CHEST PAIN
and
ISCHEMIC HEART DISEASE

Diagnosis and management in primary health care

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Pröva icke vart varje ditt steg för dig: endast den som ser långt hittar rätt.

Dag Hammarskjöld, Vägmärken, 1963

CONTENTS

ABSTRACT

Background and aims. In patients consulting for chest pain, it is of great importance to evaluate the possibility of ischemic heart disease (IHD). The aims in this thesis were to investigate the accuracy of the general practitioners' clinical assessments and the applicability of exercise testing and myocardial perfusion scintigraphy (MPS) in patients consulting for chest pain in primary care.

Statins are known to prevent IHD. A further aim was therefore to investigate if a relation could be detected on a population basis between the use of statins and the morbidity of acute myocardial infarction (AMI).

Methods. All patients from 20 to 79 years, consulting for a new episode of chest pain in three primary health care centres, were included during almost two years from 1998 to 2000. The patients were managed according to the clinical evaluation. The presence of IHD was excluded either by clinical examination only, or if stable IHD was in question, by exercise testing and if the exercise test was inconclusive by an additional MPS. If unstable IHD or myocardial infarction was suspected, referral for emergency hospital examination was made.

Correlations between statin sales and the morbidity of AMI in Sweden's municipalities were analysed in an ecological, register based study. Adjustment was made for sales of antidiabetics, socio-economic deprivation indexes and geographic coordinates.

Results. Consultations for chest pain represented 1.5% of all consultations in the ages 20 to 79 and were made by 554 patients. In 281 patients IHD was excluded by clinical examination only. In 208 patients stable IHD and in 65 unstable IHD was in question. Four patients (1.4%) evaluated as not having IHD, were diagnosed with angina pectoris or AMI within three months. Exercise testing was performed in 191 patients and revealed no IHD in 134 and IHD in 14 patients. In 43 patients the exercise test results were equivocal. Thirty-nine of these patients underwent MPS, which showed no IHD in 20 and IHD in 19 of the patients.

In a follow up almost six years later, neither mortality rate nor prevalence of IHD differed significantly between the 384 study patients evaluated not to have IHD and the population controls.

Statin sales and AMI-incidence or mortality showed no strong associations from 1998 to 2002.

Conclusions.
- Primary care is an appropriate level of care for ruling out IHD as the cause of chest pain, with sufficient safety and for diagnostics of stable IHD.
- Exercise testing and myocardial perfusion scintigraphy are useful procedures when investigating chest pain patients in primary care.
- The results indicate that preventive measures other than increased statin treatment should be considered to further decrease AMI-morbidity.

LIST OF PAPERS

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

I.   Nilsson S, Scheike M, Engblom D, Karlsson LG, Mölstad S, Åkerlind I, Örtoft K Nylander E.
 Chest pain and ischemic heart disease in primary care.
Br J Gen Pract 2003;53:378-382.

II.   Scheike M, Nilsson S, Nylander E.
Exercise testing and myocardial perfusion scintigraphy in primary care patients with chest pain of new onset.
Scand J Prim Health Care 2007;25:117-122.

III. Nilsson S, Örtoft K, Mölstad S.
The accuracy of general practitioners' clinical assessment of chest pain patients.
Submitted in September 2006.

IV. Nilsson S, Mölstad S, Karlberg C, Karlsson JE, Persson LG.
No connection between the level of exposition to statins in the population and the incidence/mortality of acute myocardial infarction.
An ecological study based on Sweden's municipalities
Submitted in July 2007.

ABBREVIATIONS

AMI	Acute Myocardial Infarction
β	Regression coefficient
CI	Confidence Interval
CK-MB	Creatine Kinase-MB Fraction
DDD	Definied Daily Doses
DDD/TID	Definied Daily Doses per 1000 Inhabitants and Day
ECG	Electrocardiogram
GP	General Practitioner
IHD	Ischemic Heart Disease
ICD 10	International Classification of Diseases and Related Health Problems 10th version
KSH97-P	Primary care version of ICD 10
NNT	Number needed to treat
MPS	Myocardial Perfusion Scintigraphy
mV	Millivolt
OR	Odds Ratio
PHCC	Primary Health Care Centre
r	Correlation coefficient

DEFINITIONS

Acute myocardial infarction
Necrosis of the myocardium, as a result of interruption of the blood supply to the area.
Angina pectoris
Symptom of paroxysmal pain, usually in the chest, consequent to ischemic heart disease and provoked by a transient stressful situation.
Chest pain
A pressure, ache, burning or stabbing sensation in the chest.
Coronary insufficiency
Insufficiency of the coronary arteries to supply the muscle tissue of the heart with enough blood. In most cases caused by arteriosclerosis.
Ischemic heart disease
A disorder of cardiac function caused by insufficient blood flow to the muscle tissue of the heart. The decreased blood flow is in most cases due to coronary arteriosclerosis or to obstruction by a thrombus of the coronary arteries. Acute myocardial infarction, unstable angina and angina pectoris are manifestations of ischemic heart disease.
Unstable angina
Angina pectoris of recent onset (<4 weeks) or impairment of previously stable angina, and possibly symptoms at rest. May precede a myocardial infarction.

INTRODUCTION

Being active as a GP for several years, a desire developed to describe the diagnostic problems in patients with chest pain, with special reference to IHD. When consulting for chest pain, a suspicion of heart disease is always considered both by the patient and the GP. Much has been written about chest pain and IHD from a secondary care perspective. Chest pain is a frequent symptom also in primary care, often less dramatic but well worth describing.

Epidemiology of chest pain and ischemic heart disease

In the world

Chest pain

Chest pain is a common symptom in the general population. A British population survey reported that 25% of a sample, 18-75 years old, with no prior diagnosis of IHD had experienced some form of chest pain (1). In a southern Chinese population above the age of 18, 21% had experienced chest pain during the past year (2). In an Australian study, 39% of a population sample above the age of 18 reported episodes of chest pain (3). In most of the population surveys, the WHO Rose chest pain questionnaire was used (4), a validated method for defining angina pectoris in epidemiological studies (5). In particular, the effort related component of chest pain has been shown to predict future IHD-events (5-7).

Ischemic heart decease

Ischemic heart disease is a cardiovascular disease. The global burden of cardiovascular disease is high. It has been estimated that almost one third of all deaths and one tenth of the total disease related burden in 1998, measured as disability adjusted life year loss (DALY), were ascribed to cardiovascular

disease (8)**.** From 1990 to 2020 the global burden of cardiovascular disease is estimated to rise with 55% in the developing countries. The highest rise is foreseen in India and China (9)**.** In India, deaths related to cardiovascular disease are expected to rise from 24.2 to 41.8% from 1990 to 2020 (9)**.** During the same thirty year period, the global burden of cardiovascular disease is expected to decline with 14.3% in developed countries (9). However, the cardiovascular mortality is estimated to increase (8). According to Yusuf et al there are five principal stages of "the epidemiologic transition": 1. Age of pestilence and famine, 2. Age of receding pandemics, 3. Age of degenerative and man-made diseases, 4. Age of delayed degenerative diseases, 5. Age of health regression and social upheaval (8)**.** In the age of degenerative and man-made disease all forms of stroke, ischemic heart disease at young ages, increasing obesity and diabetes emerge. Urban India, former socialist communities and aboriginal communities serve as examples of this stage. The typical pattern of cardiovascular epidemiology in Western Europe, North America, Australia and New Zealand is described as the age of delayed degenerative diseases. In this period, cardiovascular diseases are striking people at old age. The epidemiologic transition parallels life style changes e.g. urbanisation, smoking behaviours, changes in nutritional habits, adoption of a sedentary life style and consequently an increasing occurrence of obesity. A study of risk factors in 52 countries has shown that the risk factors associated with myocardial infarction are the same worldwide. The two most important risk factors are smoking and abnormal lipids (10). France, Greece, Italy, Spain, Switzerland and Portugal are classified as cardiovascular low-risk countries in Europe. Finland and Sweden are examples of high-risk countries (11).

In Sweden

Chest pain

In population studies from Gothenburg, Sweden, made before 1985, 15% of the men and women had experienced chest pain within a three months period (12, 13). Chest pain may become more prevalent with age. In a longitudinal population study, from middle to old age, one fifth of both men and women developed chest pain during a 24 year follow up (14). No large gender differences are reported in the occurrence of chest pain in the general

population (12, 14). Effort related non-specific chest pain, has been shown to be associated with a high long-term mortality among Swedish men (15).

Ischemic heart disease

In Sweden, as in most western countries, both the incidence and the mortality of AMI have decreased since the eighties (16). The age standardised mortality of AMI decreased from 1987 to 2004 with an average of 3.5% per year and the age standardised AMI incidence from 1987 to 2000 with 1-2% per year (17). However, the case fatality of AMI is still high. In 2004, 20% of both men and women died within 24 hours of diagnosis, 91% of them outside the hospital (17). In 2001, the number of diagnosed AMI increased due to a change in cut off levels for biochemical markers for myocardial necrosis (17, 18). Consequently, the incidence of unstable angina pectoris decreased. The prevalence of stable angina pectoris in northern Sweden declined between 1986 and 1994, especially among women, as measured by a symptom based population survey (19).

In hospital care

Chest pain

Chest pain is reported to account for 20-30% of all emergency medical admissions (20). In a Swedish study, 19% of admissions to the emergency room were due to chest pain (21). In the US, chest pain is second only to abdominal pain in the emergency room (22).

Of chest pain patients directly discharged from the emergency room, a minority had IHD, about one third had musculoskeletal pain and one fifth chest pain of uncertain origin (23, 24). In a Danish study with a thorough work up of in-patients without signs of AMI or any other immediate diagnosis, nearly one third had musculoskeletal pain and one third had IHD. Almost half of these patients had gastro-oesophageal diseases. Some patients had more than one diagnosis (24).

Ischemic heart disease

In a Swedish study, 7157 patients with chest pain admitted to the emergency room were analysed. Fifty-five percent were men and the mean age was 63 years (21). In all, 4690 (66%) of the patients were hospitalised. Twenty-four percent of all admitted chest pain patients and 36% of those who were hospitalised received a diagnosis of AMI, possible AMI or myocardial ischemia within a few days in hospital (25). In an American study one third of all hospitalised chest pain patients received an IHD-diagnosis (22).

In primary care

Chest pain

Chest pain is known to be a common cause of consultation in primary care. However, the occurrence of patients consulting for chest pain differs. In a retrospective study from Iceland, less than 1% of the consultations to an urban family practice (patients of all ages) were due to chest pain (26). Studies from the UK and US report that about 1% of primary care consultations were for chest pain (27, 28) and a study from Belgium reported 4% (29). In a Canadian study from 1977, where chest discomfort could be one of many presenting complaints, the proportion of patients consulting for chest pain was 6.7%, all ages included (30). In Sweden, a small retrospective study reported that 1% of all primary care consultations were for chest pain (31).

A diagnosis of "unspecified chest pain" after the GPs' evaluation still holds the potential of IHD. In the year 2002, less than one percent of the visits to a Swedish urban PHCC were diagnosed as chest pain (KSH97-P; R07.-P). This represents 9/1000 for the whole population, 12/1000 for men and 11/1000 for women in the 45-64 year age group (32). In the UK 15.5 /1000 of the population all ages were given a diagnosis of unspecified chest pain in conjunction with consulting a primary care physician in a given year. By age, men more often than women were given a diagnosis of unspecified chest pain. In the 70-79 year age group, the incidence rate was 32.2 and 25.8 per 1000 person-years for men and women respectively (27).

Ischemic heart disease

Ischemic heart disease, angina pectoris or myocardial infarction was the cause of chest pain in 9-18% of the cases in primary care studies (26, 29, 33). Men more often than women were diagnosed with IHD when consulting for chest pain (1, 34). The cause of chest pain was undiagnosed or non-specific in 10-16% (26, 33). Klinkman suggests that non-specific chest pain in reality represents undiagnosed angina (33). Any chest pain and exertional chest pain according to the Rose questionnaire has been shown to predict future consultations for IHD in British primary care. This was true for both men and women during a seven year follow up (1).

Diagnostic methods of ischemic heart disease in primary care

If ischemic heart disease is suspected, the management differs in relation to the probability of unstable angina or AMI. In those cases, the secondary care treatment is aiming at stabilisation and reperfusion and is often started before hospital admittance (16, 35-37). Other emergent causes of chest pain that should be considered are aortic dissection, pulmonary embolism, pneumothorax and aortic stenosis. In cases of stable angina pectoris, investigation and treatment is conceivable in primary care. The vast majority of chest pain cases are non-emergent and primarily a GP matter.

Clinical assessment

The evaluation of pain characteristics, age, gender, previous cardiovascular morbidity and other risk factors are the basis for the assessment of the probability of IHD (38). In stable angina pectoris, the pain is caused by exertion and is quickly relieved by rest. The symptoms are unchanged over a period of time (39). Ischemic pain is experienced as pressure, squeezing, burning or as a sense of heaviness over the chest. It is commonly retrosternal but sometimes emerging from the upper abdomen, the neck or lower jaw. The patient often indicates the pain with the entire hand. Pointing at the tender point by one or two fingers often represents musculoskeletal origin of pain (16). The clinical characteristics of unstable angina are, new severe angina, increased symptoms of previously stable angina or episodes of symptoms at

rest during the last month (16). Chest pain is the most common symptom of unstable angina or AMI in women as well as men. Associated symptoms as nausea, dyspnoea or vomiting are, however, more common among women than men (40, 41).

In most patients with chest pain caused by IHD, the vital functions are unimpaired, with the exception of infrequent cases with AMI. Auscultation of the heart reveals frequency and rhythm. A systolic murmur with punctum maximum in the second right intercostal space, may represent an aortic stenosis causing angina pectoris (39). Since atherosclerosis is a systemic disease, other manifestations than coronary may be a clue to the diagnosis, e.g. a systolic murmur from a carotid stenosis. An ankle-brachial blood pressure index < 0.90 indicates peripheral arterial disease. The accuracy for identifying a stenosis ≥ 50% in leg arteries is high. The sensitivity is about 90% and the specificity about 98% in well trained hands, using a Doppler ultrasonic sensor (42). Examination of the thoracic wall may reveal tenderness. Musculo-skeletal pain is shown to be one of the most common causes of non-cardiac chest pain both in primary as well as in secondary care (23, 24, 26, 31, 33, 43). However, muscular tenderness often co-exists with IHD-related pain (16). It is reported that a local injection to a muscular trigger point can diminish a referred pain of cardiac origin (44).

ECG

Rest ECG for ischemia detection in stable angina pectoris is of limited value. However, signs of left ventricular hypertrophy, arrhythmias or a pathologic Q-wave indicating an old AMI may be revealed (39).

A normal rest ECG does not rule out acute myocardial ischemia, since five to ten percent of AMI patients are reported to have normal ECGs on hospital admittance (16, 25). ST-segment changes can be temporal, and therefore not recorded on a single ECG registration (45). The earliest manifestations of myocardial ischemia are seen in the ST-segment or in the T-wave. A new ST elevation in 2 adjacent leads ≥ 0.2 mV in men or ≥ 0.15 mV in women in leads V2-V3 and/or ≥ 0.1 mV in other leads indicates acute myocardial ishemia. A new horizontal or down-sloping ST depression ≥ 0.05 mV in two adjacent leads and/or a T-wave inversion ≥ 0.1 mV in two adjacent leads with prominent R-wave are also signs of myocardial ischemia (46). Further, a new

left bundle branch block (LBBB) and/or pathologic Q-waves can be associated with myocardial infarction (46). ECG changes are sometimes difficult to interpret, e.g. ST-depression and a tall R-wave in V1-3, due to a posterior infarction (45). In cases of previously known LBBB, a pronounced left ventricular hypertrophy or a pace-maker, the ECG is difficult to interpret concerning myocardial ischemia (16).

Biochemical tests

Tests of biochemical markers with a high specificity for myocardial necrosis have been developed. According to recent guidelines, the preferred marker is cardiac troponin I or T (46). The elevation of cardiac troponin starts 2-4 hours after onset of symptoms, peaks rapidly and can persist for several days (47). Troponin testing is used in primary care and has been shown to be helpful for GPs in the triage of chest pain patients (48, 49). However, it must be emphasised that unstable angina is not associated with an elevated level of cardiac troponin. Further, there are several reasons for cardiac troponin elevation in the absence of overt ischemic heart disease (47).

Exercise test

Exercise testing is a well known and, in routine care, easily available procedure used to diagnose coronary insufficiency. Exercise is usually performed on a treadmill or a bicycle ergometer. In Sweden the latter is used almost exclusively. In cases of known ischemic heart disease, exercise testing is used to evaluate the risk profile as well. The initial workload is set in accordance to the patient's physical condition, with the aim that he or she will exercise for 6-10 minutes. The workload is increased continuously or in small steps. There are defined criteria for interruption such as blood pressure drop, severe chest pain, serious arrhythmia or severe ST-depression. The work capacity, occurrence and type of chest pain and blood pressure reaction are evaluated. The ECG reaction is analysed. A depression of the ST-segment is measured at 60 ms from the J-point, i.e. the point where the QRS ends and the ST-segment starts. A horizontal or down-sloping ST-segment depression exceeding 0.1 mV is a commonly recommended criterion indicating coronary insufficiency (50, 51). The diagnostic value of the ST-analysis is dependent on whether the age-predicted maximal heart rate is reached or not. The post test

probability for coronary artery disease is estimated from the results of the exercise testing and the patient characteristics, i.e. age, gender, symptoms and set of risk factors. The sensitivity is considered to be slightly less than 70% and the specificity around 80% (50, 52, 53). However, the sensitivity is substantially lower in diagnosing single vessel coronary artery disease (50, 54). Further, the diagnostic accuracy of the exercise test is dependant on how close the patient comes to his estimated maximal functional capacity and also on variables such as chest pain and blood pressure response during exercise. The prognostic characteristics of negative exercise tests in chest pain populations with low risk of IHD have not been well elucidated. However, two Finnish primary care studies reported a negative predictive value of 98% and 97% respectively, for patients below and above the age of 60 years (55, 56). Mark found a 99% four-year survival rate for 379 out-patients identified as at low risk on treadmill scores (57).

Gender perspective

Exercise testing is commonly viewed as being less specific in women than in men. ST depression is more often not due to coronary artery disease in younger women compared to men. Other plausible factors causing ST depression in women are syndrome X, differences in microvascular functioning and factors related to oestrogen (50, 51). However, over all the different predictive values of ST depression in men and women can be explained by the differences in the prevalence of IHD in age matched men and women (51, 52, 58). Women develop IHD in average, at least 10 years later than men (17).

Myocardial perfusion scintigraphy

Myocardial perfusion scintigraphy (MPS) is a well validated method for the investigation of myocardial perfusion. An isotope labelled tracer is injected during provocation, either with physical exercise or pharmacological vasodilatation. In Sweden, exercise is usually performed on a bicycle ergometer and pharmacological vasodilatation usually with adenosine. The distribution of the tracer in the myocardium is thereafter registered with a gamma-camera, using tomographic technique. A registration is also made without provocation and a comparison of these two studies allows assessment

of myocardial perfusion and viability. The evaluation of the MPS study is usually performed visually, often with assistance by computerised quantitative tools. In Sweden, technetium-99m labelled perfusion tracers are almost exclusively used. A description of the MPS method is given in the book "Det kliniska arbetsprovet"(51).

MPS has been shown to have a sensitivity of around 85% for revealing myocardial ischemia (59, 60), which is substantially better than the sensitivity of stress test ECG, especially in single vessel disease. The specificity is lower, in part due to attenuation artefacts caused by breast and obesity and is in the range of 75% (60). Normal findings at MPS predict a favourable prognosis (61, 62), also in the presence of significant ST-depressions on exercise ECG (63), in the presence of pathological findings on coronary angiograms (64, 65) and in patients with a history of previous AMI (66).

Diagnostic management in primary care

Stable angina

Stable angina pectoris is a symptom-based diagnosis. The main characteristics are, central chest pain brought on by effort and quickly relieved by rest (4, 39). Bass suggests structured questions for the diagnosis of IHD-related chest pain (20). Men over the age of 40 and elderly women with a typical history have a high pretest probability for IHD (39). Hence, the diagnosis may be confirmed by findings at an exercise test but should not be abolished if the findings are within normal limits. Prognostic unfavourable findings are a low maximal workload, low maximal heart rate, a blood pressure drop, severe chest pain, pronounced ST depressions during work and a slow regress of ST changes after work (51). These findings may indicate severe coronary insufficiency requiring further investigation.

AMI or unstable angina

For a possibly fatal disease, the decision taken by the GP of emergent referral for hospital investigation, necessarily involves a high sensitivity at the expense

of a low specificity. Chest pain symptoms of acute IHD may be unspecific (16). There are no typical findings at the clinical examination. Patients with unstable angina or AMI may have a normal ECG (16, 25, 45). The case fatality of AMI is high (17). The secondary care treatment is active and aiming at preserving viable myocardium by stabilisation and revascularisation of the coronary circulation (16, 35-37). In most cases of chest pain, it is advisable to make a decision whether to refer emergently or not before taking an ECG or biochemical tests. A false negative finding on any test may obscure the decision process. A negative Troponin T or I may be helpful in the decision to refrain from an emergent referral (48).

Atypical chest pain

Atypical chest pain symptoms have been shown to represent an increased risk of IHD-manifestations (1, 15, 27, 51) and consequently should make the GP act with prudence.

Non-IHD

Flook has described five major groups of non-cardiac causes of chest pain, i.e. gastrointestinal, neuromusculoskeletal, pulmonary, psychiatric and other causes. These five groups together comprise about 50 potential causes of discomfort in the chest. The prevalence of gastrooesophageal reflux is estimated to more than 50% among those with undiagnosed chest pain. A trial of acid-suppressive therapy may be helpful for the diagnosis (67). Doses of nitrates are sometimes used for differential diagnosis. However, nitrates can relieve oesophageal pain and pain from skeletal muscles as well as angina pectoris (44).

Risk factors and prevention of ischemic heart disease

Non-modifiable risk factors for IHD are male gender, age and genetic factors. Important modifiable risk factors are elevated plasma lipids, tobacco smoking, hypertension, diabetes, obesity, psychosocial factors, dietary factors and lack of physical activity (10, 11, 68). Several other risk factors for IHD have been suggested and analysed (69).

Plasma lipids

High serum cholesterol has been shown to be positively correlated to an increased risk of IHD in numerous studies (70). The relative risk of IHD-death among men is closely related to the level of serum cholesterol across cultures. However, the absolute risk of IHD-death at a given cholesterol level varies greatly, indicating that other factors, such as dietary habits are important (71). The desirable serum cholesterol level according to Swedish guidelines from 1998 is ≤ 5.0 mmol/l (72). The absolute risk of IHD is, however, related to the individual risk factor profile. A moderately increased serum cholesterol can be associated to a very wide range of risk levels, according to the risk factor profile (68). According to the ESC guidelines from 2007, the desired serum cholesterol level in general is still ≤ 5.0 mmol/l and the desired level of LDL-cholesterol < 3 mmol/L. In high risk subjects, especially those with previous manifestations of cardiovascular disease and in diabetics, the goals are much lower. Total cholesterol is desired to be < 4.5, or < 4.0 mmol/L if possible. The desired LDL- cholesterol level is <2.5 mmol/L or < 2.0 if feasible (11).

Other risk factors

Smoking has a large impact on the risk for IHD (10, 73, 74). A woman, smoking at least 20 cigarettes daily is at the same risk as a non-smoking man to get an AMI (75). The risk of IHD is increased also for passive smokers (76). Smoking has gradually decreased in Sweden during the last 30 years in women and particularly in men. The number of daily smokers in 2005 was 13 and 17 percent for men and women, respectively (77).

The present definition of hypertension is >140/90 mm Hg (68, 78, 79). With this definition, 27% of the Swedish population over the age of 20 has hypertension. There are no big gender differences concerning the prevalence of hypertension. The impact on the relative risk of IHD from a high blood pressure is about the same in women and men (79).

The risk of IHD is elevated in diabetics type II, especially in women (68). No true increase in diabetes Type II was found in a recent Swedish study (80).

Obesity is related to physical inactivity, high blood pressure, increased total- and LDL-cholesterol, insulin resistance and to increased risk of IHD (11).

Low socio-economic status and stress at work and in family life are associated to an increased risk of IHD. The psychosocial risk factors tend to cluster in the same individuals and groups (11).

A high intake of saturated fat is since long viewed as a major risk factor for IHD. However it has been questioned lately (81). A low intake of fruits and vegetables (10, 68) and alimentary fibres (82) is related to an increased risk of IHD.

Lack of physical activity is associated to an increased risk of IHD (10, 68).

An association between exposure to cold climate and high AMI-mortality has been suggested (83, 84). In addition, a regional variation in IHD in the east-west direction in mid Sweden has been suggested (85).

Prevention of ischemic heart disease

Primary prevention is aimed to prevent or delay a new onset of IHD. Secondary prevention refers to measures taken to prevent complications or new manifestations of IHD in subjects previously diagnosed with the disease (86). Accordingly, primary and secondary prevention refer to measures aimed at subjects stratified at different risk levels of IHD. Another approach is to look upon risk as a continuum (11). In general, a 40 year old healthy woman is at low risk of AMI but a 60 year old man, who had an AMI five years ago, is at high risk of another AMI. Assessment of the individual risk factor profile is complex. Physicians are shown to consider a minority of the known multiple risk factors when analysing the risk of IHD (87). Several charts and computerized programmes have been constructed to aid the risk assessment procedure. The European Society of Cardiology (ESC) suggests the SCORE chart (11). In this chart gender, age, tobacco smoking, systolic blood pressure and serum cholesterol are weighted to calculate the 10-year risk of fatal cardiovascular disease.

Statins

Randomised controlled trials have shown unequivocal benefits of statin treatment (88-91). A pill comprising 40 mg simvastatin in addition to other cardiovascular drugs has been suggested. The "Polypill" taken by everyone above the age of 55 is estimated to reduce IHD-events by 88% (92). However, in a British study, only 3% of the almost 70 000 fewer IHD-deaths in the year 2000 compared to 1981 were estimated to be attributable to statins (73). In 2006 the prevailing statins in Sweden were simvastatin, atorvastatin and prava-statin according to The Corporation of Pharmacies in Sweden (Apoteket AB).

Gender perspective

The incidence of AMI is about half for women compared to men at the same age (17). In several large trials of lipid lowering drugs, women are a minority (89, 91, 93). The results on men are often extrapolated to women. In a meta-analysis of 14 randomised trials, the relative risk reduction for an IHD-event was calculated to be about 23% for each mmol/L of LDL-cholesterol reduction irrespective of baseline risk (88). The baseline risk for women is much lower compared to men at the same age and risk factor profiles. Thus, many more women than men must be treated with statins to prevent one IHD-event. A meta-analysis of six trials on drug treatment of hyperlipidemia on a total of 11 435 women found no primary preventive effects on IHD-mortality or on total mortality in women (94). A possible primary preventive effect on IHD-events was shown only in women with diabetes (94, 95). Secondary preventive effects of statins are shown in women on IHD-mortality, IHD-events, non-fatal AMIs and coronary revascularisation, but not on total mortality (94).

AIMS OF THE STUDY

General aim

To elucidate the diagnosis and management of ischemic heart disease in primary care.

Specific aims

- To study the frequency of consultations in primary care by patients with a new episode of chest pain (I).
- To estimate the prevalence of IHD among chest pain patients (I, II).
- To study the outcome of bicycle exercise testing and myocardial perfusion scintigraphy in a primary care chest pain population (I, II).
- To evaluate the accuracy of GPs' clinical assessment of chest pain patients (III).
- To investigate if an association can be found between AMI mortality or incidence and statin sales on a population basis in Sweden's municipalities (IV).

POPULATIONS AND METHODS

This thesis is based on four papers (*Table 1*) using data acquired from;
- a prospective observational study of patients consulting primary care for chest pain (I, II, III).
- a retrieval of data from Swedish official registers concerning the sales of statins, AMI morbidity and related risk factors (IV).

Table 1. Summary of study characteristics.

Paper	Year of subject inclusion	Study population	Data sources	Level of assessment
I	1998-2000	554 patients, 20-79 years old, consulting in primary care for chest pain.	Patient history, PHCC and hospital medical records, hospital diagnosis registry, exercise testing and a postal questionnaire.	Frequency of chest pain consultations. Prevalence of IHD in the chest pain population.
II	1998-2000	191 chest pain patients, 32-79 years old, in whom stable IHD could not be excluded.	Patient history and PHCC medical records, exercise testing and MPS.	Outcome of exercise tests and MPSs.
III	1998-2000	238 chest pain patients, 30-79 years old, assessed by the GPs to have low or high probability of IHD.	GPs' statement on the probability of IHD, their stated action without study options, patient history, PHCC and hospital medical records, exercise testing and MPS.	Accuracy of clinical management.
IV	1998-2002	All male and female Swedish inhabitants, 40-79 years old.	Swedish official registers.	Correlations between sales of statins and the AMI-incidence/mortality in Sweden's municipalities.

Populations (I, II, III)

The study was performed at three PHCCs in the county of Östergötland in south-east Sweden. Each PHCC serves one primary health care area and relies on the same local hospital, within a distance of 15 to 50 kilometres, for referrals and emergencies. The PHCC on duty during nights and weekends is situated in the same town as the local hospital. Two of the PHCCs are situated in the main villages of rural areas and the third in a suburban area. The populations enrolled on the lists of the three PHCCs comprised 16 152 individuals, 20-79 years old. Each PHCC was served by, in average, four GPs during the study. In addition to the GPs, physicians under education, supervised by the GPs, also participated in the study.

From May 1998 to April 2000, all patients meeting the inclusion criteria were consecutively included by the GPs. Sessions were held Monday to Friday, from 8.00 am to 5.00 pm, corresponding to the opening hours of the three PHCCs. Due to staff holidays, no patients were included during July 1998 and June – July 1999. The total study time was 21 months.

Inclusion criteria

Patients, 20-79 years old, presenting with a new episode of chest pain met the inclusion criteria. "New" was defined as having commenced during the last six months and with a free interval of at least six months after any previous episode of the same type of complaint. "Chest pain" was defined as pressure, ache, burning or stabbing sensation in the chest. The same person could be included more than once during the two-year study period, if the inclusion criteria were met.

Exclusion criteria

Patients who, previous to their consultation for chest pain, had been diagnosed as having coronary insufficiency by physiological methods or had had an acute myocardial infarction or had been the subject of coronary revascularisation during the previous year, were excluded.

Populations (IV)

All male and female inhabitants, 40-79 years old, in 289 of Sweden's 290 municipalities, from 1998-2002.

Methods (I, II, III)

Data collection (I, II, III)

Patient data were registered in the study forms. Inclusion and exclusion criteria were provided in a study file available to all participating GPs. The patients were managed according to the GPs' clinical evaluation (*Figure 1*). The duration of the actual chest pain and the patients own concern about cardiac related chest pain/angina pectoris were noted by the GP. The visit was registered as an "emergency visit" if booked the same day or was by open access. Whether the GP thought that IHD was a possible cause of chest pain, was noted as "yes" or "no". If the answer was "no" the probable cause of chest pain was judged as, musculoskeletal, oesophageal/abdominal, infection, pulmonary/pleural non-infectious, psychogenic, other heart disease or not specified (I).

If the answer was "yes" the probability of coronary insufficiency was graded as "high" or "low". Information on the cardiovascular risk factors, diabetes, smoking, hypertension or hyperlipidemia was gathered from the patient and the PHCCs computerised patient record. In addition, information was retrieved on cardiac related morbidity i.e. atrial fibrillation, congestive heart failure, heart valve disease, previous myocardial infarction or revascularization, peripheral arterial disease or stroke/transient ischemic attack. If there was any suspicion of myocardial infarction or unstable angina, the patient was referred for emergency hospital care, according to normal clinical routines. In all cases of suspected stable IHD, the patient was referred for an exercise test. In those cases, the GPs were asked how he/she would have managed the patient if the study had not had the extended option of exercise testing. Four preset alternatives were given: 1. exercise test. 2. medication for angina. 3. second opinion 4. "wait and see". In the analysis, emergency referral to hospital and alternatives 1-3 were defined as "active decisions" (III).

Clinical evaluation by the GP		
IHD excluded	**Stable IHD?**	**Unstable IHD/AMI?**

Patients sent home or other investigation/ treatment	Referral for exercise test	Referral for emergency hospital investigation
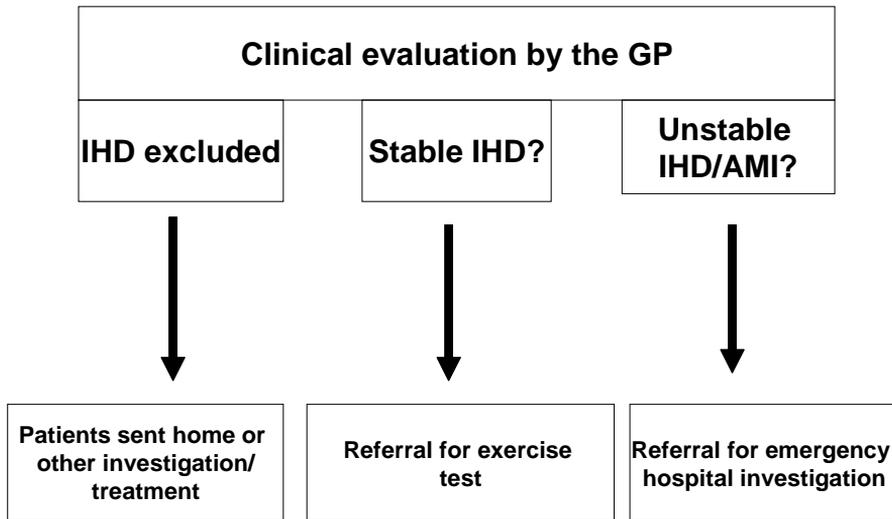
Figure 1. Principal pathways of chest pain patients in the studies (I, II, III).

Hospital medical records (I, III)

From responses to emergency referrals and from information in hospital medical records, the including GP categorised the results into six groups. A: Acute myocardial infarction, B: Coronary insufficiency verified by physiological testing, C: Coronary insufficiency not verified by physiological testing, D: No coronary insufficiency, E: Coronary insufficiency uncertain and F: Information missing. A notification was made in the study form. A - C were categorised as "IHD", D as "No IHD". E and F were categorised as "possible IHD" (I) or excluded (III).

In patients with diagnostic uncertainty at the end of hospital care, GPs had the option of referral for an exercise test at this point of the study.

Data from a hospital diagnosis registry (I)

In order to estimate the incidence of IHD in the general population and the relation between IHD cases handled in primary care and in hospital care, retrospective data on patients not managed within the study were retrieved from the diagnosis registry of the referral hospital on angina pectoris (ICD 10; I 20.0-20.9) and acute myocardial infarction (I 21.0-21.9). Patients being hospitalised with any of those diagnoses during the previous year were excluded.

Postal questionnaire (I)

Three months after inclusion, a postal questionnaire was sent to those patients believed to have had chest pain originating from causes other than IHD. One postal reminder was used. The questionnaire contained questions about ongoing symptoms and further consultations for chest pain. One question was used to evaluate if any diagnosis of myocardial infarction or angina pectoris had been given after the inclusion in the study; "Have you after visit 1 been given the diagnosis heart disease by a physician?" □ No, □Yes, myocardial infarction, □ Yes, angina pectoris, □Yes, other, please specify …
The PHCCs' computerised medical records were examined for any IHD-diagnosis of the non-responders. This was done also in cases of any possibly deceased patients.

Exercise testing (I, II, III)

Exercise tests were performed at the department of Clinical Physiology at the local county hospital within six weeks of referral. All tests were performed using a bicycle ergometer, by the same clinical physiologist physician and according to national guidelines (51). The results of the exercise tests were categorised into three groups:

1. ST-segment depression exceeding 0.1 mV and angina-like chest pain in relation to exercise or pathological Q-wave on resting ECGs was categorised as "IHD" (I, II, III).
2. Neither chest pain nor ECG changes were categorised as "No IHD" (I, II, III).
3. Chest pain but no ST-changes during or after exercise or vice versa - no chest pain but ECG changes. This group also included patients with non-assessable ECG reactions, due to e.g. left bundle branch block or digitalis medication. These were categorised as "possible IHD" (I) or an equivocal test result (II).

Myocardial perfusion scintigraphy (II, III)

Patients with equivocal exercise test results or "possible IHD", were referred for MPS. A two-day protocol was used with bicycle exercise day one followed by a study at rest within one week. Technetium-99m tetrofosmin was used as perfusion agent. For gamma camera acquisition and post-processing, a GE STARCAM 3000XR/T was used. The acquisition was performed as a single photon emission computed tomography (SPECT) study. No scatter or attenuation correction was used.

Image interpretation, validation and categorisation of results

Two experienced observers made a blinded, semiquantitative visual interpretation of the stress and rest studies. After individual interpretation, consensus was achieved and used for evaluation in the present study. The perfusion images were presented in 3 standard projections (short axis and horizontal and vertical long axis). A 13-segment left ventricular model was used. The model was designed with respect to the predominant areas of coronary perfusion (96) (*Figure 2*). Each segment was assigned a score from 0 to 3, (0 = normal perfusion, 1 = slightly reduced perfusion, 2 = mode-rately reduced perfusion, and 3 = severely reduced perfusion). Limited but significant perfusion defects that were localised in the border regions of two segments were attributed to the segment where the predominant part of the defect was localised. Summed scores for stress and rest studies were calculated. For reversibility, the summed rest score was subtracted from the summed stress score, segment by segment with the limitation that no segment could be given a difference score below 0. Reversible ischemia was defined as

a difference score ≥ 2. A myocardial scar was defined as a summed rest score ≥ 4. The results of the MPSs were categorised into two groups:

1. Summed reversibility score ≥ 2 and/or summed rest score ≥ 4 were categorised as "IHD" (II, III).
2. The remaining patients, after myocardial scintigraphy, were defined as "No IHD" (II, III).
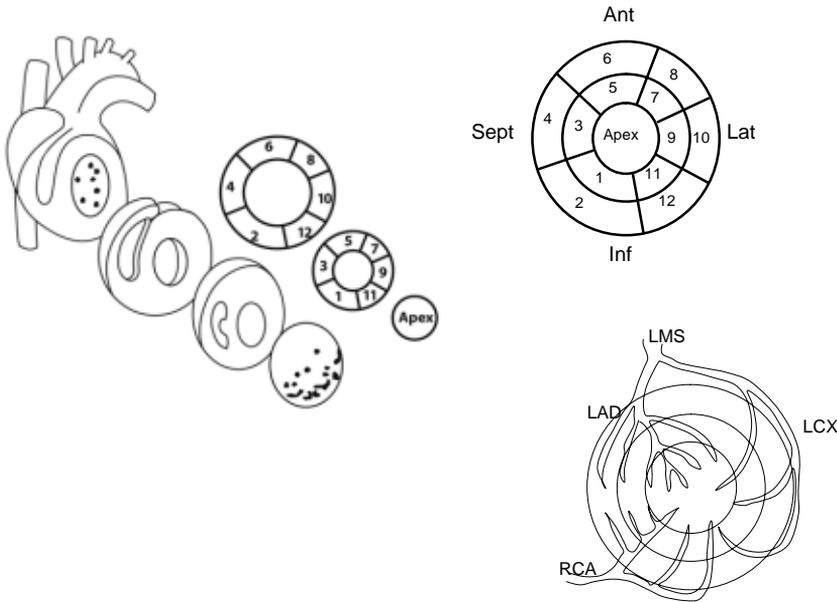
Figure 2. The 13-segment left ventricular model used for the scintigraphy analysis. LMS = Left main stem, LAD = Left anterior descending artery, LCX = Left circumflex artery, RCA = Right coronary artery.

Methods (IV)

The sales of statins, and antidiabetic drugs in 1998-2002 among outpatients, were based on the prescriptions served by The Corporation of Pharmacies in

Sweden (Apoteket AB) and expressed in Defined Daily Doses (DDD) per 1000 Inhabitants and Day (TID) (97). The DDD for simvastatin was 15 mg, atorvastatin 10 mg and pravastatin 20 mg. The DDD for antidiabetic drugs included both insulin and oral drugs.

Data on the number of AMI-deaths and the AMI-incidence were obtained from official registers at The Swedish Board of Health and Welfare (98). The AMI-incidence comprised fatal as well as non-fatal AMIs. The yearly incidence and mortality of myocardial infarction were calculated for each of the 289 Swedish municipalities for men and women and each of the age groups 40-49, 50-59, 60-69 and 70-79 years. The population sizes for the year 2000 were used. A socio-economic municipality deprivation index consisting of standardised education level, low salary and unemployment was calculated for men and women for the year 2000. Data on low education and low salary was gathered from Statistics Sweden and on unemployment from The National Labour Market Board. Data on the geographic x- and y- coordinates for each municipality was obtained from The National Land Survey of Sweden (83, 85). An official grouping of Swedish municipalities into nine groups according to number of inhabitants and infrastructure was used, in order to form subgroups of similar and enough populated municipalities (99).

Statistical methods

Detailed descriptions of the statistical methods are presented in the separate papers. StatView was used in Paper I, StatView version 5.0.1 and SPSS version 11.5.1 in Paper II, SPSS version 11 in Paper III and Minitab version 14 in Paper IV.

Bivariate variables were analysed by χ^2 and continuous variables by t-test (I, II). Univariate logistic regression was used to select explanatory variables for multivariate logistic regression analyses (II, III).

In Paper IV a simple bivariate Pearson correlation coefficient for statin sales vs. AMI-incidence/mortality was calculated for each of the years 1998-2002 and for respective age-groups and gender. In order to rank variables, for the construction of a statistical model, univariate linear regression analyses were used. AMI-incidence was used as the dependent variable and sales of statins, antidiabetic drugs, deprivation index, and geographic x- and y-coordinates for

each of the 289 municipalities as independent variables. Separate analyses were made for each of the years 1998-2002, and for respective age-groups and gender. The independent variables were ranked according to the number of significant outcomes. According to the ranking, the independent variables were included in the multivariate model in the following order, deprivation index, antidiabetic drugs, statin sales and x- and y-coordinates. The multivariate model was then used in analyses of AMI-incidence vs. the independent variables. The regression coefficients (β) and p-values for statin sales were given.

In order to minimise the effect of unusual events and small populations, the multivariate analyses were performed in a sub-group of 26 larger towns, i.e. municipality group 3, with 1857 to 4720 men aged 70-79 years (IV).

Considering the time delay for the preventive effect of statins (88, 89), the pace of increase in statin sales from 1998 to 2000 was plotted vs. AMI-incidence/mortality 2001 and 2002, and vs. the change in mortality from 2000 to 2002, for men aged 70-79 years in 149 municipalities, municipality groups 3, 4, 5 and 6. It was meaningless to include the change of AMI-incidence from 2000 to 2002 in the analyses, since the increase from 2000 to 2001 was due to a change of diagnostic methods (18) (IV).

In papers I-IV the level of significance was taken as $p < 0.05$.

Ethics

The studies were approved by the ethics committee of the Faculty of Health Sciences of Linköping University, Linköping, Sweden, Registration no. [Dnr] 98156, (Paper I-III) and 03-511 (Paper IV).

RESULTS

A total of 38 075 consultations to the GPs were made by persons aged 20-79 years between May 1998 and April 2000. Of these, 577 were for chest pain representing 1.5% of all consultations. Women accounted for 57% of all GP consultations but the proportion of consultations for chest pain was significantly lower for women than for men, 1.3% vs. 1.8%, (95% CI for difference 0.3-0.8%) (I). The 577 consultations for chest pain were made by 554 patients. Using the listed population of 16 152 patients aged 20 to 79 years, this represents a rate of 19.6 chest pain patients per 1000 consulting for chest pain during a one-year period. Twenty-three patients consulted two or three times during the study period. The results from 523 of the 554 patients, who were fully investigated, showed "IHD" in 62 (12%) and "no IHD" in 461 (88%) (I, II). In addition, during the study period, 63 patients were diagnosed as angina pectoris and 80 as AMI in the local hospital (I). These patients were from the same area of residence and had not been included by the GPs in the study. Combining the data from primary care and hospital care gave a yearly incidence of angina pectoris or AMI of 7.3 per 1000 in the studied population (I, II).

Patients (I, III)

The patient flow for the 554 chest pain patients analysed in papers I and III is shown in relation to the GPs' assessment at the time of consultation (*Figure 3*). In case of several consultations by the same patient, only the results from the first consultation were included. In 281 (51%) of the included patients, IHD was excluded as the cause of chest pain after a clinical evaluation only (I). In 208 (37%) of the patients, stable IHD could not be excluded. Subsequently, 198 of these patients were referred for exercise testing. While waiting for this investigation, six patients were hospitalised and one patient died outside hospital. Sixty-five (12%) of the patients were referred for emergency hospital investigation (I, III). In eight of these patients, an exercise test within the study was performed due to lack of diagnosis in hospital medical records. Two patients investigated by exercise test were reported as "possible IHD" in Paper I, but were re-classified into "IHD" in paper III, due to pathological Q-waves on resting ECG.
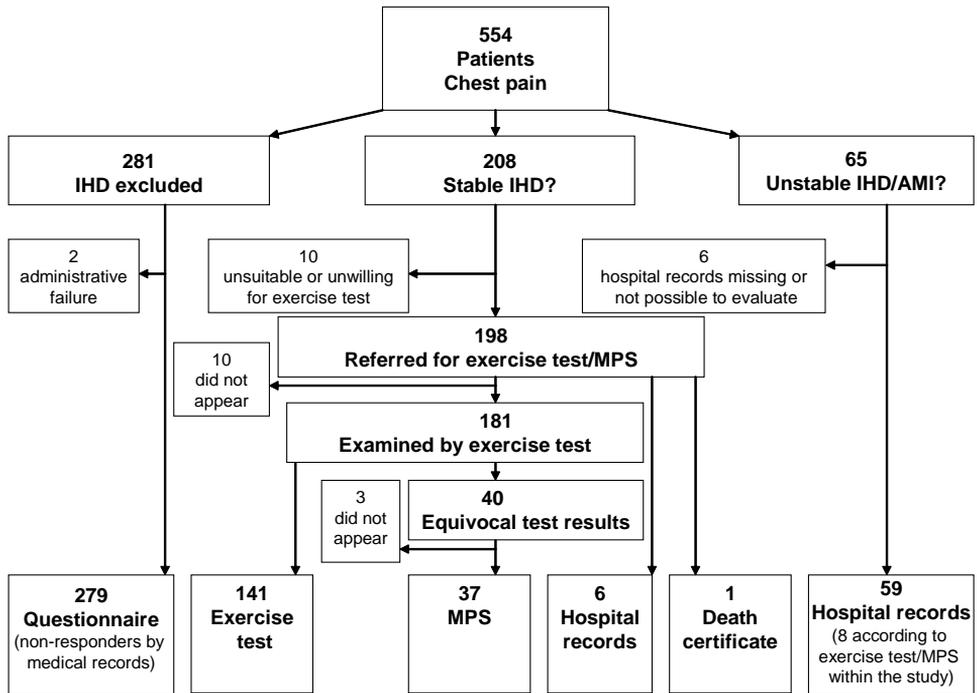
Figure 3. Patient flow (I, III), from inclusion to methods of evaluation, in relation to the GPs' initial assessment of 554 chest pain patients. IHD = ischemic heart disease, MPS = myocardial perfusion scintigraphy (I, III).

Patients (II)

In paper II, all the 577 consultations for chest pain made by 554 patients were included. In 224 of these patients, stable IHD could not be ruled out by clinical examination alone (*Figure 4*). Subsequently, 214 of these patients were referred for exercise testing of which 191 were completed. Due to equivocal test results, 43 of these patients were referred for MPS, which was completed in 39 of the patients. Two patients investigated by exercise test were reported as "possible

IHD" in Paper I, but were re-classified into "IHD" in paper II, due to pathological Q-waves on resting ECG (II).

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                    ┌─────────────────┐
                    │       224       │
                    │    Patients     │
                    │   Stable IHD?   │
                    └─────────────────┘
                             │              ┌──────────────────┐
                             │─────────────▶│        10        │
                             │              │ unsuitable or    │
                             │              │ unwilling        │
                             │              │ for exercise test│
                             ▼              └──────────────────┘
                    ┌─────────────────┐
                    │       214       │
                    │ Referred for    │
                    │ exercise test   │
                    └─────────────────┘
                             │              ┌──────────────────┐
                             │              │        23        │
                             │─────────────▶│ 17 did not appear│
                             │              │ for exercise test│
                             │              │ 6 administrative │
                             │              │ failure,         │
                             │              │ according to     │
                             │              │ study criteria   │
                             ▼              └──────────────────┘
                    ┌─────────────────┐
                    │       191       │
                    │ Examined by     │
                    │ exercise test   │
                    └─────────────────┘
                        │       │
                        │       ▼
                        │   ┌─────────┐
                        │   │   43    │
                        │   │Equivocal│
                        │   │ test    │
                        │   │ results │
                        │   └─────────┘      ┌──────────────────┐
                        │       │            │        4         │
                        │       │───────────▶│ unwilling or     │
                        │       │            │ unsuitable       │
                        │       ▼            │ for MPS          │
                        ▼   ┌─────────┐      └──────────────────┘
                  ┌─────────┐│   39    │
                  │   148   ││   MPS   │
                  │Exercise ││         │
                  │ test    │└─────────┘
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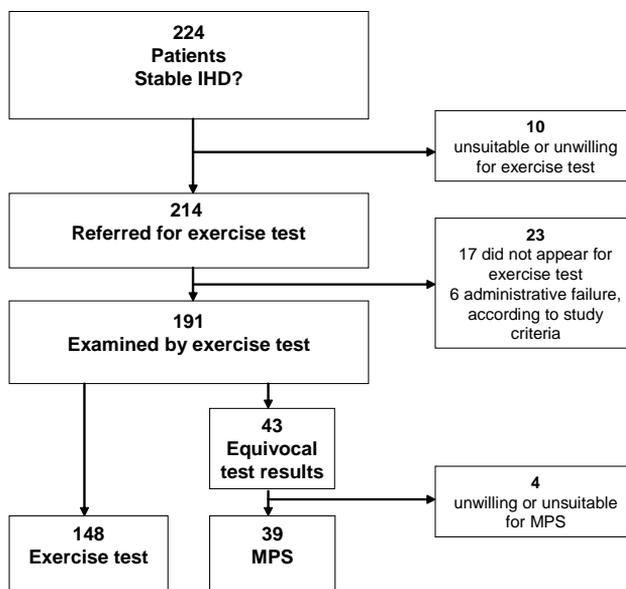
Figure 4. Patient flow (II), from study inclusion to methods of evaluation. In paper II, all the 577 consultations made by 554 patients were included. The results from conclusive exercise tests and MPSs were evaluated in 148 and 39 patients, respectively. IHD= ischemic heart disease. MPS= myocardial perfusion scintigraphy.

IHD as the cause of chest pain was excluded by the GPs' clinical evaluation (I)

IHD was excluded by clinical examination in 281 patients (I). These patients were younger ($p<0.001$) and more often female ($p<0.01$) than those where IHD was in question. Half of the patients in whom the GPs had no suspicion of IHD suspected a heart disease themselves (*Table 2*).

*Table 2. Demographic data of 554 chest pain patients in relation to the GPs'
evaluation, at enrolment in the study (I, III).*

	GPs' clinical evaluation of the chest pain patients		
	IHD excluded	*Stable IHD?*	*Unstable IHD/AMI?*
	(n=281)	*(n=208)*	*(n=65)*
Age, years (SD)	49.0 ±15	60.2 ±11	60.6 ±13
Male, n (%)	122 (43)	117 (56)	35 (54)
Female, n (%)	159 (57)	91 (44)	30 (46)
Emergency visit at the PHCC, n (%)	245 (87)	100 (48)	61 (94)
Chest pain <24 h, n (%)	66 (24)	42 (20)	33 (52)
Patient suspects heart disease, n (%)	136 (51)	156 (80)	45 (83)

Results of follow up

In 279 of the 281 patients where the GPs excluded IHD after a clinical
evaluation, a follow up was made by a postal questionnaire three months later
(*Figure 3*). The response rate was 89%. Three women and two men stated that
they had received an IHD-diagnosis, one AMI and in four cases angina
pectoris (*Table 3*). Among the non-responders no IHD-diagnosis or deaths due
to IHD were found according to a review of the PHCCs' medical records (I).

Stable IHD as the cause of chest pain could not be excluded (I, II, III)

In 208 patients, stable IHD could not be excluded (I, III). The mean age of these
patients was 60 years and they were more often of male gender. In one fifth of
the cases the discomfort in the chest had commenced during the last 24 hours
(*Table 2*).

Results after investigation and follow up

The results were analysed in 185 of the 208 patients where stable IHD could
not be ruled out by clinical examination alone (*Figure 3*). After exercise testing,
14 patients were classified as "IHD" and 127 as "No IHD" (I, III). According to
MPS results, an additional 17 patients were classified as "IHD" and 20 as "no

IHD" (III). While waiting for the exercise test, six of the patients were hospitalised with suspicion of IHD, which was confirmed in four. One patient died from myocardial infarction (I, III). Thus, 36 of these 185 patients had IHD. The IHD patients were a few years older and they were more often of male gender than those who did not have IHD (*Table 3*).

Table 3. Diagnoses after investigation and follow up in 523 patients consulting their GP for chest pain of recent onset (I, III).

Clinical evaluation	IHD excluded (n=279)		Stable IHD? (n=185)		Unstable IHD/AMI? (n=59)	
Diagnoses after investigation	"IHD" (n=5)	"No IHD" (274)	"IHD" (n=36)	"No IHD" (n=149)	"IHD" (n=21)	"No IHD" (n=38)
Age, years (min-max)	74 (48-79)	49 (20-79)	63 (33-79)	57 (32-79)	70 (47-79)	59 (30-78)
Male, n (%)	2	119 (43)	31 (86)	77 (52)	13 (62)	18 (47)
Female, n (%)	3	155 (57)	5 (14)	72 (48)	8 (38)	20 (53)

Exercise test and myocardial perfusion scintigraphy (II)

In paper II, 191 patients were investigated by exercise testing. The results revealed IHD in 14 (7%) and no IHD in 134 (70%). In 43 (23%) the exercise test results were equivocal. Thirty-nine of these patients underwent MPS, which showed "IHD" in 19 and "no IHD" in 20 of the patients. In conclusion 187 patients, 104 men and 83 women were fully investigated by exercise testing/MPS. Twenty-eight of the men and five of the women were diagnosed with IHD.

Univariate analyses in the group of 104 men showed significance for age (OR, 1.06; 95% CI, 1.01-1.11) and atrial fibrillation (OR, 10.09; 95% CI, 1.90-53.59), according to the allocation to the final outcome as "IHD" or "no IHD" (II). Only atrial fibrillation remained significant in the multivariate analyses (OR, 6.17; 95% CI, 1.04-36.73). Only five female patients were classified as "IHD". Accordingly, no further statistical analyses were performed in the female group (II).

There were no significant differences in age, gender, maximal heart rate, maximal workload (Watt) or maximal workload in % of normal value between

conclusive and equivocal exercise tests (II). Thirteen of 39 cases were referred for MPS due to chest pain at exercise testing but with a normal exercise ECG. Fourteen cases had no chest pain but abnormal exercise ECG, and were also referred for MPS (*Table 4*). After MPS, 20 patients fulfilled the criteria for "No IHD" and 19 were classified as "IHD". Six of these patients had ischemia, two of them also with myocardial scaring, and 13 patients had only myocardial scaring (*Table 4*). There were no significant differences between the main indications for referral to MPS following exercise testing and the final distribution between the "IHD" and "No IHD" groups after MPS findings.

Table 4.Classification of patients (n = 39) after myocardial perfusion scintigraphy. Listed according to main reason for referral after exercise testing (II).

Main Reason for Referral to MPS		"No IHD"	"IHD"	IHD subgroup	
				Ischemia	scar
	n	n	n	n	n
Chest pain at ET[1] but normal exercise-ECG	13	5	8	3 (1)[2]	5
No chest pain at ET but abnormal exercise-ECG	14	10	4	1	3
Blood pressure drop during ET	2	1	1	1 (1)[2]	0
Indeterminable exercise-ECG:					
Left bundle branch block at rest-ECG	3	1	2	0	2
Digitalis treatment	4	2	2	0	2
Left ventricular hypertrophy at rest-ECG	3	1	2	1	1
Total	39	20	19	6 (2)[2]	13

[1] ET= exercise test

[2] Numbers in brackets refers to patients who also had myocardial scarring

Unstable IHD or AMI could not be excluded (I, III)

In 65 patients unstable IHD or AMI could not be excluded by the GPs. The mean age of these patients was 61 years. They were more often of male gender. In half of these cases, the chest pain was of short duration. In 94%, the visit to the GP was an "emergency visit", i.e. booked the same day or made by open access (*Table 2*).

Results after investigation and follow up

The results were analysed in 59 of the 65 patients where unstable IHD or acute myocardial infarction could not be excluded (*Figure 3*). One third of these 59 patients were given an IHD-diagnosis. The IHD patients were older (p=0.001) than those without IHD (*Table 3*) (I, III).

The GPs' assessment of chest pain patients (III)

In paper III, the GPs' clinical evaluation of the probability of IHD and their stated management of chest pain patients in daily practice were analysed. The GPs assessed the probability of IHD to be high in 93 and low in 145 chest pain patients (III). In 44 (47%) of the high probability and in 13 (9%) of the low probability patients, IHD was diagnosed after investigation and follow up. These results give a sensitivity of 77% and specificity of 73% to the GPs' probability assessment (100). The negative predictive value was 91% (*Figure 5*). The sensitivity calculated on "active decisions" or "wait and see" in daily practice was 95% and the specificity 27%. In three of 49 cases where the GPs' decision would have been "wait and see" in daily practice the outcome was "IHD". Hence, the prevalence of IHD was 6% and the negative predictive value 94% in the "wait and see" group (*Figure 6*).

In 15 of 22 chest pain patients that would have been given angina medication in daily practice instead of exercise testing, the outcome was "no IHD" (III).

Factors associated to the GPs' assessment of the probability of IHD as high were, age (OR, 1.1; 95% CI, 1.03-1.10), male gender (OR, 2.2; 95% CI, 1.05-4.63), chest pain less than 24 hours (OR, 3.6; 95% CI, 1.63-7.73), hyperlipidemia (OR, 4.0; 95% CI, 1.24-12.82) and diabetes (OR, 3.4; 95% CI, 1.14-10.34). The only risk factors significantly related to the outcome "IHD" were age (OR, 1.1; 95% CI, 1.03-1.11), male gender (OR, 3.9; 95% CI, 1.77-8.46) and a previous myocardial infarction (OR, 5.0; 95% CI, 1.01-24.60) (III).

		Diagnoses after investigation			
		"IHD"	"No IHD"		
Probability of IHD	"High"	44	49	93	+PV = 44/93 = 47%
	"Low"	13	132	145	-PV = 132/145 = 91%
		57	181	238	

Se= 44/57 = 77% Sp= 132/181=73%

P = 57/238 = 24%

Figure 5. The GPs' assessment of the probability of IHD. Se= sensitivity, Sp= specificity, PV= predictive value, P= prevalence (III).

		Diagnoses after investigation			
		"IHD"	"No IHD"		
Stated action	"Active decisions"	53	123	176	+ PV= 53/176= 30%
	"Wait and see"	3	46	49	-PV = 46/49 = 94%
		56	169	225	

Se= 53/56 = 95% Sp= 46/169 =27%

P = 56/225 = 25%

Figure 6. The GPs' stated action in daily practice. Se= sensitivity, Sp= specificity, PV= predictive value, P= prevalence (III).

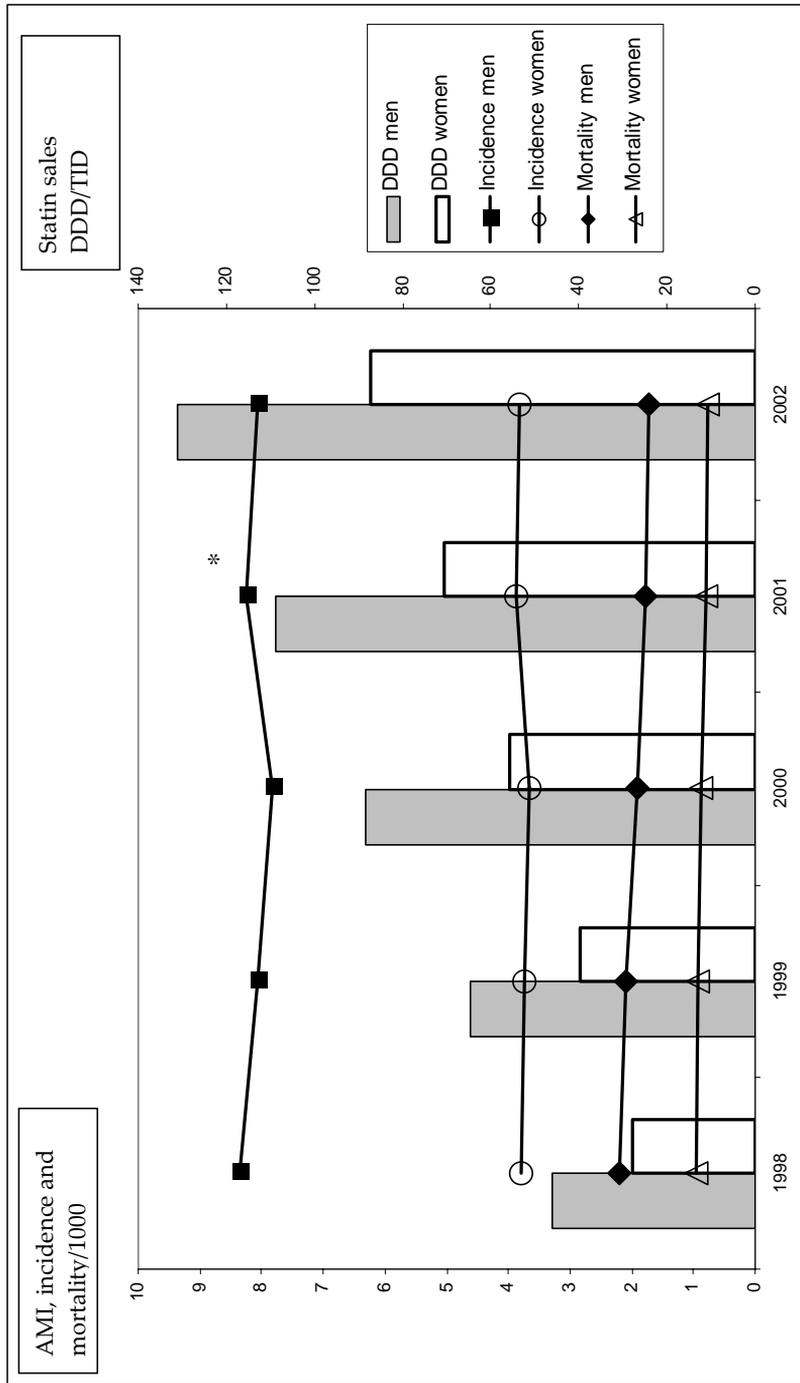# Statin sales and AMI-morbidity in Sweden between 1998 and 2002 (IV)

From 1998 to 2002 the mean sales of statins increased about three times for both men and women, from 46.2 to 131.1 and from 27.7 to 87.1 DDD/TID, respectively (*Figure 7*). The highest increase was seen in the oldest age-groups for both genders. Mortality decreased in men from 2.20 to 1.72/1000 during the five year period (*Figure 7*). The largest absolute decrease was among men 70-79 years old, from 8.74 (range 0 to 24.5) to 6.73/1000 (range 0 to 24.7). In women there was a minor decrease in mortality during the five year period from 0.97 to 0.76/1000 (*Figure 7*). During 1998-2000 the incidence of AMI decreased clearly for men but only slightly for women, from 8.37 to 7.81/1000 and from 3.79 to 3.66/1000, respectively. This decrease was followed by an increase for both men and women in 2001 (*Figure 7*) (IV).

There were very few significant correlations between statin sales and AMI-incidence in the analyses performed in different age-groups and years for men and women separately *(Table 5)*. Statin sales and AMI -incidence had a significant negative bivariate and multivariate correlation, adjusted for socio-economic deprivation, antidiabetic drugs, statin sales, x- and y-coordinates, for men 70-79 years old 1998-2000. The Pearson correlation coefficient was between -0.168 and -0.172, ($p<0.01$). The corresponding regression coefficient was between -0.026 and -0.042 ($p<0.05$). Statin sales and AMI-mortality had fewer bivariate correlations in comparison with statin sales and AMI-incidence for each of the years 1998-2002 and for respective age-groups and gender (IV).

Multivariate analysis of statin sales vs. incidence and vs. mortality of AMI for men 70-79 years old, in 26 larger towns showed no significances (IV).

The pace of increase in statin sales from 1998 to 2000 in municipality groups 3-6, for men aged 70-79 years, was plotted vs. incidence and mortality in 2001 and 2002 and vs. the change in mortality from 2000 to 2002. There were no significant correlations (IV).

The relations between five-year average statin sales and five-year average AMI-incidence are shown in figure 8.

Figure 7. Incidence and mortality of acute myocardial infarction and statin sales in the Swedish population, 40-79 years old, 1998-2002 (IV).

* Change of cut off level of Cardiac troponin T, troponin I or creatine kinase (CK-MB) for AMI.

Table 5. Correlation coefficients (r) and regression coefficients (β) for statin sales versus AMI-incidence (IV).

		Statin sales vs. AMI-incidence			
		Male		Female	
Age	Year	r	β[1]	r	β[1]
40-49	1998	0.051	0.005	0.061	0.009
	1999	0.303***	0.046***	0.165**	0.024*
	2000	0.131*	0.011	0.115	0.011
	2001	0.126*	0.017*	0.040	-0.005
	2002	0.037	0.001	-0.071	-0.008
50-59	1998	0.141*	0.007	0.086	0.004
	1999	0.287***	0.028***	0.017	-0.017*
	2000	0.141*	0.011	0.064	-0.002
	2001	-0.047	-0.016**	0.115	0.004
	2002	-0.000	-0.006	0.148*	0.003
60-69	1998	0.052	0.010	0.097	-0.0005
	1999	0.026	0.003	0.146*	0.002
	2000	-0.032	-0.001	0.146*	0.010
	2001	0.081	0.009	-0.017	-0.006
	2002	-0.042	-0.004	0.051	-0.004
70-79	1998	-0.168**	-0.042*	-0.137*	-0.031
	1999	-0.172**	-0.040*	-0.154**	-0.032*
	2000	-0.170**	-0.026*	-0.042	-0.006
	2001	-0.024	0.005	-0.062	-0.007
	2002	-0.082	-0.009	-0.036	-0.004

[1] β for statin sales in repeated multivariate linear regression analyses with AMI-incidence as dependent variable and deprivation index, sales of antidiabetic drugs, statin sales and x- and y-coordinates as independent variables.
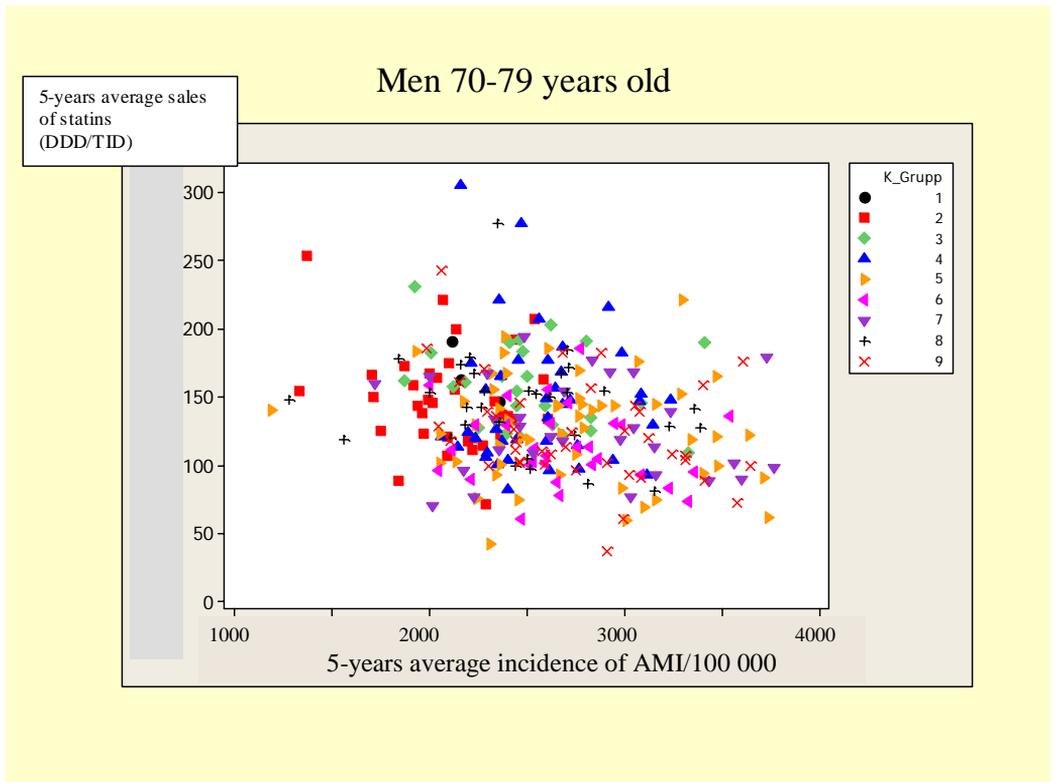
*p<0.05, **p<0.01, ***p<0.001

Figure 8. Five-year average statin sales in relation to 5-year average incidence of acute myocardial infarction(AMI) for men 70-79 years old, from 1998 to 2002. Every symbol represents one of the 289 Swedish municipalities (IV).

DISCUSSION

Chest pain represented 1.5% of all consultations to the three PHCCs in our study, made by patients aged 20-79 years. This represents 1.96% of the general population in the study area of the same age consulting for chest pain per year (I). In 12% of the consulting chest pain patients, the final diagnosis was IHD (I, II).

Patients where stable IHD could not be ruled out by clinical examination alone were investigated by exercise testing, and if equivocal, complemented by MPS. The results of the exercise tests led to a diagnostic conclusion in 77% of the cases. There were no signs of IHD in 70%, IHD was confirmed in 7% and was still in question in 23% of the patients. In these 23%, MPS indicated IHD in half of the patients. Among previously diagnosed cardiovascular disease and risk factors, only atrial fibrillation in the male group was shown to have a significant correlation to the outcome IHD (OR, 6.17; 95% CI, 1.04-36.73) (II).

The GPs' assessment of the probability of IHD as high or low in 238 chest pain patients had a sensitivity and a specificity of 77% and 73%, respectively. The GPs' stated action in daily practice resulted in a high and acceptable diagnostic sensitivity (95%) but a low specificity (27%) (III).

From 1998 to 2002 statin sales tripled in the Swedish population 40-79 years old. Bivariate and multivariate analysis for different age-groups and gender showed no correlations of importance for statin sales vs. AMI incidence or mortality (IV).

The epidemiology of chest pain and ischemic heart disease in primary care

In previous studies (26, 27, 29-31), the frequency of chest pain consultations ranged from 0.7-6.5%. In our study, the frequency was 1.5% of all consultations in the age-group 20-79 years old. The definition of chest pain was a pressure, ache, burning or stabbing sensation in the chest. These pain characteristics refer to a deep visceral pain and do not include superficial

tingling or pricking sensations. This was in contrast to the Canadian study from 1977 where chest pain could be one of many reasons for consultation. In that study, chest pain was one of the reasons for consultation in 6.7% of patients all ages (30). Hence, the frequency of chest pain as a presenting complaint varies widely, mainly due to different criteria and methods. However, it is tenable that chest pain as a presenting complaint in primary care has decreased as has the incidence and mortality of IHD (17).

Consultations for chest pain were only 1.5% of all GP consultations in the age-group 20-79 years. No more than 12% of the chest pain patients were shown to have IHD after investigation and follow up. In comparison, 19-30% of the admittances to a hospital's emergency department may be due to chest pain (20-22). Moreover, 24% of chest pain patients attending the emergency department were given an IHD-diagnosis within a few days after admittance (25). Hence, the management of chest pain patients represents a much smaller part of the daily workload of the GP compared to the emergency room physician. Further, IHD is a less common explanation to chest pain in the PHCC-setting compared to the emergency room.

Angina pectoris and myocardial infarction are commonly looked upon as mainly managed in secondary care. However, in 62 out of the 205 patients who were given an IHD-diagnosis in the general population during the study period, the GPs were actively involved.

Diagnosing ischemic heart disease

According to Sox, given a particular history based mainly on the nature of chest pain, the probability of IHD is lower in a primary care population than in a population referred for a history suggestive of IHD (101). Accordingly primary care should be an appropriate setting for ruling out IHD in chest pain patients. Ruling out IHD with sufficient safety is important since confidently assuring the patient of a non-cardiac origin of chest pain may prevent future morbidity (20).

There were 281 patients consulting for chest pain of new onset where the GPs excluded IHD as the cause of chest pain. The GPs ruled out IHD more often in younger and female patients. It is noteworthy that half of these patients suspected a heart disease themselves. In this group of 281 patients, three

women and two men reported angina pectoris or myocardial infarction in a postal questionnaire three months later. An evaluation of the information stated in the questionnaire by these five patients was done retrospectively through the PHCCs' medical records (data not included in paper I). Concerning a 48 year-old woman, who stated a myocardial infarction, the diagnosis was confirmed. Two women and one man who stated angina pectoris, had been diagnosed as angina pectoris in hospital. In one case the questionnaire was erroneously sent to a patient in whom angina pectoris was suspected by the GP in conjunction with inclusion in the study. Thus, in four of 281 (1%) of the patients where the cause of chest pain was judged to be another than IHD, the GPs' judgement could in retrospect be questioned. Accordingly the negative predictive value was 99% when the GPs ruled out IHD as the cause of chest pain by clinical evaluation. In comparison, Buntinx reports a negative predictive value of 97% for the GPs' first impression as "not serious" when evaluating chest pain patients (29).

In retrospect, 1% questionable judgements after clinical evaluation only, is almost inevitable. However, another five patients experienced emergent manifestations of IHD while waiting for an exercise test. Hence nine patients out of 554 during almost two years might not have received optimal care. In an American study, during four years, 106 AMI-patients in a population of 250 000 adults i.e. 10 in 100 000 per year were identified as missed opportunities in the primary care (102). Our results correspond to 32 in 100 000 per year and are of the same magnitude since we included angina and deaths outside hospital as well. There may be room for improvement. When there is a significant clinical suspicion of IHD, exercise testing should be available without a long delay. In addition, Troponin T testing in primary care could be of value for diagnosing of AMIs with unspecific symptoms (48, 49, 103).

In 15 of 22 patients where the GPs would have chosen medication for angina instead of exercise testing, the test results did not indicate IHD. In some cases the cause of chest pain may be another than IHD. Thus, investigation by exercise test is preferable to mere medication for angina (III).

Obviously, as indicated by the results from paper III, the grading of the probability of IHD in chest pain patients as "high" and "low" is an insufficient diagnostic measure. However, the negative predictive value of this rough estimate was as high as 91%. If the negative predictive value instead is calculated on the GPs' stated action in daily practice to "wait and see" an

increase to 94% is observed. An effort to further increase the negative predictive value in routine care, by using exercise tests in a larger proportion of "wait and see" patients, could be discussed. However, this strategy could produce a number of equivocal exercise test results claiming additional investigations to rule out IHD. Therefore, watchful waiting may be a better strategy in this group of patients.

Exercise testing

The exercise testing was conclusive in 77% of chest pain patients. In 70% of the patients the findings of exercise testing were negative and consequently exclusion of IHD as the cause of chest pain was conceivable. In 7% IHD was confirmed (II).

The probability of IHD for a certain ST depression has been calculated for different pretest likelihood levels (104). ST-segment depression exceeding 0.1 mV is a recommended criterion indicating coronary insufficiency (50), and was used in our study. We did not in this study take any notice to the slope of the ST-segment depression. If up-sloping ST-segment depression is regarded as pathologic as well as horizontal or down-sloping, the specificity of the test will be significantly lower (53). In this study we compensated for this drop in specificity by further investigations with MPS.

The evaluation of any angina-like chest pain during the exercise is known to enhance the performance characteristics of the test (50, 52). Accordingly, we required chest pain in relation to exercise in addition to ST-depression as a criterion for coronary insufficiency. There were no significant relations between the main reasons for referral for MPS after exercise testing and the final outcome as "IHD" or "no IHD" after MPS. However, if ST depression alone had been chosen as criteria for "IHD", 10 out of 20 patients with negative findings on MPS would have been classified as coronary insufficiency according to the exercise ECG. In addition, 8 patients without ST-changes but chest pain would have been erroneously classified as "no IHD" after the exercise testing (*Table 4*). Thus, our criteria for further examination after exercise testing enhanced the predictive accuracy of both positive and negative findings. The lower positive predictive value of ST depression in women was compensated for by performing MPS in all subjects with ST-depression > 0.1 mV but without chest pain. It has been suggested that further investigation of

an intermediate risk group would produce sensitivity and specificity values of around 90% (52).

Only, atrial fibrillation among risk factors was significantly correlated to the allocation to "IHD" after exercise testing or MPS, in the male group (II). We assume that the explanation for this finding is the low cardiovascular morbidity in a primary care milieu. This observation suggests an enhanced negative predictive value of the exercise test in this group of low risk patients. In other studies, a high negative predictive value of exercise testing in primary care has been reported (55-57).

Myocardial perfusion scintigraphy

About 50% of the patients with inconclusive findings on exercise testing had IHD according to MPS results (II). According to Baye's theorem, a prevalence of approximately 50% for a disease is an appropriate proportion in a population considered for a testing procedure. Further, a negative finding on MPS predicts a much favourable prognosis (61, 62, 64-66). MPS is well established and has been suggested for use in primary care (105).

Strengths and limitations

The strengths of the study were that the three participating PHCCs were chosen due to a functioning network of interested GPs. Study meetings were held regularly for all physicians and participating members of the staff (I, II, III). There was a thorough follow up of almost all included patients. The non-responders to the postal questionnaire three months after the inclusion were checked for possible IHD-diagnosis even if deceased. In those patients where there was still diagnostic uncertainty at the end of acute hospital care, GPs had the option of referral for an exercise test at this point in the study. The study was undertaken during almost two years and the patients were retrieved from almost 40 000 primary care visits.

There were some limitations. It was not possible to validate that all eligible patients with chest pain were included. Obviously, many patients with a chest pain history making unstable IHD likely were, after a telephone inquiry, directed to the emergency department of the local county hospital by the

PHCCs' nurses or the 112 alarm. Inclusion in the study was done only during office hours. However, the aim of the study was not to include all eligible chest pain patients in the general population but those who consulted their GP (I, II, III).

We did not validate the denying answers to the postal questionnaire exploring any IHD-diagnosis given within three months after study inclusion (I). It has been shown that the negative predictive value of a denying questionnaire answer on myocardial infarction is close to 100% and the positive predictive value a little more than 70% (106). The predictive accuracy of survey answers on angina pectoris diagnoses are probably lower compared to AMI. Lampe, however, found an overall agreement between self-reported diagnosis of angina pectoris and medical records in 95% of 5789 British men (107).

We did not give any preset definition of low and high probability of IHD or how this should be interpreted (III). This gave us, however, the opportunity to elucidate the daily practice and clinical decision making with regard to the chest pain patient, referral to exercise testing or acute referral to hospital (III).

The results in paper IV are based on ecological methods. Results from ecological studies are best not being interpreted at the individual level, thus avoiding the ecological fallacy (108, 109). However, the results can be used as a basis for discussion and for the generation of new alternative hypotheses (IV).

Additional data from a six year follow up

It can be discussed if subjects who consult for chest pain have a higher risk of IHD than subjects not consulting. Is the consultation an early warning sign of IHD? We therefore performed a follow up almost six years after inclusion of all patients that were judged to have another cause than IHD to their chest pain. The aim was to follow the long-term prevalence of IHD in patients who had consulted for chest pain and compare them with a control group, matched for age, gender and geographical area. The controls were chosen from The Swedish National Population Registry. A postal questionnaire was distributed to both subjects and controls. When participants claimed to have been given a diagnosis of myocardial infarction or angina pectoris, an evaluation of the information was done through medical records. Subjects with verified AMI or unstable angina were grouped together in the analysis. Those chest pain patients or controls that had had a validated diagnosis of angina pectoris or myocardial infarction prior to the inclusion day in 1998-2000 were excluded. Out of the 384 chest pain patients and their 746 controls, 16 and 28, respectively, died during the period of observation. The questionnaire was distributed to the surviving patients and controls. After one postal reminder, 279 (76%) of the chest pain patients and 530 (74%) of the controls responded to the questionnaire.

Table 6. Clinical characteristics of the 279 non-cardiac chest pain patients and their 530 population controls.

	Chest pain patients (n=279)	Controls (n=530)	p-value[1]
Age at inclusion, (years)	57 ± 11 (SD)	56 ± 11 SD)	NS
Male, n (%)	121 (43)	226 (43)	NS
Female, n (%)	158 (57)	304 (57)	NS
Information from The National Population Registry			
Mortality [2], n (%)	16 (4)	28 (4)	NS
Information from medical records			
Angina pectoris, n (%)	6 (2.2)	8 (1.5)	NS
Myocardial infarction or unstable angina, n (%)	10 (3.6)	14 (2.6)	NS
Information from postal questionnaires			
Angina pectoris, n (%)	**22 (9)**	**18 (4)**	**<0.01**
Myocardial infarction, n (%)	13 (5)	12 (2)	NS

[1] NS = not significant, [2] Mortality is calculated on all participants, i.e. 384 chest pain patients and 746 controls.

The mortality rate of the two study populations did not differ significantly (*Table 6*). According to the questionnaire, chest pain patients more often claimed to have angina pectoris (p<0.01) during follow up. Information from medical records, however, failed to verify this difference. The number of AMIs did not differ between the study groups according to the questionnaire and an evaluation of medical records confirmed this information (*Table 6*).

The important message from this six year follow up of individuals with chest pain is that GPs can exclude IHD with a high degree of certainty in a substantial number of such patients.

Are statins effective?

Despite widespread and increasing sales of statins, no correlation of importance to the incidence or mortality of AMI in the Swedish population could be detected in this ecological, explorative study (IV). It must be emphasised that some of the correlation coefficients in table 5 were significantly different from zero, but the values of the correlation coefficients were very low, so the grade of linearity is non-existent. Significance was only due to a large number of observations (IV).

The lack of observed effects can be due to low compliance. Adherence with statin therapy is shown to be rather low (110). AMI-mortality has decreased since the 1980-ies before the rise of statin treatment (17). The contribution of statins has been estimated to be no more than 3% (73). Accordingly, there are other factors of much greater importance. Tobacco smoking is a major risk factor for IHD for both men and women (10, 74, 75). Smoking has decreased in Sweden during the last thirty years. Decreased smoking has been shown to have a strong impact on the IHD-mortality (73). It is noteworthy that figures on smoking prevalence were not available by year and gender on a municipality basis in Sweden. However, to some extent smoking habits could be assumed to be included in the socio-economic deprivation index since people with low education and people with low income more often are smokers (77).

There are at least nine known modifiable risk factors of importance to consider (10), making the assessment of the risk factor profile complex. Further the propensity to follow guidelines has been shown to be low, and the practice variation high (111). Accordingly, the lack of population effects could be due to prescription habits not fully according to guidelines. The lack of effects in women is however less surprising since the preventive effect is lower in women, above all in primary but also in secondary prevention, compared to men (89, 94, 112). We do not know the indications for the statins sold from 1998-2002 but it is reasonable to assume that a substantial proportion was for primary prevention. It is well known that statins prescribed for primary prevention have a lower impact on AMI-morbidity than those prescribed for secondary prevention. An interesting finding is that in relation to the risk of

AMI, using the incidence of AMI as a proxy for risk, women were prescribed more statins than men (*Figure 7*).

To what extent can the effects of statins on AMI morbidity be calculated from known randomised controlled trials? Data from a primary preventive trial on 6595 men aged 45-64 years were used (90). A number needed to treat (NNT)/year of 235 (95% CI, 152-490) for non-fatal AMI or death from coronary heart disease was calculated. In that study 40 mg pravastatin was used. The DDD for pravastatin is 20 mg. The observed yearly, average increase in statin use in our study was, 21.2 DDD/TID and corresponds to 10.6 study-doses of pravastatin. This estimates a possible, yearly decrease in incidence of 10.6/235; 0.045 per 1000 or 4.5 per 100 000. It is appropriate to calculate the possible additional effect of statins on two years, since the preventive effect is obvious first after the initial year of treatment (88, 89). Thus, an optimal effect on AMI-incidence of statins used in primary prevention would be a decrease of only 9/100 000 from 1998 to 2000. In the present study we observed a decrease in AMI incidence of 56/100 000 for men, 40-79 year old, from 1998 to 2000.

In addition, data from a secondary preventive randomised controlled trial on 4444 patients 35-70 years old of whom 82% were men were used (89). The NNT for preventing a mortal AMI/year was estimated to 362 (95% CI 227-902). In that study the average dose of statin used corresponded to two DDDs. Hence the potential yearly decrease in AMI-mortality due to the statins was 10.6/362; 0.029 per 1000 or 2.9/100 000. This estimates a mortality decrease, calculated on four years from 1998 to 2002, of 12/100 000. In comparison, the observed mortality decrease in the present study was 48/100 000 for men 40-79 years old from 1998 to 2002.

Theoretically there are potential effects of statins on the AMI-morbidity in the population. However, our explorative study failed to reveal any correlation between statin sales and AMI-incidence/mortality. Our findings do not enhance the Poly pill strategy (92).

Conclusions

- The frequency of a new episode of chest pain bringing a patient to the GP was 1.5% of all consultations in the age-group 20-79 years (I).
- After investigation and follow up, 12% of chest pain patients received a diagnosis of ischemic heart disease (I, II).
- Exercise testing was judged to be conclusive in almost 80% of chest pain patients. Myocardial perfusion scintigraphy showed signs of IHD in 50% of patients with inconclusive exercise tests (II).
- The GPs' stated action in daily practice was in good accordance with the outcome after investigation and follow up (III).
- Despite a widespread and increasing prescribing of statins, no strong association with AMI incidence/mortality in the Swedish population, independent of age and gender, could be detected (IV).

Practical implications

Primary care is an appropriate level of care for diagnostics of stable IHD in patients with chest pain (I, II, III).

Provided a stepwise diagnostic management, the primary care setting is appropriate for ruling out IHD as the cause of chest pain with sufficient safety (I, II, III).

Exercise testing and myocardial perfusion scintigraphy are useful procedures when investigating chest pain patients in primary care (I, II).

When the alternatives are investigation or medication against angina, investigation should be chosen in some cases to prevent unwarranted diagnosis of IHD (III).

On a population level, no strong association was shown between AMI-incidence/mortality and statin sales. The results indicate that preventive measures other than increased statin treatment should be considered when discussing the allocation of public resources to further decrease AMI-morbidity (IV).

SUMMARY IN SWEDISH

Ont i bröstet är en vanlig orsak att söka läkare i primärvård. I de allra flesta fall är orsaken godartad, till exempel muskelvärk eller inflammation i matstrupen. Emellertid medför smärta i bröstet ofta oro för allvarlig hjärtsjukdom. Enligt tidigare studier har drygt en av tio som söker för bröstsmärta i primärvården en sjukdom i hjärtats kranskärl, som hjärtinfarkt eller kärlkramp, som förklaring. En klinisk bedömning kan ofta utesluta en kranskärlssjukdom men ibland behövs en kompletterande utredning med arbetsprov eller akut bedömning på sjukhus. Syftet med avhandlingen var att undersöka allmänläkares kliniska bedömning och handläggning av patienter med bröstsmärta samt hur användbara cykelarbetsprov och myocard-scintigrafi är på dessa patienter i primärvård. Ett ytterligare syfte var att analysera om det finns ett samband mellan försäljning av kolesterolsänkande läkemedel, statiner, och insjuknande i hjärtinfarkt på befolkningsnivå.

Alla patienter i åldrarna 20-79 år som sökte för bröstsmärta som debuterat senaste halvåret, erbjöds att vara med i studien. Studien pågick under nästa två år mellan 1998 och 2000 på tre vårdcentraler i Östergötland och samman-lagt inkluderades 554 patienter.

Besök för bröstsmärta utgjorde 1.5 procent av alla besök i den aktuella åldersgruppen. Detta motsvarar att omkring 2 procent av befolkningen mellan 20 och 79 år sökte för bröstsmärta på vårdcentralerna årligen.

Hos 281 av patienterna uteslöts kranskärlssjukdom efter en klinisk undersökning. För att värdera säkerheten i denna bedömning gjordes en uppföljande enkät till dessa patienter efter tre månader då 279 kunde följas upp. Den visade att fyra (1,4 %) av de 279 patienterna hade fått hjärtinfarkt eller kärlkramp diagnostiserad efter besöket på vårdcentralen.

Kranskärlssjukdom kunde uteslutas hos ytterligare 187 patienter efter utredning. Därmed hade totalt 462 patienter i studien fått bedömt att orsaken till bröstsmärtan var en annan än kranskärlssjukdom. Det kan diskuteras om patienter som söker för bröstsmärta är en riskgrupp för att senare insjukna i kärlkramp eller hjärtinfarkt. Därför gjordes en uppföljning efter nästan sex år av dessa patienter, 384 stycken som var minst 35 år vid studiestarten. Den

visade att varken dödligheten eller diagnoserna kärlkramp och hjärtinfarkt var högre bland dem som sökt för bröstsmärta, jämfört med en kontrollgrupp i normalbefolkningen. Resultaten visade att patienter som sökt för bröstsmärta och där kranskärlssjukdom inte påvisats, inte löper ökad risk att senare insjukna i kranskärlssjukdom.

Hos 208 patienter bedömdes stabil kärlkramp som en möjlig förklaring till smärtan. Utredning med arbetsprov eftersträvades hos alla dessa och i 191 av fallen gjordes också undersökningen, vilken var normal i 134 och visade kranskärlssjukdom i 14 fall. Hos 43 patienter var resultatet av arbetsprovet tvetydigt. I 39 av dessa fall utfördes myocardscintigrafi vilken var normal i 20 och visade kranskärlssjukdom i 19. Arbetsprov gav ett entydigt resultat i tre fjärdedelar av fallen och i resterande fall kunde myocardscintigrafi utesluta kranskärlssjukdom hos hälften. Resultaten visade att arbetsprov och myocardscintigrafi är värdefulla metoder för att utreda patienter med bröstsmärta i primärvård.

I de 208 fall där stabil kärlkramp bedömdes som en möjlig förklaring tillfrågades läkarna hur de hade handlagt patienten under rutinförhållanden, utan studiens ökade resurser för arbetsprov. Ett aktivt beslut om utredning eller läkemedelsbehandling hade givit 95 procent rätt diagnos, kranskärls-sjukdom. I 22 fall där endast läkemedelsbehandling hade satts in, hade 15 patienter ingen kranskärlssjukdom. I de 49 fall läkaren valt att avvakta hade endast 6 procent med kranskärlssjukdom riskerat att missas. Under väntan på utredning med arbetsprov insjuknade fem patienter med akuta symtom. Resultaten visade att allmänläkares tentativa handläggning av patienter med misstänkt kranskärlssjukdom hade god överensstämmelse med resultat av utredning. Men speciellt i de fall där endast läkemedelsbehandling hade övervägts borde även utredning ha gjorts. Studien visade även på att arbetsprov bör vara tillgängligt med kort väntetid.

Läkemedelsgruppen statiner har i ett flertal stora läkemedelsstudier visats minska risken för kranskärlssjukdom. Förhållandena i rutinsjukvård skiljer sig emellertid på många sätt från läkemedelsstudier. Därför analyserades, i en ekologisk studie, sambandet mellan användningen av statiner och sjukligheten i akut hjärtinfarkt i Sveriges kommuner, baserat på registerdata under åren 1998 till 2002. Försäljningen av statiner ökade tre gånger för både män och kvinnor under de fem åren. Dödligheten i akut hjärtinfarkt minskade något för både män och kvinnor under hela tidsperioden och insjuknandet i hjärtinfarkt

minskade för män under de första tre åren av studien. Inga samband kunde påvisas mellan mängden sålda statiner och insjuknande eller dödlighet i akut hjärtinfarkt vid jämförelse mellan kommunerna. En ekologisk studie av denna typ kan inte påvisa orsakssamband, men kan ge underlag för diskussion och hypotesgenerering. Resultaten antyder att andra preventiva åtgärder än ökad statinbehandling bör övervägas för att ytterligare minska sjukligheten i akut hjärtinfarkt.

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