. Coronary angiograms performed in secondary hospitals were not available for analysis, which reduced the power of the study.
FUTURE CONSIDERATIONS

The concept of screening for ECAD in MI patients with extensive coronary atherosclerosis deserves further exploration. By identifying a subgroup with systemic atherosclerosis at time of MI, tailored preventive measures might be taken. Based on information derived from this thesis, the most promising intervention would be directed programs to minimize sedentary behavior, but the effect of novel anti-atherosclerotic medical therapies should also be explored in this high-risk subgroup.

New methods to relate coronary anatomy and physiology to systemic atherosclerosis should be investigated. For example, the association of ECAD with coronary flow indices such as microvascular resistance and coronary flow reserve has, to our knowledge, not been described.

In the setting of acute STEMI, our studies suggest that TA as an adjunct to PCI is ineffective in optimizing perfusion and limiting myocardial damage and adverse clinical outcome, irrespective of potential infarct size and intervention methods. Other measures need to be explored. A number of pharmacological agents have been investigated for intracoronary use in the setting of acute revascularization, not only for reduction of thrombus burden, but also for reduction of reperfusion injury, including cyclosporine (83) and exenatide.(84) The path forward might be to focus investigation on mechanical and pharmacological treatment combinations, as opposed to mechanical or pharmacological treatment only.
SAMANFATTNING PÅ SVENSKA

Ateroskleros är en progressiv sjukdom som drabbar artärer i hela kroppen och som, när den manifesterar sig som hjärt- kärlsjukdom utgör den ledande orsaken till ohälsa och död globalt. Ateroskleros är en systemisk sjukdom men behandlingen är i först hand lokal och beroende på vilken hjärt- kärlhändelse som drabbar den enskilda patienten. Även om mycket redan är känt om bakomliggande riskfaktorer för ateroskleros finns fortfarande åtskilligt kvar att lära om aterosklerossjukdomens systemiska natur och om varför vissa kärlbäddar drabbas oftare än andra liksom varför vissa patienter har en högre risk för ateroskleros än andra.

Nyligen publicerade studier visar förbättrad prognos med antitrombotisk och anti-inflammatorisk behandling i breda patientgrupper med etablerad hjärt- kärlsjukdom på aterosklerotisk bas. Av hälsökonomiska skäl och för att balansera hälsovinster med komplikationsrisker, finns ett stort behov av att kunna rikta behandlingen till de grupper där den potentiella vinsten är som störst. Här har extrakardiell aterosklerotisk artärsjukdom (ECAD, ateroskleros i kroppens övriga artärer, kranstillämplig) kommit att hamna i focus som en markör för ökad risk.

Sjukvårdens resurser är begränsade och behöver därför styras till behandlingar som är så effektiva som möjligt. Därför är det viktigt att, förutom att införa nya, effektivare metoder också utrangera etablerade behandlingar som är kostnadsdrivande utan någon påvisbar nytta för patienten. Dessutom får sjukvården inte släppa fokus på livsstilsförändringar som ofta är billiga och minst lika effektiva som medicinsk behandling när det gäller att förbättra liv och hälsa för patienten.

Det finns ett behov av att förbättra verktygen för att kunna ta ett helhetsgrepp om aterosklerossjukdomen, dels för att kunna få information om prognos men framförallt för att kunna skräddarsy behandling till den individuella patienten.

I denna avhandling studerar vi hur prognosen vid kranskärlssjukdom påverkas av lokalisation och svårighetsgrad av ateroskleros både i koronarartärer och i övriga delar av kärtädet. Vi undersöker också kopplingen mellan hjärtinfarkt, grad av ateroskleros i kranstillämpliga artärer och ECAD och hur prognosen påverkas av olika interventionella behandlingsmetoder och livsstilsfaktorer.
Studie I är en retrospektiv longitudinell kohortstudie utgående från det i det närmaste heltäckande svenska koronarangiografi och angioplastik registret. Denna studie visar att återförträngning är vanligare efter stent-behandling i främre nedåtstigande koronarartärens proximala del jämfört med övriga kotronarartärer. Läkemedelsbehandlade stent i detta kranskärl var förknippade med lägre risk för återförträngning och död jämfört med metallstent.

Studie II, V och VI är prospektiva longitudinella kohortstudier utgående från Västmanland Myocardial Infarction Survey (VaMIS) vilken mellan 2005-2011 inkluderade patienter som vårdats innehållande i Västmanland för akut hjärtinfarkt. Patienterna undersöktes för ECAD som en del i studieprotokollet och en kontrollgrupp utan hjärtinfarkt rekryterades. Resultaten från dessa studier är att symtomgivande, diagnostiserad ECAD är associerad till en försämrad prognos efter hjärtinfarkt liksom förekomst av utbredd ateroskleros i kranskärlen och, i synnerhet systemisk ateroskleros definierat som kombinationen av ECAD och utbredda kranskärlsförändringar. ECAD diagnostiserad vid bred screening i hjärtinfarktspatienter visade däremot inte en sådan signifikant association till försämrad prognos. Vidare konstaterades att utbredningen av ateroskleros i koronarartärerna vid hjärtinfarkt korrelerar till ECAD. Studie II visar dessutom att fysisk inaktivitet ökar risken för hjärtinfarkt och död i studiegruppen med eller utan koronarsjukdom och ECAD.

Studie III och IV är båda subgruppsanalyser av den prospektiva, registerrandomiserade multicenterstudien Thrombus Aspiration in ST-Elevation myocardial infarction in Scandinavia (TASTE) som studerade effekten av den etablerade metoden att rutinmässigt suga ut misstänkta blodproppar (trombaspiration) vid behandling av ST- höjningsinfarkt. Dessa båda studier undersöker om effekten av trombaspiration påverkas av den teknik som i övrigt valts vid ingreppet eller om effekten av trombaspiration blir större om man behandlar patienter med hög risk och en hotande större hjärtinfarkt. Studierna bekräftar det neutrala resultatet av TASTE studien, man ser ingen effekt av trombaspiration och metoden rekommenderas inte längre som rutin.

Den sammanfattande konklusionen av studierna är att prognosen efter intervention i koronarartärerna påverkas av lokalisationen av kranskärlsförändringar. I den främre nedåtstigande koronarartären är läkemedelsbe-
handlat stent, men inte trombaspiration förenat med en förbättrad pro-
gnos. Uttalad ateroskleros i koronararterna vid hjärtinfarkt samvarierar
med ECAD. Fysisk inaktivitet, klinisk ECAD och systemisk ateroskleros är
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REFERENCES


27. Authors/Task Force m, Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, et al. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)Developed with the special contribu-
Coronary artery disease and prognosis


43. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography’s Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr. 2005;18(12):1440-63.


50. Unstable Angina and NSTEMI:

the early management of unstable angina and non-ST-segment-elevation myocardial infarction


58. Amsterdam EA, Wenger NK, Brindis RG, Casey DE, Jr., Ganiats TG, Holmes DR, Jr., et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: executive


76. Laskey WK, Yancy CW, Maisel WH. Thrombosis in coronary drug-eluting stents: report from the meeting of the Circulatory System Medi-


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