Ischaemic heart disease - risk assessment, diagnosis, and secondary preventive treatment in primary care, with special reference to the relevance of exercise ECG

Gunnar Nilsson
“Trust is the basic element of medicine”

Per Fugelli
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Abstract

**Background:** Ischaemic heart disease is a diagnostic and therapeutic challenge to most general practitioners. We sought to identify diagnostic characteristics and prognoses of patients in primary care who underwent exercise electrocardiography (ECG). We compared the ECG test results with respect to the probability of subsequent cardiologist referrals. We also aimed to identify determinants for prehospital delays and lack of statin treatment before a first-time myocardial infarction (MI).

**Methods:** Setting: Region of Jämtland Härjedalen, Sweden (adult population, approximately 99 000); study period 2010–2014. Patients and study designs: Studies I and II – 865 patients referred to exercise ECG; primary outcome – incidence of cardiovascular events (I) and cardiologist referrals within 6 months after exercise ECG (II); observed outcomes were compared to predictions from multivariable logistic models. Study III – 265 patients with first-time MI; characteristics were analysed for determinants of prehospital delay ≥2 hours. Study IV – survey of 931 patients with first-time MI; analyses of characteristics associated with rates of statin treatment in patients with previously diagnosed cardiovascular disease (CVD).

**Results:** Study I: Exercise test results were associated with exertional chest pain, a pathologic ST-T segment on resting ECG, angina diagnosis according to the patient’s report, and medication for dyslipidaemia. Cardiovascular events occurred in 52.7%, 18.3%, and 2.0% of patients with positive (ST-segment depression >1 mm and chest pain indicative of angina), inconclusive (ST depression or chest pain), or negative tests, respectively. Study II: Positive or inconclusive exercise tests were associated with cardiologist referrals. Among patients with positive exercise tests, referral rates decreased with age, after adjusting for co-morbidity. Self-employed women were referred to cardiologic evaluations more often than other employed women. Study III: The first medical contact was a primary care facility for 52.3% of patients. The prehospital delay time was ≥2 h for 67.0% of patients in primary care and 44.7% of patients who called emergency medical services or were self-referred to the hospital. Study IV: Among patients with prior CVD, 34.5% received current statin treatment before the first MI. Statin treatment rates decreased with age, after adjusting for CVD and diabetes; women ≥70 years old were treated half as often as men of the same age.
Conclusions: Clinical characteristics can be used to identify patients at low risk for cardiac events. The prognosis in patients with a negative exercise ECG was benign for 6 months after the exercise ECG. Exercise tests are important for selecting patients who require cardiologic evaluations. Age, gender, and employment status interacted with rates of referrals for cardiac evaluation. The prehospital delay time was considerably prolonged, particularly when primary care was the first medical contact. Only one third of patients with a prior CVD received statin treatment. Pre-MI statin treatment decreased with age, particularly among women ≥70 years old. In making medical decisions, it is necessary to be aware of biases regarding age, gender, and socioeconomic status. Methodologies for case-finding and follow-up need to be improved and implemented in clinical practice.

Keywords: Exercise ECG, Ischaemic heart disease, Myocardial infarction, Prehospital delay, Primary care, Prognosis, Referral, Statin, Secondary prevention
Original Papers


III. Nilsson G, Mooe T, Söderström L, Samuelsson E: Pre-hospital delay in patients with first time myocardial infarction: an observational study in a northern Swedish population. [submitted]

IV. Nilsson G, Söderström L, Samuelsson E, Mooe T: Treatment with statins prior to first time myocardial infarction, with special reference to patients with previously diagnosed cardiovascular disease: a population based survey. [submitted]

The papers will be referred to by their Roman numerals.
Sammanfattning på svenska

Bakgrund och syfte: Patienter med ischemisk hjärtsjukdom (IHD) utgör en diagnostisk och terapeutisk utmaning för läkare inom primärvården. Arbets-EKG är en vanlig metod vid utredning av patienter som söker till primärvården för besvär som kan vara förorsakade av IHD. Vi undersökte primärvårdspatienter remitterade till arbets-EKG, med avseende på de kliniska karakteristika (egenskaper och symtom) som kunde associeras med resultatet av arbets-EKG och med prognosen inom sex månader efter undersökningen. Vi jämförde arbets-EKG-svaren med avseende på efterföljande remittering för utredning vid hjärtklinik. Vi kartlade även faktorer av betydelse för tidsfördröjningen före sjukhusvård och för sekundärpreventiv behandling med kolesterol sänkande läkemedel (statiner), före insjuknande i hjärtinfarkt.

Metod: De studier som ingår i avhandlingsarbetet (studier I-IV) genomfördes i Region Jämtland och Härjedalen, befolkningsunderlag cirka 99 000 personer i åldrar från 20 år och äldre, under åren 2010-2014. Undersökta patienter och studiedesign:


Studie III: I 52.3% av samtliga fall var primärvården (personligt besök eller via telefonrådgivning) den första vårdkontakten för patienter med förstagångs hjärtinfarkt. Tidsförsökvägningen före sjukhusvård var 2 timmar eller mer bland 67.0% av alla patienter från primärvården och 44.7% bland de patienter som först ringde larmcentralen (112) eller sökte direkt till sjukhusets akutmottagning. Studie IV: Patienter med tidigare konstaterad hjärt-kärlsjukdom hade en pågående statinbehandling i 34.5% av fallen, före insjuknandet i förstagångs hjärtinfarkt. Andelen patienter med pågående statinbehandling avtog med stigande ålder, justerat för diabetes och tidigare hjärt-kärlsjukdom. Kvinnor från 70 år och äldre erhöll statinbehandling hälfen så ofta som jämförbara män.


Nyckelord och förklaringar: Arbets-EKG (kliniskt arbetsprov på ergometercykel med samtidig EKG-registriering), positivt arbets-EKG (talar för kärlkrampssjukdom), negativt arbets-EKG (talar för frånvaro av sjukdom). EKG (elektrokardiografi), hjärtinfarkt, ischemisk hjärtsjukdom (sjukdomstillstånd med otillräcklig blodtillförsel till hjärtat), sekundärprevention (förhindra återinsjuknande i tidigare genomliden sjukdom).
# Abbreviations and acronyms

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<th>Abbreviation</th>
<th>Definition</th>
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<td>AMI</td>
<td>acute myocardial infarction</td>
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<tr>
<td>AUC</td>
<td>area under the curve</td>
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<td>CABG</td>
<td>coronary artery bypass grafting</td>
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<td>CAD</td>
<td>coronary artery disease</td>
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<tr>
<td>CI</td>
<td>confidence interval</td>
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<td>CV</td>
<td>cardiovascular</td>
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<td>CVD</td>
<td>cardiovascular disease</td>
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<td>ECG</td>
<td>electrocardiography</td>
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<td>EMS</td>
<td>Emergency Medical Services</td>
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<td>ESC</td>
<td>European Society of Cardiology</td>
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<td>FMC</td>
<td>first medical contact</td>
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<td>GP</td>
<td>general practitioner</td>
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<td>HMG-CoA</td>
<td>hydroxymethylglutaryl-CoA</td>
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<td>ICD</td>
<td>International Classification of Diseases</td>
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<td>IHD</td>
<td>ischaemic heart disease</td>
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<td>IQR</td>
<td>interquartile range</td>
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<td>LDL</td>
<td>low-density lipoprotein</td>
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<td>MI</td>
<td>myocardial infarction</td>
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<td>ms</td>
<td>millisecond</td>
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mV millivolt

n number of valid cases

NA not applicable

NAILED ACS Nurse-Based Age-Independent Intervention to Limit Evolution of Disease After Acute Coronary Syndrome

NSTEMI non-ST elevation myocardial infarction

NPV negative predictive value

OR odds ratio

PAD peripheral artery disease

PCI percutaneous coronary intervention

PPV positive predictive value

ROC receiver operating characteristic

SCORE Systematic Coronary Risk Estimation

SD standard deviation

SEI Swedish socioeconomic classification

SHD Swedish Healthcare Direct

STEMI ST-elevation myocardial infarction

TIA transitory ischaemic attack
Introduction

Cardiovascular disease (CVD) is still the leading cause of death in Europe, despite decreasing coronary heart disease mortality since the 1980s [1, 2]. In Sweden, CVD according to the International Classification of Diseases, tenth revision (ICD-10), codes I00-I99 [3], was the most common cause of death among women (37%) and men (36%) in 2014 [4]. The decreasing CVD mortality in the years 1987–2014 was particularly evident among men in the northern part of Sweden [5]. Worldwide, ischaemic heart disease (IHD) was the leading cause of death during the past decade, accounting for 7.4 million deaths in 2012, followed by stroke, chronic obstructive lung disease, and lower respiratory infections [6]. At the global level, CVD is estimated to be the most important somatic cause of loss of productivity [7].

Classification: CVD can be divided into the diagnostic categories of IHD (ICD-10 codes I20–I25) and other groups of vascular diseases. IHD can be subdivided into specific diagnostic groups: angina pectoris (ICD-10 codes I20.0–I20.9), acute myocardial infarction (AMI) (ICD-10 codes I21.0–I21.9), chronic IHD (ICD-10 codes I25.0–I25.9), and coronary disease (ICD-10 code I25.1).

Background

Rationale

Research on CVD is conducted primarily from the perspective of hospital-based care, so that results are not always applicable in primary care. Thus, there are several reasons to research CVD from a primary care perspective [8-11]. In countries with developed primary healthcare services, general practitioners (GPs) have a certain responsibility for diagnosis and treatment of CVD, before emergence of complications, such as unstable angina and myocardial infarction (MI) [7]. Although knowledge of risk factors for CVD and MI is paramount for prevention of disease [12], our scope was not to study individuals primarily from a risk factor perspective.

We conducted follow-up of patients contacting primary healthcare for symptoms suggestive of IHD and warranting an exercise ECG (studies I and II), and retrospective studies of patients hospitalized with first-time MI, with respect to measures taken before hospital care (studies III and IV).
Evaluation of chest pain

Observing and interpreting symptoms and signs, in the light of medical history and epidemiologic baseline characteristics, remain the core essence of medical practice. A symptom of certain interest for physicians meeting patients in primary care and emergency clinics is chest pain or discomfort in the chest [13-15]. The symptoms of IHD can vary in intensity: from a silent IHD with few symptoms, to angina pectoris on exertion, unstable angina, AMI, or a sudden cardiac death [16]. Chest pain is classified as typical angina related to exertion, atypical angina, and other chest pain [17]. Chest pain, an onset symptom of IHD, is an often-reported symptom in population-based surveys [18-20]. Chest pain may be related to several different underlying conditions (cardiac, pulmonary, intestinal, chest-wall syndromes, and more), making the diagnostic process a challenge to GPs and other physicians evaluating patients for pain or discomfort in the chest [10, 11, 21-37]. New-onset chest pain is the reason for contact in 1.4–1.8% of consultations to GPs [19, 26, 38].

Medical actions in patients consulting for chest pain are normally conducted to confirm or exclude IHD as the underlying cause, triggered by the potential seriousness of the condition. As an endpoint diagnosis among patients accessing primary care for chest pain symptoms, IHD is diagnosed in 8–18% of all cases [26, 27, 38-40]. IHD and coronary disease are more prevalent among patients seen in coronary units [10, 11].

For assessment of angina symptoms, the questionnaire “Rose Angina” has been used in epidemiologic research [41, 42]. The Rose-form, originally a questionnaire of seven questions, was also validated in a version consisting of three questions focused on exertional chest pain [43, 44]. A Marburg-based research group described in several reports their development of a clinical prediction rule for evaluating chest pain symptoms among patients seen in primary care [21, 45-47]. Such prediction rules may be helpful in clinical practice, to avoid assessment of patients by single risk factors.
Exercise electrocardiography (ECG)

Exercise ECG is an established method for assessing and diagnosing IHD, but the test results should be interpreted with respect to the prevalence of disease in the population [48-51]. In Sweden, the exercise ECG is conducted as a bicycle ergometer test, with simultaneous ECG recording and registration of chest pain symptoms, according to validated rating scales [48, 52]. Clinical assessment, supported by basal biochemical characteristics and a resting ECG, is conducted before referral of patients to clinical exercise testing. Because of the uncertainty in the clinical diagnosis of IHD, exercise ECG is often required as a complementary diagnostic tool. The 2-year prognosis in patients with a negative exercise ECG is reported to be benign, with manifestations of coronary disease in 2–3% of patients during follow-up [53, 54].

Sensitivity and specificity: The sensitivity of exercise ECG, compared to coronary angiography as a reference standard, depends on the underlying type of coronary disease. The average sensitivity is estimated at 66%, with a range between 40% and 90%, depending on the presence of one-, two-, or three-vessel coronary disease [55, 56]. The sensitivity of exercise ECG is increased by radionuclide imaging techniques, which is recommended for complementary diagnostic use [51, 56]. Use of radionuclide imaging has so far been infrequent in primary care because of availability and cost limitations. The specificity of exercise ECG is estimated at 84% at the cut-off level of ST-segment depression >1 mm (0.1 mV) as the criterion for a positive exercise ECG, with coronary angiography as reference [55].

Exercise ECG in primary care: Exercise ECG holds a prime position as a complement to history and physical examination for diagnosing IHD in primary care. In the region of Jämtland Härjedalen, the present study setting, 3463 exercise ECGs and 119 myocardial radionuclide-imaging procedures were performed from 2003 to 2008 by request from GPs in the region. The department of clinical physiology at Östersund Hospital was the only clinic taking referrals from primary care clinics during the study period.

Exercise ECG in different populations: In patients seen in primary care, the prevalence of advanced coronary disease is lower than in patients seen in coronary units or emergency departments [10]. The sensitivity of exercise ECG testing is lower in patients with one- or two-vessel disease compared to patients with three-vessel disease. This reduced sensitivity has implications for the interpretation of exercise ECG results. The predictive value of a positive exercise ECG can be calculated using a web-based calculator [57]. At an estimated sensitivity of 0.66 and specificity of 0.84, the predictive value of a positive test (PPV) will be 0.51 with an underlying disease prevalence of 20%.
At a 10% disease prevalence, the PPV will be only 0.31, indicating an increase in false-positive test results at lower disease prevalence in the target population. The predictive value of a negative test result (NPV) is 0.96 at an underlying disease prevalence of 10%, with a sensitivity of 0.66 and specificity of 0.84.

**Referrals to cardiologic evaluation**

**Gender bias and socioeconomic bias:** In deciding which patients to refer for further evaluation, GPs may be influenced by irrelevant presumptions, leading to biased referral decisions. Gender bias is described as “unintended but systematic neglect of either women or men” [58]. In the same way, socioeconomic bias can be defined as discrimination against patients for unintended socioeconomic reasons.

Gender bias in examination and treatment of heart diseases is reported repeatedly: Female IHD patients are reported to be less likely to access comprehensive management for stable angina in primary care [59], to receive secondary preventive drug treatment [60], to access cardiac rehabilitation or prevention programmes [61, 62], or to undergo revascularization, adjusted for confounding and eligibility for intervention [63].

But the presence of gender bias has also been questioned [64-67] or reported with equivocal results. Female patients were less likely to receive revascularization after hospital stay for non-ST elevation MI (NSTEMI) but not for ST-elevation MI (STEMI), and no differences in long-term mortality were observed adjusted for age [68]. Overuse of referrals to cardiologic evaluation was reported in men, without suboptimal management of female chest pain patients seen in primary care [69].

Socioeconomic inequality in access to coronary artery bypass grafting (CABG) was reported among male, but not female, Swedish patients during 1991 to 2000 [63]. The use of cardiologic procedures must also be evaluated relative to the need for procedures, which may differ by social gradient in CVD patients [70, 71].

**Socioeconomic status and mortality:** Differences in IHD mortality have been explored in a European multi-centre survey, in which Sweden did not participate [72]. Considerable differences in mortality from CVD have also been reported in the Swedish adult population, according to the Swedish registry on causes of death: “Death rates for heart disease are more than twice as high among women with only primary education compared to women with tertiary education, aged 65–79 years” [4]. Therefore, controlling for the influence of socioeconomic conditions is of obvious importance in epidemiologic CVD research.
**Socioeconomic classification:** Socioeconomic status can be determined from various aspects: educational level, professional background, and income [73]. In Sweden, socioeconomic status can be determined by the classification system “Swedish socioeconomic classification” (SEI) [74]. The SEI is based on professional background and level of qualification. Within SEI, it is also possible to classify retired persons by their previous professional background, and those who are self-employed. Socioeconomic classification according to profession may be misleading due to changes in formal educational requirements, e.g., if nurses and certain teaching professionals were educated in a former education system. It could therefore be convenient to conduct socioeconomic classification by educational level in parallel with the SEI classification.

**Prehospital delay**

Time to treatment is of vital importance for treatment possibilities and prognoses in patients with AMI [75-79], but time from symptom onset until cardiology care has remained largely unchanged [80-82]. A time span of 2.0–6.5 hours from symptom onset until availability of cardiology care, i.e., prehospital delay, has been reported since the 1980s [83, 84]. Any cut-off time to define a prolonged prehospital delay is arbitrary, however, because mortality rate increases with time to reperfusion [75, 85]. Nevertheless, a 2-hour cut-off is frequently applied because AMI patients who receive reperfusion therapy within that time span have the most clinical benefit [86, 87].

**Time fractions of prehospital delay:** Total prehospital delay time can be divided into subcategories according to time from symptom onset until the patient’s decision to call professional healthcare (“decision time”), and time from call for medical help to hospital admission (“transport time”) [88]. Total prehospital delay is the time from onset of symptoms until arrival at the hospital, or time until the presence of advanced cardiology care [89, 90]. In studies where total prehospital delay, decision time, and transport time could be determined separately, decision time is usually the major part of total prehospital delay [88, 91-93].

The terminology related to prehospital delay and its determinants is, however, not consistent, and comparisons among different studies can therefore be difficult; e.g., delay may contribute to the individual patient’s decision time (from symptom onset until call for medical help), but also to time required for the doctor’s decision-making [94, 95].
**Determinants of prehospital delay:** Determinants associated with a prolonged time to cardiologic care are high age, female sex, single-household living, low educational level, difficulties in assessment of symptoms, self-medication, mental stress and fear, co-morbidities (e.g., diabetes and angina pectoris), atypical symptom presentation, and characteristics associated with the healthcare provider [95-102]. Patients with a first medical contact (FMC) with primary care are reported not only to have increased prehospital delay but also to have less severe cardiac events compared to patients with FMC to the emergency medical services (EMS) [103-107].

**Symptoms of AMI:** Onset of AMI symptoms is frequently not identified by patients as cardiac, explaining why primary care or telephone-counselling services may be the preferred FMC [104, 106, 108]. The symptoms at onset of AMI may be vague or atypical compared to expected symptoms and therefore cause delayed care [109-112]. The influence from previous experience of AMI on prehospital delay is reported in different directions, with shorter [113-116], longer [117, 118], or neutral [104, 119] impact on prehospital delay.

**Delayed care and context:** Because prehospital delay is related to context, proper healthcare and demographic data should be included in the research process. Relevant data in a Northern Sweden context are distance to hospital, availability of ambulance services by road and by air, low educational level, and high average age of the population. Prehospital delay can also be related to misinterpretation of symptoms at triage of patients, causing a “doctor’s delay”, which should be evaluated apart from other causes of prehospital delay.

**Data sources:** The time for onset of symptoms suggestive of MI is normally registered at patient triage, by admission to hospital, or according to ambulance records. Time for ambulance call and time required for transport are available from ambulance and triage records. The patient’s self-assessment of symptoms and any help from friends or relatives are data not uniformly recorded in medical records but such information may be obtained from questionnaires.
Assessment of cardiovascular risk

Persons with known CVD are high-risk patients in need of active management of risk factors [120].

In asymptomatic patients, cardiovascular (CV) risk factors are essential for assessment of CV risk, with nine determinants (abnormal lipids, smoking, hypertension, diabetes, abdominal obesity, psychosocial factors, dietary habits, alcohol, and regular physical activity), except age, accounting for about 90% of the population-attributable risk of MI in men (90%) and women (94%) [12].

The relevance of risk factor control and preventive measurements is clarified by the declining coronary-mortality curves derived from the Northern Sweden MONICA cohorts 1986–2009 [121, 122]. The 2013 guidelines from the European Society of Cardiology (ESC) emphasize the GP’s responsibility to identify persons with symptomatic disease or increased risk of IHD and to inform and follow up patients with stable IHD [123]. Thus, the challenge is not lack of evidence but how to organize healthcare to reach set treatment goals according to guidelines and established evidence.

Scoring algorithms: Evaluation of single patients with suspected IHD is made from a baseline assumption of the probability of disease, based on knowledge of prevalence of disease in the population relative to patient characteristics. This assumption will always involve a degree of error and subjectivity. For assessment of CV risk in individuals without established CVD, scoring algorithms based on European or US population samples have been developed [124].

A scoring algorithm calibrated for use in the Swedish population was put forth in 2003 [125, 126]. In this algorithm, “The Swedish SCORE chart for cardiovascular risk” (SCORE), the 10-year risk of fatal CV events is calculated from age, sex, smoking status, systolic blood pressure, and total serum cholesterol. Use of SCORE is developed and validated for use in patients aged 40–65 years, which is a restriction because patients older than 65 years of age also may be eligible for preventive treatment. A SCORE risk ≥5% is the proposed cut-off to define high CV risk, where preventive drug treatment should be considered as one part of a comprehensive treatment strategy [7].

Use of a scoring algorithm for CV risk assessment will account for the multifactorial aspects of CVD whereas single-risk-factor assessment can lead to false conclusions, with potential overuse of medication.

A risk-scoring algorithm reflects the morbidity of the population in which the scoring chart was developed. When the CV morbidity of an entire population is decreasing, use of scoring charts based on older population samples will overestimate the true risk, and vice versa [7].

Another issue concerning scoring charts is whether to estimate fatal CV events only, or total CV events (fatal+non-fatal CVD). SCORE estimates the 10-year risk of CV death whereas the Framingham Risk Score estimates 10-year risk of coronary heart disease or CVD [127, 128].
Application of scoring charts developed in the US will lead to overestimation of the true risk of CV events in European populations [129].

Risk calculation based on fatal events is a harder endpoint compared to total events assessment, where different diagnostic traditions may interfere. A high risk of fatal CV events will inevitably imply a higher total CV event rate [7].

From a public health perspective, there is also concern about the consequences of clinical guidelines and scoring algorithms for preventive treatment applied to entire populations, with potential overuse of pharmacotherapy [130, 131].

**Secondary prevention:** Patients with previously diagnosed CVD are all at very high risk and should be considered for secondary prevention, including treatment with lipid-lowering drugs [120]. Other groups with very high or high CV risk are patients with diabetes (type 2 diabetes, or type 1 diabetes with microalbuminuria), chronic kidney disease, and those with very high levels of individual risk factors [120, 132].

**Statin treatment**

Lipid-lowering treatment with hydroxymethylglutaryl-Co-A (HMG-Co-A) reductase inhibitors, known by their generic name as “statins”, reduces mortality and morbidity in patients at elevated risk for CV events [133-138]. The mechanism in common to all statins is inhibition of the rate-controlling enzyme of cholesterol synthesis, HMG-Co-A reductase, while efficiency depends on the dose and type of statin [139, 140]. Since the 4S study group in 1994 reported beneficial outcomes from statin treatment of patients with angina pectoris or previous MI and elevated levels of serum cholesterol, several statins have become available as generic drugs [133, 141].

Statin treatment in persons with raised CV risk, but without previous CV events (primary prevention), has been evaluated in meta-analyses of published trials, with the finding of a reduction in all-cause mortality and in major CV events related to statin treatment [138, 142, 143]. A Cochrane review on statin treatment for primary prevention of CVD concluded that “Of 1000 people treated with a statin for five years, 18 would avoid a major CVD event”, and statin treatment for primary prevention of CVD was not associated with an increased risk of serious side effects or with cancer [138].

A meta-analysis focused on more intensive statin treatment regimens (patients with or without prior vascular diseases or diabetes, 27% women, enrolled in 26 randomized trials) found a 10% reduction in all-cause mortality and a 20% reduction in coronary death per 1.0 mmol/L reduction in low-density lipoprotein (LDL) cholesterol [134].
The safety of long-term statin treatment was evaluated in a follow-up of the original 4S study for up to 8.3 years (median 7.4 years). The relative risk reduction of total death was 0.73 (95% CI 0.60–0.82), with no excess risk for cancers or non-CV death [144].

**Adverse effects:** Among the common statin-related adverse effects are myalgia and asymptomatic elevation of liver enzymes [145-147]. The risk of incident diabetes is slightly increased by statins (approximately 0.5% absolute risk increase), but this risk is outweighed by the reduction in total risk for patients receiving statin treatment [148-150]. A serious but rare adverse event associated with statins is rhabdomyolysis, with an approximate incidence of 3/100,000 treated person-years [146]. The incidence of statin-related adverse effects in placebo-controlled trials is reported as equal to placebo treatment [148]. The incidence of adverse effects in observational studies is generally higher; between 5% and 10% are common estimates of side effects or intolerance associated with statins [145, 151]. An even higher statin-related event rate is reported (17.4%), although most patients rechallenged with statins were able to tolerate statin therapy long-term [152]. The true incidence of the most common statin-related side effect, myalgic symptoms, can be hard to evaluate appropriately because of the absence of consensus on a definition of statin-related myopathy [153].

**Gender and age aspects:** Women and men are recommended statin treatment with the same therapeutic targets [120, 134, 142, 154]. In patients with established CVD, there is evidence for the same relative risk reduction from treatment up to ages 75–80 years [155, 156], and statin treatment is recommended for the same indications in these patients [120, 134, 142].

**Monitoring of treatment:** The best way to monitor statin treatment has been a scientific controversy. The European position is to treat towards a pre-defined target level of serum LDL cholesterol, while the US position is to treat patients by estimated CV risk level with a predetermined statin dose [120, 157]. This discrepancy, from a theoretical perspective, is not necessarily reflected in differences in treatment in clinical practice, however.

In patients with myalgic symptoms linked to statins, an expert panel recommended evaluation of symptoms associated with discontinuation of treatment and rechallenge with the same therapy [158].
**Discontinuation of treatment:** Discontinuation of pharmacotherapy is a common problem in long-term treatment of chronic conditions [159]. Long-term adherence to statins (measured over 2–5 years) is assessed at approximately 50% among high-risk patients and even lower when statins are prescribed for primary prevention [160-162]. Discontinuation of statin treatment is linked to adverse CV outcomes and death, in high-risk patients [163-166] and at the population level [167]. Low adherence to medication is associated with patients’ inadequate perception of risk related to disease, low continuity of care, and difficulties in the relationship between the patient and healthcare provider [159, 168].

Patient adherence and awareness of CV risk profile are linked phenomena, because awareness of risk is associated with health literacy and finally with adherence to preventive actions [169]. Subjective underestimation of CV risk, especially related to age, is reported among urban-living women [170] and might be an even more widespread phenomenon.

**Barriers to implementation of clinical guidelines**

Barriers to implementation of preventive strategies must be identified before appropriate actions can be recommended [171-174]. Primary care in Northern Sweden is hampered by a lack of permanent-staff GPs and a need to recruit GPs on short-term contracts, which might cause difficulties in treatment of chronic conditions, such as IHD. GPs have a particular role in identifying patients at high CV risk, but the adherence to clinical guidelines may be insufficient.

Barriers to implementation of clinical guidelines are many and include inadequate knowledge, lacking time, and insufficient patient adherence [175-177]. An insufficient healthcare framework to provide primary and secondary prevention of CVD was reported by physicians from various European countries [175]. The importance of maintaining healthcare organizations that provide a supportive professional framework for all categories of healthcare professionals is probably underestimated.

Achievements in diagnosing and treating CVD before occurrence of further complications, such as AMI, could serve as a measurement of the quality of preventive-care services. As a contribution to assess statin treatment in practice compared to clinical guidelines, we designed a survey of patients with a first-time MI.
Aims

The overall aim was to investigate IHD with respect to risk assessment, diagnosis, and secondary preventive treatment in primary care and with special reference to the relevance of exercise ECG.

Specific study aims:

I. To identify clinical characteristics that predict exercise ECG test results and to describe the occurrence of CV events within 6 months after testing, related to the test results.

II. To assess the utility of exercise ECG in selecting primary care patients for referral to further cardiologic evaluation and to identify if referral decisions are biased by socioeconomic status or gender.

III. To evaluate prehospital delay in patients with a first-time MI and to identify determinants for a prolonged prehospital delay.

IV. To assess treatment with statins before a first-time MI, with reference to patients with prior CVD, and to evaluate treatment differences related to primary care clinic use of GPs on short-term contracts.
Methods

Setting

Studies I–IV were conducted in the region of Jämtland Härjedalen, in the northern part of Sweden. The studies recruited patients ≥20 years of age, registered at primary care clinics within the study region. The study population (individuals ≥20 years old) was approximately 99 000 inhabitants in 2012. In 2012, 47% of the population lived in the central municipality of Östersund while the other portion lived in one of seven rural communities [178]. The distance from patients’ places of residence to the central hospital in Östersund ranged from 0.4 to 234 km by road.

Organization of healthcare: Primary care clinics were located in all communities. Östersund Hospital was the only hospital taking referrals from primary care clinics. At the time of the study, the cardiology unit of Östersund Hospital referred patients in need of revascularization to the University Hospital in Umeå, with a distance by road of 365 km from Östersund. Primary care clinics were run by the region (n=21) or by private clinics (n=7), with contracts to provide primary care from the regional healthcare authorities.

Ambulance services: Ambulance service stations were located in each rural community and in the central community of Östersund. Airborne ambulance was available during daytime in certain cases of emergency. The ambulance services were organized from the Emergency Care Centre, Östersund Hospital. Ambulances were equipped to perform ECG recordings and to give thrombolytic therapy. Primary care, ambulance, and emergency care services were subject to moderate patient charges of approximately 15–27 Euro.

Telephone counselling services: Public telephone counselling was provided by primary care clinics during office hours and by the Swedish Healthcare Direct (SHD) at all hours during the week. The SHD was a part of the primary care organization and staffed by district nurses with training in telephone counselling. From the SHD, patients could be directed over to the EMS or to a primary care clinic, whichever was determined to be more appropriate.
Participants

Study I and study II, the exercise ECG cohort: We identified eligible study patients through referrals to exercise ECG, from GPs working at primary care clinics within the study area: 1191 potentially eligible study patients were identified; 265 declined to give consent, 8 were unable to perform an exercise ECG, and 53 were referred for reasons other than IHD. The final study sample was 865 patients (427 women).

The study patients were examined with an exercise ECG according to standards of normal care, at the department of clinical physiology, Östersund Hospital. After the completed examination, the referring GP received a written testimony of the test result, stating the relevant findings. The referring GP then decided which patients required referral for further cardiologic evaluation and which ones should be treated within primary care. Patients who were referred to exercise ECG for reasons other than IHD were excluded from evaluation and follow-up, within the study context.

Study III, assessment of prehospital delay in patients with first-time MI: We identified 317 patients from the population-based secondary prevention study, the Nurse-Based Age-Independent Intervention to Limit Evolution of Disease After Acute Coronary Syndrome (NAILED ACS) trial [179]. Within 6 months after hospital care, 10 patients were deceased, 19 declined to give consent, and 23 were lacking data for assessment of prehospital delay. The final study sample consisted of 265 consenting patients (89 women).

Study IV, treatment with statins prior to first-time MI: We recruited 931 patients (345 women) from the NAILED ACS trial, after a first-time MI. Three had data lacking on statin treatment. Determinants of current statin treatment were based on 928 patients. Patients were recruited from the 21 primary care clinics run by the regional health authorities of Jämtland Härjedalen.
Recruitment and follow-up

**Study I:** Recruitment period, February 2010 until the end of February 2012. Follow-up of CV events (hospitalization for MI or unstable angina, cases of recurrent angina treated in primary care, decisions on revascularization, and fatal CV events) within 180 days from exercise ECG. Patients on the waiting list for revascularization were followed with respect to date and type of procedure.

**Study II:** Recruitment period, February 2010 until the end of February 2012. Follow-up of referral to cardiologic evaluation, hospitalization for MI or unstable angina, and fatal CV events within 180 days. Revascularizations were recorded within 250 days from exercise ECG.

**Study III:** Recruitment period, November 2009 until the end of March 2012.

**Study IV:** Recruitment period, November 2009 until the end of December 2014.

Data sources and measurements

**Studies I and II**

A postal pre-test questionnaire was sent to patients along with the notice for the exercise ECG. The questionnaires were answered by patients and collected by nursing staff before the exercise ECG procedure. The pre-test questionnaire addressed medication, smoking habits, medical history, chest pain symptoms, level of education, employment status, and one question about the patient’s own opinion regarding the nature of chest pain symptoms. Medical history and present medication were determined by questions with fixed alternatives. Chest pain symptoms were evaluated according to the shortened, three-question version of the Rose Angina Questionnaire [44]: “Do you ever have chest pain or discomfort in the chest?”; “Do you have chest pain walking at an ordinary pace on the level?” and "Do you have chest pain walking uphill or in a hurry?". The questionnaire is provided in the Appendices section as Appendix A.

**The exercise ECG procedure:** Exercise ECGs were conducted as bicycle ergometer tests with simultaneous 12-lead ECG registration, registration of systolic blood pressure, respiratory rate, and recording of chest pain symptoms and perceived exertion by the Borg rating scales [48, 52]. A resting ECG was registered before exercise ECG and classified according to the Minnesota Code guidelines [180, 181].
The physician responsible for the exercise ECG procedure assessed the resting ECG, classified the exercise ECG result, and provided an answer back to the referring GP.

The exercise ECG results were classified as follows. Positive test: depression of the ST segment, horizontal or down sloping, >1 mm (0.1 mV) at 60 ms after the inflection point between the QRS segment and the ST segment, and chest pain symptoms suggestive of angina during the test. Inconclusive test: either chest pain symptoms or ST-segment depression during the test. In negative exercise tests, there was neither chest pain nor ST-segment depression during the test procedure. A small number of tests were classified as non-assessable due to left bundle branch block, pacemaker ECG, or ST-segment artefacts caused by digitalis medication.

**Socioeconomic classification:** Patient employment status was used to determine socioeconomic status according to the SEI [74]. We used the aggregated version of the SEI, with the main categories of manual workers, non-manual employees, and self-employed or employees. Educational level was determined from each patient’s highest achieved educational level.

**Follow-up of CV events and referrals:** During the follow-up period, hospitalizations for unstable angina, MI, fatal CV events, recurrence of angina pectoris treated in primary care, revascularizations, and referral decisions were recorded from medical records. MI diagnoses were determined according to the universal definition of MI [182]. Revascularizations were patients with CABG or percutaneous coronary intervention (PCI) within 250 days from the day of exercise ECG. Fatal CV events were registered when cause of death was sudden cardiac death, MI, or congestive heart failure. Causes of death were provided from the Swedish registry of Causes of Death.
Study III

Data sources used in study III.

1. Demographic and baseline data provided from the baseline file of the NAILED ACS trial.

2. A postal questionnaire (Appendix B), with two reminders, within 3–6 months after hospitalization for MI. The questionnaire covered symptoms, sequence of events, and patient’s FMC before admission for first-time MI. Chest pain symptoms prior to MI were recorded according to the shortened Rose Angina Form [44].

3. Record data: Ambulance records were scrutinized for relevant data: time for call to the EMS, time for admission to hospital, and symptoms recorded at triage. For patients with private transport, time for hospital admission and triage data were provided according to records from the EMS.

Time intervals:

1. Total prehospital delay was determined as the time from onset of symptoms suggestive of MI until admission to hospital.

2. Decision time was determined as the time from onset of symptoms until the call to the EMS.

3. Transport time was the time from the call to the EMS until hospital admission.

Assessment of onset time: Time for onset of symptoms suggestive of MI was determined by nursing staff during the hospital stay. The time for symptom onset was recorded with an estimate of uncertainty, with hours more or less relative to the recorded time for onset of symptoms. In patients with private transportation to the hospital, only total prehospital delay was possible to estimate.

Assessment of distance: The distance from the patient’s place of residence to the central hospital in Östersund was in kilometres by road, according to the web-based application Google Maps (https://maps.google.com) [183].
**FMC at onset of symptoms suggestive of MI**: FMC was determined according to a fixed-alternatives question, with the possibility of providing complementary information in free text. FMC was classified as “Personal visit to a GP before referral”, “Referral by call to a primary care centre or the Swedish Healthcare Direct”, “Called the Emergency Medical Services”, or “Self-referred to hospital”.

**Presenting symptoms**: The presenting symptoms reported by patients at triage were classified as “Predominantly chest pain symptoms”, e.g., pain, ache, burn, or pressure in the chest; “predominantly other pain symptoms”, e.g., pain in the abdomen, arm, shoulder, or neck; and “predominance of symptoms other than pain”, e.g., severe fatigue, syncope, or circulatory shock. Chest pain symptoms at triage were assessed from visual analogue scales, used by ambulance staff or EMS nursing staff, as a procedure of normal care.

**Doctor’s delay**: All patient records were scrutinized for cases in which a medical error may have caused a prehospital delay of 2 hours or more.

**No sub-classification of MI**: The universal definition of MI type 1 was used to determine a MI, but MI diagnoses were not classified as STEMI or NSTEMI [182]. We regarded sub-classification of MI to be an outcome measurement, from a prehospital perspective.

**Study IV**

Study patients were recruited from the NAILED ACS trial. The baseline file from the NAILED ACS trial was used to identify determinants associated with statin treatment before first-time MI. Patients were stratified according to diagnoses of CVD before the first MI episode.

CVD comprised the following diagnoses: angina pectoris (as a clinical diagnosis), revascularization (CABG or PCI), ischaemic stroke or transitory ischaemic attack (TIA), and peripheral artery disease (PAD). PAD comprised leg artery disease, a stenosing lesion of the carotid, or atherosclerotic aneurysm.

**CV risk assessment**: In patients without previously diagnosed CVD or diabetes, aged 40–65 years, the CV risk was assessed according to SCORE [125]. The SCORE estimates the 10-year risk of fatal CV events by sex, age, smoking status, systolic blood pressure, and total serum cholesterol. A SCORE risk ≥5% defined the cut-off level of high CV risk.
Primary care clinics: Primary care clinics run by the region of Jämtland Härjedalen were classified by their use of GPs working on short-term contracts and GPs working as permanent staff. Data were provided by the regional health authorities, as total salaries paid to permanent staff GPs and to GPs working on short-term contracts, per primary care clinic during 2010–2014. The primary care clinics were stratified into three levels: low (0–9%), medium (10–39%), and high short-term clinics (≥40%).

Study design, studies I–IV

I. Prospective observational study
II. Prospective observational study
III. Retrospective observational study
IV. Population-based survey

Statistics

Patient characteristics are presented as proportions or as means or medians. For comparison of proportions, we used the chi-squared test or Fisher’s exact test (two sided) as appropriate. For comparison of means and medians, we used the Students t-test (two sided) or the Mann–Whitney U test. For highly skewed distributions, the median and interquartile range (IQR) was preferred. The level of significance was determined as p<0.05.

Study I: Univariate logistic regression was used to identify determinants associated with exercise ECG test results, positive or inconclusive vs. negative. Significant variables identified in univariate analysis were entered into a multivariable logistic model, which was reduced stepwise until only significant variables remained. In the final model, the significant variables and variables assessed as clinically important were retained. Variables identified in the final model were used as a predictive model of the exercise ECG test result. We used a 10% probability cut-off to detect CV events in relation to the predicted test result.

We evaluated the multivariable predictive model through a bootstrapping procedure, based on random samples with replacement from 865 patients, with 100 replicates. The statistical analyses were carried out in IBM SPSS version 20. Diagnostic characteristics for outcome of the exercise ECG tests were computed in WINPEPI (version 11.26) [57]. The bootstrapping procedure was performed in Stata (version 12).
Study II: Univariate logistic regression was used to identify determinants associated with referral to cardiologic evaluation after exercise ECG. Baseline characteristics were entered into a multivariable prediction model, and the model was reduced stepwise by exclusion of the least significant variables until only significant variables remained. Significant variables were adjusted for age and gender in the final model. Separate adjusted models were computed to detect determinants of referral, stratified by gender. The statistical analyses were carried out in IBM SPSS version 22.

Study III: Univariate logistic regression was used to identify determinants associated with a prehospital delay ≥2 hours. Determinants with a p<0.25 were entered into a multivariable logistic model. The multivariable model was reduced stepwise by exclusion of the least significant variable until only significant variables remained. Receiver operating characteristic (ROC) curves were computed to evaluate the discriminatory power of the multivariable model [184, 185]. The statistical analyses were carried out in IBM SPSS version 22.

Study IV: Univariate logistic regression, with patients stratified by previous CVD, was used to identify determinants associated with statin treatment. Age was dichotomized by the mean age of the study population (70 years). Because of a possible bidirectional causality between statin treatment and estimated CV risk according to SCORE, we did not include SCORE risk in the regression model. In the regression model, we applied an interaction term, “age ≥70 by female gender”, with diabetes and prior CVD as covariates.

Ethical approval

Studies I, II, and III: The studies were approved by the Regional Ethical Review Board at Umeå University (Dnr 09-133M and 2010/302-32M). Participating patients provided informed consent.

Study IV: Use of baseline data collected in the secondary preventive trial (NAILED ACS) was approved by the Regional Ethical Review Board at Umeå University (Dnr 09-142M, 2013-204-32M and 2014-416-32M).
Results

Study I

**Descriptive data:** The study sample consisted of 865 patients referred for exercise ECG due to a suspected IHD. Of these patients, 55 (6.4%) had a positive exercise ECG, 653 (75.5%) were negative, 142 (16.4%) were inconclusive, and 15 (1.7%) had an exercise ECG that was not assessable. Patients with inconclusive exercise ECGs had significant ST-depressions in 89 cases (51% men) and angina-like chest pain in 53 cases (47% men).

**Demographics:** The mean ages of men and women were 63 and 64 years, respectively. More women (22.1%) than men (12.7%) had higher education (university or college degree). Prior CV events (MI, revascularization, stroke, or a TIA) were reported more often among men (21.3%) than women (11.2%). More men (33.3%) than women (23.0%) were on medication for dyslipidaemia. Chest pain symptoms were commonly reported among men (63.8%) and women (76.5%). Pathologic ST-T segment on resting ECGs were equally common among men and women, but most patients had a normal resting ECG (Table 1).

Patients with a positive/inconclusive exercise ECG were older and had more often experienced prior CV events compared to patients with a negative exercise ECG. The former were more often treated for dyslipidaemia and hypertension; they had more often chest pain on exertion or angina diagnosis according to the patient’s opinion. A pathologic resting ECG was more common among patients with a positive/inconclusive exercise ECG (Table 2).
Table 1 Patient characteristics (n=865)

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=438 (50.6%)</td>
<td>n=427 (49.4%)</td>
<td></td>
</tr>
<tr>
<td><strong>Age, mean (SD)</strong></td>
<td>63 (12)</td>
<td>64 (11)</td>
<td>0.030</td>
</tr>
<tr>
<td><strong>University or college degree</strong></td>
<td>50/394 (12.7%)</td>
<td>84/380 (22.1%)</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Current or previous smoker</strong></td>
<td>245/436 (56.2%)</td>
<td>210/424 (49.5%)</td>
<td>0.050</td>
</tr>
<tr>
<td><strong>Medical history</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>57/434 (13.1%)</td>
<td>20/424 (4.7%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Revascularization</td>
<td>60/436 (13.8%)</td>
<td>15/426 (3.5%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stroke or TIA</td>
<td>27/433 (6.2%)</td>
<td>24/422 (5.7%)</td>
<td>0.735</td>
</tr>
<tr>
<td>Previous cardiovascular event</td>
<td>92/432 (21.3%)</td>
<td>47/420 (11.2%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Current medical conditions</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension, medication for</td>
<td>248/435 (57%)</td>
<td>216/421 (51.3%)</td>
<td>0.094</td>
</tr>
<tr>
<td>Diabetes mellitus, treatment for</td>
<td>56/434 (12.9%)</td>
<td>40/423 (9.5%)</td>
<td>0.110</td>
</tr>
<tr>
<td>Dyslipidaemia, medication for</td>
<td>144/433 (33.3%)</td>
<td>97/421 (23.0%)</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Chest pain</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever have chest pain or discomfort in the chest</td>
<td>272/426 (63.8%)</td>
<td>315/412 (76.5%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chest pain walking at an ordinary pace on the level</td>
<td>59/431 (13.7%)</td>
<td>65/412 (15.8%)</td>
<td>0.392</td>
</tr>
<tr>
<td>Chest pain walking uphill or in a hurry</td>
<td>198/427 (46.4%)</td>
<td>210/411 (51.1%)</td>
<td>0.171</td>
</tr>
<tr>
<td><strong>Angina diagnosis according to patient</strong></td>
<td>111/404 (27.5%)</td>
<td>100/396 (25.3%)</td>
<td>0.476</td>
</tr>
<tr>
<td><strong>Systolic blood pressure (mmHg), mean (SD)</strong></td>
<td>148 (19)</td>
<td>147 (20)</td>
<td>0.503</td>
</tr>
<tr>
<td><strong>Resting ECG</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal resting ECG</td>
<td>303/438 (69.2%)</td>
<td>336/427 (78.7%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>27/438 (6.2%)</td>
<td>11/427 (2.6%)</td>
<td>0.010</td>
</tr>
<tr>
<td>Atroventricular block</td>
<td>17/438 (3.9%)</td>
<td>6/427 (1.4%)</td>
<td>0.024</td>
</tr>
<tr>
<td>Signs of myocardial scarring</td>
<td>45/438 (10.3%)</td>
<td>28/427 (6.6%)</td>
<td>0.049</td>
</tr>
<tr>
<td>Pathologic ST-T segment on resting ECG</td>
<td>59/438 (13.5%)</td>
<td>47/427 (11.0%)</td>
<td>0.269</td>
</tr>
</tbody>
</table>

SD: standard deviation. TIA: transitory ischaemic attack. ECG: electrocardiogram. Cardiovascular event: myocardial infarction, revascularization, stroke, or TIA. Myocardial scarring: pathologic Q-wave or altered R-wave progression compared to previous ECG.
Table 2 Characteristics of participants according to exercise ECG result (n=850)

<table>
<thead>
<tr>
<th></th>
<th>Exercise ECG result</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive/inconclusive*</td>
</tr>
<tr>
<td><strong>Patients</strong></td>
<td>n=197 (23.2%)</td>
</tr>
<tr>
<td><strong>Age, mean (SD)</strong></td>
<td>66 (11)</td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td>106 (53.8%)</td>
</tr>
<tr>
<td><strong>Medical history</strong></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>25 (12.8%)</td>
</tr>
<tr>
<td>Revascularization</td>
<td>30 (15.2%)</td>
</tr>
<tr>
<td>Stroke or TIA</td>
<td>16 (8.1%)</td>
</tr>
<tr>
<td>Previous cardiovascular event</td>
<td>47 (24.0%)</td>
</tr>
<tr>
<td><strong>Current medical conditions</strong></td>
<td></td>
</tr>
<tr>
<td>Hypertension, medication for</td>
<td>120 (61.5%)</td>
</tr>
<tr>
<td>Diabetes mellitus, treatment for</td>
<td>24 (12.2%)</td>
</tr>
<tr>
<td>Dyslipidaemia, medication for</td>
<td>78 (40.0%)</td>
</tr>
<tr>
<td><strong>Chest pain</strong></td>
<td></td>
</tr>
<tr>
<td>Ever have chest pain or discomfort in the chest</td>
<td>138 (72.3%)</td>
</tr>
<tr>
<td>Chest pain walking at an ordinary pace on the level</td>
<td>50 (26.0%)</td>
</tr>
<tr>
<td>Chest pain walking uphill or in a hurry</td>
<td>134 (69.1%)</td>
</tr>
<tr>
<td><strong>Angina diagnosis according to patient</strong></td>
<td>80 (43.2%)</td>
</tr>
<tr>
<td><strong>Systolic blood pressure (mm Hg), mean (SD)</strong></td>
<td>151 (21)</td>
</tr>
<tr>
<td><strong>Resting ECG</strong></td>
<td></td>
</tr>
<tr>
<td>Normal resting ECG</td>
<td>132 (67.0%)</td>
</tr>
<tr>
<td>Pathologic ST-T segment on resting ECG</td>
<td>42 (21.3%)</td>
</tr>
</tbody>
</table>

*Positive exercise test: angina symptoms and depression of ST segment >0.1 mV during the test. Inconclusive test: angina or ST depression. **Negative test: neither angina nor ST depression. SD: standard deviation. TIA: transitory ischaemic attack. ECG: electrocardiogram. Cardiovascular event: myocardial infarction, revascularization, stroke, or TIA.
**Multivariable models:** We analysed the exercise ECG results, dichotomized as positive/inconclusive tests vs. negative tests. Exercise ECG results were predicted by chest pain on exertion (odds ratio (OR) 2.46; 95% confidence interval (CI) 1.69–3.59), pathologic ST-T segment on resting ECG (OR 2.29; 95% CI 1.44–3.63), angina diagnosis according to patient opinion (OR 1.70; 95% CI 1.13–2.55), and medication for dyslipidaemia (OR 1.51; 95% CI 1.02–2.23), adjusted for age, systolic blood pressure, previous CV events, and gender (Table 3). In regression models of patients stratified by gender, exertional chest pain and ST-T segment changes on resting ECG were independently significant among women and men; self-assessment of angina was significant among women (OR 1.86; 95% CI 1.04–3.34) but did not reach significance among men (OR 1.48; 95% CI 0.83–2.63). Medication for dyslipidaemia was not included as a determinant in the final model because pre-treatment serum cholesterol levels were unavailable and prescription of lipid-lowering drugs is dependent on prescription traditions.

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**Table 3 Adjusted ORs for positive/inconclusive vs. negative exercise ECG (n=850)**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest pain walking uphill or in a hurry</td>
<td>2.46 (1.69–3.59)</td>
</tr>
<tr>
<td>Pathologic ST-T segment on resting ECG</td>
<td>2.29 (1.44–3.63)</td>
</tr>
<tr>
<td>Angina diagnosis according to patient’s opinion</td>
<td>1.70 (1.13–2.55)</td>
</tr>
<tr>
<td>Dyslipidaemia, medication for</td>
<td>1.51 (1.02–2.23)</td>
</tr>
<tr>
<td>Age</td>
<td>1.01 (0.99–1.03)</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>1.01 (1.00–1.02)</td>
</tr>
<tr>
<td>Previous cardiovascular event</td>
<td>1.02 (0.63–1.64)</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.16 (0.82–1.64)</td>
</tr>
</tbody>
</table>

OR: odds ratio. CI: confidence interval. ECG: electrocardiogram. TIA: transitory ischaemic attack. Cardiovascular event: myocardial infarction, revascularization, stroke, or TIA. Positive exercise ECG: angina symptoms and depression of ST segment >0.1 mV during the test. Inconclusive exercise ECG: angina or ST depression. Negative exercise ECG: neither angina nor ST depression.
**Diagnostic accuracy of predicting variables:** The diagnostic accuracy of predicting variables was evaluated one by one (Table 4a) and in combinations (Table 4b). The pre-test probability for a positive/inconclusive exercise ECG was 23.2%, equal to the prevalence of positive/inconclusive exercise ECG results (n=197) out of all assessable results (n=850). In the single characteristics model of exercise ECG outcome, the number of patients per positive/inconclusive exercise ECG was 3.0 for exertional chest pain, 2.5 for pathologic ST-T segment on resting ECG, and 2.6 for angina diagnosis according to patient’s opinion. In the combined characteristics model, the number of patients per positive/inconclusive exercise ECG decreased to 1.4 for the combination of exertional chest pain, pathologic ST-T segment, and angina diagnosis according to patient’s opinion, corresponding to a net gain of 48.3% (95% CI 31.6–60.7) for the combination of all three predicting variables (Table 4b).

In a theoretical simulation of ROC curves of predictive variables, the area under the curve (AUC) increased up to 0.82 for the combination of three predictive variables of exertional chest pain, pathologic ST-T segment, and angina diagnosis according to patient opinion.

**CV events within 180 days:** CV events occurred in 52.7% of patients with a positive exercise ECG result, compared to 18.3% and 2.0% in patients with inconclusive or negative exercise ECGs, respectively. Within the entire patient cohort, CV events occurred in 8% (69), and 4% (35) of patients had a revascularization. Only two CV events occurred in patients with a predicted negative exercise ECG result (2/104), according to the model. Cases of CV death all involved patients with a positive (n=1) or inconclusive exercise ECG result (n=2). The ORs for any CV event were 54.6 (95% CI 25.5–117.0) in patients with a positive exercise ECG and 11.3 (95% CI 5.6–22.6) in patients with an inconclusive exercise ECG, with negative exercise ECG result as reference.

Evaluation of the predictive model through a bootstrapping procedure demonstrated a good fit between observed data and the model.
Table 4a Diagnostic characteristics of exercise ECG outcome (positive/inconclusive vs. negative)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Exertional chest pain* (95% CI)</th>
<th>Pathologic ST-T segment** (95% CI)</th>
<th>Angina diagnosis according to the patient’s opinion† (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients with characteristic</td>
<td>134</td>
<td>42</td>
<td>80</td>
</tr>
<tr>
<td>Likelihood ratio for positive test</td>
<td>1.7 (1.4–1.9)</td>
<td>2.3 (1.6–3.2)</td>
<td>2.1 (1.7–2.6)</td>
</tr>
<tr>
<td>Likelihood ratio for negative test</td>
<td>0.5 (0.4–0.7)</td>
<td>0.9 (0.8–0.9)</td>
<td>0.7 (0.6–0.8)</td>
</tr>
<tr>
<td>Net gain after positive result</td>
<td>10% (7.2–13.3)</td>
<td>17.2% (9.0–26.0)</td>
<td>15.2% (10.0–20.7)</td>
</tr>
<tr>
<td>Number of patients with characteristic per positive/inconclusive exercise ECG</td>
<td>3.0</td>
<td>2.5</td>
<td>2.6</td>
</tr>
</tbody>
</table>

Chest pain when walking uphill or in a hurry. **Pathologic ST-T segment on resting electrocardiogram. †Patient’s opinion of angina diagnosis: yes, or no. Positive exercise ECG: angina symptoms and ST-segment depression >0.1 mV during the test. Inconclusive exercise ECG: angina or ST depression. Negative exercise ECG: neither angina nor ST depression.

Table 4b Composite diagnostic characteristics of exercise ECG outcome (positive/inconclusive vs. negative)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Exertional chest pain* and pathologic ST-T segment** (95% CI)</th>
<th>Exertional chest pain and angina diagnosis according to patient’s opinion† (95% CI)</th>
<th>Exertional chest pain and pathologic ST-T segment and angina diagnosis according to patient’s opinion (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients with characteristic</td>
<td>26</td>
<td>74</td>
<td>15</td>
</tr>
<tr>
<td>Likelihood ratio for positive test</td>
<td>4.9 (3.1–7.9)</td>
<td>2.7 (2.1–3.4)</td>
<td>8.3 (4.0–18.0)</td>
</tr>
<tr>
<td>Likelihood ratio for negative test</td>
<td>0.7 (0.6–0.8)</td>
<td>0.5 (0.4–0.7)</td>
<td>0.7 (0.6–0.9)</td>
</tr>
<tr>
<td>Net gain after positive result</td>
<td>36.7% (25.0–47.3)</td>
<td>21.8% (16.0–27.7)</td>
<td>48.3% (31.6–60.7)</td>
</tr>
<tr>
<td>Number of patients with characteristic per positive/inconclusive exercise ECG</td>
<td>1.7</td>
<td>2.2</td>
<td>1.4</td>
</tr>
</tbody>
</table>

*Chest pain when walking uphill or in a hurry. **Pathologic ST-T segment on resting electrocardiogram. †Patient’s opinion of angina diagnosis: yes, or no. Positive exercise ECG: angina symptoms and ST-segment depression >0.1 mV during the test. Inconclusive exercise ECG: angina or ST depression. Negative exercise ECG: neither angina nor ST depression.
Study II

**Descriptive data:** The study population consisted of 865 patients (427 women and 438 men) examined with exercise ECG. Half of the patients were manual workers (women 46.9%; men 49.9%). Self-employment was more common among men than among women (18.8% vs. 8.3%; \(p<0.001\)). Most self-employed patients ran single-person companies (63.5%), and few were employers of five persons or more (8%). The medical characteristics of the study patients were previously described in study I (Table 1).

**Main results:** After exercise ECG, all study patients completed follow-up of 180 days for referrals to cardiologic evaluation and 250 days for revascularizations. Of this group, 99 patients were referred to cardiologic evaluation, 79 patients had coronary angiography (6 as emergency cases and 73 after referral for an elective procedure), and 35 patients had revascularizations (18 with bypass grafting and 17 by percutaneous intervention).

**Referrals:** Referral to cardiologic evaluation occurred for 67.3%, 26.1%, 3.5%, and 13.3% of patients with positive, inconclusive, negative, or non-assessable exercise ECG, respectively. Overall, the socioeconomic level, assessed by the SEI classification or by employment status, did not discriminate for referral to cardiologic evaluation. Within non-manual employees, referrals to cardiologic evaluation occurred less frequently among women (5.8%) than men (14.8%) \((p=0.009)\); this difference remained significant after adjustment for exercise ECG result, exertional chest pain, and age (OR 0.40; 95% CI 0.16–1.00; \(p=0.049\)).

**Interaction between gender and socioeconomic status:** The probability of referral to cardiologic evaluation was higher among self-employed women compared to women who were employees, adjusted for age, exertional chest pain, and exercise test result (OR 3.62; 95% CI 1.19–10.99). Employed men had a higher OR for referral compared to employed women but not to significance (OR 1.73; 95% CI 0.99–3.01), adjusted for confounding (Table 5).
Table 5 ORs (95% CIs) for referral to cardiologic evaluation according to gender and employment status

<table>
<thead>
<tr>
<th>Gender</th>
<th>Employment status</th>
<th>ORs (95% CIs)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Employed</td>
<td>Self-employed</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1.00 (n=352)</td>
<td>3.62 (1.19–10.99) (n=32)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1.73 (0.99–3.01)  (n=332)</td>
<td>1.87 (0.76–4.61) (n=77)</td>
<td></td>
</tr>
</tbody>
</table>

ORs were adjusted for age, exertional chest pain, and positive/inconclusive exercise ECG outcome vs. negative exercise ECG outcome. Referrals to cardiologic evaluation occurred within 6 months from exercise ECG procedure. Employed females were reference.

Self-employed patients: Characteristics for self-employed patients showed no significant differences between women and men, except for previous revascularizations, which were 13.2% and 0% among self-employed men and women, respectively (p=0.032).

Multivariable models: In the comprehensive model (n=865), a positive/inconclusive exercise ECG (vs. negative exercise ECG results) (OR 12.43; 95% CI 7.49–20.64) and exertional chest pain (OR 2.71; 95% CI 1.57–4.68) were associated with referral to cardiologic evaluation, adjusted for age and gender.

Predictive variables of referral were calculated in adjusted models stratified by gender. In the female patient model, exercise ECG result (positive/inconclusive vs. negative), exertional chest pain, prior revascularization, and self-employment were all associated with referral, adjusted for age. In the male patient model, exercise ECG result, exertional chest pain, and ST-T wave abnormalities on the resting ECG were associated with referral to cardiologic evaluation (Table 6).
**Employment status:** Among employees, the probability for referral in women compared to men was just below the level of significance (OR 0.58; 95% CI 0.33–1.01; p=0.053), adjusted for exercise ECG result, exertional chest pain, and age. The probability of referral was not associated with the employment grade according to SEI (among employees) or with the number employed in enterprise (among self-employed/employers).

**Age gradient in the probability of referral:** Among patients with a positive exercise ECG, the proportion of patients who were referred to cardiologic evaluation decreased by increasing age, in decades (p=0.024 for trend) (Table 7). This age gradient in referrals was still significant after adjusting for confounding from co-morbidity (revascularization, MI, TIA, stroke, or exertional chest pain symptoms) (p=0.042).

**CV events among patients with a positive exercise ECG:** Among patients with a positive exercise ECG without subsequent referral to cardiologic evaluation, CV events occurred in 22.2% (4/18; two revascularizations, one patient hospitalized for unstable angina, and one CV death), compared to a 56.8% CV event rate (21/37) in referred patients.

In 33.3% (6/18), the non-referred patients were re-evaluated, with few symptoms on medication. In 55.5% (10/18) of ECG-positive non-referred patients, the medical records did not provide any information about decisions based on exercise ECG outcome.
Table 6 Multivariable models of characteristics for referral to cardiologic evaluation in women and men

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>OR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women (n=427)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive/inconclusive exercise ECG vs negative</td>
<td>11.07 (5.11–23.95)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Exertional chest pain symptoms</td>
<td>2.40 (1.03–5.63)</td>
<td>0.043</td>
</tr>
<tr>
<td>Prior revascularization</td>
<td>5.15 (1.33–19.97)</td>
<td>0.018</td>
</tr>
<tr>
<td>Self-employment</td>
<td>3.92 (1.29–11.92)</td>
<td>0.016</td>
</tr>
<tr>
<td>Age</td>
<td>0.99 (0.96–1.03)</td>
<td>0.589</td>
</tr>
<tr>
<td>Men (n=438)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive/inconclusive exercise ECG vs negative</td>
<td>13.60 (6.77–27.33)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Exertional chest pain symptoms</td>
<td>3.22 (1.52–6.85)</td>
<td>0.002</td>
</tr>
<tr>
<td>Pathologic ST-T segment on resting ECG</td>
<td>2.42 (1.07–5.49)</td>
<td>0.034</td>
</tr>
<tr>
<td>Age</td>
<td>1.01 (0.98–1.04)</td>
<td>0.655</td>
</tr>
</tbody>
</table>

Follow-up of referrals until 6 months after exercise ECG. Positive exercise ECG: angina symptoms and depression of ST segment >0.1 mV during the test. Inconclusive exercise ECG: angina or ST depression. Negative exercise ECG: neither angina nor ST depression.
Table 7 Referral to cardiologic evaluation within 6 months, patients with positive exercise ECG results, stratified by age (n=55)

<table>
<thead>
<tr>
<th>Years of age</th>
<th>Patients referred to cardiologic evaluation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>40–49</td>
<td>4 (100%)</td>
</tr>
<tr>
<td>50–59</td>
<td>5 (83.3%)</td>
</tr>
<tr>
<td>60–69</td>
<td>14 (73.7%)</td>
</tr>
<tr>
<td>70–79</td>
<td>12 (57.1%)</td>
</tr>
<tr>
<td>80–89</td>
<td>2 (40%)</td>
</tr>
<tr>
<td>All ages</td>
<td>37 (67.3%)</td>
</tr>
</tbody>
</table>

Two-sided exact test for trend, p=0.024.

Study III

**Descriptive data:** The study sample was 265 patients (89 women) identified after a first-time MI. The mean age of the study patients was 68.1 years (women 72.6 years), and the majority were manual workers (62.7%). Most patients used ambulance transport to the hospital (76.6%), 5 by air ambulance and 198 by road ambulance. A primary care facility was the FMC for 52.3% of all patients, in 22.3% as a personal consultation with a GP and in 30% by telephone counselling from a primary care clinic or from the SHD. The EMS was the FMC in 37.3%, and 10.4% of patients were self-referred to the hospital. MIs were finally classified as STEMI (97 patients) or NSTEMI (168 patients).

**Main results:** The prehospital delay of the entire study sample was a median 5.1 (IQR 18.1) hours, decision time was a median 3.1 hours (IQR 10.4), and transport time was a median 1.2 hours (IQR 1.0). No significant differences in prehospital delay, decision time, or transport time were observed between men and women. Median transport time was longer among patients living in a rural community (1.65 hours; IQR 1.1), compared to the central community (0.78 hours; IQR 0.5).

Patient decision time was not significantly different in rural communities compared to the central community. Total prehospital delay and decision time had highly skewed distributions, with some very high values.

The estimated uncertainty in time of symptom onset was median 0.0 hours (IQR 1.0), with an 80th percentile of 2.0 hours.
**Univariate analysis:** Patients with a prolonged prehospital delay (≥2 hours), lived at a greater distance from the hospital, were more often diagnosed with diabetes, reported recurrent angina symptoms more frequently, and reported a personal visit to a GP before referral in 26.9% of cases. Patients with shorter prehospital delay (<2 hours) had more often called the EMS or used self-referral to the hospital, and they reported chest pain symptoms at triage more frequently. Chest pain was the predominating symptom at triage, with a predominance of chest pain in patients with prehospital delay ≥2 hours (80.6%) and <2 hours (92.3%).

**A multivariable model:** Consultation with a GP was associated with total prehospital delay (OR 10.77; 95% CI 2.39–48.59) and decision time ≥2 hours (OR 3.85; 95% CI 1.66–8.90) in a multivariable regression model. A telephone call to a primary care facility before referral was associated with a total prehospital delay ≥2 hours (OR 3.82; 95% CI 1.68–8.68) and with a decision time ≥2 hours (OR 2.00; 95% CI 1.03–3.87). A predominance of chest pain symptoms was associated with shorter prehospital delay (OR 0.24; 95% CI 0.08–0.77) and decision time (OR 0.34; 95% CI 0.12–0.90). Distance from the patient’s place of residency to the hospital was associated with a longer total prehospital delay but not with decision time. The determinants of the multivariable model were evaluated for discriminatory ability according to ROC curves of total prehospital delay (AUC=0.84; 95% CI 0.79–0.90; p<0.001) and decision time (AUC=0.68; 95% CI 0.60–0.76; p<0.001).

**First medical contact (FMC):** Total prehospital delay for patients with FMC to a primary care facility (by personal visit or telephone call) was 8.7 (IQR 33.3) hours. The prehospital delay increased sharply in primary care patients with private transport to the hospital (20.9 hours; IQR 69.1) and in primary care patients with private transport and rural residency (74.0 hours; IQR 140.8).

A total of 67% of primary care patients had a decision time ≥2 hours, compared to 44.7% of patients who called EMS or self-referred to the hospital (p=0.002). Compared to other patients, patients with FMC to a primary care facility were approximately 3 years younger, lived farther from the hospital, had recurrent angina symptoms before MI more often, reported a lower pain intensity at triage, and had less often obtained help from friends or relatives to contact healthcare. Finally, primary care patients were less often diagnosed with STEMI (Table 8).

**Doctor’s delay:** Three cases were identified in which a medical error contributed to a prehospital delay ≥2 hours. In two cases, patients were sent home but returned to the primary care clinic because of persistent symptoms; one patient was kept waiting ≥2 hours before referral to the hospital by ambulance.
Table 8 Characteristics of patients with first-time myocardial infarction (MI), stratified by first medical contact (FMC)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>FMC</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Primary care facility, by personal visit or telephone call</td>
<td>Call to EMS or self-referral to hospital</td>
</tr>
<tr>
<td>Decision time ≥2 hours, % of patients with characteristic</td>
<td>67.0%</td>
<td>44.7%</td>
</tr>
<tr>
<td>Mean age, years (SD)</td>
<td>66.3 (12.0)</td>
<td>69.7 (10.9)</td>
</tr>
<tr>
<td>Median distance to hospital, km (IQR)</td>
<td>37.5 (10.0–99.5)</td>
<td>21.0 (4.0–68.5)</td>
</tr>
<tr>
<td>Recurrent angina before MI, % of patients with characteristic</td>
<td>34.6%</td>
<td>21.8%</td>
</tr>
<tr>
<td>Pain intensity at triage, mean value (SD)*</td>
<td>5.1 (3.1)</td>
<td>6.3 (2.9)</td>
</tr>
<tr>
<td>Accessed healthcare by help from relative/friend, % of patients with characteristic</td>
<td>20.5%</td>
<td>38.8%</td>
</tr>
<tr>
<td>STEMI, % of patients with characteristic</td>
<td>25.7%</td>
<td>49.2%</td>
</tr>
</tbody>
</table>

Study IV

**Descriptive data:** We recruited 931 patients (345 women) hospitalized with a first-time MI. The mean ages of the women and men were 74.7 and 68.2 years, respectively. The complete background of the study population has been described previously [179].

Of all study participants, 4.1% reported a previous revascularization and 5.6% a previous ischaemic stroke or TIA. Angina pectoris, hypertension, diabetes, and PAD were current diagnoses in 11.7%, 54.9%, 18.5%, and 2% of patients, respectively. Current statin treatment was reported by 17.3% of all patients, and 17.8% had a prior diagnosis of CVD. Prior-CVD patients (mean age 78.3 years) compared to non–prior-CVD patients (mean age 68.9 years) received more pharmacotherapy for CVD and for diabetes (p<0.002). The mean LDL cholesterol level was 3.0 (1.1 SD) in patients with prior CVD and 3.3 (1.1 SD) mmol/L in patients without prior CVD (p=0.010).

Simvastatin was the most prescribed statin (139/161 patients), at a median dose of 20 mg, while other patients were treated with other statins, as single drugs or in combination with other classes of lipid-lowering agents.

Many primary care clinics within the study region were lacking permanent staff GPs, and recruitment of GPs serving on short-term contracts was often necessary. A total of 26% of patients were registered to a primary care clinic classified as high short-term clinic while 38% were registered to a low short-term clinic.

**Main results:** In patients with previously diagnosed CVD, 34.5% received statin treatment, compared to 13.6% in patients without known CVD (p<0.001). In the entire study cohort, 49.1% of patients with diabetes received statin treatment. Patients treated by permanent-staff GPs received statins less frequently compared to patients registered to clinics with medium or high short-term GPs (Table 9). The sample size was considered too small to detect significant differences in the probability of statin treatment between types of primary care clinics, stratified by prior CVD. A SCORE risk was computed for patients aged 40–65 years without known CVD or diabetes. Among patients with a SCORE risk ≥5%, only 4.3% (3/70) received statin treatment.

**Patients with prior CVD:** There was a decreasing trend of statin treatment by age (p<0.003 for trend) (Table 10); the same trend applied also with patients stratified by type of primary care clinics: low short-term clinics (p=0.037 for trend) and medium-to-high short-term clinics (p=0.010 for trend) (Figure 1). Treatment with other major classes of CV drugs, including acetylsalicylic acid, did not diminish with increasing age.

Age ≥70 (OR 0.30; 95% CI 0.13–0.66) and female gender (OR 0.39; 95% CI 0.20–0.78) were inversely associated with statin treatment whereas diabetes had a positive correlation with statin treatment (OR 3.52; 95% CI 1.75–7.08) (Table 11).
**Statin treatment by gender and age, the entire patient cohort:** There was an interaction between age and female gender: age ≥70 years (OR 1.29; 95% CI 0.79–2.11), female gender (OR 1.88; 95% CI 1.02–3.50), and age ≥70 by female gender (OR 0.24; 95% CI 0.11–0.54), with diabetes and prior CVD as covariates (Table 11).

The probability of statin treatment was approximately three times as high in women <70 years compared to women ≥70 years (OR 3.24; 95% CI 1.64–6.38), and in patients ≥70 years, the probability of statin treatment was twice as high among men (OR 2.22; 95% CI 1.31–3.76), adjusted for prior CVD and diabetes (female patients ≥70 served as reference).

**Table 9 Statin treatment before the first-time myocardial infarction, by primary care clinic types (n=928)**

<table>
<thead>
<tr>
<th>Primary care clinic types</th>
<th>Proportion (%) of patients receiving statin treatment</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–9% (low short-term clinics)</td>
<td>48/351 (13.7%)</td>
<td>0.047</td>
</tr>
<tr>
<td>10–39% (medium)</td>
<td>54/255 (21.2%)</td>
<td></td>
</tr>
<tr>
<td>≥40% (high)</td>
<td>59/322 (18.3%)</td>
<td></td>
</tr>
</tbody>
</table>

Primary care clinic types: Proportion of total GP salaries paid to GPs working on short-term contracts. P: Chi-squared test for a 2×3 table.

**Table 10 Statin treatment prior to first-time myocardial infarction in patients with known CVD, by age (n=165)**

<table>
<thead>
<tr>
<th>Age, years</th>
<th>Proportion of patients with statin treatment (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤59</td>
<td>3/5 (60%)</td>
</tr>
<tr>
<td>60–79</td>
<td>35/79 (44.3%)</td>
</tr>
<tr>
<td>≥80</td>
<td>19/81 (23.5%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>57/165 (34.5%)</td>
</tr>
</tbody>
</table>

CVD: cardiovascular disease, a composite of diagnoses including angina pectoris, prior revascularization, ischaemic stroke/transitory ischaemic attack, or peripheral artery disease (PAD). PAD comprised leg artery disease, a stenosing lesion of the carotid, or atherosclerotic aneurysm. P<0.003 for trend.
Figure 1 Estimated probability of statin treatment in patients with prior CVD, by age and primary care clinic types
Table 11 Probability of statin treatment (crude and adjusted ORs; 95% CI) in patients with prior cardiovascular disease (CVD) and in the entire study cohort

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients with prior CVD (n=165)</th>
<th>Patients from the entire cohort (n=928)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Crude OR (95% CI)</td>
<td>Adjusted OR (95% CI)</td>
</tr>
<tr>
<td>Age ≥70 years</td>
<td>0.30 (0.13–0.66)</td>
<td>1.29 (0.79–2.11)</td>
</tr>
<tr>
<td>Female gender</td>
<td>0.39 (0.20–0.78)</td>
<td>1.88 (1.02–3.50)</td>
</tr>
<tr>
<td>Age ≥70 by female gender*</td>
<td>NA</td>
<td>0.24 (0.11–0.54)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>3.52 (1.75–7.08)</td>
<td>8.55 (5.72–12.79)</td>
</tr>
<tr>
<td>Prior CVD</td>
<td>NA</td>
<td>3.27 (2.08–5.13)</td>
</tr>
</tbody>
</table>

Discussion

Primary care patients examined with exercise ECG

Patients with a negative exercise ECG had a very low risk of CV events within 6 months of follow-up (study I). The likelihood of CV events in patients with a positive or inconclusive exercise ECG was considerably increased compared to patients with a negative exercise ECG. The observed outcome rate in patients with a negative exercise ECG was about equal to the predicted rate, according to a multivariable predictive model. The predictive model consisted of three variables that were independently associated with the exercise ECG outcome: exertional chest pain, a pathologic ST-T segment on the resting ECG, and angina diagnosis according to the patient’s opinion.

Referral decisions and bias

Referrals to cardiologic evaluation (study II) were strongly associated with exercise ECG outcome and exertional chest pain. Overall, we found no differences in referral rates related to age, gender, or socioeconomic status. With respect to referral rates, gender and socioeconomic status interacted; self-employed women were about three times more likely to be referred compared to employed women, adjusted for exercise ECG result, exertional chest pain, and age. Among non-manual employees, women were less often referred to cardiologic evaluation compared to men, adjusted for confounding. Among patients with a positive exercise ECG, the referral rates decreased significantly with increasing age.

Prehospital delay

The median total prehospital delay (study III) was 5.1 hours, and transport time to the hospital contributed less than decision time. Shorter prehospital delay was associated with chest pain as the presenting symptom. A prolonged prehospital time (≥2 hours) was associated with patient FMC with a primary care facility. About half of patients reported their FMC as a primary care facility, either as a personal visit or as primary care telephone counselling.
Statin treatment before a first-time AMI

Current statin treatment was reported only among one third of patients with known CVD, despite evidence in support of statin treatment in patients at high CV risk. Among patients with prior CVD, higher age and female gender were associated with a lower probability of statin treatment. The probability of statin treatment among diabetes patients was higher compared to non-diabetics.

The probability of statin treatment in women <70 years was about three times the probability of statin treatment in women ≥70 years; and the probability of statin treatment in men ≥70 years was about twice the probability of treatment in women of the same age, adjusted for confounding from diabetes and prior CVD.

Within the entire cohort, patients treated by permanent staff GPs received statin treatment less often, compared to patients who were registered at clinics with GPs working on short-term contracts.

Comparisons and interpretation of findings

Studies I and II

The low CV event rate during follow-up among our study patients with a negative exercise ECG result was comparable to findings in a Finnish cohort. Those previous authors reported a 2% to 3% CV event rate within 2 years in middle-aged and elderly patients with negative exercise ECG tests [53, 54].

At the cut-off level of 1 mm ST-segment depression on exercise ECG, the estimated likelihood ratio for disease after a positive exercise ECG is 2.79, and after a negative test 0.44 [50], which are only moderately strong estimates. Interpretation of exercise ECG results should therefore be made in consideration of the risk profile and clinical history. The marked differences in CV event rates observed among our study patients supported the use of exercise ECG outcome as a proxy for underlying coronary disease.

The classification of exercise ECG results by dynamic ECG changes and chest pain symptoms was according to Swedish standards for exercise ECG testing [48, 52] but deserve some consideration. In the regression models, we applied a bivariate approach: Patients with positive and inconclusive exercise ECG results were treated as one group and compared to patients with a negative exercise ECG. This approach has similarities in clinical decision-making because chest pain symptoms as well as ECG changes indicative of coronary insufficiency need to be considered for appropriate treatment.

Exertional chest pain: The association between chest pain symptoms and IHD is established knowledge [15]. Chest pain on exertion was an independent predictor of exercise ECG outcome among our study patients, and this finding was expected.
Self-assessment of angina: We used self-assessment of angina as a bivariate variable: “Angina pectoris according to the patient’s own opinion” with “yes” or “no”. This approach was used to avoid uncertainty about patient evaluation of symptoms. In the entire study cohort, patient self-assessment of angina was a significant predictor of the exercise ECG outcome (Table 3). In the regression models, self-assessment of angina remained significant among women but did not reach the level of significance among men. It is likely that the smaller sample size after stratification for gender was relevant for this inconsistency.

Comparisons with the Marburg Heart Score: Self-assessment of angina was also used by the authors of the “Marburg Heart Score”, described as “Patient assumes pain is of cardiac origin” [8].

In our study cohort, neither age nor prior CV events remained as significant determinants of disease in the multivariable model, a contrast compared to the findings in the Marburg cohort. Possible explanations for these disparities are considered below.

First, in our study, we applied a pragmatic approach, with enrolment of patients due to a suspected IHD according to the referring GP, not because of chest pain symptoms explicitly. In addition, patients with atypical pain symptoms could be included in our cohort. This approach is close to decision-making in clinical practice because patients with atypical chest pain symptoms also should be carefully evaluated because of an increased risk of CV events [15, 186].

Second, treatment of age as a continuous variable, or dichotomized as in the Marburg cohort, could have contributed to different results.

Third, in our study cohort, we included the resting ECG reading as a determinant of exercise ECG outcome. A resting ECG is normally recorded and evaluated at the GP’s office, before referral for exercise ECG testing. During the exercise ECG procedure, a dynamic ST-segment depression is used as a criterion for myocardial ischemia during exercise. The often observed ST-T wave abnormalities on resting ECGs are not to be confused with the dynamic ST depressions observed during exercise ECG testing [48]. Resting ECG outcome was not included as a determinant of the Marburg score.

Another reason to perform a resting ECG before exercise ECG referral is that certain resting ECG abnormalities, e.g., left bundle branch block, make evaluation of the ECG reaction during exercise non-assessable.
The prognostic importance of resting ECG recordings: The usefulness of a resting ECG for assessment of coronary disease in primary care is described with different results. Pathologic Q waves and ST-T segment abnormalities have been associated with coronary disease and survival prognosis, within 3 years [187]. A review of several prior studies focused on the relevance of resting ECG and concluded that resting ECG has only limited value for evaluation of suspected angina in primary care patients [24].

Among our study patients, we found that ST-T segment abnormalities on the resting ECG were associated with exercise ECG outcome. Pathologic Q waves on the resting ECG, a sign of myocardial scarring, were not associated with the outcome of exercise ECG among our patients.

Recent reports indicate that the prognostic importance of resting ECG recordings, deserves to be re-evaluated [188, 189].

Different reference standards: Comparison of our study results with findings in other cohorts is not a straightforward operation because of differences in reference standards. The Marburg score research team used an external expert panel as reference standard, and they described “Pain not reproduced by palpation” as a specific modality of chest pain [8]. Such methodological differences are likely to have contributed to differences in comparison with our findings.

Observed and predicted CV event rates: A delayed-type of reference standard was used in several previous studies, focused on symptom evaluation in primary care [14, 23, 26, 38, 190, 191]. Validation of CAD by angiography is not routine in primary care, where the expected prevalence of disease is lower than in hospital care. As long as follow-up for CV outcome is complete, a delayed-type of reference standard is clinically relevant. Among our study patients, the observed CV event rate to 180 days was very low in patients with a negative exercise ECG result; only 4/653 patients had a revascularization, and no cases of CV death occurred among the exercise ECG–negative patients.

We applied a ≥10% probability cut-off to detect CV events for the predictive model to be clinically useful. Clinical usefulness depends on the trade-off between the ability to rule in high-risk patients (in the hospital setting) and ruling out of low-risk patients (in the primary care setting). Evaluation of prediction models intended for use in clinical practice should consider the main purpose and the clinical context in which the model is to be used [192].
Age, gender, and socioeconomic status: The reasons that age, and interactions between gender and socioeconomic position, affected referral rates after exercise testing deserve consideration. A framework from a theoretical viewpoint is provided from gender theory and intersectionality [58, 193, 194]. Within the framework of intersectionality, described as “the relationships among multiple dimensions and modalities of social relations and subject formations” [194], different dimensions of social identity (gender, socioeconomic class, education, age, ethnicity) within various fields of health-related research may be brought under study [193].

Among our female patients, self-employed women had a higher probability of referral compared to other women, but we observed no such gradient among male patients. Thus, GP referrals were biased by employment status and gender combined.

Among employed patients, the difference in probability of referral between women and men bordered on significant. We can therefore not rule out that male employees had a higher probability of referral compared to female employees. Such gender-related differences have been described previously [59].

Reasons for a referral bias related to gender and self-employment combined may trace to preconceptions about professional normality, in which self-employed females may be viewed as different compared to a stereotyped view of self-employed professionals.

The declining referral rates, noted from ages 40–49 years and higher in patients with a positive exercise ECG, was an unexpected finding. A genuine age-related bias in clinical decision-making is plausible because the declining referral gradient with increasing age remained significant after adjustment for co-morbidity. Patient willingness to undergo invasive cardiac procedures might also be decreased at greater ages, an option not explored within our study.

A previous revascularization was a significant determinant of referral only among women, and ST-T segment abnormalities on resting ECG were important only among men. These findings, without any obvious medical explanations, may reflect opinions about “normality”, in which unexpected findings gain more attention and subsequent referrals.

The reason that some patients with a positive exercise ECG were not considered for cardiologic evaluation was not always supported by documentation in medical records. One cause of incomplete documentation might have been a lack of continuity of care in primary care clinics, with a high proportion of GPs serving on short-term contracts.
**Study III**

The total prehospital delay among our study patients (5.1 hours) was longer than we had expected from previous reports. A prehospital delay of 2–3 hours was reported in the European study arm of the Global Registry of Acute Coronary Events (GRACE) cohort, years 2000–2006 [113]. A prehospital delay ≥2 hours was found in 64% of diabetes patients and in 58% of those without diabetes in a report based on the Northern Sweden MONICA cohort [90]. A prehospital delay roughly comparable to ours was reported from a recent Irish patient cohort in which a median prehospital delay of 4.1 hours was found among acute coronary syndrome patients [106].

We recruited patients without an upper age limit, but age was not a determinant of prehospital delay ≥2 hours in our patient cohort. In the MONICA cohort, an upper age of 74 years was applied.

**Prehospital delay and context:** We found that FMC to a primary care clinic was associated with prolonged total prehospital delay and with longer decision time. The relation between patient and healthcare provider may have contributed to prehospital delay, especially if patients hold the view that calling primary care always is the most appropriate action [95, 103-107, 195-197].

Among our study patients, manual workers were the predominant social class, and few patients had a higher educational level. At any rate, socioeconomic status was not a determinant of prehospital delay in our study, in contrast to some previous reports [101, 116, 198, 199]. These diverging findings might arise from differences in accessibility of healthcare and from different definitions of socioeconomic status.

**Transport time and decision time:** Transport time was not the major factor in total prehospital delay, despite the fact that many patients lived at considerable distances from the hospital. This outcome underlines that decision time commonly is the major portion of prehospital time and that transport time is a minor, but sometimes crucial, contributor.

Ambulance transport was used by 76.6% of our study patients, a high proportion compared to other Swedish and international cohorts. A common estimate is 40%–50% of patients with acute coronary syndromes transported to hospital by ambulance [200-202]. Of patients with FMC to a GP before hospital admission, 72.4% used an ambulance to get to the hospital. Among patients who called the EMS as FMC, 99% were transported by ambulance.

Patient decision time as the major component of prehospital delay has been reported repeatedly [88, 91-93], despite differences in total prehospital delay. Reasons for a prolonged decision time despite urgent symptoms are largely unexplained.
Health literacy: The concept of health literacy, described as “the cognitive and social skills which determine the motivation and ability of individuals to gain access to, understand and use information in ways which promote and maintain good health” [203], is correlated with outcomes of several medical conditions, adherence to medication, and healthy lifestyle choices [204-207]. Low health literacy may be important in otherwise unexplained cases of prolonged prehospital delay, although this hypothesis was not explored in our study.

Doctor’s delay: Doctor’s delay was rarely a cause of prolonged prehospital time among participating patients. Covering the entire scope of shortcomings in medical decision-making would have required including patients who died after out-of-hospital cardiac arrest in the patient cohort.

Study IV

Among patients with previously diagnosed CVD, we found barriers to statin treatment, risk assessment, and implementation of guidelines on CVD prevention.

The total prescription of statins in the study area (98.1 defined daily doses/1000 inhabitants/day) was comparable to the average Swedish prescription of statins (101.6 defined daily doses/1000 inhabitants/day in 2010–2015) [208]. A regional difference in use of statins is unlikely to account for the underuse of statin treatment observed in our study.

External validity: Our study patients were of low average educational level, and many lived at a distance from the hospital in different rural communities. Thus, the external validity of our observations should be evaluated within a larger national or international study sample.

The Swedish RIKS-HIA registry of patients recruited from all Swedish clinics providing acute coronary care is a possibility for such validation [209]. Data provided from the RIKS-HIA registry, 1998–2014, revealed that 38.7% of patients with known CVD (ischaemic stroke, revascularization, or PAD; n=13793) received statin treatment before their first MI episode, with a rising trend up to 54.2% in 2014 (data on file). Patients in our study sample also included those with clinical angina diagnoses but were otherwise comparable to patients in the RIKS-HIA registry, indicating that underuse of statins was not a phenomenon restricted to our study population.

The mean level of LDL cholesterol in our prior CVD patients was 3.0 mmol/L, exceeding the recommended levels according to Swedish guidelines from 2006 (<2.5 mmol/L) [210] and the target level according to the 2012 European guidelines for CVD prevention in risk patients (1.8 mmol/L) [7].
Accordingly, the one third of prior CVD patients treated with statins was consistent with an underuse of cholesterol-lowering therapy among patients in our study population.

**Possible reasons for underuse of statins:** lack of routines for secondary prevention, case-finding, and follow-up of patients with known CVD; decreasing adherence to pharmacotherapy with time from first prescription; statin-related side effects; and insufficient adherence to clinical guidelines among physicians providing care for CVD patients.

**Access to preventive services:** The quality of care provided to CVD patients is associated with access to preventive services, such as case-finding and follow-up routines, and the possibility of CVD risk assessment within the electronic medical record system [211]. Follow-up programmes delivered in primary care or as a nurse-based follow-up programme directed to patients after hospital care are described with improved risk factor management among patients with known CVD [179, 212-214].

**Negative media reporting:** Negative media reporting and general concern about statin-related side effects in relation to perceived need for treatment are associated with discontinuation of long-term drug treatment [167, 215].

**Adherence to therapy:** Long-term adherence to statin therapy is low among elderly patients in primary as well as in secondary prevention [162]. Adherence to statin therapy, estimated as proportion of days covered, was only about 55% in a population-based cohort of patients aged 45–75 years [216]. The defining CV event among our study patients might have occurred long before the first-time MI; thus, a declining adherence to treatment over time was probably important.

Patients treated by permanent-staff GPs received statin treatment less often compared to patients registered at primary care clinics with more short-term GPs. The reason remains unexplained, but this finding is contradictory to an association between adherence to medication and continuity of healthcare [159].

**Statin related side effects:** Our baseline file did not provide data on statin-related side effects, but discontinuation due to myalgic side effects is likely to have reduced the number of patients taking statins. The reported incidence of patients with myalgic side effects diverges by cohort type and study approach. A frequently cited incidence rate of statin-associated myalgia is 10.5% in the PRIMO survey, an observational study conducted in France [145].
Even if side effects are one reason for discontinuation of treatment, continuity of care and follow-up remain essential for evaluation of symptoms experienced during drug therapy.

Most patients with interrupted treatment due to side effects related to statins were able to tolerate long-term treatment after rechallenge with statins, according to a cohort study of patients followed in a routine care setting [152].

Guidelines for CVD prevention: Updated European clinical guidelines for CVD prevention were published in 2012 [7], but adherence to guidelines for CVD prevention is often incomplete in clinical practice [175, 217-219]. New treatment targets may be adopted slowly by GPs, explaining why treatment according to new targets often is a slow process in primary care [171-173]. Patients with diabetes have a raised CV risk, and statin treatment is often indicated. In our patient cohort, statin treatment among diabetic patients (49.1%) exceeded statin treatment among prior-CVD patients (34.5%), although both values were below expected percentages if patients were treated by current guidelines.

Low treatment rate among risk patients: Very few patients with a risk SCORE ≥5% received statin treatment. However, comparison with external population-based cohorts should be made with caution because preventive treatment with statins may be correlated with disease in a bidirectional way of causality.

According to a longitudinal study on ageing, the “TILDA” cohort [220], statin treatment was reported in 57.4% of diabetes patients, in 68.8% of patients with prior CVD, and in 19.7% of patients with a SCORE risk ≥5%. The low statin treatment rate among our risk patients may have been related to incomplete follow-up of patients with prior CVD and incomplete risk scoring in other patient groups. A recall and follow-up programme for diabetes patients in our study area may have contributed to the higher statin treatment rate among diabetes patients compared to prior-CVD patients.

Lower probability of statin treatment in women ≥70 years: The considerably lower probability of statin treatment in women ≥70 years compared to younger women and to men ≥70 years could arise from a combination of reasons. Age and female gender are both associated with an increased risk of statin-related muscle symptoms [158]. Age is associated with underestimation of personal CV risk, according to a survey conducted in urban women, despite the fact that age is a strong independent predictor [170].

Statin treatment in clinics with permanent staff GPs: Within the entire patient cohort, the proportion of patients receiving statin treatment was lower in clinics staffed by predominantly permanent-staff GPs (low short-term clinics) compared to medium and high short-term clinics, for reasons not explained by the study data.
One hypothesis is that permanent-staff GPs were less likely to treat patients according to new guidelines, compared to younger colleagues who served on short-term contracts. Acceptance of patient reluctance to medicate from a risk perspective might differ between permanent-staff and short-term GPs. The down-sloping curve of statin treatment with increasing age was nevertheless similar between types of primary care clinics (Figure 1).

Limitations

General limitations

Socioeconomic status could be determined in different ways; we used employment status and education level. Other measurements could have been income, housing conditions, or liquid assets [221]. We did not treat retired patients as a separate category. Thus, influence from retirement was not possible to assess separately from age.

Some results were based on small numbers or with CIs close to the level of significance; such results should be confirmed in larger samples. Another possibility is that the number of study patients was too small to detect differences with clinical relevance.

Alternative study approaches, such as focus groups, or other qualitative methods, could have been used to understand why GPs fail to undertake medical actions recommended by current guidelines and why certain patients delay seeking care despite urgent symptoms.

Those who died from out-of-hospital cardiac arrest were not included in the study cohort, so the results are not applicable to that subset of patients.

Limitations, studies I and II

Patients contacting primary care for chest pain or discomfort without referral to exercise ECG were not included in the study cohort. Methodologies for differential diagnosing of chest pain is another important field of study.

Blinding of the exercise ECG outcome was not possible because medical records were used without pre-selection of data. Regardless of that, the exercise ECG results were determined by a physician not involved with the research team.

We did not use a method for reference diagnosing of IHD. An external expert panel for reference diagnosing is sometimes applied in clinical research [9, 27-30, 45, 222], but neither external reference panels nor coronary angiography as reference standard are routine in primary care.
Recording of baseline data from a questionnaire is not free from error. An alternative would have been to use medical record data, but neither method is faultless. Medication lists in records are not always up to date, and patient adherence to medication lists may be incomplete. The validity of patient-reported diagnoses of angina has support in previous research [223].

The prediction model (Study I) was evaluated through a bootstrapping procedure. An alternative approach would have been validation in a separate external validation cohort or by dividing the cohort into one derivation cohort and one validation cohort. Dividing of the study cohort would have reduced the statistical power, and an external validation cohort was not available. Validation in an external cohort would be valuable before application of our predictive model in clinical practice.

Among patients not re-examined after exercise ECG, there were probably remaining cases of significant coronary disease. Within an observational study, it is impossible to avoid that kind of limitation.

**Limitations, study III**

Time for onset of symptoms suggestive of MI is the weakest part in assessment of prehospital delay [94]. Time for symptom onset was determined at hospital stay by nursing staff, and we included an estimate of uncertainty in onset time. Among patients with private transport to the hospital, only the total prehospital delay was possible to obtain, and not decision time and transport time separately.

A postal questionnaire with questions on prehospital events and symptoms was sent to patients 3–6 months after the MI episode. Recall bias could therefore not be ruled out.

Prehospital delay could also have been treated as a continuous variable. We applied a 2-hour cut-off for determinants of prehospital delay. This limitation allowed for comparisons with other studies that used a similar cut-off [90, 93, 105, 113, 224].

**Limitations, study IV**

Data were lacking about the date of initiation of statin treatment and discontinuation of treatment. A more comprehensive dataset would have been useful to explore reasons for lacking treatment with statins in patients at high CV risk.

Angina pectoris was determined as a clinical diagnosis and not confirmed by invasive procedures because invasive procedures are not always justified in the primary care setting [187, 225].
Because pre-treatment levels of cholesterol were unavailable, statin treatment in patients without prior CVD was evaluated from data obtained by admission to hospital.

To compare statin treatment in different types of primary care clinics, we applied an economic measurement, “salaries paid to GPs working on short-term contracts”, and not a direct measurement at the provider–patient level. Firm conclusions regarding the importance of continuity of care would require a measurement at the level of care.

Clinical importance and future aspects

Referrals to exercise ECG and to cardiologic evaluation: A predictive model of clinical characteristics was useful for identification of low-risk patients, before referral to exercise ECG. Exercise ECG results were relevant for referral decisions of primary care patients to further cardiologic evaluation, but interactions between gender, socioeconomic status, and age affected the referral rates. To avoid bias, heuristics to support clinical decision-making need to be developed and validated in normal care.

Prehospital delay: Determinants of prehospital delay were related to patient decision processes and symptoms at onset of disease. The substantial prehospital delay among MI patients seen in primary care highlights the importance of educating patients to call the EMS in cases of new-onset chest pain. Limited health literacy, as a possible contributor to prolonged decision time in MI patients, should be researched further to target appropriate actions.

Statin treatment: The age- and gender-related aspects of deficient treatment with statins in patients at high CV risk have not gained sufficient previous attention. Because of the high risk of CV death or new events, patients with prior CVD should be targeted for designed recall and follow-up programmes. Electronic medical records should be developed as tools for efficient management of at-risk patients. The use of risk assessment by scoring algorithms should be encouraged in patients without known CVD.
Conclusions

- Patients with a negative exercise ECG result have a benign prognosis up to 6 months. Patient characteristics, combined in a predictive model, could be used for identification of low-risk patients before an exercise test is requested.

- Exercise ECG results are important for selection of primary care patients for cardiologic evaluation. Referral rates are also affected by bias related to gender, socioeconomic status, and age, with decreasing probability of referral by increasing age in patients with a positive exercise ECG.

- Patients with a first-time MI had a considerably prolonged prehospital delay, particularly if the FMC was to a primary care facility. To reduce prehospital delay in patients with first-time MI, it is necessary to increase the use of EMS and shorten patient decision time.

- In patients with known CVD, we found a deficient use of statin therapy, in particular to the disadvantage of women and elderly patients. Overall, patients treated by permanent-staff GPs were less often on current statin treatment before a first-time MI.

- To bridge the gap between clinical guidelines and treatment in practice, it is necessary to improve and implement methods for case-finding, recall, and follow-up of patients in clinical practice.
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Appendices
Appendix A

Primärvården i Jämtlands län i 
samarbete med 
Fysiologavdelningen Östersunds 
sjukhus

Enkätfrågor

Alla svar är viktiga för undersökningen.

Om du är tveksam, svara efter bästa förmåga.

Frågor 1-15, om din medicinska bakgrund.

1. Kön:

□ Man
□ Kvinna

2. När är du född?

__________________________ (årtal)
3. Den doktor som remitterade mig var:

☐ Man

☐ Kvinna

4. Är du rökare?

☐ Jag är rökare

☐ Jag har tidigare rökt, men slutat.

☐ Jag har aldrig varit rökare.

5. Medicinerar du för högt blodtryck?

☐ Ja

☐ Nej

6. Har du sockersjuka, behandlad med kost, tabletter eller insulin?

☐ Ja

☐ Nej
7. Medicinerar du för höga blodfetter/högt kolesterolvärde?

☐ Ja

☐ Nej

8. Medicinerar du för hjärtsvikt/svagt hjärta?

☐ Ja

☐ Nej

9. Har du tidigare vårdats för hjärtinfarkt?

☐ Ja

☐ Nej

10. Har du tidigare undersöks med arbets-EKG?

☐ Ja

☐ Nej
Om du svarade Ja, vid vilket sjukhus blev du undersökt?

____________________________________________________(sjukhusets namn)

11. Har du tidigare undersöks med kranskärlsröntgen?

□ Ja

□ Nej

Om du svarade Ja, vid vilket sjukhus blev du undersökt?

____________________________________________________

12. Har du tidigare undersökt hjärtat med s.k. scintigrafi, ”isotopröntgen”

□ Ja

□ Nej

Om du svarade Ja, vid vilket sjukhus blev du undersökt?

____________________________________________________
13. Har du opererat hjärtats kransärl, med ”bypass” eller ballongvidgning?

□ Ja
□ Nej

Om du svarade Ja, vid vilket sjukhus blev du opererad?
_____________________________________________________________(sjukhusets namn)

14. Har du tidigare drabbats av slaganfall i hjärnan, så kallad TIA eller stroke?

□ Ja
□ Nej

15. Har du fönstertittarsjuka, artärsjukdom i benen?

□ Ja
□ Nej
Här följer några frågor om dina förväntningar eller farhågor inför undersökningen. Vilken är Din Egen uppfattning?

16. Är din egen uppfattning att du har kärlkramp i hjärtat?

☐ Ja

☐ Nej

17. Tror Du själv att undersökningen med arbets-EKG kommer att visa att Du har kärlkramp i hjärtat?

☐ Ja

☐ Nej

18. Vilka är Dina känslor inför undersökningen med arbets-EKG

Markera med X på den heldragna linjen hur Du känner dig

Helt lugn

Mycket stark oro
Frågor om eventuell smärta i bröstet: [Frågor 19-21 användes i översättning från formuläret ”Rose Angina questionnaire”]

Kryssa för det alternativ som gäller för dig.

19. Brukar du ha smärta eller obehag i bröstet?

□ Ja

□ Nej

20. När du går i normal takt på plan mark, får du då ont i bröstet?

□ Ja

□ Nej
21. När du går i motlut eller måste skynda dig, får du då ont i bröstet?

☐ Ja

☐ Nej
Här följer några frågor om utbildning och yrkesliv. [Frågor 22-32 är enligt SEI klassifikationen; Socioekonomisk indelning (SEI) 1982. Mis 1982:4, SCB; nytryck 1984, Bilaga 1]

22. Vad gjorde Du förra veckan? Kryssa för det eller de alternativ som gällde för Dig.

Jag var:

- [ ] Anställd
- [ ] Tjänstledig (inklusive barnledig, sjukskriven och ledig för studier)
- [ ] Skötte eget lantbruk
- [ ] Skötte eget företag
- [ ] Studerade
- [ ] Arbetslös, permitterad eller väntade på arbete
- [ ] Arbetslös sedan mer än ett halvt år
- [ ] Hjälpte till i familjemedlems lantbruk
- [ ] Hjälpte till i familjemedlems företag
- [ ] Förtidspensionerad
- [ ] Ålders eller tjänstepensionerad
- [ ] Skötte hushållet
- [ ] Gjorde militärtjänst
- [ ] Sjukskriven
- [ ] Annat. Ange vad __________________________
23. Vilket av alternativen i FRÅGA 22, är normalt Din huvudsakliga sysselsättning?

Sätt en ring kring rutan för denna – se ovanstående fråga på föregående sida.
BESVARAS AV DIG SOM ÄR GIFT ELLER SAMMANBOENDE

24. Vad gjorde din make/maka/sambo förra veckan?

Kryssa för de alternativ som gällde för honom/henne.

Min make/maka/sambo var:

☐ Anställd

☐ Tjänstledig (inkusive barnledig, sjukskriven och ledig för studier)

☐ Skötte eget lantbruk

☐ Skötte eget företag

☐ Studerade

☐ Arbetslös, permitterad eller väntade på arbete

☐ Arbetslös sedan mer än ett halvt år

☐ Hjälpte till i familjemedlems lantbruk

☐ Hjälpte till i familjemedlems företag

☐ Förtidspensionerad

☐ Ålders eller tjänstepensionerad

☐ Skötte hushållet

☐ Gjorde militärtjänst

☐ Sjukskriven

☐ Annat. Ange vad __________________________
25. Vilket av alternativen i FRÅGA 24, är normalt din make/makas/sambos huvudsakliga sysselsättning?

Sätt en ring kring rutan för denna – se ovanstående fråga på föregående sida.

Undvik allmänna yrkesbeteckningar såsom hantverkare, lärare, tjänsteman m fl. Skriv utförligare; t ex bilplåtslagare, gymnasielärare, eller socialsekreterare.

Beskriv kortfattat dina arbetsuppgifter!

□ Har aldrig förvärvsarbetat
BESVARAS AV DIG SOM ÄR GIFT ELLER SAMMANBOENDE

27. Vilket är Din make/maka/sambos/ yrke eller befattning?

Förvärvsarbetar han/hon inte nu ska Du ange yrke/sysselsättning som han/hon tidigare huvudsakligen haft.

Undvik allmänna yrkesbeteckningar såsom hantverkare, lärare, tjänsteman m fl. Skriv utförligare; t ex bilplåtslagare, gymnasielärare, eller socialsekreterare.

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Beskriv kortfattat hans/hennes arbetsuppgifter!

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□ Har aldrig förvärvsarbetat
BESVARAS AV DIG SOM ÄR FÖRVÄRVSARBETANDE

28. Är någon personal direkt underställd dig?

□ Ja

□ Nej

________________________________________________

BESVARAS AV DIG SOM BOR I ETT LANTBRUKARHUSHÅLL

(GÄLLER ÄVEN FÖRE DETTA LANTBRUKARHUSHÅLL)

29. Ange lantbrukets storlek

Hektar åkerjord ________________________________

Hektar skog ____________________________________

________________________________________________
BESVARAS AV FÖRETAGARHUSHÅLL
(GÄLLER ÄVEN FÖRE DETTA FÖRETAGARHUSHÅLL)

30. Ange företagets storlek

Antal anställda ___________________________

BESVARAS AV STUDERANDE

31. På vilken nivå studerar Du?

□ Grundskolenivå

□ Gymnasienivå

□ Universitet eller högskola

□ Annat.

Beskriv! ____________________________________________
BESVARAS AV DIG SOM HAR MAKE/MAKA/SAMBO SOM STUDERAR

32. På vilken nivå studerar Din make/maka/sambo?

- □ Grundskolenivå
- □ Gymnasienivå
- □ Universitet eller högskola
- □ Annat.

Beskriv! __________________________________________
33. Vad har Du för utbildning?

Ange den längsta utbildningen som du avslutat.

□ Grundskola, realskola eller folkskola
□ Tvåårig gymnasieutbildning
□ Tre eller fyraårig gymnasieutbildning
□ Examen från universitet eller högskola
□ Annan utbildning efter gymnasieskola, ange vilken!

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Plats för eventuella egna kommentarer

Stort tack för din medverkan!

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Appendix B

Primärvården i Jämtlands län i samarbete med Hjärtenheten Östersunds sjukhus

Enkätfrågor

Alla svar är viktiga för undersökningen.

Om du är tveksam, svara efter bästa förmåga.

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Här följer två frågor om misstankar eller farhågor under tiden före hjärtinfarkten.

1. Var din egen uppfattning att du hade kärlkramp i hjärtat/angina pectoris, innan den dagen då du fick hjärtinfarkt?

□ Ja

□ Nej

____________________________________________________
2. Hade någon läkare konstaterat att du hade kärlkramp i hjärtat/angina pectoris någon gång före hjärtinfarkten?

□ Ja

Om Ja: Ange om möjligt vilken slags läkare

□ Läkare på sjukhuset

□ Läkare utanför sjukhuset, t. ex distriktsläkare

□ Nej

Här följer sex frågor om hur det var den dagen du drabbades av hjärtinfarkt.

3. Trodde Du själv att det var hjärtinfarkt, den dagen du drabbades av hjärtinfarkt?

□ Ja

□ Nej
4. Den dagen Du blev inlagd för hjärtinfarkt: Vad hände?

Sätt ett kryss i den ruta som stämmer bäst på dig!

☐ Jag beslutade helt själv att kontakta sjukvården

☐ Jag rådgjorde först med någon anhörig, vän eller arbetskamrat, innan jag sökte vård

☐ Någon anhörig, vän eller arbetskamrat tog kontakt i mitt ställe

5. Den dagen du drabbades av hjärtinfarkt: Hur fort sökte du vård?

Sätt ett kryss i den ruta som stämmer bäst på dig!

☐ Sjukvården kontaktades sedan jag hade känt symtom under några minuter till en högst en timme

☐ Sjukvården kontaktades sedan jag hade känt symtom sedan mer än en timme till högst ett dygn

☐ Sjukvården kontaktades sedan jag hade känt symtom sedan mer än ett dygn
6. Den dagen då du blev inlagd för hjärtinfarkt: Vilka förväntningar hade Du på sjukvården när du sökte?

Sätt ett kryss på linjen nedanför, där det passar bäst på dig!

| Mycket låg förväntan | Bästa tänkbara hjälp |

7. När du fick diagnosen hjärtinfarkt: Vilka förväntningar hade Du på din framtida hälsa efter infarkten?

Sätt ett kryss på linjen nedanför, där det passar bäst på dig!

| Mycket dålig hälsa | Fullt frisk igen |
8. Den dagen då du blev inlagd för hjärtinfarkt:

Sätt ett kryss i den ruta som stämmer bäst på dig!

☐ Besökte jag först distriktsläkare och fick remiss till sjukhuset

☐ Ringde jag/någon närstående först till hälsocentralen och blev hänvisad direkt till sjukhuset, efter telefonsamtalen

☐ Ringde jag/någon närstående först till Sjukvårdsrådgivningen, SVR, och blev sedan hänvisad direkt till sjukhuset

☐ Ringde jag/någon närstående till larmcentralen, telefon 112, och blev sedan hänvisad direkt till sjukhuset

☐ Kommer jag inte ihåg vad som hände

☐ Annat händelseförlopp; beskriv vad som hände!

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Tre frågor om hur det känns efter hjärtinfarkten

Kryssa för det alternativ som passar för dig.

9. Brukar du ha smärta eller obehag i bröstet?

□ Ja
□ Nej

10. När du går i normal takt på plan mark, får du då ont i bröstet?

□ Ja
□ Nej

11. När du går i motlut eller måste skynda dig, får du då ont i bröstet?

□ Ja
□ Nej
Tre frågor om hur det kändes före hjärtinfarkten

Kryssa för det alternativ som passar för dig.

12. Brukade du ha smärta eller obehag i bröstet?

□ Ja
□ Nej

13. När du gick i normal takt på plan mark, fick du då ont i bröstet?

□ Ja
□ Nej
14. När du gick i motlut eller måste skynda dig, fick du då ont i brösten?

☐ Ja

☐ Nej

Plats för eventuella egna kommentarer

Stort tack för din medverkan!

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