In Non ST-Elevation Acute Coronary Syndromes

Similarities and differences between women and men

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ISSN 0345-0082 ISBN: 978-91-7393-565-4 "Afterthought first
Then, hard work"
I-or

To Lena and Johannes, Hilda and Hugo

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Abstract

Background

Non ST-elevation Acute Coronary Syndromes are the most frequent manifestations of acute ischemic heart disease. Gender differences in treatment intensity, including differences in level of care, have been reported. Also differences in benefit from certain treatments, especially invasive treatment, have been discussed. Finally, difference in outcome between men and women, have been proposed. Results have been inconsistent, partly depending on if and how adjustment for differences in background characteristics has been made.

The aims of the studies in this thesis were to assess differences between the genders in baseline characteristics, level of care, medical treatment and non-invasive and invasive cardiac procedures. The aims were also to determine gender differences in short and long-term mortality, including impact of level of care, and to determine differences between the genders in benefit from an invasive strategy, with special reference to benefit in women.

Method

We used prospectively collected data from the RIKS-HIA register in two studies (Paper I and IV). In one study we merged data from patients admitted to general wards in the south-east region of Sweden (The AKUT register), with data from patients admitted to CCU's (RIKS-HIA) at participating hospitals during the same time (Paper II). We also randomly assigned women to a routine invasive or a selective invasive treatment strategy, and performed a meta-analysis, to determine gender differences in benefit from a routine invasive strategy (Paper III).

Results

Women were older than men and more likely to have a history of diabetes and hypertension, while men were more likely to have a history of myocardial infarction and revascularisation. Women were also more likely to have normal coronary arteries on the angiogram. After adjustment for baseline differences there were only minor, and directionally inconsistent, differences between women and men in pharmacological treatment. Men were more often referred for coronary angiography, even after adjustment. While CABG-rate was lower in women, after adjustment PCI-rate was similar or even higher compared to men. After adjustment for differences in age, long-term outcome was better in women.

In our small but randomised trial there was no benefit from a routine invasive strategy in women. A meta-analysis indicated interaction between gender and treatment strategy, with lack of benefit in women, in contrast to in men. However, our large observational study indicated no gender difference with an invasive strategy. Moreover, benefit was similar in women and men with invasive treatment.

Conclusion

There are substantial differences between women and men in baseline characteristics that affect management and outcome more than gender per se. After adjustment women have better long-term outcome than men. There appear to be a difference in benefit from a routine invasive strategy between the genders, with less benefit in women, but in routine clinical management there was no difference between women and men managed with an invasive strategy.

ist of original Papers

This thesis is based on the following papers, which will be referred to by their Roman numerals.

I Alfredsson J, Stenestrand U, Wallentin L, Swahn E.

Gender differences in management and outcome in non-ST-elevation acute coronary syndrome.

Heart. 2007; 93:1357-62.

II Alfredsson J, Sederholm-Lawesson S, Stenestrand U, Swahn E.

Although women are less likely to be admitted to Coronary Care Units, they are treated equally to men and have better outcome. A prospective cohort study in patients with Non ST-Elevation Acute Coronary Syndromes.

Accepted for publication in Acute Cardiac Care

III Swahn E, Alfredsson J, Afzal R, Budaj A, Chrolavicius S, Fox K, Jolly S, Mehta S. R, de Winter R, Yusuf S.

Early invasive compared with a selective invasive strategy in women with non-ST-elevation acute coronary syndromes: a substudy of the OASIS 5 trial and a meta-analysis of previous randomized trials.

Eur Heart J. 2009 Feb 7. [Epub ahead of print]

IV Alfredsson J, Stenestrand U, Wallentin L, Lindbäck J, Swahn E Similar outcome in women and men with an invasive strategy.

In manuscript

Abbreviations

(In alphabetical order)

ACC American College of Cardiology
ACE Angiotensin Converting Enzyme

ACS Acute Coronary Syndrome
ADP Adenosine DiPhosphate
AHA American Heart Association

Apo Apolipoprotein

BMI Body Mass Index

BSA Body Surface Area

CAD Coronary Artery Disease
CCB Calcium Channel Blockers

CCU Coronary Care Unit
CHD Coronary Heart Disease
CHF Congestive Heart Failure
CI Confidence Interval

CKMB Creatinine Kinase Muscle Brain

COPD Chronic Obstructive Pulmonary Disease

CRP C-Reactive Protein

CVD CardioVascular Disese ECG ElectroCardioGram

ESC European Society of Cardiology

GP IIb/IIIa Glycoprotein IIb/IIIa

HDL High Density Lipoprotein

HF Heart Failure
HR Hazard Ratio

IHD Ischemic Heart Disease

ICCU Intensive Coronary Care Unit

LDL Low Density Lipoprotein

LM Left Main

LBBB Left Bundle Branch Block

LMWH Low Molecular Weight Heparin

MI Myocardial Infarction

NHLBI National Heart, Lung, and Blood Institute
NSTEMI Non ST-elevation Myocardial Infarction

NSTE ACS Non ST-Elevation Acute Coronary Syndrome

OR Odds Ratio

PAR Population Attributable Risk

PCI Percutaneous Coronary Intervention

RCT Randomised Controlled Trial

RR Relative Risk

STEMI ST-Elevation Myocardial Infarction

UAP Unstable Angina Pectoris
UFH UnFractionated Heparin
ULN Upper Limit Normal

WHO World Health Organisation

Acronyms

(In alphabetical order)

ACUITY Acute Catheterization and Urgent Intervention Triage

strategy

ACOS Acute Coronary Syndromes Registry

AKUT Akut Kranskärslsjukdom UTanför HIA

BARI Bypass Angioplasty Revascularization Investigation

CRUSADE Can Rapid Risk Stratification of Unstable Angina Patients

Suppress Adverse Outcomes with Early Implementation of

the ACC/AHA Guidelines

CURE Clopidogrel in Unstable Angina to Prevent Recurrent Events

FRISC Fragmin and Revascularization during Instability in

Coronary artery disease

GRACE Global Registry of Acute Coronary Events

GUSTO Global Utilization of Streptokinase and Tissue Plasminogen

Activator for Occluded Coronary Arteries

ICTUS Invasive Versus Conservative Treatment in Unstable

Coronary Syndromes

MONICA Multinational MONItoring of trends and determinants in

CArdiovascular disease

OASIS Organization For The Assessment Of Strategies For

Ischemic Syndromes

PRAIS (UK) Prospective Registry of Acute Ischaemic Syndromes in the

UK

PROSPER The Prospective Study of Pravastatin in the Elderly at Risk

RIKS-HIA Register of Information and Knowledge about

Swedish Heart Intensive care Admissions

RITA 3 Third Randomized Intervention Trial of Unstable Angina

SCAAR Svenska Coronar Angiografi- och Angioplastik Registret

TACTICS-TIMI 18 Treat angina with Aggrastat and determine Cost of Therapy

with an Invasive or Conservative Strategy-Thrombolysis In Myocardial Infarction 18

TRITON Trial to Assess Improvement in Therapeutic Outcomes

by Optimizing Platelet Inhibition with Prasugrel

ntroduction

The myocardial infarction mortality has decreased markedly during recent decades, in Sweden and the rest of the Western world; a decrease that have multiple causes. (1-3) In spite of improvements, the incidence of acute MI has remained high and cardiovascular disease is still the leading cause of death, afflicting almost 50 % of both

men and women. Coronary heart disease accounts for most of the cardiovascular events,

and MI is the single most important contributor to mortality and morbidity. (4, 5)

Historically, fewer women than men have been included in studies on CHD. Whether this is caused by lower incidence in women, especially at younger age, or actual exclusion of women from the trials have been debated. (6, 7) The consequence is that evidence base for several treatments are less firm for women than for men. Lack of gender-specific knowledge has emerged as an important issue in management of non ST-elevation acute coronary syndromes where some data have indicated difference in benefit from a routine invasive strategy according to gender. (8-10)

There are also reports that women have been managed less intensively, with worse outcome, compared to men. For example, women have less often received reperfusion therapy, early antithrombotic therapy and antiplatelet therapy at discharge. Moreover, men have more often been referred for coronary angiography. (11-15)

There are several important differences in background characteristics between a female and a male population with acute coronary syndromes (ACS); for example, females are older and have more co-morbid conditions.

Studies comparing management and outcome in men and women are, for obvious reasons, not randomised why fair comparisons rely on statistical methods to adjust for observed differences in background characteristics. To decide whether it is gender per se or other characteristics that account for observed differences in management and outcome between the genders, large study populations, with information on potential confounders, are needed to perform proper adjustments.

To improve the individual management of NSTE ACS patients it is important to clarify if we, in real life clinical practice, treat women differently than men.

It is also important to evaluate if there are differences in effect of treatments between the genders, and if observed differences are due to gender per se.

Background

Definitions

Coronary Heart Disease is an initially silent and progressive disease that eventually can be manifested as stable angina pectoris or as an acute coronary syndrome.

Acute Coronary Syndromes

- · Sudden Cardiac Death
- M yocardial Infarction
 - ST-Elevation Myocardial Infarction
 - Non ST-Elevation Myocardial Infarction

Unstable Angina Pectoris

Non ST-Elevation Acute Coronary Syndromes

ACS comprises sudden cardiac death, ST-elevation myocardial infarction (STEMI), non ST-elevation myocardial infarction (NSTEMI) and unstable angina pectoris (UAP). Due to similarities in pathophysiology and treatment, NSTEMI and UAP are often referred to as non ST-elevation acute coronary syndromes (NSTE ACS).

Patients with NSTE ACS are the focus of this thesis.

In earlier literature MI was usually divided in Q-wave myocardial infarction and non Q-wave myocardial infarction depending on development of a Q-wave on the ECG, as a result of myocardial necrosis.

However, with the development of new treatment strategies, the distinction between STEMI and NSTEMI upon presentation have become more important to guide early treatment and decision making, e.g. fibrinolysis or referral for primary percutaneous coronary intervention.

In patients with ACS the proportion of NSTEMI to STEMI, and in NSTE ACS the proportion of UAP to NSTEMI, is higher for women than for men. (16)

Diagnosis

Diagnosis of **myocardial infarction** is based on biochemical markers, symptoms and ECG-changes. In the joint European Society of Cardiology (ESC) / American College of Cardiology (ACC) consensus document on redefinition of MI from 2000 (17) MI is defined by either:

- 1. Typical rise and fall (troponin) of biochemical markers of myocardial necrosis together with at least one of the following:
 - a. Ischemic symptoms
 - b. Development of pathologic Q waves on the ECG
 - c. ECG changes indicative of ischemia (ST elevation or depression)
 - d. Coronary artery intervention
- 2. Post-mortem findings of an acute MI.

Unstable angina is defined according to Braunwald classical definition (18) as either of:

- 1. New onset of severe angina or accelerated angina
- 2. Angina at rest.
- 3. Angina less than 14 d after MI.

UAP patients may have elevated biochemical markers (below the MI diagnosis level) but it is not obligatory for UAP diagnosis. Definitions of MI and UAP are the same in men and women.

Epidemiology

During the last two decades mortality in myocardial infarction has decreased by about 50 % in Sweden and in most industrialised countries. (19) The decrease is evident for both men and women, although somewhat more pronounced in men. Explanations for the marked decrease in mortality are a combination of improved risk factor situation, acute treatment and prevention.

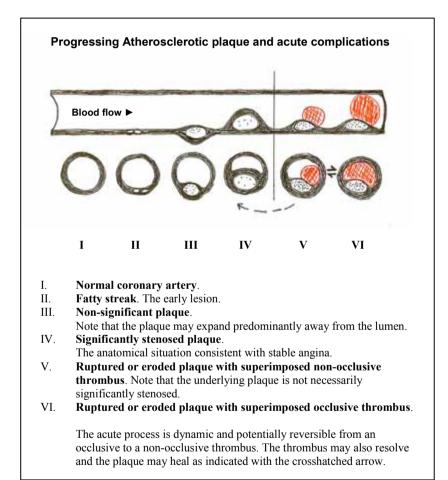
The prevalence of risk factors for atherosclerosis has improved in the general population. While the prevalence of diabetes and obesity have increased, prevalence of smoking, hypertension, hyperlipidemia and physical inactivity have all decreased with a net positive effect on cardiovascular risk. Medical treatment for primary prevention of identified risk factors, as well as secondary prevention, including antihypertensive treatment, statins and antiplatelet therapy, after an acute coronary event have improved. Finally, acute treatment of an acute coronary syndrome has gone through an intense progress during the latest three decades with development of antithrombotic strategies, including fibrinolysis and antiplatelet therapies, catheterisation techniques, including stents and primary PCI, and organisational improvements, such as pre-hospital management and intensive monitoring of patients with the highest risk. (1-3)

Even so, incidence of MI has remained high and cardiovascular diseases, with coronary heart disease being the most prevalent, are the most common causes of death in both men and women. (20)

The most apparent difference between the genders in epidemiology is the higher incidence of MI, especially at younger age, and consequently higher mortality in men. (21)

Patophysiology

Pathogenesis of NSTE ACS involves two different processes. A slow atherosclerotic process, with low degree of reversibility, that lasts for decades, and a fast, dynamic and potentially reversible process characterized by plaque rupture or erosion, with subsequent thrombus formation.



Dysfunction of the endothelium, recognised as one of the earliest signs of atherosclerosis, may be caused by mechanical stress, turbulent blood flow or smoking and is associated with diabetes, hypertension, hyperlipidemia and also genetic mechanisms. Injured endothelium has increased adhesiveness and permeability of

inflammatory cells and lipid cells that accumulates in the vessel wall. Hence the atherosclerotic process has been increasingly linked to inflammation. Atherosclerosis begins early in life and already in the early teens the first signs, fatty streaks, which consists of inflammatory cells and low-density lipoprotein, are evident. (22, 23)

A plaque that has become large enough to compromise blood flow is the anatomical foundation for stable angina. An ACS, on the other hand, is usually characterised by a sudden erosion of the endothelial wall or rupture of a plaque. (24, 25)

Plaque instability, indicating high propensity for rupture, is determined by the plaque's characteristics such as inflammatory activity and thickness of the fibrous cap more than size or stenosis severity. (26, 27) Plaque rupture leads to presentation of thrombogenic factors to the blood elements, with immediate activation of platelets, which is a pivotal part of the pathophysiological process of ACS, and activation of the coagulation cascade. (28)

Endothelial erosion is more common in younger ACS patients and women. (24, 29)

Risk Factors

A large number of risk factors for atherosclerosis and CVD have been described. In this section only the most established will be mentioned, with special reference to gender differences.

Early longitudinal studies revealed that there are gender differences in risk factor prevalence, especially in the young and middle ages. Although there are differences between men and women in impact of a certain risk factor (diabetes and smoking being the most obvious), the most striking impression is the similarity between the genders in relative risk associated with most of the classical risk factors. (30-32)

Schnohr et al reported from a 21-year follow-up from the Copenhagen city Heart Study (33) on 5599 men and 6478 women aged 30 to 79 years at baseline. The risk ratios for CHD were similar in men and women for hypertension, hypercholesterolemia, physical inactivity and obesity. In contrast, relative risk for CHD associated with diabetes and smoking was higher in women than in men.

The INTERHEART study, a case-control study of over 12 000 cases (3000 women) and more than 14 000 controls from 52 countries all over the world, investigated the

association of nine potentially modifiable risk factors for a first MI. (34, 35) The six factors positively associated with increased risk for a first MI were hyperlipidemia (ApoB/ApoA1 ratio), smoking, hypertension, diabetes, abdominal obesity and psychosocial stress. The three factors negatively associated with MI (i.e. protected from MI) were physical activity, low risk diet (daily vegetables and fruits) and moderate alcohol consumption. The study confirmed that CHD determinants were the same in women and men, and these nine factors accounted for 90% of the population attributable risk in men and 94% in women. However, there were small differences between the genders in the strength of a certain risk factor. Hypertension, diabetes, physical inactivity and lack of alcohol intake were more strongly associated with MI in women than men. The study also indicated that the higher risk for MI in younger men (<60 years) compared to women of the same age was mainly due to difference in risk factor burden.

Smoking

Smoking is a strong risk factor for both genders but several studies have shown that smoking is even more powerful as a risk factor for women. (30-33, 36)

A 12 year follow-up of the Finnmark Study of 11 843 men and women aged 35 to 52 at entry showed that the MI incidence was 4.6 times higher in men compared to women. (30) The RR for smokers was 3.6 (95% CI, 2.2-6.0) in women and 2.4 (95% CI, 1.7-3.4) in men. Moreover there was an indication of difference in "dose-response" between the genders. The RR for suffering an MI for women smoking 1-9 cigarettes / day was 2.3 (95% CI, 1.2-4.2) and for men 2.3 (95% CI, 1.5-3.5). In contrast the RR for women smoking more than 20 cigarettes/day was 5.9 (95% CI, 2.9-11.8), more than twice the corresponding rate for men, 2.8 (95% CI, 1.9-4.2).

The antiestrogenic effect of smoking has been proposed as an explanation for the higher RR associated with smoking in women, (37) beside effects on atherosclerosis (38) and haemostasis. (39)

Decline in smoking habits during the latest decades is regarded as the major contributor to the decrease in CHD mortality. (1) In Sweden, smoking incidence has decreased in both men and women, but more so in men. In the latest National health report from the Swedish national board of health and welfare, with data from 2005, 18% of women and 15% of men were smokers compared to 27% in both men and women in 1988. (40)

Diabetes

A history of diabetes has been reported to be a more powerful risk factor for MI in women than in men in prospective studies (30, 32, 33) and case-control studies. (35)

The enhanced risk for cardiovascular death, in women compared to men, is even more pronounced. (30, 41) In a prospective study of 14 786 middle-aged men and women in Finland the RR for CHD incidence associated with diabetes was 2.00 (95% CI, 1.51-2.61) for men and 2.29 (95% CI, 1.57-3.35) for women, while, the RR for CHD mortality was much higher in women 4.26 (95% CI, 2.42-7.60) vs. 2.37 (95% CI, 1.63-3.44). (30)

In a meta-analysis published in the British Medical Journal 2006, including 447 064 patients, the RR for fatal CHD for diabetics compared to non-diabetics was significantly higher in women, 3.50 (95% CI, 2.70-4.53) vs. 2.06 (95% CI, 1.81-2.34) The difference persisted but was attenuated with adjustment for other risk factors (women vs. men) RR 1.46 (95% CI, 1.14-1.88). (42)

A study from the Swedish RIKS-HIA register showed that at least younger women with diabetes (<65 years) have higher mortality after an MI compared to their male counterparts. The excess risk was mainly attributed to an increased risk factor burden, and after adjustment the difference was no longer statistically significant (women vs. men) 1.14 (95% CI, 0.98-1.33). (43)

Dyslipidemia

Elevated total cholesterol and LDL cholesterol are established risk factors for both men and women. (30, 33, 44) The increase in risk with increased cholesterol values appears more obvious in men. (45) However, a recent report from Copenhagen City Heart Study suggests that the increased risk associated with elevated total cholesterol is most pronounced in relatively young individuals (<60 years) and at that age, the risk increment is actually more pronounced in women than in men. (46) Interaction between age and sex may explain the divergent findings regarding impact of cholesterol and LDL in different studies.

Decreased HDL cholesterol and elevated triglycerides, the dyslipidemia typical for the metabolic syndrome, are important risk indicators in both genders, with a stronger impact in women (45) especially elderly women. (47, 48)

Apolipoprotein B has repeatedly been shown to predict CVD risk more accurately than LDL in both men and women (45, 49, 50) Also, during recent years increased attention has been paid to the protective role of HDL or Apolipoprotein A1 in prediction of risk. Accordingly, the ratios of ApoB:ApoA1 or Cholesterol:HDL has been superior in risk prediction compared to all other lipid values, and the former being somewhat better in both genders. (45, 49, 50)

Clinical presentation and symptoms

Typical symptoms in NSTE ACS are virtually the same as in MI.

Chest pain is the most common symptom in both men and women.(51-56) The typical ischemic chest pain or chest discomfort is characterized by a retrosternal heaviness or squeezing sensation. The chest pain is often, but not always, radiating to left or right arm, to the neck, jaws, back, shoulders or epigastrium. Dyspnoea, dizziness or diaphoresis are often accompanying the chest sensations. Absence of chest pain in patients with an acute MI appear common in both men and women, but in most studies somewhat more common in women, (52, 54-57) sometimes even after adjustment for age and medical history. (51)

In a report from a large cohort with more than 400 000 patients in the American National Registry of Myocardial Infarction 33% (29% of men vs. 39% of women) of the patients with a diagnosis of MI presented without chest pain. Patients without chest pain were older and more often diabetics. (52)

Presenting without chest pain has been associated with longer delay time, less intensive treatment and worse outcome. (52, 54, 58)

Milner et al showed that chest pain was more common in men compared to women with acute MI. Age, however, had higher impact on prevalence of chest pain than gender. In the youngest (<65 years) 73.1% of women and 81.0% of men experienced chest pain compared to 45.5% of women and 56.3% of men among the oldest (≥75 years). (57)

In a recent report from Northern Sweden MONICA study 81% of female and 86% of male patients with MI presented with typical symptoms. (59)

A large meta-analysis by Canto et al supported difference in chest pain prevalence between women and men, but the authors concluded: "Women are significantly less likely to report chest pain or discomfort compared with men. These differences, however, are not likely large enough to warrant sex-specific public health messages regarding the symptoms of ACS at the present time". (60)

A large review by Patel et al found differences in prevalence of chest pain between the genders but the differences were small and most often non-significant. Importantly, concomitant symptoms like back or jaw pain, nausea, dyspnoea and palpitations were more common in women, (61) which is in line with several studies that have suggested that women report more symptoms than men. (61, 62)

Difference between the genders in interpretation of symptoms has been observed (63) but in another paper difference in awareness of symptoms suggestive of ischemia did not appear to be lower in women. (64)

In patients with symptoms suspected of MI, significantly fewer women than men are finally diagnosed as MI or UAP. (57, 65, 66)

Risk Stratification

The NSTE ACS population is very heterogeneous, with a large variation in risk for future ischemic events or death. Therefore, stratification of patients according to risk for future cardiac events, but also to identify patients with the highest benefit from intensive treatment, have become an integrated part of the management of NSTE ACS patients. (67, 68)

The two most established single objective findings used in risk stratification are ECG-changes (in NSTE ACS, mainly ST-depression) and elevation of myocardial damage markers (today preferably, troponins). Several studies have confirmed ST-depression as a marker of risk of death and MI (69, 70) and as a marker to properly identify patients with the highest benefit from a more intensive treatment. (71) In the same way, troponins are established markers for prediction of MI and death, (72-74) presence of significant coronary stenosis or thrombus (75) and benefit from an invasive strategy. (9, 76) In a meta-analysis of seven clinical trials and 19 cohort studies on patients with NSTE ACS, patients with elevated troponin had higher mortality in clinical trials (OR = 3.0, 95% CI, 1.8-5.0) but even more so in cohort studies (OR = 23.7, 95% CI, 6.6-85.6). (74)

A combination of ST-depression and troponin elevation has better prognostic capacity than either of them alone. (77, 78)

Little is known about differences between men and women in prognostic value of ECG-changes and biomarkers.

Randomised trials comparing invasive to a conservative treatment strategy in NSTE ACS indicate similar prevalence of ST-depression but higher prevalence of troponin elevation in men compared to women. (8-10) TACTICS TIMI-18 showed similar benefit with an invasive strategy in women and men with troponin elevation. In patients with ST-depression benefit from an invasive approach was more pronounced in men (OR = 0.49, 95% CI, 0.32-0.75) than in women (OR = 0.66, 95% CI, 0.38-1.15) although directionally the same. (9)

Several other risk markers have been put forward. Among numerous markers of inflammation, high sensitive CRP is the most widely used, and the FRISC II trial confirmed that elevated high sensitivity CRP levels is associated with long-term mortality. (79)

Markers of neurohormonal activation (80, 81) or renal dysfunction (81) also carry important prognostic information, especially regarding mortality. One small study indicated that renal dysfunction may have more severe prognostic information in women than men. (82)

Since NSTE ACS is a complex event different markers may reflect different pathophysiological aspects of the disease. Combining markers for myocardial necrosis, inflammation, neurohormonal activation and renal dysfunction in a multimarker approach has been proposed and studies have demonstrated that a multimarker approach improves risk stratification. (81) Wiviott et al reported in a substudy from the TACTICS TIMI 18 that a multimarker approach identified a higher proportion of high risk women, but lack of any marker elevation also identified very low risk women. Men were more likely to have elevated CK-MB or troponin while women were more likely to have elevated CRP or BNP. (83)

A number of, more or less complex, risk factor scores have been constructed, among them the GRACE-score, the TIMI-score and the FRISC-score.

The GRACE-score has a very good discriminative power but is complex and require special tools. (84) The TIMI-score is simple and have been widely accepted in spite of less accuracy. (85) The more recently constructed FRISC-score has been used to adequately identify patients with highest benefit from an early invasive strategy. (86)

In one rather small study the TIMI-score was shown to correctly predict 30-days death/MI/revascularisation in both men and women. (87) Whether the GRACE and FRISC-scores perform equally in men and women is not well known.

Level of care

It is often difficult to establish the NSTE ACS diagnosis in the emergency unit. Therefore many patients with a suspected ACS need to be hospitalised for repeated testing of biochemical markers and ECG monitoring.

Earlier studies have found that male patients were more likely to be admitted to coronary care units, (88-92) and it has been suggested that this could have an impact on differences in treatment intensity between the genders. (88, 92) Compared to general wards, CCU's have been associated with more intensive care (88, 89) and better outcome. (89) However, these studies included patients with both STEMI and NSTEMI, which could explain differences in both level of care and treatment intensity. No earlier trials have assessed consequences of level of care from a gender perspective.

Non-invasive diagnostic testing

Prevalence of significant coronary obstruction in patients with chest pain, suspicious of ischemia, is substantially lower in women than in men, affecting diagnostic accuracy. (93)

Exercise ECG test

The exercise ECG test is easily available and the most frequently used non invasive diagnostic test, despite reports of low accuracy, especially in women. Inadequate workload is more common in women and consequently lower sensitivity. Higher prevalence of false-positive ECG-changes in women contributes to a lower specificity. (94) In a meta-analysis by Kwok et al, in both symptomatic and asymptomatic women

and men, a mean specificity (for coronary obstruction) of 0.70 vs. 0.77 and a mean specificity of 0.61 vs. 0.68 was found for women and men respectively. (95) Diagnostic accuracy is improved in both genders if other factors than symptoms and ST-depression, such as maximum heart rate and maximum work load, are taken into account.

It has been shown that early symptom-limited exercise test can be conducted safely in the context of NSTE ACS, (96, 97) and prognostic information in this clinical setting is just as useful in women as in men. (98, 99) Exercise test and troponins in combination identifies a very low risk group even better in women than in men. (100)

Stress Echocardiography

In a prospective study on patients with intermediate risk of coronary heart disease, dobutamine stress echocardiography accurately predicted significant coronary stenosis (>70%) with at least as high sensitivity and specificity for women (90% and 85%) as for men (80% and 77%). Stress echocardiography with pharmacological stress is especially useful in older women with insufficient workload. (101)

Myocardial perfusion scintigraphy

In a meta-analysis, perfusion scintigraphy performed somewhat better in men, with a sensitivity and specificity of 85% and 85% respectively compared to 78% and 64% in women. (95) The lower accuracy in women was explained by lower sensitivity for single-vessel disease in women (102) and female breast attenuation artifacts.(103) However, a normal perfusion scintigraphy carries an excellent prognostic value and an abnormal scan indicates significant risk for an adverse event, similar in both genders. (104, 105)

Medical treatment

Anti ischemic drugs

Beta-blockers

Evidence for beta-blockers in the context of NSTE ACS is based on a very limited amount of randomised trial data, and most of the studies were performed more than two decades ago. Recommendations are also based on extrapolation from trials in stable angina and unselected MI. (106) In a meta-analysis treatment with beta-blockers vs. placebo, in patients with UAP, was associated with 13% risk reduction in progression to STEMI. (107)

In patients with ACS undergoing PCI pooled results from recent trials indicated effect on mortality at 30 days (0.6% vs. 2.0%, p < 0.001) and 6 months (1.7% vs. 3.7%, p < 0.001) with beta-blocker therapy. (108)

Although there is a paucity of gender specific data, there were no obvious differences in effect between the genders in one trial. (109)

In patients with congestive heart failure (CHF) and left ventricular dysfunction there is evidence for benefit with beta-blocker treatment. (110-112) A meta-analysis, including four major beta-blocker trials in CHF, indicated similar effect on mortality in men and women. (113)

Beta-blockers are recommended for secondary prevention in the absence of contraindications, without difference between the genders. Indication is stronger in patients with left ventricular systolic dysfunction.

Nitrates

In an early and small randomised trial a reduction in infarct size and left ventricular dysfunction associated with nitroglycerin-infusion was indicated. In the sub-group with anterior MI even reduction in mortality was noted. (114)

More recent and large scale trials showed no benefit with nitroglycerin treatment. (115, 116)

There are no placebo-controlled randomised trials in the context of NSTE ACS assessing effect of nitrates.

Nitrates are recommended and used primarily for symptom relief, without any known difference in effect between men and women.

Calcium channel blockers

There are three subclasses of CCB with different proportion of vasodilatation and heart rate reduction.

The small randomised trials regarding the use of calcium channel blockers in NSTE ACS have shown diverging results which could, at least in part, be due to different mode of action of different classes of CCB. (117-119)

There are no known differences in effect between the genders.

Lipid lowering treatment

Statin therapy improves long-term outcome (120) and is recommended to be initiated early in all patients with NSTE ACS. (121-124) Men were in majority in most statin trials, and still gender-specific data are scarce, with somewhat contradictory results. There are studies reflecting secondary prophylaxis, (125) primary prevention in high risk individuals (124) and primary prevention in individuals with low cholesterol but elevated CRP; (126) with no apparent difference in effect between the genders. However, with a lower event rate in women, benefit was more uncertain. Moreover, the PROSPER trial (including 2 804 men and 3 000 women with a history of, or risk factors for, vascular disease) found a significant beneficial effect only in men. (127) In the guidelines, there are no differences in recommendations between men and women. (67)

ACE-inhibitor / A2-receptor blockers

Several studies have shown that ACE-inhibitors are beneficial in reducing remodelling and improving survival in patients with reduced left ventricular systolic function after MI. (128-130) In patients who are intolerant to ACE-inhibitors angiotensin-2 receptor blockers are indicated. (131, 132) In more recent years a number of trials have suggested an anti-atherogenic effect of ACE-inhibitors, irrespective of LV-function in

patients with established atherosclerotic disease or high risk for atherosclerotic disease. (133-135)

Treatment is indicated in all NSTE ACS patients with left ventricular dysfunction, diabetes or hypertension. (128-130)

A meta-analysis (based on 10 267 men and 2 396 women) indicated similar effect in men and women. (136)

Antithrombotic treatment

Antithrombotic therapy is fundamental in the acute treatment of NSTE ACS to prevent progression of the thrombotic process in the afflicted coronary artery, and it is also essential in long-term treatment of NSTE ACS to prevent new ischemic events. Antithrombotic treatment is especially important in clinical settings involving PCI.

Acetylsalicylic acid

Randomised trials of aspirin compared with placebo, already in the 1980s, showed consistent benefit for patients with UAP/NSTEMI by reducing the risk for non-fatal MI by approximately 50%. (137-139)

Indirect comparison of maintenance doses has shown similar effect in a broad range (75-1500 mg) but a dose-dependant increase in bleeding. (140) Hence a maintenance dose of 75 to 162 mg per day is recommended. A very recent meta-analysis revealed similar effect in men and women in secondary prevention. (141)

Adenosine Diphosphate-receptor antagonists

The thienopyridines ticlopidine and clopidogrel are ADP-receptor antagonists. Both drugs seem at least as effective as aspirin. (142, 143) However the adverse effects of ticlopidine have limited its use, especially after introduction of clopidogrel as an alternative. Clopidogrel has proved effective in combination with aspirin after NSTE ACS in the CURE study, with another 20% risk reduction of the composite endpoint cardiovascular death, MI or stroke [9.3% vs. 11.4%, RR = 0.80, 95% CI (0.72-0.90)]. Risk reduction was directionally the same in men and women but lower and not statistically significant in women. (144) The overall benefit was larger in a sub-group of patients undergoing PCI. (145)

In the TRITON trial, the more recently developed ADP-receptor antagonist, prasugrel was compared to clopidogrel in ACS patients (74% NSTE ACS), on top of aspirin. The combined end point death from cardiovascular causes, nonfatal MI or nonfatal stroke was reduced with prasugrel [9.9% vs. 12.1%, HR = 0.81, 95% CI (0.73-0.90)]. However the rate of major bleedings was significantly higher in patients receiving prasugrel (2.4% vs. 1.8%, p = 0.03). (146) Gender differences paralleled those in the CURE trial, with less pronounced and statistically not significant, although directionally the same, risk reduction in women.

Other ADP-receptor antagonists have been developed. For example ticagrelor and cangrelor have been investigated and phase III clinical trials are undertaken or under way. (147, 148)

Other antiplatelet drugs

Several thrombin-receptor antagonists are currently being investigated in trials. (149)

Non-responders to antiplatelet treatment

Substantial inter-individual variation in effect of both aspirin and clopidogrel has been observed (150, 151) and these so called "non-responders" or "low-responders" appear to be at increased risk for new ischemic events. (152, 153) Optimal individual management of antiplatelet therapy may therefore in the near future involve monitoring of platelet activity and individual tailoring of treatment (i.e. choice of drug or dose adjustment) based on individual responsiveness.

There are reports on differences in the proportion of men and women that could be defined as non-responders, why monitoring of responsiveness might be even more important in women. (154)

Glycoprotein (GP) IIb/IIIa antagonists

Abciximab is a Fab fragment of an antibody, with strong affinity for the receptor. Eptifibatide is a peptide and tirofiban mimics a peptide that contains the part of fibringen that binds to the receptor. (155)

A meta-analysis of the six large randomised GP IIb/IIIa antagonist trials in patients with UAP/NSTEMI, not routinely scheduled to undergo coronary angiography, showed a modest benefit by reducing the combined endpoint death /MI by 30 days [11.8% vs. 10.8%, OR = 0.91, 95% CI (0.84-0.98)]. Effect was mainly restricted to patients with

high risk features such as elevated troponin or ST-depression. Patients undergoing PCI or CABG had greater risk reduction compared to those not revascularized. (156) In the same meta-analysis, a subgroup analysis revealed significant interaction with gender. While men had a significant benefit in reduction of death/MI by 30 days, harm was indicated in women (OR = 0.81 vs. 1.15, p for interaction < 0.0001).

Unfractionated Heparin (UFH)

A meta-analysis indicated a 33% reduction of death or MI (RR = 0.67, 95% CI, 0.44-1.02) by adding heparin to aspirin in patients with UAP. (157)

Low-Molecular-Weight Heparin (LMWH)

Trials of LMWH added to treatment with aspirin have generally shown favourable results for the combination in the acute phase, but extended treatment after hospital discharge has been less convincing. (158)

For example in the FRISC trial treatment with dalteparin vs. placebo resulted in a marked risk reduction for the primary end-point death/new MI during the first 6 days [1.8% vs. 4.8%, RR = 0.37, 95% CI (0.20-0.68)], but after extended 40 days of treatment the difference, although directionally consistent with outcome at 6 days, was no longer statistically significant [8% vs. 10.7%, RR = 0.75, 95% CI (0.54-1.03)]. (159) In the FRISC II trial, patients with NSTE ACS were randomised to 90 days of dalteparin treatment vs. placebo after 5-7 days of open label treatment. There was a 47% risk reduction in the combined end point death/MI 30 days but after 3 months there was no statistically significant difference. (160)

The FRISC trial indicated a more pronounced effect of dalteparin treatment in women compared to men in death/new MI during 6 days of treatment [RR = 0.16 (95% CI, 0.05-0.56) vs. 0.55 (95% CI, 0.28-1.11)]. (159)

Direct thrombin inhibitors

Hirudin has been extensively studied but with mixed results, including excess bleeding. (161, 162) The synthetic hirudin analogue bivalirudin was compared to UFH/enoxaparin in ACS-patients (65% NSTE ACS) in the ACUITY trial. Bivalirudin alone was non-inferior to bivalirudin+GPIIB/IIIa or UFH/LMWH+GPIIb/IIIa in the composite ischemic endpoint death/MI/unplanned revascularisation at 30 days, but with lower rate of bleeding. Subgroup analysis revealed that effect on the ischemic endpoint

was restricted to patients receiving thienopyridines. Bleeding rates were lower with bivalirudin in all subgroups. (163) Although several subgroup analyses were performed, data on gender differences was not presented.

In the published 1 year follow-up non-inferiority with bivalirudin alone persisted. Subgroup analysis according to gender showed no difference in effect. (164)

Lack of difference in effect between the genders was confirmed in a separate analysis on patients that had PCI performed. (165)

Factor Xa inhibitors

In the OASIS 5 trial, more than 20 000 patients with NSTE ACS were randomised to fondaparinux or enoxaparin for a maximum of 8 days. The composite primary efficacy outcome death, MI or refractory ischemia at 9 days was 5.7% with fondaparinux vs. 5.8% with enoxaparin, which satisfied the prespecified non-inferiority criteria. Rates of major bleeding were lower with fondaparinux (2.2% vs. 4.1%), hence the composite efficacy and safety endpoint was in favour of fondaparinux. At 6 months the composite death, MI and stroke was significantly lower with fondaparinux [2.5% vs. 11.3%, HR = 0.89, 95% CI (0.82-0.97)]. At all time-points bleeding rate was lower with fondaparinux. (166)

Subgroup analyses regarding the primary outcome revealed no gender interaction.

Bleeding complications

Different bleeding complications are the most frequent non-ischemic complications in NSTE ACS patients. For example, the CURE trial reported significantly higher rate of major bleeding with the aspirin/clopidogrel combination compared to aspirin alone (3.7% vs. 2.7%, p = 0.001). (144) Data from real life management in the GRACE register showed rates of major bleeding between 2.7% (in UAP) and 4.7% (in NSTEMI). (167) Independent predictors of major bleeding included female sex, age, renal dysfunction, history of bleeding and use of GP IIb/IIIa inhibitors. In a multivariate analysis the adjusted OR for bleeding was 1.71 (95% CI, 1.35-2.17) in women compared to men. (167) In the CRUSADE register about 14% of the patients were given red blood cell transfusion (and significantly more of these patients were treated

with an early invasive strategy) indicating higher bleeding rates in real life clinical circumstances. (168)

Recent trials have highlighted a strong impact on prognosis with bleeding complications in ACS. (167, 169, 170) In two large scale meta-analyses increase in bleeding was associated with a stepwise increase in mortality. Not only mortality, but also ischemic events increased with major bleeding. (171, 172) In a recent analysis from the OASIS 5 trial, after adjustment for baseline differences and bleeding propensity, the 180 days risk (for patients experiencing a major bleeding vs. no bleeding) was: 3.11 (95% CI, 2.55-3.79) for death, 2.63 (95% CI, 2.13-3.25) for MI and 4.25 (95% CI, 2.93-6.15) for stroke. The risk was directionally the same for minor bleedings, but the magnitude was lower. (170)

Female sex has been an independent predictor of bleeding in several ACS trials with different anticoagulation strategies. (169, 173, 174)

There are several factors that may explain worse outcome associated with major bleeding. Among them, potential confounders such as older age, comorbidity and renal failure, but also more causative factors such as hemodynamic instability and the possibility that bleeding triggers pro-thrombotic and pro-inflammatory processes. Furthermore, discontinuation of antiplatelet and antithrombotic therapy as a consequence of bleeding has been put forward as a major reason for increased risk of ischemic events. (172) Women appear to be at higher risk for excess doses of antithrombotic medication and as a consequence, higher bleeding rate. (173, 174) Also, impaired renal function is more common among female patients, and associated with higher bleeding rates. (174)

Revascularisation

Revascularisation is performed in the setting of NSTE ACS to relieve symptom and to prevent progression to extended myocardial ischemia and death.

Routine invasive vs. selective invasive strategy

In a subgroup of NSTE ACS patients with ongoing ischemic symptoms or hemodynamic or rhythm instability there is consensus that urgent catheterisation is the preferred treatment strategy.

For the majority of patients with NSTE ACS, without need for urgent revascularisation, there was an intense debate during the 90s whether an invasive approach, with routine coronary angiography, (followed by revascularisation if feasible), was superior to a more conservative approach, with pharmacological stabilisation and coronary angiography only if the patient experienced symptoms or signs of ischemia (spontaneous or during a stress test). These two treatment strategies have been compared in a number of randomised trials. Most (175-179) but not all (180-182) of the studies have been in favour of a routine invasive strategy. A meta-analysis of seven of the earlier trials showed a reduced rate of death at the end of follow-up [12.2% vs. 14.4%, OR = 0.82, 95% CI (0.72-0.93) p=0.001] for routine invasive vs. selective invasive. The long term benefit came with an early hazard during initial hospitalisation, with a significantly higher risk of death or MI [5.2 vs. 1.1%, OR = 1.36, 95% CI (1.12-1.66) p=0.002 in the routine invasive strategy arm. Many of the included trials in this meta-analysis do not reflect contemporary management strategies, and the use of stents and GP IIb/IIIA-inhibitors was low. The current paradigm was challenged by the ICTUS trial in which there was no difference between a routine invasive vs. a more selective invasive strategy in the composite of death, MI or rehospitalisation for angina pectoris within 1 year [22.7 vs. 21.2%, RR = 1.07, 95% CI (0.87-1.33) p = 0.33]. (182) A small difference in revascularisation rate between the two groups and a regular use of thienopyridines in the ICTUS trial may at least partly explain the difference in result between the ICTUS trial and earlier trials.

Today an early invasive treatment strategy, with coronary angiography and revascularisation if feasible, has become the treatment strategy of choice in patients with NSTE ACS, and is a class 1-recommendation in both American College of Cardiology/American Heart Association (ACC/AHA) (68) and European Society of Cardiology (ESC) (67) guidelines on NSTE ACS, at least for patients with medium or high risk features.

Gender aspects on routine invasive vs. selective invasive strategy

Only three of the trials comparing a routine with a selective invasive treatment have prespecified analyses according to gender, and data on this matter are conflicting.

The FRISC II trial randomised 1704 men and 749 women. (8) In contrast to a clear favorable outcome with a routine invasive strategy for the primary combined endpoint death/MI for men (9.6% vs. 15.8%, p < 0.001) there was no benefit in women (12.4% vs. 10.5%, ns). In a multivariate regression analysis, adjusting for baseline differences between the genders, male gender was an independent risk factor for death/MI in the non invasive strategy arm [OR for death/MI women vs. men 0.64 (95% CI, 0.43-0.97)]. In the routine invasive strategy arm, on the other hand, female gender indicated worse outcome [OR for death/MI women vs. men 1.46 (95% CI, 0.96-2.23)].

Results from the RITA 3 trial (682 women and 1208 men) were similar to those of the FRISC II trial. (10) Men had a lower incidence of the primary end-point death/MI with a routine invasive strategy (7.0% vs. 10.1%) while the opposite was indicated for women (8.6% vs. 5.1%), with a significant interaction test (p = 0.011).

Contrasting the two former trials, the TACTICS TIMI-18 trial (757 women and 1463 men) indicated a beneficial effect of an early intervention for both men and women. (9) The primary outcome, a composite of death/MI/rehospitalisation for ACS, was lower with an invasive strategy in both genders, but did not reach statistical significance in women. In a subgroup analysis of high risk patients there was a similar benefit regarding the primary end-point in troponin-positive females (OR = 0.56, 95% CI, 0.32-0.97) and males (OR = 0.53, 95% CI, 0.35-0.79).

Gender aspects on revascularisation

Percutaneous coronary intervention

In the early days of percutaneous coronary interventions, data from registries indicated differences in several aspects between the genders. Women were older and more likely to have hypertension, diabetes and heart failure. Women were also more likely to be referred for catheterisation in an acute situation. (183, 184) Most of these early reports indicated increased risk for complications, including in-hospital death, for women after PCI. (184-188) However, despite higher age and comorbidity, women and men had comparable long term outcome. (184, 186, 187)

Comparison of data from 1993-1994 and 1985-1986 with data from 1997-1998 in the NHLBI dynamic register showed that, although women in the more recent register were older and had a higher incidence of comorbidity, they had greater success rate and comparable rate of mortality, MI and need for emergency CABG surgery. After controlling for potential confounders in baseline factors gender was not a significant predictor of death or death/MI. (189) However women more often reported angina symptoms, limiting activity and quality of life, during one-year follow-up.(190)

In another comparative study of patients undergoing PCI 1979-1995 and 1996-2004

30 days mortality was significantly reduced in both men and women. After adjustment for risk factors there was no difference between the genders in the later group, neither in short-term nor long term mortality. (191) The observed improvement could probably be explained by improvements in operator experience, technique and equipment.

Difference in coronary artery size and body size between men and women has been proposed as important factors for observed differences in outcome and in a report by Peterson et al on more than 100 000 patients there was no difference in mortality between men and women after adjustment for body surface area. (192) In another small study on patients who underwent PCI to lesions in vessels with a reference diameter of < 3.0 mm, there was no difference between the genders in procedural success or inhospital cardiac events. (193)

More contemporary studies have continued to show worse crude outcome for women, but after adjustment for confounding baseline variables outcome have most often been similar, (194-196) or even better long-term outcome in women. (197) Hence much of the observed difference in outcome could be explained by differences in comorbidity and age.

However, in the youngest subgroup women still appear to have worse outcome, even after adjustment for clinical and procedural factors. (198)

There is a paucity of data concerning gender differences in benefit from bare metal stents or drug eluting stents, but the benefit appear to be similar. (199, 200)

Although differences in outcome between the genders after PCI have diminished and although rate of vascular site complications have improved over time there is still evidence of more vascular site and bleeding complications among women, even after multiple adjustment. (195)

Coronary artery bypass graft surgery

In a majority of studies, women undergoing CABG surgery have had greater early mortality compared to their male counterparts. (201-207) However, after adjustment for differences in baseline risk-factors, mortality rates for women have often, (201, 202, 204, 208, 209) but not always (203, 205-207) been similar to that of men.

At least three factors could contribute to observed differences. There are marked differences between the genders in age and comorbidity, (with more heart failure, hypertension, renal insufficiency and diabetes in women) surgical risk factors (more often emergency or urgent CABG, smaller body surface area inferring smaller vessels and consequently a more technically challenging procedure) and finally use of internal mammary artery (less often used in women). (201, 203-206, 209) Diabetes confer an important excess risk in CABG surgery (210) and appears to be an even stronger risk-factor in women. (211) Difference in BSA has been proposed as a major contributor to differences in outcome in CABG surgery, and difference in outcome between the genders have sometimes (201) but not always (206) disappeared after adjustment for BSA.

Also, impact of gender may differ if we assess short or long term mortality. In a work by Guru et al on >50 000 patients (>12 000 women) that had CABG surgery performed; after adjustment women still had higher short term (30 days) mortality, but lower long-term (1year) mortality. (212) A report from the BARI trial, in which patients with multivessel disease were randomised to CABG or PCI, indicated better long-term outcome in women compared to men. At an average of 5.4 years follow-up crude mortality in the CABG group was similar in men and women, but after adjustment women had significantly lower risk of death. (213)

Over time things have improved, with decreasing mortality associated with CABG, despite higher age and more comorbidity, especially for women. (214)

Hence the discussion whether there are gender differences in outcome associated with CABG surgery has not come to an end.

Gender differences in treatment and outcome

During the last two decades increased attention has been paid to gender differences in treatment of ACS. However, there are major differences in baseline characteristics between a female and a male population with ACS that may affect the attending physician's choice of treatment, appropriateness of a certain treatment and maybe even the patient's preferences for a therapy. Also difference in outcome between the genders has been increasingly highlighted. But again, there are obvious differences between men and women in baseline characteristics that have to be accounted for to evaluate impact of gender per se.

Treatment

Many early studies, (11-15, 215-217) but not all, (218) indicated that women were treated less intensively in the acute phase of ACS. In some of the studies, after adjustment for age, comorbidity and severity of the disease, most of the differences disappeared. (15, 216) There is also conflicting evidence on gender differences in evidence-based treatment at discharge.(11, 14, 15, 215, 217, 219, 220) The majority of these studies were performed in patients with acute MI, both STEMI and NSTEMI. Data on medical treatment in a population with NSTE ACS are scarce, but Stone et al. reported from the TIMI III register of patients with UAP or non-Q-wave AMI, that women were less likely to receive heparin and IV nitroglycerin in the acute phase, as well as aspirin at discharge, even after age-adjustment.(11)

Outcome

After an acute MI a higher short-term mortality in women is documented in several studies. (12, 14, 15, 216, 221-223) Even after adjustment for age and comorbidity some difference has usually, (12, 14, 221, 222) but not always, (220, 223) remained. On the other hand, most studies assessing long-term outcome, have found no difference between the genders, or even better outcome in women, at least after adjustment. (216, 219, 222, 223)

Earlier studies focusing on gender differences in outcome after an ACS have usually studied patients with MI, including both STEMI and NSTEMI. (12, 14, 15, 216, 221-223) Not only the pathophysiology and initial management differs between these two conditions, (224) but also outcome according to gender. (16, 220) In contrast to in STEMI, (225) women with NSTEMI or UAP seem to have equal or better outcome, after adjustment for age and comorbidity. (11, 13, 16, 217, 220, 226) Different impact of gender at different ages has also been indicated. Young women appear to have worse outcome while elderly women seem to have better outcome compared to men of the same age. (225, 227)

Gender differences in recruitment to trials

It is a fact that fewer women than men have been included in most clinical studies regarding CHD. As an example, even in the trials comparing a routine invasive to a selective invasive strategy, with a pre-specified gender analysis, the proportion of women has been 30% to 38%. (9, 10, 177) The proportions have been similar in other trials in the area of NSTE ACS. (144, 159, 166) Whether this reflects a lower incidence in women, especially at younger age, or actual exclusion of women from the trials have been debated. (6, 7) In trials with age exclusion criteria the proportion of women was lower than in trials without exclusion of the elderly, indicating that difference in age between a male and a female ACS population may be an important contributor to difference in inclusion rate. (228) Moreover, willingness to participate in clinical trials may differ between the genders. (229) The consequence, regardless of reason, is that evidence is less firm for women than for men regarding quite a few of the established

treatments. To be able to present evidence-based treatment recommendations, valid for both men and women; more women need to be recruited to clinical trials in the future.

Pims of the studies in this thesis

The aims of the studies on patients with NSTE ACS were

- To assess differences between the genders in baseline characteristics, acute pharmacological treatment, non-invasive and invasive cardiac procedure and pharmacological treatment at discharge.
- To determine gender differences in short and long term outcome.
- To evaluate differences between men and women in level of care and impact on management and outcome.
- To determine benefits and risks with a routine invasive strategy compared to a selective invasive strategy in women.
- To determine difference in effect between the genders, in real life patients, with an invasive and non-invasive treatment.

Material and Methods

Different types of studies

Studies comparing healthcare interventions can be divided into randomised controlled trials (RCT) and non-randomised trials (often register trials). Both methods have strengths and limitations. The RCT is the gold standard as the randomisation procedure makes sure that studied subjects differ only in exposure to the considered intervention. However many individuals to whom results will later be applied differ from patients included in the RCTs. Therefore non-randomised studies in real-life clinical circumstances are important to ensure that results obtained in the randomised trials hold true in real-life situations. Non-randomised trials are also important for generating hypotheses that can later be tested in an RCT. But while non-randomised trials are less selective regarding recruitment they have an inherited risk of selection bias in allocation to a certain treatment. Selection bias results in differences in baseline characteristics, which has to be adjusted for. Large scale registries provide us with data from clinical practice and generalisability depends on how well the register covers the population we aim to describe. (230-232)

If a study is performed to assess differences in treatment provided by healthcare practitioners to certain groups, an observational study design is necessary. In comparisons between groups that one could not randomise to, for example gender, the study, for obvious reasons, has to be non-randomised.

When single trials do not have enough power to provide a statistically significant answer regarding effect of a certain treatment, a meta-analysis may be undertaken. Increasing the number of studied subjects by merging studies in a meta-analysis improves the probability to obtain a statistically significant answer. However meta-analyses have limitations, heterogeneity being one of the most important. Heterogeneity in effect between included studies is usually tested but there may also be other problems

with heterogeneity concerning difference in inclusion and exclusion criteria and difference in outcome definition. (233)

In this study we have used all the types of trials described above, to answer the study questions.

Data Sources

RIKS-HIA

The Register of Information and Knowledge about Swedish Heart Intensive care Admissions (RIKS-HIA) registers all patients admitted to the coronary care units of participating Swedish hospitals. The register started in 1995 with 19 participating hospitals and has increased gradually. In 1997 46 CCU's participated and in 2002 70 of 78 CCU's participated. Today all CCU's in Sweden continuously deliver data to the register.

Information is reported on case record forms, today directly on-line. On admission about 30 variables are recorded including age, gender, risk factors, medical history, previous medications, symptoms and ECG findings. During the hospital stay another 37 variables are recorded regarding biochemical markers, treatments, investigations and major complications. Finally, at discharge further 33 variables are recorded, including outcomes during hospital stay, discharge medication and final diagnosis. Source data verification is performed by an external monitor comparing the register information with actual hospital records in randomly selected patients from about 20 different hospitals annually. More than 40,000 measurements are checked annually and the agreement between the registered information and patient records has been between 94-96 % every year.

The complete protocol is also available at the RIKS-HIA website: http://www.riks-hia.se.

Data from RIKS-HIA is used in Paper I, II and IV.

The AKUT-register

In Paper II data from CCU's in RIKS-HIA is complemented with data from general wards collected in the AKUT-register, described more in detail in the methods section to paper II. The protocol in the AKUT-register was almost identical to the RIKS-HIA protocol.

The Swedish National Cause of Death Register and The National Patient Register

RIKS-HIA is repeatedly merged with data from the Swedish National Cause of Death Register. The Cause of Death Register covers all Swedish residents, whether the person in question was a Swedish citizen or not and irrespective of whether the death occurred in Sweden or not.

The National Patient Register comprises all diagnoses of patients hospitalised in Sweden from 1987 and onwards. By merging with the RIKS-HIA, data on comorbidity, such as previous history of heart failure, stroke, dementia, cancer, chronic obstructive pulmonary disease and renal failure were obtained.

The National Board of Health and Welfare are responsible for both these registers.

Data from The Cause of Death Register and Patient Register was used in Paper I, II and IV.

Women Sub-Study

The study was performed as a substudy to the OASIS-5 study comparing the effect of fondaparinux to enoxaparin in NSTE ACS. (166) The population is described more in detail under the heading Paper III.

Paper 1

Data presented in this paper was obtained from the RIKS-HIA register, from five years between 1998 and 2002. All patients with a discharge diagnosis of AMI or UAP, and no ST-segment elevation or left bundle branch block on admission ECG, were included. Patients treated with fibrinolysis or primary PCI were excluded in order not to include patients that developed STEMI during hospital stay. Finally, only the first time an individual appeared in the register with NSTEMI or UAP was included for analysis. Standardized criteria for the diagnosis of acute myocardial infarction and unstable angina, according to WHO, were used by all participating centers. (234) Biochemical criteria were revised during the study period in accordance with the ESC/ACC consensus document. (17) Finally, diagnoses were coded according to the International Classification of Diseases, version 10, at treating physicians' discretion.

Ethics approval

The RIKS-HIA register and the process of merging with other registries were approved by the Swedish Data Inspection Board. This study complies with the Declaration of Helsinki and was approved by the local ethics committee.

Statistical analysis

Group differences based on continuous variables were assessed using the t-test and differences based on categorical variables were assessed using the squared chi-test.

Gender differences in background characteristics were assessed with logistic regression analysis. In the first model gender was included as the sole independent variable. In the second model gender and age were included. Differences between the genders in performed procedures, pharmacological treatment, both acute and at discharge, and outcome were assessed in the same way. To further adjust for differences in background characteristics a third logistic regression model was created which included 23 covariates. For information on included variables see Paper 1. To further explore the importance of age on differences in management, rates of treatments and procedures were assessed in four age-strata.

To identify differences in outcome between the genders during 1-year follow-up, hazard ratios (HR) were calculated in four different age-intervals, using Cox regression

survival analysis, with the same covariates included as in the logistic regression analysis.

All statistical analyses were performed using SPSS version 13.0 software (SPSS Inc, Chicago III).

Paper 2

Seven hospitals in the southeast region of Sweden participated in this study. All patients admitted to CCU's were, by routine, registered in The RIKS-HIA register. At the same time-period we registered patients with suspected ACS, admitted to general wards. Dedicated nurses actively screened general wards for patients hospitalised because of a suspected ACS. Patients prescribed a series of troponin analyses were regarded as suspected of having an ACS, and registered in the same manner as in the RIKS-HIA register. Data from patients admitted to CCU's were then merged with data from patients admitted to general wards, comprising all patients with a suspected ACS admitted to the seven participating hospitals during the study period. Survival status was obtained by merging our database with the Swedish National Cause of Death Register, and information on comorbidity was obtained by merging with the National Patient Register.

Data was collected during three months in 2002. Only patients with NSTE ACS were included in this analysis. We used an "intention-to-treat" approach based on initial admission. This means that if a patient was initially admitted to a general ward and later transferred to a CCU, the study protocol handled the patient as allocated to the primary admitting ward. For outcome analyses, in order to avoid double-counting, only the first time a patient appeared in the database was included.

Standardised criteria for the diagnosis of acute MI and UAP according to WHO were used by all participating centers, (234) in accordance with the ESC/ACC consensus document. (17) Diagnoses were coded according to the International Classification of Diseases, version 10, at treating physicians' discretion.

Ethical consideration

All patients were informed of their participation in the register, and their right to deny participation. Data for research purposes have had all personal identifiers removed. The study complies with the Declaration of Helsinki and was approved by the local ethics committee.

Statistical analysis

Group differences based on continuous variables were analysed using the t-test and differences based on categorical variables were analysed using the squared chi-test, all tests were two-sided. P-values ≥ 0.05 were considered not significant.

We calculated a modified TIMI-score. (85) Age > 65 years, ST-depression \ge 1 mm, Aspirin treatment on admission, known CHD (defined as history of MI or revascularisation), elevated markers (defined as Troponin T \ge 0.05 or CKMB \ge 5) and \ge three of four risk factors (diabetes, hypertension, smoking and treatment for hyperlipidemia) each gave one point. Accordingly patients could have a TIMI-score between 0 and 6. (Detailed information on anginal events during last 24 hours before admission was not possible to obtain.)

To adjust for baseline differences between women and men, logistic regression models were created. In the first model only gender was included as independent covariate, in the second, age was added. In the third model, in addition to age and gender, we included history of diabetes, hypertension, MI, coronary revascularisation, heart failure, dementia, stroke, chronic obstructive pulmonary disease, renal failure, and diagnosed malignancy during the last three years, smoking habits and pharmacological treatment before admission (including aspirin and/or clopidogrel, warfarin, beta-blockers, ACE-inhibitors, angiotensin receptor blockers, digoxin, diuretics, long-acting nitrates and lipid lowering drugs), ST-depression (≥ 1 mm in two adjacent leads) and elevated troponin T or I (defined as above upper limit of normal (ULN) for the method used at each hospital). In the last model level of care, expressed as admittance to CCU or not, was added. The 95% CI were calculated and presented.

All statistical analyses were performed using SPSS version 14.0 software (SPSS Inc, Chicago III).

Paper 3

This study was a randomised, prospectively designed substudy of the OASIS 5 trial, an international, multi-centre, randomised, double blind trial in which fondaparinux was compared to enoxaparin in patients with UAP or NSTEMI.

Study design (235) and results (166) of the OASIS 5 main study are presented in detail earlier.

Study patients

In the OASIS 5 trial patients were randomly assigned to receive fondaparinux or enoxaparin within 24 hours after onset of symptoms. Inclusion and exclusion criteria for the substudy were identical to those of the OASIS 5 main study. Patients were eligible if they met at least two of the following three criteria: an age of at least 60 years, an elevated level of troponin or CK-MB above upper limit of normal (ULN) or electrocardiographic changes indicative of ischemia (defined as ST depression at least 1 mm in 2 contiguous leads or T-wave inversion >3 mm or any dynamic ST shift or transient ST elevation). Patients with contraindications to low-molecular-weight heparin, recent hemorrhagic stroke, indications for anticoagulation other than an ACS, age <21, pregnancy, comorbid condition with life expectancy <6 months or severe renal insufficiency [defined as a serum creatinine level of at least 3 mg per deciliter (265 µmol per liter)] were excluded.

At the same time as randomisation to fondaparinux or enoxaparin; female patients participating in this substudy were randomised to a routine coronary angiography (within 4 days of admission and, if appropriate, revascularisation within 7 days of admission) or to a selective invasive strategy with coronary angiography only if they experienced symptoms or signs of severe ischemia. Indications for coronary angiography in the selective invasive arm were: 1. Refractory ischemia, defined as recurrent chest pain/ischemic symptoms (with documented characteristic ECG changes: Horizontal ST depression ≥1mm indicative of ischemia) lasting more than 5 minutes, while on "optimal" medical therapy [defined as at least 2 anti-anginal treatments (nitrate, β-blocker, calcium antagonist)]. 2. New ST-elevation in two contiguous leads, without Q-waves or T-wave inversion (>3 mm). 3. Development of hemodynamic instability, or severe heart failure (Killip class 4). 4. Intractable life-threatening

arrhythmia. **5**. Incapacitating angina or severe ischemia at a stress test before discharge or later during follow-up. **6**. Reinfarction during follow-up. In both study groups the mode of revascularisation, PCI or CABG, was left to the discretion of the attending physicians and was based on patient characteristics and preferences, extent of disease, comorbidity and left ventricular function. If PCI was performed, the use of stents was strongly encouraged. Prior to PCI, all patients should be pre-treated with aspirin and clopidogrel. Aspirin dose was left to the discretion of the investigator but doses <100 mg was recommended. Treatment with intravenous GP IIb/IIIa was encouraged in association with PCI.

Ethical consideration

The study complies with the Declaration of Helsinki. Local ethics committees approved the study protocol, and all patients provided written informed consent.

Outcomes

The primary outcome was the composite of death, MI or stroke at 2 years. Secondary outcomes included: 1. Each of death, MI and stroke evaluated separately. 2. Composites of death, MI and death, MI, stroke or refractory ischemia (i.e. ischemia driven revascularisation).

A central committee of clinicians blinded to the allocated management strategy adjudicated death classified by cause, MI, refractory ischemia, stroke and major bleedings.

For definition of major bleeding and refractory ischemia, see the original paper.

Sample size estimate and statistical analysis

Based on the overall results of the FRISC II trial, a reduction in the rate of death or MI from 17.5% to 12.5% at 3 years was assumed, with a routine invasive strategy. To detect a relative risk reduction of 28.5%, with 80% power, a sample size of 1 600 was planned. Because of slow inclusion rate in the substudy only 184 patients were recruited when the OASIS 5 main trial was stopped. However, a decision to follow all randomised patients, in a blinded fashion, until 2 years was made.

Means and percentages are used to describe baseline and other characteristics. Outcomes are presented as hazard ratios with 95% CI. Selected outcomes are summarised by Kaplan-Meier curves. A meta-analysis of randomised trials of routine invasive vs. selective invasive strategies, with separate data for the genders, was undertaken using the method described by Yusuf and Peto.(236) This approach uses an assumption free model and weights the analyses in proportion to the information (number of events) contributed from each trial. FRISC II, RITA 3, and TACTICS TIMI-18 (published results) ICTUS (personal communication by coauthor Robbert de Winter) and OASIS 5 women substudy were included in the meta-analysis. OR with 95% CI for death and death/MI are reported. Heterogeneity was assessed with Q statistic. The level of significance was 0.05 (two-sided). Statistical software used for the meta-analysis was Comprehensive Metaanalysis V 2.0 (Biostat Inc, Englewood, NJ).

Paper 4

We included consecutive patients from the RIKS-HIA register with a discharge diagnosis of acute MI, UAP or angina pectoris admitted to hospital between 2000 and 2006. All included patients had elevated biochemical markers (defined as TnT >0.03 μ g/l or CK-MB \geq 5 μ g/l or TnI above decision limit for MI, for the method used). Patients with ST-elevation or left bundle branch block on admission ECG were excluded, as were patients treated with thrombolysis or primary PCI. Because of an increased risk of comorbidity, potentially interfering with the decision to treat invasively or not, patients above the age of 80 were excluded. All patients earlier diagnosed with dementia were excluded.

To avoid double counting only the first register-recorded hospitalisation, in agreement with inclusion and exclusion criteria, was included.

Standardised criteria for the diagnosis of acute MI and UAP according to WHO were used by all participating centers, and from 2001, in accordance with the ESC/ACC/AHA consensus document. (17) Diagnoses were coded according to the International Classification of Diseases, version 10, at treating physicians' discretion.

Information on revascularisation procedures was obtained by matching data with the national registries on coronary angiography and PCI and thoracic surgery. Reinfarction was defined as a rehospitalisation with a discharge diagnosis of MI. A new MI causing immediate death before hospitalisation was not included in the reinfarction rate but in the mortality rate.

Two different risk scores were applied in order to investigate gender differences in benefit from an early invasive strategy according to risk profile.

A modified TIMI-score (85) was calculated: Age >65 years, ST-depression ≥ 1 mm, Aspirin treatment on admission, known CHD (defined as history of AMI or revascularisation), elevated markers and ≥ 3 of 4 risk factors (diabetes, hypertension, smoking and treatment for hyperlipidemia) each gave one point.

We also calculated a modified FRISC-score. (86) Age >65 years, a history of diabetes, a history of MI, ST-segment depression on admission, elevated myocardial damage markers and elevated CRP each gave one point.

Ethical considerations

All patients for whom data were entered into the RIKS-HIA register were informed of their participation and long-term follow-up. On admission to the CCU patients received written information about RIKS-HIA and other quality registries. They had the right to deny participation immediately or have data removed later. According to Swedish law written informed consent is not necessary. Data used for research purposes have had all personal identifiers removed. The study complies with the Declaration of Helsinki and was approved by the ethics committee.

Statistical analysis

Group differences based on continuous variables were assessed using the t-test and differences based on categorical variables were assessed using the χ 2 test. Our primary outcome was one-year mortality. The cumulative risk of death in women and men respectively was calculated using a Cox regression analysis. Separate analyses were made for patients managed with an invasive strategy and a non-invasive strategy.

The main analyses were performed on patients that were discharged alive and alive 14 days after admission, in order not to include patients in the early non-invasive arm that were so severely ill (for different reasons) that it precluded them from being referred for coronary angiography. However sensitivity analyses were made, including patients that

died during the first 14 days after admission, to confirm that gender was not associated with early excess mortality.

A propensity score method was used to compensate for the non-randomised study design. A comparison between men and women isn't possible to perform in a randomised fashion and baseline differences between the compared study groups were inevitable. The propensity score method (237, 238) produces a summary score of the background characteristics for all patients and was used to balance for baseline differences between the genders. The score is usually calculated, in a logistic regression model (given baseline information available), to estimate the probability of being allocated to a certain treatment strategy that is studied. When comparing men and women, the score is the estimated probability of being female, estimated from a logistic regression model, given the baseline characteristics that were available. We calculated two different scores for the early non-invasive and the early invasive group respectively. The propensity score model included age, smoking status, previous MI, PCI or CABG surgery, history of hypertension, diabetes, congestive heart failure, renal failure, stroke, chronic obstructive pulmonary disease or malignant disease, medical treatment on admission (including ACE inhibitors/Angiotensin receptor blockers, clopidogrel, β-blockers, lipid lowering drugs, diuretics, digitalis, long-acting nitroglycerin and calcium antagonists), ST-segment depression on admission, Killip class and year of admission.

To compare risk for mortality and for the combined end-point mortality or MI between men and women, within treatment strategy, Cox regression survival analyses were performed including propensity score as a continuous variable and medical treatment at discharge (including ACE inhibitors/Angiotensin receptor blockers, aspirin, clopidogrel, β -blockers, statins, diuretics, digitalis, long-acting nitroglycerin and calcium antagonists). In a similar way difference outcome with an early invasive compared to a non-invasive strategy was assessed, with adjustment for propensity for an invasive strategy and discharge medication.

Results were presented as relative risk (RR) and 95% confidence intervals. Model performance was evaluated with the c index.

Analyses were performed with the statistical software SPSS (version 16.0) and R (version 2.9.0).

Results

Paper 1

Baseline and Management

Between 1998 and 2002, 53 781 patients (37% women) with a discharge diagnosis of either NSTEMI or UAP were included in this study. Women were older than men (73 vs. 69 years, p < 0.001) and more often had a history of diabetes, hypertension and heart failure. Men more often had a history of MI and revascularisation. There were only minor differences between the genders in the proportion of patients diagnosed as NSTEMI and in the proportion of patients with elevated biochemical markers (Table 1) Before adjustment, men were more often treated with heparin/low molecular weight heparin and GP IIb/IIIa inhibitor during hospital stay, and aspirin, β-blockers and lipid lowering drugs at discharge. Men were also more likely to have a stress test, echocardiography, coronary angiography, PCI and CABG performed. (Table 2) After adjustment for difference in age, there remained no significant differences in pharmacological treatments, except for treatment with GPIIb/IIIa inhibitors, and ACE inhibitors at discharge, which were more often used in men. However, age adjusted OR for procedure use, such as stress test, echocardiography, coronary angiography, PCI and CABG, were all higher in men. Further adjustment with another 21 covariates, did not change these associations except that there remained no significant difference in PCI rate. (Table 2)

Table 1								
Baseline characteristics								
	Men (n=34 020)	Women (n=19 761)	Un-adjusted OR* (95 % CI)	Age-adjusted OR* (95 % CI)				
Age, (years)	69 (±12)	73 (±11)	-	-				
(mean \pm (SD),								
Risk factors								
Hypertension	35	43	0.71 (0.69-0.74)	0.74 (0.71-0.77)				
Diabetes	21	24	0.84 (0.80-0.87)	0.86 (0.82-0.89)				
Current Smoker	21	17	1.28 (1.22-1.34)	0.96 (0.91-1.01)				
History of MI	36	30	1.27 (1.23-1.32)	1.44 (1.38-1.49)				
History of PCI	9	6	1.56 (1.45-1.68)	1.35 (1.26-1.45)				
History of CABG	9	5	1.97 (1.83-2.13)	1.94 (1.79-2.09)				
Medical treatment before	re admission		,	,				
ACE-inhibitor	21	21	0.99 (0.94-1.03)	1.03 (0.99-1.08)				
Aspirin/ other platelet	53	52	1.04 (1.01-1.08)	1.15 (1.11-1.20)				
inhibitor			`	` ′				
Oral anticoagulant	6	5	1.21 (1.12-1.31)	1.36 (1.25-1.47)				
β-blocker	46	47	0.95 (0.92-0.98)	0.97 (0.93-1.00)				
Digitalis	7	10	0.69 (0.64-0.73)	0.89 (0.83-0.95)				
Diuretic	26	41	0.50 (0.49-0.52)	0.63 (0.60-0.65)				
Long-acting nitrates	29	31	0.88 (0.85-0.92)	1.04 (0.99-1.08)				
Lipid lowering therapy	22	19	1.23 (1.18-1.29)	1.06 (1.01-1.11)				
Medical history								
Stroke	12	12	1.02 (0.97-1.08)	1.27 (1.20-1.35)				
Renal failure	1.9	1.3	1.44 (1.25-1.66)	1.56 (1.35-1.80)				
COPD	6	7	0.78 (0.72-0.83)	0.86 (0.80-0.93)				
Heart failure	13	17	0.72 (0.68-0.75)	0.93 (0.88-0.98)				
Cancer last 3 years	4.8	3.8	1.26 (1.15-1.37)	1.50 (1.37-1.64)				
Ischemic signs				` ` ` ` ` ` ` ` ` ` ` ` ` ` ` ` ` ` ` `				
ST-depression †	34	38	0.83 (0.80-0.86)	0.95 (0.92-0.99)				
CKMB $\geq 5 \mu g/L$ or	79	79	1.02 (0.99-1.06)	1.16 (1.11-1.21)				
TnT ≥0.06 μg/L §			()	(
CKMB ≥10 µg/L or	72	71	1.05 (1.01-1.09)	1.20 (1.15-1.25)				
TnT ≥0.1 μg/L §			` ,	, ,				
Diagnosis at discharge								
NSTEMI	72	73	0.91 (0.88-0.95)	1.09 (1.05-1.14)				
UAP	29	27	1.10 (1.05-1.14)	0.92 (0.88-0.96)				

Data are presented as percentages unless otherwise indicated.

Abbreviations: MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; ACE, angiotensin converting enzyme; COPD, chronic obstructive pulmonary disease; ICCU, intensive coronary care unit; NSTEMI, non-ST-elevation myocardial infarction; UAP, unstable angina pectoris; CKMB, creatinine kinase muscle/brain; TnT, troponin T; OR, odds ratio and CI, confidence interval.

^{*} Odds ratios were obtained by logistic regression analysis and presented for male vs. female gender. \dagger ST depression was defined as ≥ 1 mm depression of the ST-segment in ≥ 2 leads, on admission electrocardiogram.

[§] Valid values for CKMB or TnT were available in 47 348 (88%).

Table 2 Procedures, treatments and outcome							
rrocedures, trea	Men	Women	Odds Ratios*	Odds Ratios*	Odds Ratios*		
	(%)	(%)	Before	After	After		
	(n=	(n=	adjustment	age-	multiple		
	34 020)	19 761)	(95% CI)	adjustment (95% CI)	adjustment † (95% CI)		
Treatment							
Heparin/LMWH	59	56	1.11	1.02	1.02		
•			(1.07-1.15)	(0.98-1.06)	(0.98-1.07)		
Nitroglycerin i.v.	32	32	1.00	0.99	0.98		
<i>U</i> 3			(0.96-1.03)	(0.96-1.03)	(0.94-1.03)		
GPIIb/IIIa	6	4	1.43	1.22	1.18		
inhibitor			(1.31-1.56)	(1.11-1.34)	(1.07-1.30)		
Procedures ‡			/	/	,		
Stress test	28	20	1.56	1.31	1.34		
			(1.50-1.63)	(1.25-1.37)	(1.27-1.40)		
Echocardiography	44	40	1.17	1.10	1.11		
217			(1.13-1.21)	(1.06-1.14)	(1.06-1.15)		
Coronary	37	29	1.44	1.12	1.10		
angiography			(1.38-1.49)	(1.07-1.16)	(1.05-1.15)		
PCI	18	14	1.35	1.07	1.03		
-	-		(1.28-1.42)	(1.02-1.13)	(0.97-1.09)		
CABG	7	5	1.55	1.40	1.43		
		•	(1.43-1.68)	(1.29-1.52)	(1.31-1.57)		
Medication at disc	harge		(1112 1111)	(-1-> -10-)	(=======		
ACE-inhibitor	37	36	1.04	1.10	1.13		
			(1.00-1.07)	(1.06-1.14)	(1.07-1.19)		
Aspirin/Other	88	85	1.22	1.04	1.02		
platelet inhibitor			(1.15-1.28)	(0.98-1.09)	(0.96-1.09)		
β-blocker	82	78	1.23	1.04	1.06		
'			(1.17-1.28)	(1.00-1.09)	(1.00-1.12)		
Lipid lowering	51	45	1.30	0.99	0.98		
drugs	-		(1.25-1.35)	(0.95-1.03)	(0.94-1.03)		
Mortality (all-caus	se)		(' ' ' ' ' ' ' '	(**************************************	(***		
In-hospital	5	7	0.74	1.03	1.03		
•			(0.69 - 0.80)	(0.96-1.11)	(0.94-1.13)		
30 days	7	9	0.76	1.05	1.07		
J			(0.71-0.81)	(0.98-1.12)	(0.99-1.15)		
1 year	16	19	0.77	1.11	1.12		
•			(0.74-0.81)	(1.05-1.16)	(1.06-1.19)		

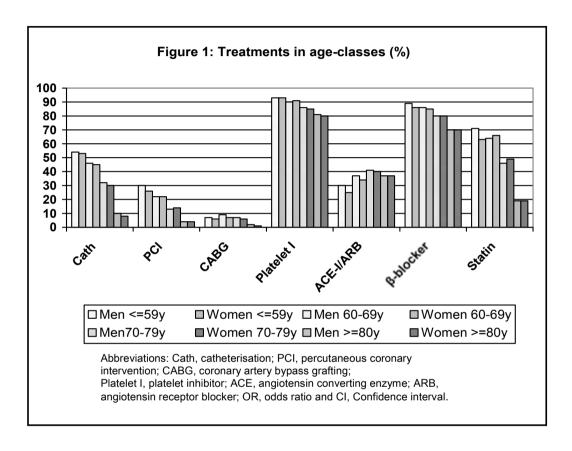
Data are given as percentages unless otherwise indicated.

Abbreviations: LMWH, low molecular weight heparin; GPIIb/IIIa, glycoprotein IIb/IIIa; ACE, angiotensin converting enzyme; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting and CI, confidence interval.

^{*}Odds ratios were obtained by logistic regression analysis and presented as OR for male vs. female. †For information on included covariates methods section in original Paper I.

[‡] Performed during hospital stay.

To further assess the impact of age on gender differences in management we stratified the population into four age-groups. There were large differences in treatment intensity between age-classes, but within age-classes observed differences between men and women were small. (Figure 1)

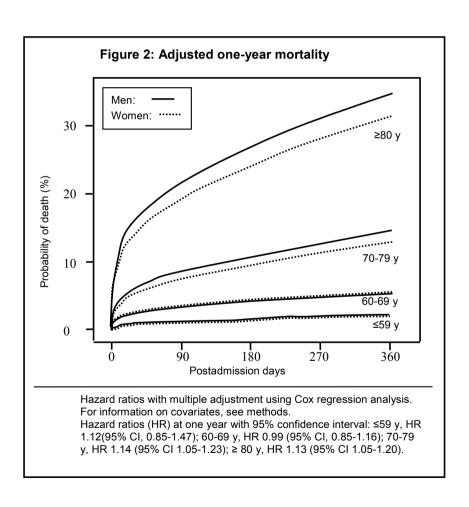


Outcome

Crude short-term and long-term mortality were higher in women. However, after adjustment for age, there was no difference in mortality during hospital stay or at 30 days. At one year female gender was even associated with a lower mortality, which persisted after including further 21 covariates in a multivariate logistic regression analysis. (Table 2)

We assessed all-cause mortality as main outcome measure, but there was no important difference between men and women in proportion of cardiovascular cause of death during hospital stay (89% vs. 90%), at 30 days (89% vs. 89%) or at 1 year (82% vs. 84%).

When 1-year mortality was calculated in a Cox regression analysis, with extensive adjustment for covariates, and presented in four age-strata, we found no significant differences between men and women in patients younger than 70 years. In patients older than 70 years the relative risk of death at one year was significantly higher in men. (Figure 2)



Paper 2

During the study period 2 959 patients [1 313 women (44%) and 1 646 men (56%)] were admitted to participating hospitals with a suspected ACS. Patients were similarly distributed to CCU's [1 378 (47%)] and general wards [1 581 (53%)]; but women were less likely to be admitted to CCU's [534 (41%)] compared to men [844 (51%)].

After inclusion and exclusion criteria for this analysis had been applied, 570 patients [231 (41%) women and 339 (59%) men] with a confirmed NSTE ACS diagnosis at discharge remained.

Baseline characteristics

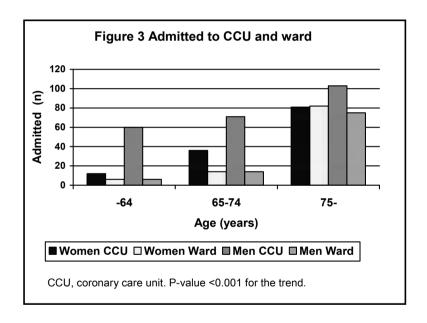
Women were older than men (78 vs. 73 years, p < 0.001). Of note, both men and women were markedly older in this study compared to patients from CCU's only. (Paper1) Differences in baseline characteristics, between men and women, were similar to what was observed in our study on patients from CCU's (Paper I). There were only minor differences between the genders in the proportion of patients (women vs. men) with chest pain (85% vs. 80%, p = 0.102), diagnosed as NSTEMI (84% vs. 81%, p = 0.47), and with elevated biochemical markers (83% vs. 81%, p = 0.491).

Gender differences in level of care

Women in our study were less likely to be admitted to CCU [129 (56%) vs. 234 (69%), p = 0.002], even after adjustment for age and comorbidity. (Table 3)

When analysed in three different age intervals, we found that the proportion of women admitted to general wards was larger in all age categories. (Figure 3)

A TIMI risk-score was calculated and the study population was divided into three TIMI-classes. There was no significant difference between the genders in risk according to calculated TIMI-class (data not shown). However, the proportion admitted to CCU was significantly higher for men in TIMI-scores 0-2 (71% vs. 51%, p = 0.004) and 3-4 (67% vs. 56%, p < 0.05) while there was no difference within TIMI-score 5-6 (70% vs. 74%, p = 0.79).



Gender differences in treatments and procedures

We found no significant difference between the genders in pharmacological treatment, but men were more likely to have a stress test, coronary angiography and CABG performed. However, after adjustment for differences in age and baseline characteristics, the only statistically significant differences in management between the genders were that PCI was more frequently performed in women, and women were more often prescribed lipid lowering drugs. (Table 3)

Table 3								
Management and Outcome								
	Women (n=231)	Men (n=339)	Crude	Adjusted for age	Adjusted for background characteristics †	Adjusted for background characteristics and level of		
	n (%)	n (%)	OR* (95 % I)	OR* (95 %CI)	OR*(95 % I)	care OR* (95 % CI)		
CCU care	129(56)	234(69)	0.58(0.40- 0.80)	0.70(0.49- 1.00)	0.65(0.43- 0.98)	n.a.		
Heparin / LMWH	134(58)	184(55)	1.14(0.81- 1.60)	1.37(0.96- 1.95)	1.20(0.81- 1.78)	1.15(0.78- 1.71)		
Stress test	18(8)	53(16)	0.45(0.26- 0.79)	0.58(0.32- 1.04)	0.56(0.29- 1.06)	0.58(0.30- 1.11)		
Echo	98(43)	148(44)	0.93(0.67- 1.31)	1.14(0.80- 1.63)	1.15(0.77- 1.71)	1.25(0.83- 1.87)		
Coronary angiography ‡	63(27)	124(37)	0.65(0.45- 0.94)	1.20(0.78- 1.86)	1.23(0.76- 2.00)	1.28(0.78- 2.08)		
PCI ‡	32(14)	40(12)	1.20(0.73- 1.98)	2.12(1.21- 3.72)	2.37(1.26- 4.48)	2.49(1.31- 4.73)		
CABG ‡	7(3)	24(7)	0.42(0.17- 0.97)	0.54(0.22- 1.32)	0.47(0.18- 1.20)	0.47(0.18- 1.23)		
PCI / CABG ‡	39(17)	64(19)	0.87(0.56- 1.35)	1.45(0.89- 2.37)	1.43(0.84- 2.44)	1.48(0.86- 2.55)		
Medical treati	nent at dis	scharge		·				
Aspirin and/or Clopidogrel	210(91)	296(89)	1.38(0.76- 2.38)	1.78(0.98- 3.21)	1.24(0.62- 2.50)	1.29(0.64- 2.61)		
Platelet inhibitor or Anticoagulant	214(93)	310(93)	1.04(0.54- 2.00)	1.28(0.65- 2.52)	1.12(0.52- 2.44)	1.16(0.53- 2.53)		
β-blocker	201(87)	285(85)	1.19(0.73- 1.95)	1.41(0.85- 2.35)	1.13(0.63- 1.99)	1.16(0.65- 2.06)		
ACE-I / ARB	108(47)	166(50)	0.90(0.64- 1.25)	0.82(0.58- 1.16)	1.03(0.66- 1.61)	1.10(0.70- 1.75)		
Lipid lowering drug	120(52)	198(59)	0.75(0.53- 1.05)	1.37(0.91- 2.04)	2.02(1.19- 3.43)	2.08(1.22- 3.55)		

Abbreviations: CCU, coronary care unit; LMWH, low molecular weight heparin; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; OR, odds ratio and CI, Confidence interval.

^{*}Odds ratios were obtained by logistic regression analysis. Presented as OR for female vs. male gender.

[†] For information on covariates see methods section.

[‡] Performed during hospital stay.

Gender differences in outcome

There were no differences in crude in-hospital, 30-days, or 1-year mortality. However, adjustment for age revealed better outcome for women, at least at one year. Further adjustment for background characteristics in a third model, and level of care in a fourth model confirmed the association. (Table 4)

Table	4					
Morta	lity					
	Women (n=205)	Men (n=309)	Crude	Adjusted for age	Adjusted for background characteristics †	Adjusted for background characteristics and level of care
	n (%)	n (%)	OR (95% CI)*	OR (95% CI)*	OR (95% CI)*	OR (95% CI)*
In- hospital	12(5.9)	18(5.8)	1.01 (0.47- 1.13)	0.63 (0.29- 1.38)	0.73 (0.31-1.72)	0.72 (0.30-1.71).
30 days	20(9.8)	32(10.4)	0.94 (0.52- 1.69)	0.58 (0.31- 1.08)	0.62 (0.32-1.23)	0.63 (0.31-1.24)
1 year	45(22.0)	70(22.7)	0.96 (0.63- 1.47)	0.58 (0.36-0.92)	0.58 (0.34-0.99)	0.59 (0.35-1.01)

Abbreviations: CCU, coronary care unit; LMWH, low molecular weight heparin; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; ARB, angiotensin receptor blocker; OR, odds ratio and CI, Confidence interval.

^{*}Odds ratios were obtained by logistic regression analyses. Presented as OR for female vs. male. †For information on included variables see methods section in Paper II.

Paper 3

A total of 92 patients were randomly assigned to a routine invasive strategy and 92 patients to a selective invasive strategy. Baseline characteristics are shown in Table 5. Mean age was 68 years in both groups. Almost 80% of the patients had troponin or CKMB above ULN.

Baseline characteristic	Routine invasive	Selective
	(n=92)	invasive
	(')	(n=92)
Age (yrs) (mean \pm SD)	68.2 (± 9.2)	$67.8 (\pm 8.8)$
Comorbidity and Risk	n (%)	n (%)
factors		
History of MI	22(24)	18(20)
Previous PCI	7(8)	11(12)
Previous CABG	5(5)	3(3)
Stroke	4(4)	4(4)
Hypertension	57(62)	63(67)
Diabetes Mellitus	19(21)	27(29)
Current Smoker	9(10)	24(26)
Medications at the time		
of randomization		
Aspirin	70(76)	71(77)
Clopidogrel or ticlopidine	27(29)	28(30)
Unfractionated Heparin	4(4)	2(2)
Low-molecular-weight	27(29)	26(28)
heparin		
ACE-inhibitor or ARB	44(48)	45(50)
3-blocker	62(67)	61(66)
Lipid lowering drug	26(28)	37(40)
Ischemic symptoms and		
signs		
ST-depression (≥1mm)	44 (48)	42(46)
Any ECG abnormality	79(86)	79(86)
Troponin or CKMB	73(79)	72(78)
elevation		
Diagnosis at study entry		
Unstable angina	33(36)	27(29)
Suspected MI	59(64)	65(71)

Abbreviations: MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; CKMB, creatinine kinase muscle/brain.

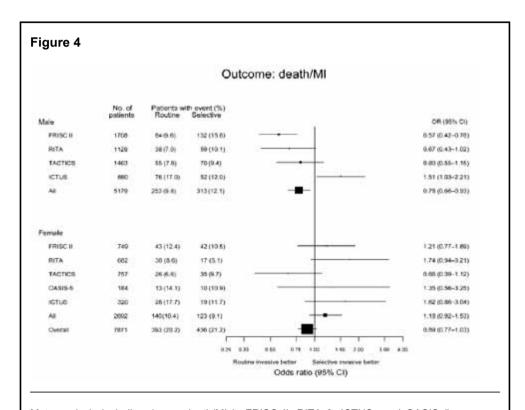
During initial hospitalisation 88 patients (96%) in the routine invasive arm and 37 patients (40%) in the selective invasive arm underwent coronary angiography, followed by revascularisation in 53 patients (58%) and 28 patients (30%) respectively. During the whole study period 89 patients (97%) in the routine invasive and 60 patients (65%) in the selective invasive group had a coronary angiography performed. In the routine invasive group 44 patients (48%) had a PCI performed and 15 patients (16%) underwent CABG compared to 36 patients (39%) and 11 patients (12%) respectively in the selective invasive group. The proportion of patients receiving thienopyridines before or during PCI was similar in the two arms but a larger proportion of patients in the routine invasive arm received GP IIb/IIIa inhibitors (34% vs. 22%) and a larger proportion of patients in the selective invasive arm received unfractionated heparin (47% vs. 39%). Complications were more frequent in the routine invasive arm (16% vs. 0%). Among patients subjected to PCI there was a slightly higher success rate (96% vs. 88%) and use of stents (83% vs. 73%) in the selective invasive group compared to the routine invasive group.

There was no statistically significant difference in the primary outcome of death/MI/stroke (21.0% in the routine invasive group vs. 15.4% in the selective invasive group, HR = 1.46, 95% CI, 0.73-2.94) or in the secondary composite outcome of death/MI. We found no significant differences when MI and stroke was evaluated separately. However, at 30 days there was a trend towards a higher rate of death with a routine invasive strategy as compared to a selective invasive strategy [4.3% vs. 1.1%, HR = 4.47, 95% CI (0.49-40.70)]. At 1 year there was a statistically significant difference in mortality with 8 deaths in the routine invasive arm compared to one death in the selective invasive arm [8.8% vs. 1.1%, HR = 9.01, 95% CI (1.11-72.90)]. The observed difference in mortality at one year persisted until the end of follow-up at two years, although the statistical significance was borderline [8.8% vs. 2.2%, HR = 4.65, 95% CI (0.97-22.20)]. (Table 6)

Table 6			
Outcomes			
	Routine invasive	Selective invasive	Hazard Ratio
	(n=92)	(n=92)	(95% CI)
	n(%)	n(%)	
2 years			
Death/MI/stroke	19(21.0)	14(15.4)	1.46 (0.73-2.94)
Death/MI	17(18.8)	13(14.3)	1.39 (0.67-2.88)
Death	8(8.8)	2(2.2)	4.65 (0.97-22.20)
Major bleeding	9(10.0)	2(2.2)	6.90 (1.48-32.13)
30 days			
Death/MI/stroke	9(9.8)	4(4.3)	2.18 (0.66-7.17)
Death/MI	8(8.7)	4 (4.3)	1.97 (0.58-6.63)
Death	4(4.3)	1(1.1)	4.47 (0.49-40.70)
Major bleeding	8(8.8)	1(1.1)	11.45 (1.43-91.96)
180 days			
Death/MI/stroke	14(15.2)	8(8.7)	1.75 (0.73-4.20)
Death/MI	13(14.1)	7(7.6)	1.84 (0.73-4.65)
Death	7(7.6)	1(1.1)	7.47 (0.91-61.52)
Major bleeding	8(8.8)	1(1.1)	11.45 (1.43-91.96)
1 year			
Death/MI/stroke	15(16.0)	11(12.0)	1.45 (0.66-3.20)
Death/MI	13(14.1)	10(10.9)	1.36 (0.59-3.13)
Death	8(8.8)	1(1.1)	9.01 (1.11-72.90)
Major bleeding	9(10.0)	1(1.1)	13.35 (1.68-105.9)
Abbreviations: MI,	myocardial infarction;	RI, Refractory Ischemia	a

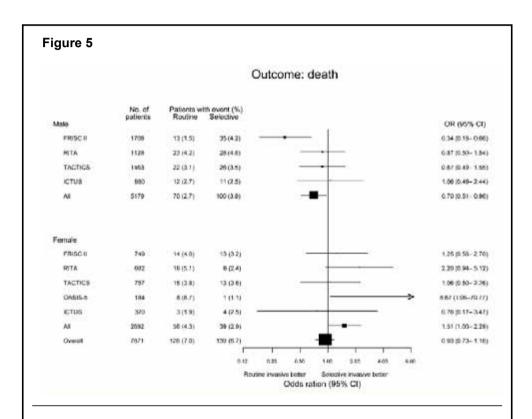
To evaluate whether any of the invasive treatment modalities were associated with worse outcome, we assessed outcomes according to treatment with PCI or CABG, regardless of initial allocation. At two years follow-up there were 2 deaths (7.7%) among the 26 patients who had a CABG performed, 6 deaths (7.5%) among the 80 patients subjected to PCI and only 2 (2.6%) deaths in the 78 patients not revascularized. The rate of major bleedings was substantially higher in patients randomised to the routine invasive strategy at 30 days [8.8% vs. 1.1%, HR = 11.45, 95% CI (1.43-91.96)] and the difference persisted during long-term follow-up at 730 days [10.0% vs. 2.2%, HR = 6.90, 95% CI (1.48-32.13)]. (Table 6) Of the 11 patients who had experienced a major bleeding at 2 years follow-up, 8 occurred among patients that were subjected to PCI and 2 among patients that had CABG performed. However there were only 2 deaths among these 11 patients.

We conducted a meta-analysis based on previously published data from FRISC II, RITA 3 and TACTICS TIMI-18, from ICTUS (data from the study investigators) and the present trial. The meta-analysis indicated benefit with a routine invasive strategy in men but not in women. Odds ratio for death /MI, for the routine invasive compared to a selective invasive strategy, showed no significant benefit in women (OR = 1.18, 95% CI, 0.92-1.53) in contrast to in men (OR = 0.78, 95% CI, 0.66-0.93) (Figure 4).



Meta-analysis including 1-year death/MI in FRISC II, RITA 3, ICTUS and OASIS 5 women substudy and 180 days outcome in TACTICS TIMI-18. OR was calculated for routine vs. selective invasive strategy. p-value for interaction (strategy and gender) 0.01

For men, the routine invasive strategy was associated with lower mortality (OR = 0.70, 95% CI, 0.51-0.96), while the opposite was found in women (OR = 1.51, 95% CI, 1.00-2.29) (Figure 5). Heterogeneity testing indicated heterogeneity between men and women for a routine invasive compared to a selective invasive strategy regarding both death/MI (p = 0.01) and death (p = 0.01).



Meta-analysis including 1-year mortality in FRISC II, RITA 3, ICTUS and OASIS 5 women substudy and 180 days outcome in TACTICS TIMI-18. OR was calculated for routine vs. selective invasive strategy. p-value for interaction (strategy and gender) 0.01

Paper 4

We included 46 455 patients, 14 819 women (32%) and 31 636 men (68%). A larger proportion of men than women was treated with an early invasive approach (63% vs. 56%).

There were significant differences in baseline characteristics between men and women in both treatment strategy arms. Women were older, more likely to have hypertension, diabetes and chronic obstructive pulmonary disease, but less likely to have a history of MI and revascularisation. (Table 7) Differences were well balanced after adjustment with a propensity score (data not shown).

Table 7								
Baseline Characteristics								
	Early non-in	vasive strategy	Early invasiv	e strategy				
	Women (n=6 573)	Men (n=11 770)	Women (n=8 246)	Men (n=19 886) p-value				
Age (year)	70.3 (±8.4)	68.0 (±9.3)	66.0 (±9.7)	63.5 (±9.7)				
$(mean \pm SD)$								
Risk factors								
Hypertension	45	40	46	38				
Diabetes	31	28	23	21				
Current Smoker	22	24	27	26				
History of MI	33	42	20	26				
History of	15	24	13	18				
PCI/CABG								
Medical history								
Stroke	13	15	6.4	6.0				
Renal failure	3.5	4.7	1.2	1.2				
COPD	16	11	9.0	5.5				
Heart failure	18	18	6.1	5.4				
Cancer last 3	3.8	5.1	2.3	2.4				
years								
Medication at dis	charge							
ACE-I/ ARB	47	48	49	50				
Aspirin	81	82	91	93				
Clopidogrel	19	19	61	62				
β-blocker	82	84	88	89				
Statin	61	62	82	84				

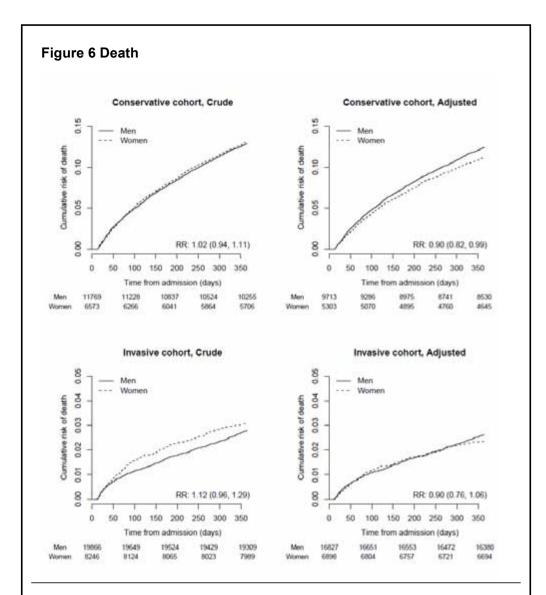
Data are given as percentages unless otherwise indicated. Abbreviations: SD, standard deviation; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery by-pass grafting; COPD, chronic obstructive pulmonary disease; ARB, angiotensin receptor blocker; ACE-I, angiotensin-converting enzyme inhibitor.

In a subset of patients in the early invasive arm with complete angiographic data (7 057 women and 16 854 men) we analyzed the degree of CHD. Women were more likely to have no significant stenosis and men more likely to have three-vessel or left main stem disease. (Table 8)

Table 8								
Findings on angiography								
	Women (n=7 057) (%)	Men (n=16 854) (%)	p-value					
Normal /atheromatosis	22	6.9	_					
1-2 vessel disease	52	58						
3-vessel/main stem disease	26	3	< 0.001					
Treatment after angiograp	hy							
	Women	Men	p-value					
	(n=8 246)	(n=19 866)						
	(%)	(%)						
Medical treatment	42	32						
PCI	52	58						
CABG	6.8	9.3	< 0.001					

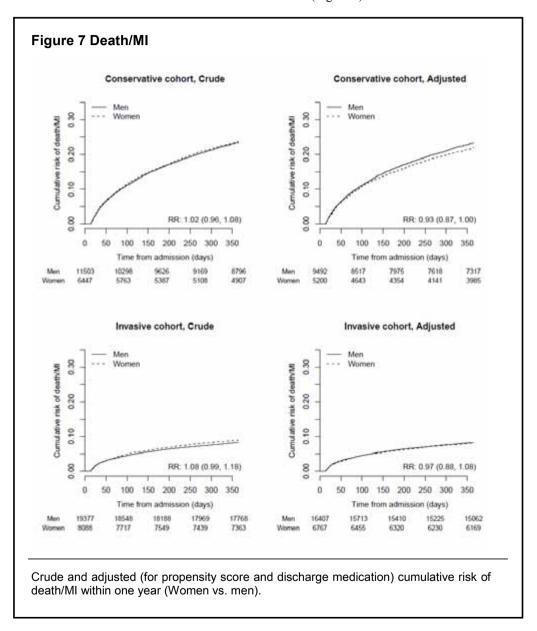
Abbreviations: PCI, percutaneous coronary intervention; CABG, coronary artery by-pass grafting. Complete data on angiography findings were available for 85% of the early invasively treated patients. Treatment after angiography is reported for all early invasively treated patients.

We found no significant difference in one-year mortality between the genders, within treatment strategy. In the non-invasive strategy arm RR of death before adjustment was (women vs men) 1.02 (95% CI, 0.94-1.11) and in the invasive strategy arm 1.12 (95% CI, 0.96-1.29). After adjustment for baseline differences between the genders with a propensity score (different scores for conservative and invasive treatment strategy) and discharge medication there was a trend towards worse outcome among men (RR = 0.90, 95% CI, 0.82-0.99) in the conservative group while there was still no significant difference in the invasive group (RR = 0.90, 95% CI, 0.76-1.06). (Figure 6)



Crude and adjusted (for propensity score and discharge medication) cumulative risk of death within one year (Women vs. men).

We also calculated the occurrence of the combined end-point death or MI during one year after index admission, but there was no difference between men and women, neither in the conservative nor in the invasive cohort. (Figure 7)



Two different risk scores were applied, the FRISC-score and the TIMI-score. Both scores predicted 1-year mortality well. Patients treated with an early invasive strategy

were generally at lower predicted risk according to both the FRISC-score and the TIMI-score.

The 1-year mortality was higher with increasing score and with a conservative strategy in both the TIMI score and the FRISC score, but without significant difference between men and women in any of the calculated risk-score classes.

To further explore impact of revascularisation on outcome, we analyzed outcome according to mode of revascularisation in the early invasive group. Before adjustment, but not after, women as compared to men had higher mortality in the PCI-treated group. Most of the difference seemed to be explained by older age. On the other hand, among the medically treated patients, after adjustment, women had lower mortality compared to their male counterparts. (Table 9)

One year mortality according to angiographic finding							
Women	Men	RR	RR	RR			
(n=	(n=	(95% CI)	(95% CI)	(95% CI)			
7 057)	16 854)	Women vs.	Adjustment	Full			
(%)	(%)	Men	for age	Adjustment			
2.0	1.8	1.13	1.01	0.82			
		(0.65-1.97)	(0.57-1.77)	(0.43-1.55)			
2.0	1.6	1.25	1.05	0.97			
		(0.94-1.65)	(0.79-1.39)	(0.71-1.32)			
5.1	4.5	1.14	1.01	0.91			
		(0.90-1.44	(0.80-1.28)	(0.69-1.20)			
	Women (n= 7 057) (%) 2.0	Women (n= (n= 7057) Men (n= 6854) (%) (%) 2.0 1.8	Women (n=) Men (n=) RR (95% CI) 7 057) 16 854) Women vs. (%) (%) Men 2.0 1.8 1.13 (0.65-1.97) 2.0 1.6 1.25 (0.94-1.65) 5.1 4.5 1.14	Women (n=) Men (n=) RR (95% CI) (95% CI) RR (95% CI) 7 057) 16 854) Women vs. Adjustment for age (%) (%) Men for age 2.0 1.8 1.13 (0.65-1.97) (0.57-1.77) 2.0 1.6 1.25 (0.94-1.65) (0.79-1.39) 5.1 4.5 1.14 (1.01)			

One year mortality according to treatment after anglography						
	Women	Men	RR	RR	RR	
	(n=	(n=	(95% CI)	(95% CI)	(95% CI)	
	8 246)	19 866)	Women vs.	Adjustment	Full	
	(%)	(%)	Men	for age	Adjustment	
Medical	4.0	4.6	0.89	0.84	0.78	
treatment			(0.72 - 1.09)	(0.68-1.03)	(0.61-0.98)	
PCI	2.3	1.8	1.29	1.06	1.06	
			(1.02-1.63)	(0.84-1.35)	(0.80-1.39)	
CABG	3.7	2.8	1.35	1.13	0.91	
			(0.81-2.23)	(0.68-1.89)	(0.49-1.69)	

Abbreviations: PCI, percutaneous coronary intervention; CABG, coronary artery by-pass grafting; RR, risk ratio; CI, Confidence interval. Complete data on angiography findings were available for 85% of the early invasively managed patients. Treatment after angiography is reported for all early invasively managed patients. Relative risks are presented for women vs. men. Full Adjustment means adjustment with propensity score and discharge medication. For information on included variables, see methods section.

In our main analyses all included patients had to be alive the first 14 days after admission, but we also performed separate sensitivity analyses for several time-points after admission (day 0-365, 1-365, 30-365 and 45-365). In all time intervals there was a similar RR within treatment strategy, as compared to what we found in our main analysis.

A larger proportion of men than women were treated with an early invasive approach (63% vs. 56%).

The relative risks of death for invasive vs. conservative treatments were similar for women (RR = 0.46, 95% CI, 0.38-0.55) and men (RR = 0.45, 95% CI, 0.40-0.52). The corresponding result for death/MI was for women (RR = 0.57, 95% CI, 0.51-0.64) and men (RR = 0.60, 95% CI, 0.56-0.65). Tests for interaction for between gender and treatment strategy were not significant. (Table 10)

Table 10					_
One-year mortality					
Invasive vs. non-invasive strategy					
	Invasive (n= 28 112) (%)	Non- invasive (n= 18 343) (%)	RR (95% CI)	RR (95% CI) Full Adjustment	Interaction p-value
Death					
Women	3.1	13	0.23 (0.20-0.26)	0.46 (0.38-0.55)	0.611
Men	2.8	13	0.21 (0.19-0.23)	0.45 (0.40-0.52)	
Death/MI					
Women	11	25	0.40 (0.36-0.43)	0.57 (0.51-0.64)	0.684
Men	11	25	0.39 (0.37-0.42)	0.60 (0.56-0.65)	

Abbreviations RR, Relative Risk; CI, Confidence interval.

Cox regression analysis, crude and adjusted for Propensity score and discharge medication (for information on included variables see methods section)..

Discussion

Background characteristics

In agreement with earlier findings, we found major differences in background characteristics between women and men. (11, 215, 217) Women were older, more likely to have a history of heart failure, diabetes and hypertension; while men were more likely to be smokers and have a history of MI and revascularisation. (Table 1) If patients admitted to general wards were included, age and comorbidity increased in both men and women.

Before admission, men were somewhat more likely to be treated with platelet inhibitors and statins, even after adjustment, which probably reflect the higher rate of history of MI. Women were more likely to be treated with β -blockers and diuretics which may reflect the higher rate of hypertension and heart failure.(Table 1)

Baseline differences between a female and male population with NSTE ACS is partly explained by difference in age. It is well known that women experience their first MI several years later than men, with implications on baseline characteristics. In the INTERHEART study almost 70% of women experiencing their first MI were over the age of 60 years compared to 40% of men. (35)

Studies comparing gender differences in management and outcome are for obvious reasons not randomised. However, if the aim is to assess gender differences per se, it is of utmost importance to adjust the analyses for baseline differences. A large scale register, like RIKS-HIA, with information on a large number of variables, makes adjustment for a multitude of confounders possible.

Management

Level of care

The NSTE ACS population is very heterogeneous, ranging from very high risk, including cardiogenic shock, to very low risk without detectable myocardial damage with echo or markers. Moreover, early on, establishing the diagnosis is difficult and admission for repeated blood tests and repeated or continuous ECG-recordings is often necessary. Although many of the NSTE ACS patients are admitted to CCU's, it's well known that quite a few are admitted to general wards. Former trials have indicated that more men than women were admitted to CCU's. (88-90, 239) However, these trials included both STEMI and NSTEMI, which could have implications on level of care since STEMI is more common among men, especially in younger patients. Older age and higher comorbidity have been suggested as reasons for women being admitted to general wards. (239, 240) We found that also among NSTE ACS patients, men were significantly more likely than women to be admitted to CCU's. This is supported by a recent report from the PRAIS (UK) study, a register of NSTE ACS-patients admitted to 56 UK hospitals, where a large proportion of NSTE ACS patients were admitted to cardiology wards or general medical wards; patients admitted to general wards were older and more often women. (241) Our data further extends knowledge and shows that older age and comorbidity among women seem to explain only a minor part of observed difference in admittance to CCU's.

We applied a TIMI-score and found that the patients in our study were at medium or low risk, with a distribution similar to the TIMI III-register, (242) but there was no difference between men and women. In TIMI-score 0-4, men were more likely to be admitted to CCU's. Hence, predicted risk, expressed as a TIMI-score, did not explain differences between the genders in level of care. It has been proposed that difference between the genders in prevalence of chest pain could account for the difference in admittance to CCU's, (90) but in our study chest pain was as common in women as in men (85% vs. 80%, p = 0.102). Recent trials confirm that although a substantial proportion of patients with NSTE ACS do not have typical chest pain, difference between men and women is rather small. (58-61) However difference in character of the pain, number of accompanying symptoms (61) and difference in way of describing

symptoms (243, 244) have been reported, which could have implications for risk evaluation and initial level of care.

Medical treatment

After age adjustment there was no difference between the genders in treatment with heparin/LMWH. GP IIb/IIIa-inhibitors were used infrequently in both men and women in our data, but less often in women. (Table 2)

At discharge men were prescribed ACE-inhibitors, β -blockers, platelet inhibitors and lipid lowering drugs more often, but the difference seemed to be almost entirely explained by difference in age. (Table 2)

When patients admitted to general wards were studied together with patients admitted to CCU's we found no significant difference in acute treatment with heparin/LMWH or discharge treatment with ACE-I, platelet inhibitors, β-blockers or lipid lowering drugs. In contrast to our findings, reports from the TIMI III register and from the CRUSADE register indicated lower likelihood of both acute and discharge treatment in women, even after adjustment. (11, 217) However the most recent report, from the ACOS register in Germany, at least partly supports our findings; after age-adjustment they found no difference in discharge medication, except for clopidogrel. (245) In our data from Swedish CCU's (Table 2) and CCU's and general wards assessed together, (Table 3) differences between the genders in pharmacological treatment were small and not directionally consistent. The observed differences between our study and others may, at least partly be explained by differences in time of recruitment. In recent years there has been increased attention in heart disease in women and in the elderly. Lack of any large differences in medical treatment between patients admitted to general wards and CCU's lends support from a recent paper from the PRAIS (UK) register. (241)

Invasive treatment

Referral for coronary angiography and subsequent revascularisation was more common in men. The difference, although substantially attenuated, persisted after age adjustment (Table 2), which is in agreement with earlier findings. (11, 13, 226) While CABG rate

was more common in men, even after adjustment for age and comorbidity, there was no difference in PCI rate, which is in line with an earlier report on patients with UAP. (226) In a recent paper by Blomkalns et al from the CRUSADE register, lower use of catheterisation, PCI and CABG was reported in women, and in contrast to what we found, difference in PCI rate persisted even after adjustment. (217) This may partly be explained by the higher use of coronary angiography in the CRUSADE register and a more selective invasive approach in our data.

The fact that women were more likely to be admitted to general wards did not imply that the difference between the genders in invasive treatment was larger than in a CCU-population. On the contrary, overall PCI rate was actually higher in women than men when a complete NSTE ACS population from both CCU's and general wards was studied. Although the numbers were too small to draw firm conclusions; at the general wards both angiography-rate (22% vs. 21%) and PCI-rate (9% vs. 6%) was at least as high in women as in men. Difference between the genders in invasive treatment was small but the overall rate of catheterisation was low indicating room for substantial improvement.

Impact of age on treatment

Older age accounted for a major part of the difference between men and women in medical as well as invasive treatment in our studies. There were minor differences between men and women within an age-class. (Figure 1) Large impact of age on treatment has earlier been shown. (11, 226) Lack of difference in treatment or inconsistency in direction of observed difference, between the genders, within age classes has, to our knowledge, not been shown before.

Outcome

Several earlier trials have reported worse outcome, especially short-term, in women with MI, when NSTEMI and STEMI were assessed together. (12, 14, 15, 216, 221, 222) However in accordance with our data, women with UAP appeared to have equal or better outcome after adjustment for differences in age and comorbidity. (13, 226) In our study from Swedish CCU's, crude mortality was higher in women, but after adjustment

there was no difference in short-term mortality and even better outcome for women regarding long-term mortality, (Table 2) which is in agreement with other contemporary observational data. (217, 245) In a separate analysis in four age classes, better outcome in women seemed to be restricted to older patients (Figure 2). Interaction between gender and age in early outcome after an ACS has earlier been shown in patients with MI. In a report from the National Registry of Myocardial Infarction by Vaccarino et al worse outcome among young women compared to men was revealed. In contrast there was a trend towards better outcome in old women compared to men at the same age.(227)

Better outcome associated with CCU-treatment has been proposed. (89) But in our study including NSTE ACS patients admitted to both CCU's and general wards; women, in spite of being admitted to general wards more often, still had better outcome. Earlier trials included both STEMI and NSTEMI and it is likely that immediate CCU care is more important for STEMI patients, with need for immediate reperfusion treatment and arrhythmia monitoring.

Benefit from invasive treatment

Gender differences in benefit from an invasive strategy have been intensively debated and data are conflicting.

In our observational data from CCU's women were managed less invasively. Men were significantly more often referred for coronary angiography (37% vs. 29%), even after adjustment (OR = 1.10, 95% CI, 1.05-1.15). In spite of that, after adjustment for age alone women had better long-term outcome (OR for 1-year mortality 1.11, 95% CI, 1.05-1.16). This may indicate that women, as a group, have less to gain from an early invasive strategy.

Randomised trials

In the OASIS 5 WSS (Paper III) there was no statistical difference between the routine invasive and the selective invasive strategies in the primary outcome measure death/MI/stroke or the secondary outcome death/MI during one year. However, although the numbers were small, there was a significantly higher rate of death with a routine invasive strategy at one year. (Table 6)

Three earlier randomised trials comparing a routine invasive with a selective invasive strategy in NSTE ACS have reported outcomes separately for women and men.

In the FRISC II trial (8), in contrast to a clear favorable outcome with a routine invasive strategy for the primary endpoint death/MI in men (9.6% vs. 15.8%, p < 0.001) there was no benefit in women (12.4% vs.10.5%, ns), which was similar to the findings in our study. After adjustment male sex was an independent risk factor for death/MI in the non invasive strategy arm [OR for death/MI women vs. men 0.64 (95% CI, 0.43-0.97)]. In the routine invasive strategy arm, on the other hand, female sex was associated with worse outcome [OR for death/MI, women vs. men 1.46 (95% CI, 0.96-2.23)].

In the RITA 3 trial (10) results were similar to those of the FRISC II trial. While men had a lower incidence of the primary end-point death/MI with a routine invasive strategy (7.0% vs. 10.1%) there was a trend towards the opposite for women (8.6% vs. 5.1%) (p for interaction 0.007). After adjustment for baseline variables the OR for death with an invasive compared to conservative strategy was 0.78 (0.44-1.41) for men and 2.43 (1.01-5.84) for women (interaction p = 0.031).

Accordingly, in most ways the findings in our study parallel data from the FRISC II trial and the RITA 3 trial. The increased rate of death associated with a routine invasive strategy observed in our trial, although directionally consistent with FRISC II and RITA 3, is likely to be an exaggeration perhaps due to the play of chance and has to be interpreted with great caution.

In contrast, the TACTICS-TIMI 18 (9) trial indicated similar benefit in men and women with a routine invasive strategy, but mainly restricted to those with elevated markers.

Meta-analyses

None of the randomised studies had enough power to show a statistically significant difference in outcome according to treatment strategy, in women. We therefore conducted a meta-analysis which was presented together with data from the OASIS 5 WSS. The meta-analysis suggested a clear benefit with a routine invasive strategy compared to a selective invasive strategy in men for death/MI (OR = 0.78, 95% CI, 0.66-0.93) that could not be seen in women (OR = 1.18, 95% CI, 0.92-1.53, p-value for interaction = 0.01). (Figure 4) Also regarding death, men had significantly better outcome with a routine invasive strategy (OR = 0.70, 95% CI, 0.51-0.96) while the

opposite was indicated in women (OR = 1.51, 95% CI, 1.00-2.29, p-value for interaction = 0.01). (Figure 5)

Another meta-analysis by O'Donoghue et al published in JAMA 2008 included 8 trials (3 075 women and 7 075 men) (246) and showed no significant difference in outcome with a routine invasive vs. a more selective invasive strategy in the endpoint death/MI, either for men or women. This is in contrast to results of the meta-analysis we performed and probably reflects difference in studies included.

Observational studies

Some of the randomised trials have indicated not only lack of benefit, but even harm associated with an invasive strategy, in women. On the other hand, Meuller et al presented register data indicating that women with NSTE ACS treated predominantly with PCI had at least as good outcome as men. (247) We therefore conducted a study in a real-life setting with patients from the RIKS-HIA register. Among more than 28 000 patients (8 246 women and 19 886 men) subjected to an invasive strategy there was no difference between the genders in one year mortality before (RR = 1.12, 95% CI, 0.96-1.29) or after adjustment for confounders (RR = 0.90, 95% CI, 0.76-1.06). (Figure 6) Neither did we find any significant difference between the genders in the combined outcome death/MI. (Figure 7) Accordingly, in a real life setting we found no evidence of harm against women with an early invasive strategy. In the non-invasive strategy arm, we also found similar outcome in women and men but adjustment revealed lower mortality in women (RR = 0.90, 95% CI, 0.82-0.99).

However, in this clinical setting, where referral to coronary angiography was based on treating physicians' discretion, a larger proportion of men (63%) than women (56%) were treated invasively. While there was no difference in outcome between the genders within treatment strategy, both men and women in the non-invasive arm had worse outcome as compared to invasively managed patients. Regarding mortality, there was a similar benefit in women (HR = 0.46, 95% CI, 0.38-0.55) and men (HR = 0.45, 95% CI, 0.40-0.52) with an invasive strategy (interaction p-value 0.611). The risk reduction was similar with the combined endpoint death/MI, and again without interaction according to gender.

There are several possible reasons for less benefit from an invasive strategy in women with NSTE ACS, and for difference in outcome between earlier studies.

Degree of coronary artery disease

A common finding in the FRISC II, RITA 3 and TACTICS-TIMI 18 was that women have less obstructive CHD. In the routine invasive strategy arms, the rate of no significant stenosis was lower in men (9.5% vs. 24.6%, 12% vs. 37% and 10% vs. 18%) in FRISC II, RITA 3 and TACTICS-TIMI 18 respectively. In the FRISC II trial patients without significant stenosis had an excellent prognosis with no deaths during one year follow-up. In our study from a real-life clinical setting, comparing early invasive strategy in men and women, (Paper IV) we could confirm differences in severity of CHD, with a larger proportion of women with no significant stenosis (22% vs. 6.9%) and fewer women having 3-vessel disease or main stem disease (26% vs. 36%). (Table 9)

The relative paucity of obstructive CHD may obviously dilute the treatment benefit with an invasive strategy. The lower event rate in women managed in a selective invasive strategy in women in FRISC II and RITA 3 may well largely be explained by the high proportion of women with a low degree of CHD. Our data from a large cohort in RIKS-HIA confirmed that outcome differed substantially between 1-2 vessel disease and 3-vessel /main stem-disease, but with similar degree of coronary disease there was no difference in outcome between the genders. (Table 9) Even if the higher number of diseased vessels in men reasonably indicates that men would have more to gain from an invasive strategy, it made no overall difference in outcome between the genders among invasively treated patients, indicating that catheterisation per se did not result in too high risk for the large proportion of women without significant stenosis. In line with our results the TACTICS-TIMI 18 trials indicated similar benefit in men and women, in spite of similar difference in rate of obstructive CHD, but mainly restricted to patients with marker elevation.

Risk stratification with biomarkers

Not only has a difference between the genders been shown in severity of CHD, but also in proportion of patients with elevated markers. Both in the FRISC II trial and the TACTICS-TIMI 18 trial, men were significantly more likely to have elevated

troponin T compared to women, (62% vs. 47% and 57% vs. 47% respectively). Troponin is a marker of myocardial necrosis and is predictive of degree of CHD and even probability of visible thrombus on the angiogram, indicative of plaque rupture. (248)

In a subgroup analysis of high risk patients in the TACTICS TIMI-18, there was a similar benefit on the primary end-point death/MI/revascularisation in troponin positive female (OR = 0.56, 95% CI, 0.32-0.97) and troponin positive male (OR = 0.53, 95% CI, 0.35-0.79) patients. However in troponin negative women there was an indication of harm (OR = 1.46, 95% CI, 0.78-2.72) that was not seen in men (OR = 1.02, 95% CI, 0.64-1.62). These data was further supported in the meta-analysis by O'Donoghue et al, where benefit with an invasive strategy in women appeared to be restricted to patients with elevated markers. Our report from the RIKS-HIA register (Paper IV) parallels these findings. In our study all included patients had elevated biochemical markers, and we found no difference in outcome between the genders, within treatment strategy.

Difference between the genders in proportion of troponin negative patients may well explain a substantial part of the overall difference between men and women in effect of a routine invasive strategy.

Mode of revascularisation

Several earlier trials have indicated higher risk associated with an invasive strategy for women, especially regarding CABG. The higher event rate in women compared to men, treated with a routine invasive strategy, in the FRISC II trial seemed largely due to an increased rate of death (9.9% vs. 1.2%) and recurrent MI (12% vs. 5%) in women that had CABG surgery performed.

The ratio of PCI to CABG was approximately 1 in the invasive arm in the FRISC II trial, while in the invasive arm in TACTICS-TIMI 18 trial, where there was no significant difference between men and women with an invasive strategy, the PCI/CABG-ratio was about 2, which lends support to the notion that PCI/CABG-ratio in revascularised patients may be an important contributor to gender differences in invasively treated patients with NSTE ACS. Our data from RIKS-HIA supports the importance of PCI/CABG-ratio. In patients referred for early angiography the PCI/CABG-ratio was 7.6 for women and 6.3 for men, with no difference in outcome between the genders. Whether worse outcome in women with CABG is explained by difference in coronary artery size, comorbidity or yet other factors, is still not clear. In

support of our results, the recently published TIMACS trial (comparing early and delayed catheterisation in NSTE ACS patients), in which about 14% of the patients were revascularised with CABG, indicated no gender difference in effect of a very early compared to a delayed invasive strategy. (249) In the FRISC II trial and TACTICS TIMI-18 trial there was no difference in outcome between the genders in patients undergoing PCI. Our study indicates that there may be a higher rate of adverse outcome associated with higher age and comorbidity, but not gender per se, in both PCI and CABG-treated patients. In the OASIS 5 WSS we also assessed mortality according to mode of revascularisation. There were two deaths among CABG treated patients (7.5%) and six deaths among PCI-treated patients (7.5%). Hence CABG did not seem to explain the higher mortality associated with a routine invasive strategy in this study. Notably, the lowest mortality rate was found in patients who did not undergo any revascularisation. The use of evidence-based medication was high in the OASIS 5 WSS, including use of aspirin (100% vs. 99%) and thienopyridines (86% vs. 76%). With an optimal medical therapy there may be less to gain from an invasive therapy, especially in women with lower rate of significant stenosis and higher risk associated with invasive procedures.

Bleeding complications

An important finding in the OASIS 5 WSS was the high rate of bleedings associated with a routine invasive strategy. The difference in bleeding was evident already at 30 days (8.8% vs. 1.1%, p = 0.004). Increased risk of major bleeding was consistent and statistically significant at all time points of the study. In agreement with what we found, higher rate of bleeding associated with an invasive procedure has repeatedly been shown in earlier studies comparing an invasive with a conservative strategy. (177-179, 182) Moreover earlier trials have revealed higher rate of bleeding among women. For example in the TACTICS-TIMI 18 the rate of major bleeding was substantially higher in women (8.3% vs. 2.9%, p = 0.001) even after adjustment for differences in baseline variables (OR = 3.6, 95% CI, 1.6-8.3, p= 0.0001). Although the numbers in the OASIS 5 WSS are too small to draw firm conclusions we found a three times higher mortality among patients that experienced a major bleeding compared to those who did not (18% vs. 6%). However, supporting our findings, several recent studies have highlighted both short-term and long-term risk of death in ACS patients with bleeding complications. (169, 171, 172)

Higher bleeding rate in women associated with an invasive strategy may also contribute to difference in effect from an invasive strategy between the genders. Reasons for higher bleeding rates in women are not fully understood but impaired renal function, which is more common among female patients, and higher risk for excess doses of antithrombotic medication has been proposed. (174)

Further studies are warranted to elucidate reasons behind the higher bleeding rates among women.

Future research

Stratification for risk of a new ischemic event is a cornerstone in the management of patients with NSTE ACS. A challenge for future research will be to find ways to identify patients with highest net clinical benefit from an early invasive strategy, maybe by a multimarker approach as suggested in a sub-study of the TACTICS-TIMI 18 (83), or maybe by novel markers, more specific in identifying plaque rupture. Risk-indicators for adverse events, e.g. bleeding, associated with a certain treatment, are also strongly needed. Risk-indicators for adverse events may be even more important in women with documented higher risk associated with invasive procedures, and less extensive CHD. An individually tailored treatment strategy to balance early procedural risk with long-term reduction of cardiac events will benefit both women and men with NSTE ACS. The FRISC II trial indicated benefit with an invasive strategy only in patients with medium or high risk features.(86) Hence the optimal proportion of men and women respectively that will benefit from an early invasive strategy is still to be decided.

To answer the question whether there are true differences between men and women in outcome according to treatment strategy, and to find the optimal treatment strategy for women and men, a large randomised trial with sufficient number of women and proper risk stratification is needed.

Conclusions

- There are substantial differences in baseline characteristics between a male and a female population with NSTE ACS.
 - Women are older and more likely to have a history of diabetes, hypertension and congestive heart failure.
 - Men are more likely to have a history of myocardial infarction and revascularisation.
 - o Women have lower rate of significant coronary stenosis.
- Women are less likely to be admitted to coronary care units.
- After adjustment for age and baseline characteristics
 - there are minor differences between men and women in pharmacological treatment.
 - o women are less likely to undergo coronary angiography and CABG.
 - o women appear at least as likely as men to undergo PCI.
- Crude mortality rates are higher in women. After adjustment for difference in age,
 or age and other baseline characteristics, mortality rates are similar in men and
 women or even lower in women. Especially long-term outcome seems favourable in
 women.
 - The observation that women were less likely to be admitted to CCU's does not imply worse outcome in women with NSTE ACS.

- A routine invasive strategy in patients with NSTE ACS
 - o does not appear to benefit women.
 - o is associated with higher risk of bleeding complications in women.
- In real life management of NSTE ACS patients, with elevated markers,
 - there is no difference in outcome between men and women, within treatment strategy.
 - o risk reduction with an invasive strategy is similar in men and women.

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References

- 1. Unal B, Critchley JA, Capewell S. Explaining the decline in coronary heart disease mortality in England and Wales between 1981 and 2000. Circulation. 2004 Mar 9;109(9):1101-7.
- 2. Ford ES, Ajani UA, Croft JB, Critchley JA, Labarthe DR, Kottke TE, et al. Explaining the decrease in U.S. deaths from coronary disease, 1980-2000. N Engl J Med. 2007 Jun 7;356(23):2388-98.
- 3. Bjorck L, Rosengren A, Bennett K, Lappas G, Capewell S. Modelling the decreasing coronary heart disease mortality in Sweden between 1986 and 2002. Eur Heart J. 2009 May;30(9):1046-56.
- 4. The Swedish National board of Health and Welfare. National Cause of Death Register.
- The Swedish National board of Health and Welfare. The National Patient Register.
- 6. Meinert CL. The inclusion of women in clinical trials. Science 1995 Aug 11:269(5225):795-6.
- 7. Lee PY, Alexander KP, Hammill BG, Pasquali SK, Peterson ED. Representation of elderly persons and women in published randomized trials of acute coronary syndromes. Jama 2001 Aug 8;286(6):708-13.
- 8. Lagerqvist B, Safstrom K, Stahle E, Wallentin L, Swahn E. Is early invasive treatment of unstable coronary artery disease equally effective for both women and men? FRISC II Study Group Investigators. J Am Coll Cardiol 2001;38(1):41-8.
- 9. Glaser R, Herrmann HC, Murphy SA, Demopoulos LA, DiBattiste PM, Cannon CP, et al. Benefit of an early invasive management strategy in women with acute coronary syndromes. Jama 2002 Dec 25;288(24):3124-9.
- 10. Clayton TC, Pocock SJ, Henderson RA, Poole-Wilson PA, Shaw TR, Knight R, et al. Do men benefit more than women from an interventional strategy in patients with unstable angina or non-ST-elevation myocardial infarction? The impact of gender in the RITA 3 trial. Eur Heart J 2004 Sep;25(18):1641-50.
- 11. Stone PH, Thompson B, Anderson HV, Kronenberg MW, Gibson RS, Rogers WJ, et al. Influence of race, sex, and age on management of unstable angina and non-Q-wave myocardial infarction: The TIMI III registry. Jama 1996;275(14):1104-12.
- 12. Chandra NC, Ziegelstein RC, Rogers WJ, Tiefenbrunn AJ, Gore JM, French WJ, et al. Observations of the treatment of women in the United States with myocardial infarction: a report from the National Registry of Myocardial Infarction-I. Arch Intern Med 1998;158(9):981-8.
- 13. Roger VL, Farkouh ME, Weston SA, Reeder GS, Jacobsen SJ, Zinsmeister AR, et al. Sex differences in evaluation and outcome of unstable angina. Jama 2000;283(5):646-52.

- 14. Gan SC, Beaver SK, Houck PM, MacLehose RF, Lawson HW, Chan L. Treatment of acute myocardial infarction and 30-day mortality among women and men. N Engl J Med 2000;343(1):8-15.
- 15. Mahon NG, McKenna CJ, Codd MB, O'Rorke C, McCann HA, Sugrue DD. Gender differences in the management and outcome of acute myocardial infarction in unselected patients in the thrombolytic era. Am J Cardiol 2000;85(8):921-6.
- 16. Hochman JS, Tamis JE, Thompson TD, Weaver WD, White HD, Van de Werf F, et al. Sex, clinical presentation, and outcome in patients with acute coronary syndromes. Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes IIb Investigators. N Engl J Med 1999;341(4):226-32.
- 17. Myocardial infarction redefined--a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. Eur Heart J. 2000 Sep;21(18):1502-13.
- 18. Braunwald E. Unstable angina: an etiologic approach to management. Circulation. 1998 Nov 24;98(21):2219-22.
- 19. Socialstyrelsen. Hjärtinfarktregistret. .
- 20. Socialstyrelsen wss. Dödsorsaksregistret
- 21. Socialstyrelsen. Hjärtinfarktregistret; 2002 Contract No.: Document Number.
- 22. Ross R. Atherosclerosis--an inflammatory disease. N Engl J Med. 1999 Jan 14:340(2):115-26.
- 23. Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. Circulation. 2002 Mar 5;105(9):1135-43.
- 24. Fuster V, Moreno PR, Fayad ZA, Corti R, Badimon JJ. Atherothrombosis and high-risk plaque: part I: evolving concepts. J Am Coll Cardiol. 2005 Sep 20;46(6):937-54.
- 25. Arbustini E, Dal Bello B, Morbini P, Burke AP, Bocciarelli M, Specchia G, et al. Plaque erosion is a major substrate for coronary thrombosis in acute myocardial infarction. Heart. 1999 Sep;82(3):269-72.
- 26. van der Wal AC, Becker AE, van der Loos CM, Das PK. Site of intimal rupture or erosion of thrombosed coronary atherosclerotic plaques is characterized by an inflammatory process irrespective of the dominant plaque morphology. Circulation. 1994 Jan;89(1):36-44.
- 27. Falk E, Shah PK, Fuster V. Coronary plaque disruption. Circulation. 1995 Aug 1;92(3):657-71.
- 28. Corti R, Farkouh ME, Badimon JJ. The vulnerable plaque and acute coronary syndromes. Am J Med. 2002 Dec 1;113(8):668-80.
- 29. Arbustini E, Dal Bello B, Morbini P, Burke AP, Bocciarelli M, Specchia G, et al. Plaque erosion is a major substrate for coronary thrombosis in acute myocardial infarction. Heart 1999;82(3):269-72.
- 30. Jousilahti P, Vartiainen E, Tuomilehto J, Puska P. Sex, age, cardiovascular risk factors, and coronary heart disease: a prospective follow-up study of 14 786 middle-aged men and women in Finland. Circulation 1999;99(9):1165-72.
- 31. Njolstad I, Arnesen E, Lund-Larsen PG. Smoking, serum lipids, blood pressure, and sex differences in myocardial infarction. A 12-year follow-up of the Finnmark Study. Circulation 1996;93(3):450-6.
- 32. Tunstall-Pedoe H, Woodward M, Tavendale R, A'Brook R, McCluskey MK. Comparison of the prediction by 27 different factors of coronary heart disease

- and death in men and women of the Scottish Heart Health Study: cohort study. BMJ. 1997 Sep 20;315(7110):722-9.
- 33. Schnohr P, Jensen JS, Scharling H, Nordestgaard BG. Coronary heart disease risk factors ranked by importance for the individual and community. A 21 year follow-up of 12 000 men and women from The Copenhagen City Heart Study. Eur Heart J. 2002 Apr;23(8):620-6.
- Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet. 2004 Sep 11-17;364(9438):937-52.
- 35. Anand SS, Islam S, Rosengren A, Franzosi MG, Steyn K, Yusufali AH, et al. Risk factors for myocardial infarction in women and men: insights from the INTERHEART study. Eur Heart J. 2008 Apr;29(7):932-40.
- 36. Jonsdottir LS, Sigfusson N, Gudnason V, Sigvaldason H, Thorgeirsson G. Do lipids, blood pressure, diabetes, and smoking confer equal risk of myocardial infarction in women as in men? The Reykjavik Study. J Cardiovasc Risk 2002 Apr;9(2):67-76.
- 37. Michnovicz JJ, Hershcopf RJ, Naganuma H, Bradlow HL, Fishman J. Increased 2-hydroxylation of estradiol as a possible mechanism for the anti-estrogenic effect of cigarette smoking. N Engl J Med. 1986 Nov 20;315(21):1305-9.
- 38. Mjos OD. Lipid effects of smoking. Am Heart J. 1988 Jan;115(1 Pt 2):272-5.
- 39. FitzGerald GA, Oates JA, Nowak J. Cigarette smoking and hemostatic function. Am Heart J. 1988 Jan:115(1 Pt 2):267-71.
- 40. Socialstyrelsen. Folkhälsorapport
- 41. Abbott RD, Donahue RP, Kannel WB, Wilson PW. The impact of diabetes on survival following myocardial infarction in men vs women. The Framingham Study. JAMA. 1988 Dec 16;260(23):3456-60.
- 42. Huxley R, Barzi F, Woodward M. Excess risk of fatal coronary heart disease associated with diabetes in men and women: meta-analysis of 37 prospective cohort studies. BMJ. 2006 Jan 14;332(7533):73-8.
- 43. Norhammar A, Stenestrand U, Lindback J, Wallentin L. Women younger than 65 years with diabetes mellitus are a high-risk group after myocardial infarction: a report from the Swedish Register of Information and Knowledge about Swedish Heart Intensive Care Admission (RIKS-HIA). Heart. 2008 Dec:94(12):1565-70.
- 44. Sharrett AR, Ballantyne CM, Coady SA, Heiss G, Sorlie PD, Catellier D, et al. Coronary heart disease prediction from lipoprotein cholesterol levels, triglycerides, lipoprotein(a), apolipoproteins A-I and B, and HDL density subfractions: The Atherosclerosis Risk in Communities (ARIC) Study. Circulation. 2001 Sep 4;104(10):1108-13.
- 45. Walldius G, Jungner I, Holme I, Aastveit AH, Kolar W, Steiner E. High apolipoprotein B, low apolipoprotein A-I, and improvement in the prediction of fatal myocardial infarction (AMORIS study): a prospective study. Lancet. 2001 Dec 15;358(9298):2026-33.
- 46. Iversen A, Jensen JS, Scharling H, Schnohr P. Hypercholesterolaemia and risk of coronary heart disease in the elderly: impact of age: the Copenhagen City Heart Study. Eur J Intern Med. 2009 Mar;20(2):139-44.

- 47. Manolio TA, Pearson TA, Wenger NK, Barrett-Connor E, Payne GH, Harlan WR. Cholesterol and heart disease in older persons and women. Review of an NHLBI workshop. Ann Epidemiol. 1992 Jan-Mar;2(1-2):161-76.
- 48. Cooney MT, Dudina A, De Bacquer D, Wilhelmsen L, Sans S, Menotti A, et al. HDL cholesterol protects against cardiovascular disease in both genders, at all ages and at all levels of risk. Atherosclerosis. 2009 Mar 19.
- 49. Kastelein JJ, van der Steeg WA, Holme I, Gaffney M, Cater NB, Barter P, et al. Lipids, apolipoproteins, and their ratios in relation to cardiovascular events with statin treatment. Circulation. 2008 Jun 10;117(23):3002-9.
- 50. McQueen MJ, Hawken S, Wang X, Ounpuu S, Sniderman A, Probstfield J, et al. Lipids, lipoproteins, and apolipoproteins as risk markers of myocardial infarction in 52 countries (the INTERHEART study): a case-control study. Lancet. 2008 Jul 19;372(9634):224-33.
- 51. Goldberg RJ, O'Donnell C, Yarzebski J, Bigelow C, Savageau J, Gore JM. Sex differences in symptom presentation associated with acute myocardial infarction: a population-based perspective. Am Heart J 1998;136(2):189-95.
- 52. Canto JG, Shlipak MG, Rogers WJ, Malmgren JA, Frederick PD, Lambrew CT, et al. Prevalence, clinical characteristics, and mortality among patients with myocardial infarction presenting without chest pain. Jama 2000 Jun 28;283(24):3223-9.
- 53. Milner KA, Funk M, Richards S, Wilmes RM, Vaccarino V, Krumholz HM. Gender differences in symptom presentation associated with coronary heart disease. Am J Cardiol 1999 Aug 15:84(4):396-9.
- 54. Dorsch MF, Lawrance RA, Sapsford RJ, Durham N, Oldham J, Greenwood DC, et al. Poor prognosis of patients presenting with symptomatic myocardial infarction but without chest pain. Heart. 2001 Nov;86(5):494-8.
- 55. Gupta M, Tabas JA, Kohn MA. Presenting complaint among patients with myocardial infarction who present to an urban, public hospital emergency department. Ann Emerg Med. 2002 Aug;40(2):180-6.
- 56. Arslanian-Engoren C, Patel A, Fang J, Armstrong D, Kline-Rogers E, Duvernoy CS, et al. Symptoms of men and women presenting with acute coronary syndromes. Am J Cardiol. 2006 Nov 1;98(9):1177-81.
- 57. Milner KA, Vaccarino V, Arnold AL, Funk M, Goldberg RJ. Gender and age differences in chief complaints of acute myocardial infarction (Worcester Heart Attack Study). Am J Cardiol. 2004 Mar 1;93(5):606-8.
- 58. Brieger D, Eagle KA, Goodman SG, Steg PG, Budaj A, White K, et al. Acute coronary syndromes without chest pain, an underdiagnosed and undertreated high-risk group: insights from the Global Registry of Acute Coronary Events. Chest. 2004 Aug;126(2):461-9.
- Isaksson RM, Holmgren L, Lundblad D, Brulin C, Eliasson M. Time trends in symptoms and prehospital delay time in women vs. men with myocardial infarction over a 15-year period. The Northern Sweden MONICA Study. Eur J Cardiovasc Nurs. 2008 Jun;7(2):152-8.
- 60. Canto JG, Goldberg RJ, Hand MM, Bonow RO, Sopko G, Pepine CJ, et al. Symptom presentation of women with acute coronary syndromes: myth vs reality. Arch Intern Med. 2007 Dec 10;167(22):2405-13.
- 61. Patel H, Rosengren A, Ekman I. Symptoms in acute coronary syndromes: does sex make a difference? Am Heart J 2004 Jul;148(1):27-33.

- 62. DeVon HA, Ryan CJ, Ochs AL, Shapiro M. Symptoms across the continuum of acute coronary syndromes: differences between women and men. Am J Crit Care. 2008 Jan;17(1):14-24; quiz 5.
- 63. Fukuoka Y, Dracup K, Moser DK, McKinley S, Ball C, Yamasaki K, et al. Is severity of chest pain a cue for women and men to recognize acute myocardial infarction symptoms as cardiac in origin? Prog Cardiovasc Nurs. 2007 Summer:22(3):132-7.
- 64. Greenlund KJ, Keenan NL, Giles WH, Zheng ZJ, Neff LJ, Croft JB, et al. Public recognition of major signs and symptoms of heart attack: seventeen states and the US Virgin Islands, 2001. Am Heart J. 2004 Jun;147(6):1010-6.
- 65. Herlitz J, Starke M, Hansson E, Ringvall E, Karlson B, Waagstein L. Characteristics and outcome among women and men transported by ambulance due to symptoms arousing suspicion of acute coronary syndrome. Med Sci Monit 2002;8(4):CR251-6.
- 66. Kohn MA, Kwan E, Gupta M, Tabas JA. Prevalence of acute myocardial infarction and other serious diagnoses in patients presenting to an urban emergency department with chest pain. J Emerg Med. 2005 Nov;29(4):383-90.
- 67. Bassand JP, Hamm CW, Ardissino D, Boersma E, Budaj A, Fernandez-Aviles F, et al. Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes. Eur Heart J. 2007 Jul;28(13):1598-660.
- 68. Anderson JL, Adams CD, Antman EM, Bridges CR, Califf RM, Casey DE, Jr., et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-Elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction) developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. J Am Coll Cardiol. 2007 Aug 14;50(7):e1-e157.
- 69. Cannon CP, McCabe CH, Stone PH, Rogers WJ, Schactman M, Thompson BW, et al. The electrocardiogram predicts one-year outcome of patients with unstable angina and non-Q wave myocardial infarction: results of the TIMI III Registry ECG Ancillary Study. Thrombolysis in Myocardial Ischemia. J Am Coll Cardiol. 1997 Jul;30(1):133-40.
- 70. Savonitto S, Cohen MG, Politi A, Hudson MP, Kong DF, Huang Y, et al. Extent of ST-segment depression and cardiac events in non-ST-segment elevation acute coronary syndromes. Eur Heart J. 2005 Oct;26(20):2106-13.
- 71. Holmvang L, Clemmensen P, Lindahl B, Lagerqvist B, Venge P, Wagner G, et al. Quantitative analysis of the admission electrocardiogram identifies patients with unstable coronary artery disease who benefit the most from early invasive treatment. J Am Coll Cardiol 2003 Mar 19;41(6):905-15.
- 72. Hamm CW, Ravkilde J, Gerhardt W, Jorgensen P, Peheim E, Ljungdahl L, et al. The prognostic value of serum troponin T in unstable angina. N Engl J Med. 1992 Jul 16:327(3):146-50.
- 73. Antman EM, Tanasijevic MJ, Thompson B, Schactman M, McCabe CH, Cannon CP, et al. Cardiac-specific troponin I levels to predict the risk of mortality in patients with acute coronary syndromes. N Engl J Med. 1996 Oct 31;335(18):1342-9.

- 74. Heidenreich PA, Alloggiamento T, Melsop K, McDonald KM, Go AS, Hlatky MA. The prognostic value of troponin in patients with non-ST elevation acute coronary syndromes: a meta-analysis. J Am Coll Cardiol. 2001 Aug;38(2):478-85.
- Lindahl B, Diderholm E, Lagerqvist B, Venge P, Wallentin L. Mechanisms behind the prognostic value of troponin T in unstable coronary artery disease: a FRISC II substudy. J Am Coll Cardiol. 2001 Oct;38(4):979-86.
- 76. Morrow DA, Cannon CP, Rifai N, Frey MJ, Vicari R, Lakkis N, et al. Ability of minor elevations of troponins I and T to predict benefit from an early invasive strategy in patients with unstable angina and non-ST elevation myocardial infarction: results from a randomized trial. JAMA. 2001 Nov 21;286(19):2405-12.
- 77. Diderholm E, Andren B, Frostfeldt G, Genberg M, Jernberg T, Lagerqvist B, et al. The prognostic and therapeutic implications of increased troponin T levels and ST depression in unstable coronary artery disease: the FRISC II invasive troponin T electrocardiogram substudy. Am Heart J. 2002 May;143(5):760-7.
- 78. Sabatine MS, Morrow DA, McCabe CH, Antman EM, Gibson CM, Cannon CP. Combination of quantitative ST deviation and troponin elevation provides independent prognostic and therapeutic information in unstable angina and non-ST-elevation myocardial infarction. Am Heart J. 2006 Jan;151(1):25-31.
- 79. Lindahl B, Toss H, Siegbahn A, Venge P, Wallentin L. Markers of myocardial damage and inflammation in relation to long-term mortality in unstable coronary artery disease. FRISC Study Group. Fragmin during Instability in Coronary Artery Disease. N Engl J Med. 2000 Oct 19;343(16):1139-47.
- 80. Jernberg T, Stridsberg M, Venge P, Lindahl B. N-terminal pro brain natriuretic peptide on admission for early risk stratification of patients with chest pain and no ST-segment elevation. J Am Coll Cardiol. 2002 Aug 7;40(3):437-45.
- 81. James SK, Lindahl B, Siegbahn A, Stridsberg M, Venge P, Armstrong P, et al. N-terminal pro-brain natriuretic peptide and other risk markers for the separate prediction of mortality and subsequent myocardial infarction in patients with unstable coronary artery disease: a Global Utilization of Strategies To Open occluded arteries (GUSTO)-IV substudy. Circulation 2003 Jul 22;108(3):275-81.
- 82. Chen R, Kumar S, Timmis A, Feder G, Yaqoob MM, Hemingway H. Comparison of the relation between renal impairment, angiographic coronary artery disease, and long-term mortality in women versus men. Am J Cardiol. 2006 Mar 1;97(5):630-2.
- 83. Wiviott SD, Cannon CP, Morrow DA, Murphy SA, Gibson CM, McCabe CH, et al. Differential expression of cardiac biomarkers by gender in patients with unstable angina/non-ST-elevation myocardial infarction: a TACTICS-TIMI 18 (Treat Angina with Aggrastat and determine Cost of Therapy with an Invasive or Conservative Strategy-Thrombolysis In Myocardial Infarction 18) substudy. Circulation 2004 Feb 10;109(5):580-6.
- 84. Fox KA, Dabbous OH, Goldberg RJ, Pieper KS, Eagle KA, Van de Werf F, et al. Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study (GRACE). BMJ. 2006 Nov 25;333(7578):1091.
- 85. Antman EM, Cohen M, Bernink PJ, McCabe CH, Horacek T, Papuchis G, et al. The TIMI risk score for unstable angina/non-ST elevation MI: A method for

- prognostication and therapeutic decision making. Jama. 2000 Aug 16;284(7):835-42.
- 86. Lagerqvist B, Diderholm E, Lindahl B, Husted S, Kontny F, Stahle E, et al. FRISC score for selection of patients for an early invasive treatment strategy in unstable coronary artery disease. Heart. 2005 Aug;91(8):1047-52.
- 87. Karounos M, Chang AM, Robey JL, Sease KL, Shofer FS, Follansbee C, et al. TIMI risk score: does it work equally well in both males and females? Emerg Med J. 2007 Jul;24(7):471-4.
- 88. Clarke KW, Gray D, Keating NA, Hampton JR. Do women with acute myocardial infarction receive the same treatment as men? Bmj 1994;309(6954):563-6.
- 89. Rotstein Z, Mandelzweig L, Lavi B, Eldar M, Gottlieb S, Hod H. Does the coronary care unit improve prognosis of patients with acute myocardial infarction? A thrombolytic era study. Eur Heart J 1999 Jun;20(11):813-8.
- 90. Lundberg V, Wikstrom B, Bostrom S, Asplund K. Exploring sex differences in case fatality in acute myocardial infarction or coronary death events in the northern Sweden MONICA Project. J Intern Med 2002 Mar;251(3):235-44.
- 91. Herlitz J, Karlson BW, Karlsson T, Svensson L, och Bjorn Kalin EZ. A description of the characteristics and outcome of patients hospitalized for acute chest pain in relation to whether they were admitted to the coronary care unit or not in the thrombolytic era. Int J Cardiol. 2002 Mar:82(3):279-87.
- 92. Hanratty B, Lawlor DA, Robinson MB, Sapsford RJ, Greenwood D, Hall A. Sex differences in risk factors, treatment and mortality after acute myocardial infarction: an observational study. J Epidemiol Community Health 2000;54(12):912-6.
- 93. Foussas SG, Adamopoulou EN, Kafaltis NA, Fakiolas C, Olympios C, Pisimissis E, et al. Clinical characteristics and follow-up of patients with chest pain and normal coronary arteries. Angiology. 1998 May;49(5):349-54.
- 94. Cerqueira MD. Diagnostic testing strategies for coronary artery disease: special issues related to gender. Am J Cardiol. 1995 Apr 13;75(11):52D-60D.
- 95. Kwok Y, Kim C, Grady D, Segal M, Redberg R. Meta-analysis of exercise testing to detect coronary artery disease in women. Am J Cardiol. 1999 Mar 1;83(5):660-6.
- Swahn E, Areskog M, Wallentin L. Early exercise testing after coronary care for suspected unstable coronary artery disease--safety and diagnostic value. Eur Heart J. 1986 Jul;7(7):594-601.
- 97. Nyman I, Wallentin L, Areskog M, Areskog NH, Swahn E. Risk stratification by early exercise testing after an episode of unstable coronary artery disease. The RISC Study Group. Int J Cardiol. 1993 May;39(2):131-42.
- 98. Safstrom K, Nielsen NE, Bjorkholm A, Wiklund G, Swahn E. Unstable coronary artery disease in post-menopausal women. Identifying patients with significant coronary artery disease by basic clinical parameters and exercise test. IRIS Study Group. Eur Heart J. 1998 Jun;19(6):899-907.
- 99. Safstrom K, Swahn E. Early symptom-limited exercise test for risk stratification in post menopausal women with unstable coronary artery disease. FRISC study group. Fragmin during Instability in Coronary Artery Disease. Eur Heart J. 2000 Feb;21(3):230-8.
- 100. Safstrom K, Lindahl B, Swahn E. Risk stratification in unstable coronary artery disease--exercise test and troponin T from a gender perspective. FRISC-Study

- Group. Fragmin during InStability in Coronary artery disease. J Am Coll Cardiol. 2000 Jun;35(7):1791-800.
- 101. Schannwell CM, Lazica D, Plehn G, Leschke M, Strauer BE. [The current status of noninvasive cardiac diagnosis in women with suspected coronary heart disease]. Med Klin (Munich). 2002 Sep 15;97(9):513-21.
- 102. Iskandrian AE, Heo J, Nallamothu N. Detection of coronary artery disease in women with use of stress single-photon emission computed tomography myocardial perfusion imaging. J Nucl Cardiol. 1997 Jul-Aug;4(4):329-35.
- 103. Goodgold HM, Rehder JG, Samuels LD, Chaitman BR. Improved interpretation of exercise Tl-201 myocardial perfusion scintigraphy in women: characterization of breast attenuation artifacts. Radiology. 1987 Nov;165(2):361-6.
- 104. Geleijnse ML, Elhendy A, van Domburg RT, Cornel JH, Reijs AE, Fioretti PM. Prognostic significance of normal dobutamine-atropine stress sestamibi scintigraphy in women with chest pain. Am J Cardiol. 1996 May 15;77(12):1057-61.
- Iskander S, Iskandrian AE. Risk assessment using single-photon emission computed tomographic technetium-99m sestamibi imaging. J Am Coll Cardiol. 1998 Jul;32(1):57-62.
- Metoprolol in acute myocardial infarction (MIAMI). A randomised placebocontrolled international trial. The MIAMI Trial Research Group. Eur Heart J. 1985 Mar;6(3):199-226.
- 107. Yusuf S, Wittes J, Friedman L. Overview of results of randomized clinical trials in heart disease. II. Unstable angina, heart failure, primary prevention with aspirin, and risk factor modification. JAMA. 1988 Oct 21;260(15):2259-63.
- 108. Ellis K, Tcheng JE, Sapp S, Topol EJ, Lincoff AM. Mortality benefit of beta blockade in patients with acute coronary syndromes undergoing coronary intervention: pooled results from the Epic, Epilog, Epistent, Capture and Rapport Trials. J Interv Cardiol. 2003 Aug;16(4):299-305.
- 109. Hjalmarson A, Elmfeldt D, Herlitz J, Holmberg S, Malek I, Nyberg G, et al. Effect on mortality of metoprolol in acute myocardial infarction. A double-blind randomised trial. Lancet. 1981 Oct 17;2(8251):823-7.
- 110. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. Lancet. 1999 Jan 2;353(9146):9-13.
- 111. Hjalmarson A, Goldstein S, Fagerberg B, Wedel H, Waagstein F, Kjekshus J, et al. Effects of controlled-release metoprolol on total mortality, hospitalizations, and well-being in patients with heart failure: the Metoprolol CR/XL Randomized Intervention Trial in congestive heart failure (MERIT-HF). MERIT-HF Study Group. JAMA. 2000 Mar 8;283(10):1295-302.
- 112. Dargie HJ. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: the CAPRICORN randomised trial. Lancet. 2001 May 5;357(9266):1385-90.
- 113. Shekelle PG, Rich MW, Morton SC, Atkinson CS, Tu W, Maglione M, et al. Efficacy of angiotensin-converting enzyme inhibitors and beta-blockers in the management of left ventricular systolic dysfunction according to race, gender, and diabetic status: a meta-analysis of major clinical trials. J Am Coll Cardiol. 2003 May 7;41(9):1529-38.
- 114. Jugdutt BI, Warnica JW. Intravenous nitroglycerin therapy to limit myocardial infarct size, expansion, and complications. Effect of timing, dosage, and infarct location. Circulation. 1988 Oct;78(4):906-19.

- 115. GISSI-3: effects of lisinopril and transdermal glyceryl trinitrate singly and together on 6-week mortality and ventricular function after acute myocardial infarction. Gruppo Italiano per lo Studio della Sopravvivenza nell'infarto Miocardico, Lancet. 1994 May 7:343(8906):1115-22.
- 116. ISIS-4: a randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58,050 patients with suspected acute myocardial infarction. ISIS-4 (Fourth International Study of Infarct Survival) Collaborative Group. Lancet. 1995 Mar 18;345(8951):669-85.
- 117. Yusuf S, Held P, Furberg C. Update of effects of calcium antagonists in myocardial infarction or angina in light of the second Danish Verapamil Infarction Trial (DAVIT-II) and other recent studies. Am J Cardiol. 1991 Jun 1;67(15):1295-7.
- 118. Furberg CD, Psaty BM, Meyer JV. Nifedipine. Dose-related increase in mortality in patients with coronary heart disease. Circulation. 1995 Sep 1;92(5):1326-31.
- 119. Smith NL, Reiber GE, Psaty BM, Heckbert SR, Siscovick DS, Ritchie JL, et al. Health outcomes associated with beta-blocker and diltiazem treatment of unstable angina. J Am Coll Cardiol. 1998 Nov;32(5):1305-11.
- Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet. 1994 Nov 19:344(8934):1383-9.
- 121. Schwartz GG, Olsson AG, Ezekowitz MD, Ganz P, Oliver MF, Waters D, et al. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial. JAMA. 2001 Apr 4;285(13):1711-8.
- 122. de Lemos JA, Blazing MA, Wiviott SD, Lewis EF, Fox KA, White HD, et al. Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes: phase Z of the A to Z trial. JAMA. 2004 Sep 15;292(11):1307-16.
- 123. Hulten E, Jackson JL, Douglas K, George S, Villines TC. The effect of early, intensive statin therapy on acute coronary syndrome: a meta-analysis of randomized controlled trials. Arch Intern Med. 2006 Sep 25;166(17):1814-21.
- 124. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet. 2002 Jul 6;360(9326):7-22.
- 125. Miettinen TA, Pyorala K, Olsson AG, Musliner TA, Cook TJ, Faergeman O, et al. Cholesterol-lowering therapy in women and elderly patients with myocardial infarction or angina pectoris: findings from the Scandinavian Simvastatin Survival Study (4S). Circulation. 1997 Dec 16;96(12):4211-8.
- 126. Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM, Jr., Kastelein JJ, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med. 2008 Nov 20;359(21):2195-207.
- 127. Shepherd J, Blauw GJ, Murphy MB, Bollen EL, Buckley BM, Cobbe SM, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. Lancet. 2002 Nov 23;360(9346):1623-30.
- 128. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. Lancet. 1993 Oct 2;342(8875):821-8.
- 129. Pfeffer MA, Braunwald E, Moye LA, Basta L, Brown EJ, Jr., Cuddy TE, et al. Effect of captopril on mortality and morbidity in patients with left ventricular

- dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. N Engl J Med. 1992 Sep 3;327(10):669-77.
- 130. Torp-Pedersen C, Kober L. Effect of ACE inhibitor trandolapril on life expectancy of patients with reduced left-ventricular function after acute myocardial infarction. TRACE Study Group. Trandolapril Cardiac Evaluation. Lancet. 1999 Jul 3;354(9172):9-12.
- 131. Dickstein K, Kjekshus J. Effects of losartan and captopril on mortality and morbidity in high-risk patients after acute myocardial infarction: the OPTIMAAL randomised trial. Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan. Lancet. 2002 Sep 7;360(9335):752-60.
- 132. Pfeffer MA, McMurray JJ, Velazquez EJ, Rouleau JL, Kober L, Maggioni AP, et al. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. N Engl J Med. 2003 Nov 13;349(20):1893-906.
- 133. Fox KM. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). Lancet. 2003 Sep 6;362(9386):782-8.
- 134. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. N Engl J Med. 2000 Jan 20;342(3):145-53.
- 135. Braunwald E, Domanski MJ, Fowler SE, Geller NL, Gersh BJ, Hsia J, et al. Angiotensin-converting-enzyme inhibition in stable coronary artery disease. N Engl J Med. 2004 Nov 11;351(20):2058-68.
- 136. Flather MD, Yusuf S, Kober L, Pfeffer M, Hall A, Murray G, et al. Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction: a systematic overview of data from individual patients. ACE-Inhibitor Myocardial Infarction Collaborative Group. Lancet. 2000 May 6;355(9215):1575-81.
- 137. Risk of myocardial infarction and death during treatment with low dose aspirin and intravenous heparin in men with unstable coronary artery disease. The RISC Group. Lancet. 1990 Oct 6;336(8719):827-30.
- 138. Lewis HD, Jr., Davis JW, Archibald DG, Steinke WE, Smitherman TC, Doherty JE, 3rd, et al. Protective effects of aspirin against acute myocardial infarction and death in men with unstable angina. Results of a Veterans Administration Cooperative Study. N Engl J Med. 1983 Aug 18;309(7):396-403.
- 139. Cairns JA, Gent M, Singer J, Finnie KJ, Froggatt GM, Holder DA, et al. Aspirin, sulfinpyrazone, or both in unstable angina. Results of a Canadian multicenter trial. N Engl J Med. 1985 Nov 28;313(22):1369-75.
- 140. Peters RJ, Mehta SR, Fox KA, Zhao F, Lewis BS, Kopecky SL, et al. Effects of aspirin dose when used alone or in combination with clopidogrel in patients with acute coronary syndromes: observations from the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) study. Circulation. 2003 Oct 7;108(14):1682-7.
- 141. Baigent C, Blackwell L, Collins R, Emberson J, Godwin J, Peto R, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative metaanalysis of individual participant data from randomised trials. Lancet. 2009 May 30;373(9678):1849-60.

- 142. Balsano F, Rizzon P, Violi F, Scrutinio D, Cimminiello C, Aguglia F, et al. Antiplatelet treatment with ticlopidine in unstable angina. A controlled multicenter clinical trial. The Studio della Ticlopidina nell'Angina Instabile Group. Circulation. 1990 Jul;82(1):17-26.
- 143. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee. Lancet. 1996 Nov 16:348(9038):1329-39.
- 144. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med. 2001 Aug 16;345(7):494-502.
- 145. Mehta SR, Yusuf S, Peters RJ, Bertrand ME, Lewis BS, Natarajan MK, et al. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. Lancet. 2001 Aug 18;358(9281):527-33.
- 146. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2007 Nov 15;357(20):2001-15.
- 147. James S, Akerblom A, Cannon CP, Emanuelsson H, Husted S, Katus H, et al. Comparison of ticagrelor, the first reversible oral P2Y(12) receptor antagonist, with clopidogrel in patients with acute coronary syndromes: Rationale, design, and baseline characteristics of the PLATelet inhibition and patient Outcomes (PLATO) trial. Am Heart J. 2009 Apr;157(4):599-605.
- 148. Greenbaum AB, Grines CL, Bittl JA, Becker RC, Kereiakes DJ, Gilchrist IC, et al. Initial experience with an intravenous P2Y12 platelet receptor antagonist in patients undergoing percutaneous coronary intervention: results from a 2-part, phase II, multicenter, randomized, placebo- and active-controlled trial. Am Heart J. 2006 Mar;151(3):689 e1- e10.
- 149. Angiolillo DJ, Bhatt DL, Gurbel PA, Jennings LK. Advances in antiplatelet therapy: agents in clinical development. Am J Cardiol. 2009 Feb 2;103(3 Suppl):40A-51A.
- Wiviott SD. Clopidogrel response variability, resistance, or both? Am J Cardiol. 2006 Nov 20:98(10A):18N-24N.
- 151. Cheng X, Chen WH, Simon DI. Aspirin resistance or variable response or both? Am J Cardiol. 2006 Nov 20;98(10A):11N-7N.
- 152. Eikelboom JW, Hirsh J, Weitz JI, Johnston M, Yi Q, Yusuf S. Aspirin-resistant thromboxane biosynthesis and the risk of myocardial infarction, stroke, or cardiovascular death in patients at high risk for cardiovascular events. Circulation. 2002 Apr 9;105(14):1650-5.
- 153. Matetzky S, Shenkman B, Guetta V, Shechter M, Bienart R, Goldenberg I, et al. Clopidogrel resistance is associated with increased risk of recurrent atherothrombotic events in patients with acute myocardial infarction. Circulation. 2004 Jun 29:109(25):3171-5.
- 154. Chen WH, Cheng X, Lee PY, Ng W, Kwok JY, Tse HF, et al. Aspirin resistance and adverse clinical events in patients with coronary artery disease. Am J Med. 2007 Jul;120(7):631-5.
- 155. Topol EJ, Byzova TV, Plow EF. Platelet GPIIb-IIIa blockers. Lancet. 1999 Jan 16;353(9148):227-31.
- 156. Boersma E, Harrington RA, Moliterno DJ, White H, Theroux P, Van de Werf F, et al. Platelet glycoprotein IIb/IIIa inhibitors in acute coronary syndromes: a

- meta-analysis of all major randomised clinical trials. Lancet. 2002 Jan 19;359(9302):189-98.
- 157. Oler A, Whooley MA, Oler J, Grady D. Adding heparin to aspirin reduces the incidence of myocardial infarction and death in patients with unstable angina. A meta-analysis. JAMA. 1996 Sep 11;276(10):811-5.
- 158. Eikelboom JW, Anand SS, Malmberg K, Weitz JI, Ginsberg JS, Yusuf S. Unfractionated heparin and low-molecular-weight heparin in acute coronary syndrome without ST elevation: a meta-analysis. Lancet. 2000 Jun 3;355(9219):1936-42.
- 159. Low-molecular-weight heparin during instability in coronary artery disease, Fragmin during Instability in Coronary Artery Disease (FRISC) study group. Lancet. 1996 Mar 2;347(9001):561-8.
- 160. Long-term low-molecular-mass heparin in unstable coronary-artery disease: FRISC II prospective randomised multicentre study. FRagmin and Fast Revascularisation during InStability in Coronary artery disease. Investigators. Lancet 1999 Aug 28;354(9180):701-7.
- 161. Effects of recombinant hirudin (lepirudin) compared with heparin on death, myocardial infarction, refractory angina, and revascularisation procedures in patients with acute myocardial ischaemia without ST elevation: a randomised trial. Organisation to Assess Strategies for Ischemic Syndromes (OASIS-2) Investigators. Lancet. 1999 Feb 6;353(9151):429-38.
- 162. Direct thrombin inhibitors in acute coronary syndromes: principal results of a meta-analysis based on individual patients' data. Lancet. 2002 Jan 26;359(9303):294-302.
- 163. Stone GW, McLaurin BT, Cox DA, Bertrand ME, Lincoff AM, Moses JW, et al. Bivalirudin for patients with acute coronary syndromes. N Engl J Med. 2006 Nov 23;355(21):2203-16.
- 164. Stone GW, Bertrand ME, Moses JW, Ohman EM, Lincoff AM, Ware JH, et al. Routine upstream initiation vs deferred selective use of glycoprotein IIb/IIIa inhibitors in acute coronary syndromes: the ACUITY Timing trial. JAMA. 2007 Feb 14;297(6):591-602.
- 165. Stone GW, White HD, Ohman EM, Bertrand ME, Lincoff AM, McLaurin BT, et al. Bivalirudin in patients with acute coronary syndromes undergoing percutaneous coronary intervention: a subgroup analysis from the Acute Catheterization and Urgent Intervention Triage strategy (ACUITY) trial. Lancet. 2007 Mar 17;369(9565):907-19.
- 166. Yusuf S, Mehta SR, Chrolavicius S, Afzal R, Pogue J, Granger CB, et al. Comparison of fondaparinux and enoxaparin in acute coronary syndromes. N Engl J Med. 2006 Apr 6;354(14):1464-76.
- Moscucci M, Fox KA, Cannon CP, Klein W, Lopez-Sendon J, Montalescot G, et al. Predictors of major bleeding in acute coronary syndromes: the Global Registry of Acute Coronary Events (GRACE). Eur Heart J. 2003 Oct;24(20):1815-23.
- 168. Bhatt DL, Roe MT, Peterson ED, Li Y, Chen AY, Harrington RA, et al. Utilization of early invasive management strategies for high-risk patients with non-ST-segment elevation acute coronary syndromes: results from the CRUSADE Quality Improvement Initiative. JAMA. 2004 Nov 3;292(17):2096-104
- 169. Manoukian SV, Feit F, Mehran R, Voeltz MD, Ebrahimi R, Hamon M, et al. Impact of major bleeding on 30-day mortality and clinical outcomes in patients

- with acute coronary syndromes: an analysis from the ACUITY Trial. J Am Coll Cardiol. 2007 Mar 27;49(12):1362-8.
- 170. Budaj A, Eikelboom JW, Mehta SR, Afzal R, Chrolavicius S, Bassand JP, et al. Improving clinical outcomes by reducing bleeding in patients with non-ST-elevation acute coronary syndromes. Eur Heart J. 2009 Mar;30(6):655-61.
- 171. Rao SV, O'Grady K, Pieper KS, Granger CB, Newby LK, Van de Werf F, et al. Impact of bleeding severity on clinical outcomes among patients with acute coronary syndromes. Am J Cardiol. 2005 Nov 1;96(9):1200-6.
- 172. Eikelboom JW, Mehta SR, Anand SS, Xie C, Fox KA, Yusuf S. Adverse impact of bleeding on prognosis in patients with acute coronary syndromes. Circulation. 2006 Aug 22;114(8):774-82.
- 173. Alexander KP, Chen AY, Roe MT, Newby LK, Gibson CM, Allen-LaPointe NM, et al. Excess dosing of antiplatelet and antithrombin agents in the treatment of non-ST-segment elevation acute coronary syndromes. Jama. 2005 Dec 28;294(24):3108-16.
- 174. Alexander KP, Chen AY, Newby LK, Schwartz JB, Redberg RF, Hochman JS, et al. Sex differences in major bleeding with glycoprotein IIb/IIIa inhibitors: results from the CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines) initiative. Circulation. 2006 Sep 26;114(13):1380-7.
- 175. Spacek R, Widimsky P, Straka Z, Jiresova E, Dvorak J, Polasek R, et al. Value of first day angiography/angioplasty in evolving Non-ST segment elevation myocardial infarction: an open multicenter randomized trial. The VINO Study. Eur Heart J. 2002 Feb;23(3):230-8.
- 176. Effects of tissue plasminogen activator and a comparison of early invasive and conservative strategies in unstable angina and non-Q-wave myocardial infarction. Results of the TIMI IIIB Trial. Thrombolysis in Myocardial Ischemia. Circulation 1994 Apr;89(4):1545-56.
- 177. Invasive compared with non-invasive treatment in unstable coronary-artery disease: FRISC II prospective randomised multicentre study. FRagmin and Fast Revascularisation during InStability in Coronary artery disease Investigators. Lancet 1999 Aug 28;354(9180):708-15.
- 178. Fox KA, Poole-Wilson PA, Henderson RA, Clayton TC, Chamberlain DA, Shaw TR, et al. Interventional versus conservative treatment for patients with unstable angina or non-ST-elevation myocardial infarction: the British Heart Foundation RITA 3 randomised trial. Randomized Intervention Trial of unstable Angina. Lancet 2002 Sep 7;360(9335):743-51.
- 179. Cannon CP, Weintraub WS, Demopoulos LA, Vicari R, Frey MJ, Lakkis N, et al. Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. N Engl J Med. 2001 Jun 21;344(25):1879-87.
- 180. McCullough PA, O'Neill WW, Graham M, Stomel RJ, Rogers F, David S, et al. A prospective randomized trial of triage angiography in acute coronary syndromes ineligible for thrombolytic therapy. Results of the medicine versus angiography in thrombolytic exclusion (MATE) trial. J Am Coll Cardiol. 1998 Sep;32(3):596-605.
- 181. Boden WE, O'Rourke RA, Crawford MH, Blaustein AS, Deedwania PC, Zoble RG, et al. Outcomes in patients with acute non-Q-wave myocardial infarction randomly assigned to an invasive as compared with a conservative management strategy. Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital

- (VANQWISH) Trial Investigators. N Engl J Med. 1998 Jun 18;338(25):1785-92.
- 182. de Winter RJ, Windhausen F, Cornel JH, Dunselman PH, Janus CL, Bendermacher PE, et al. Early invasive versus selectively invasive management for acute coronary syndromes. N Engl J Med. 2005 Sep 15;353(11):1095-104.
- 183. Welty FK, Mittleman MA, Healy RW, Muller JE, Shubrooks SJ, Jr. Similar results of percutaneous transluminal coronary angioplasty for women and men with postmyocardial infarction ischemia. J Am Coll Cardiol. 1994 Jan;23(1):35-9.
- 184. Weintraub WS, Wenger NK, Kosinski AS, Douglas JS, Jr., Liberman HA, Morris DC, et al. Percutaneous transluminal coronary angioplasty in women compared with men. J Am Coll Cardiol. 1994 Jul;24(1):81-90.
- 185. Kelsey SF, James M, Holubkov AL, Holubkov R, Cowley MJ, Detre KM. Results of percutaneous transluminal coronary angioplasty in women. 1985-1986 National Heart, Lung, and Blood Institute's Coronary Angioplasty Registry. Circulation. 1993 Mar;87(3):720-7.
- 186. Bell MR, Holmes DR, Jr., Berger PB, Garratt KN, Bailey KR, Gersh BJ. The changing in-hospital mortality of women undergoing percutaneous transluminal coronary angioplasty. JAMA. 1993 Apr 28;269(16):2091-5.
- 187. Mehilli J, Kastrati A, Dirschinger J, Bollwein H, Neumann FJ, Schomig A. Differences in prognostic factors and outcomes between women and men undergoing coronary artery stenting. Jama 2000;284(14):1799-805.
- 188. Watanabe CT, Maynard C, Ritchie JL. Comparison of short-term outcomes following coronary artery stenting in men versus women. Am J Cardiol 2001 Oct 15;88(8):848-52.
- 189. Jacobs AK, Johnston JM, Haviland A, Brooks MM, Kelsey SF, Holmes DR, Jr., et al. Improved outcomes for women undergoing contemporary percutaneous coronary intervention: a report from the National Heart, Lung, and Blood Institute Dynamic registry. J Am Coll Cardiol 2002 May 15;39(10):1608-14.
- 190. Holubkov R, Laskey WK, Haviland A, Slater JC, Bourassa MG, Vlachos HA, et al. Angina 1 year after percutaneous coronary intervention: a report from the NHLBI Dynamic Registry. Am Heart J. 2002 Nov;144(5):826-33.
- 191. Singh M, Rihal CS, Gersh BJ, Roger VL, Bell MR, Lennon RJ, et al. Mortality differences between men and women after percutaneous coronary interventions. A 25-year, single-center experience. J Am Coll Cardiol. 2008 Jun 17:51(24):2313-20.
- Peterson ED, Lansky AJ, Kramer J, Anstrom K, Lanzilotta MJ. Effect of gender on the outcomes of contemporary percutaneous coronary intervention. Am J Cardiol 2001;88(4):359-64.
- 193. Ashby DT, Mehran R, Aymong EA, Lansky AJ, Iakovou I, Weisz G, et al. Comparison of outcomes in men versus women having percutaneous coronary interventions in small coronary arteries. Am J Cardiol. 2003 Apr 15;91(8):979-81, A4, A7.
- 194. Chiu JH, Bhatt DL, Ziada KM, Chew DP, Whitlow PL, Lincoff AM, et al. Impact of female sex on outcome after percutaneous coronary intervention. Am Heart J. 2004 Dec;148(6):998-1002.
- 195. Argulian E, Patel AD, Abramson JL, Kulkarni A, Champney K, Palmer S, et al. Gender differences in short-term cardiovascular outcomes after percutaneous coronary interventions. Am J Cardiol. 2006 Jul 1;98(1):48-53.

- 196. Abbott JD, Vlachos HA, Selzer F, Sharaf BL, Holper E, Glaser R, et al. Gender-based outcomes in percutaneous coronary intervention with drug-eluting stents (from the National Heart, Lung, and Blood Institute Dynamic Registry). Am J Cardiol. 2007 Mar 1;99(5):626-31.
- 197. Berger JS, Sanborn TA, Sherman W, Brown DL. Influence of sex on in-hospital outcomes and long-term survival after contemporary percutaneous coronary intervention. Am Heart J. 2006 May;151(5):1026-31.
- 198. Srinivas VS, Garg S, Negassa A, Bang JY, Monrad ES. Persistent sex difference in hospital outcome following percutaneous coronary intervention: results from the New York State reporting system. J Invasive Cardiol. 2007 Jun;19(6):265-8.
- 199. Lansky AJ, Costa RA, Mooney M, Midei MG, Lui HK, Strickland W, et al. Gender-based outcomes after paclitaxel-eluting stent implantation in patients with coronary artery disease. J Am Coll Cardiol. 2005 Apr 19;45(8):1180-5.
- 200. Holmes DR, Jr., Leon MB, Moses JW, Popma JJ, Cutlip D, Fitzgerald PJ, et al. Analysis of 1-year clinical outcomes in the SIRIUS trial: a randomized trial of a sirolimus-eluting stent versus a standard stent in patients at high risk for coronary restenosis. Circulation. 2004 Feb 10;109(5):634-40.
- 201. O'Connor GT, Morton JR, Diehl MJ, Olmstead EM, Coffin LH, Levy DG, et al. Differences between men and women in hospital mortality associated with coronary artery bypass graft surgery. The Northern New England Cardiovascular Disease Study Group. Circulation. 1993 Nov;88(5 Pt 1):2104-10.
- 202. Hammar N, Sandberg E, Larsen FF, Ivert T. Comparison of early and late mortality in men and women after isolated coronary artery bypass graft surgery in Stockholm, Sweden, 1980 to 1989. J Am Coll Cardiol 1997;29(3):659-64.
- 203. Edwards FH, Carey JS, Grover FL, Bero JW, Hartz RS. Impact of gender on coronary bypass operative mortality. Ann Thorac Surg 1998;66(1):125-31.
- 204. Abramov D, Tamariz MG, Sever JY, Christakis GT, Bhatnagar G, Heenan AL, et al. The influence of gender on the outcome of coronary artery bypass surgery. Ann Thorac Surg 2000;70(3):800-5; discussion 6.
- 205. Vaccarino V, Abramson JL, Veledar E, Weintraub WS. Sex differences in hospital mortality after coronary artery bypass surgery: evidence for a higher mortality in younger women. Circulation 2002 Mar 12;105(10):1176-81.
- 206. Blankstein R, Ward RP, Arnsdorf M, Jones B, Lou YB, Pine M. Female gender is an independent predictor of operative mortality after coronary artery bypass graft surgery: contemporary analysis of 31 Midwestern hospitals. Circulation. 2005 Aug 30:112(9 Suppl):I323-7.
- 207. Woods SE, Noble G, Smith JM, Hasselfeld K. The influence of gender in patients undergoing coronary artery bypass graft surgery: an eight-year prospective hospitalized cohort study. J Am Coll Surg. 2003 Mar;196(3):428-34.
- 208. Koch CG, Khandwala F, Nussmeier N, Blackstone EH. Gender and outcomes after coronary artery bypass grafting: a propensity-matched comparison. J Thorac Cardiovasc Surg. 2003 Dec;126(6):2032-43.
- 209. Guru V, Fremes SE, Austin PC, Blackstone EH, Tu JV. Gender differences in outcomes after hospital discharge from coronary artery bypass grafting. Circulation. 2006 Jan 31;113(4):507-16.
- 210. Szabo Z, Hakanson E, Svedjeholm R. Early postoperative outcome and mediumterm survival in 540 diabetic and 2239 nondiabetic patients undergoing coronary artery bypass grafting. Ann Thorac Surg. 2002 Sep;74(3):712-9.

- 211. Ritchison A, Smith JM, Engel AM. Gender differences in diabetic patients following coronary artery bypass graft surgery. J Card Surg. 2007 Sep-Oct;22(5):401-5.
- 212. Guru V, Fremes SE, Tu JV. Time-related mortality for women after coronary artery bypass graft surgery: a population-based study. J Thorac Cardiovasc Surg. 2004 Apr;127(4):1158-65.
- 213. Jacobs AK, Kelsey SF, Brooks MM, Faxon DP, Chaitman BR, Bittner V, et al. Better outcome for women compared with men undergoing coronary revascularization: a report from the bypass angioplasty revascularization investigation (BARI). Circulation 1998;98(13):1279-85.
- 214. O'Rourke DJ, Malenka DJ, Olmstead EM, Quinton HB, Sanders JH, Jr., Lahey SJ, et al. Improved in-hospital mortality in women undergoing coronary artery bypass grafting. Northern New England Cardiovascular Disease Study Group. Ann Thorac Surg 2001;71(2):507-11.
- 215. Scirica BM, Moliterno DJ, Every NR, Anderson HV, Aguirre FV, Granger CB, et al. Differences between men and women in the management of unstable angina pectoris (The GUARANTEE Registry). The GUARANTEE Investigators. Am J Cardiol 1999;84(10):1145-50.
- 216. Gottlieb S, Harpaz D, Shotan A, Boyko V, Leor J, Cohen M, et al. Sex differences in management and outcome after acute myocardial infarction in the 1990s: A prospective observational community-based study. Israeli Thrombolytic Survey Group, Circulation 2000:102(20):2484-90.
- 217. Blomkalns AL, Chen AY, Hochman JS, Peterson ED, Trynosky K, Diercks DB, et al. Gender disparities in the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes: large-scale observations from the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the American College of Cardiology/American Heart Association Guidelines) National Quality Improvement Initiative. J Am Coll Cardiol. 2005 Mar 15;45(6):832-7.
- 218. Raine RA, Black NA, Bowker TJ, Wood DA. Gender differences in the management and outcome of patients with acute coronary artery disease. J Epidemiol Community Health 2002 Oct;56(10):791-7.
- 219. Mehilli J, Kastrati A, Dirschinger J, Pache J, Seyfarth M, Blasini R, et al. Sexbased analysis of outcome in patients with acute myocardial infarction treated predominantly with percutaneous coronary intervention. Jama 2002 Jan 9:287(2):210-5.
- 220. Hasdai D, Porter A, Rosengren A, Behar S, Boyko V, Battler A. Effect of gender on outcomes of acute coronary syndromes. Am J Cardiol 2003 Jun 15;91(12):1466-9, A6.
- 221. Marrugat J, Sala J, Masia R, Pavesi M, Sanz G, Valle V, et al. Mortality differences between men and women following first myocardial infarction. RESCATE Investigators. Recursos Empleados en el Sindrome Coronario Agudo y Tiempo de Espera. Jama 1998;280(16):1405-9.
- Maynard C, Every NR, Martin JS, Kudenchuk PJ, Weaver WD. Association of gender and survival in patients with acute myocardial infarction. Arch Intern Med 1997;157(12):1379-84.
- 223. Moen EK, Asher CR, Miller DP, Weaver WD, White HD, Califf RM, et al. Long-term follow-up of gender-specific outcomes after thrombolytic therapy for acute myocardial infarction from the GUSTO-I trial. Global Utilization of

- Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries. J Womens Health 1997;6(3):285-93.
- 224. Braunwald E, Antman EM, Beasley JW, Califf RM, Cheitlin MD, Hochman JS, et al. ACC/AHA 2002 guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction--summary article: a report of the American College of Cardiology/American Heart Association task force on practice guidelines (Committee on the Management of Patients With Unstable Angina). J Am Coll Cardiol. 2002 Oct 2;40(7):1366-74.
- 225. Champney KP, Frederick PD, Bueno H, Parashar S, Foody J, Merz CN, et al. The joint contribution of sex, age and type of myocardial infarction on hospital mortality following acute myocardial infarction. Heart. 2009 Jun;95(11):895-9.
- 226. Kim C, Schaaf CH, Maynard C, Every NR. Unstable angina in the myocardial infarction triage and intervention registry (MITI): short- and long-term outcomes in men and women. Am Heart J 2001 Jan;141(1):73-7.
- Vaccarino V, Parsons L, Every NR, Barron HV, Krumholz HM. Sex-based differences in early mortality after myocardial infarction. National Registry of Myocardial Infarction 2 Participants. N Engl J Med 1999 Jul 22;341(4):217-25.
- 228. Gurwitz JH, Col NF, Avorn J. The exclusion of the elderly and women from clinical trials in acute myocardial infarction. Jama 1992;268(11):1417-22.
- 229. Ding EL, Powe NR, Manson JE, Sherber NS, Braunstein JB. Sex differences in perceived risks, distrust, and willingness to participate in clinical trials: a randomized study of cardiovascular prevention trials. Arch Intern Med. 2007 May 14;167(9):905-12.
- 230. McKee M, Britton A, Black N, McPherson K, Sanderson C, Bain C. Methods in health services research. Interpreting the evidence: choosing between randomised and non-randomised studies. BMJ. 1999 Jul 31;319(7205):312-5.
- Benson K, Hartz AJ. A comparison of observational studies and randomized, controlled trials. N Engl J Med. 2000 Jun 22;342(25):1878-86.
- 232. Barton S. Which clinical studies provide the best evidence? The best RCT still trumps the best observational study. BMJ. 2000 Jul 29;321(7256):255-6.
- 233. Eysenck HJ. Meta-analysis and its problems. BMJ. 1994 Sep 24;309(6957):789-92
- 234. Tunstall-Pedoe H, Kuulasmaa K, Amouyel P, Arveiler D, Rajakangas AM, Pajak A. Myocardial infarction and coronary deaths in the World Health Organization MONICA Project. Registration procedures, event rates, and casefatality rates in 38 populations from 21 countries in four continents. Circulation. 1994 Jul;90(1):583-612.
- 235. Mehta SR, Yusuf S, Granger CB, Wallentin L, Peters RJ, Bassand JP, et al. Design and rationale of the MICHELANGELO Organization to Assess Strategies in Acute Ischemic Syndromes (OASIS)-5 trial program evaluating fondaparinux, a synthetic factor Xa inhibitor, in patients with non-ST-segment elevation acute coronary syndromes. Am Heart J. 2005 Dec;150(6):1107.
- 236. Yusuf S, Peto R, Lewis J, Collins R, Sleight P. Beta blockade during and after myocardial infarction: an overview of the randomized trials. Prog Cardiovasc Dis. 1985 Mar-Apr;27(5):335-71.
- 237. Joffe MM, Rosenbaum PR. Invited commentary: propensity scores. Am J Epidemiol. 1999 Aug 15;150(4):327-33.
- 238. Rubin DB. Estimating causal effects from large data sets using propensity scores. Ann Intern Med. 1997 Oct 15;127(8 Pt 2):757-63.

- 239. Herlitz J, Karlson BW, Karlson T, Svensson L, och Bjorn Kalin EZ. A description of the characteristics and outcome of patients hospitalized for acute chest pain in relation to whether they were admitted to the coronary care unit or not in the thrombolytic era. Int J Cardiol 2002 Mar;82(3):279-87.
- 240. Porath A, Arbelle JE, Grossman E, Gilutz H, Cohen E, Greenfield S, et al. A comparison of management and short-term outcomes of acute myocardial infarction patients admitted to coronary care units and medical wards: the importance of case mix. Eur J Intern Med. 2002 Dec;13(8):507-13.
- 241. Jones I, Flather M, Johnson M, Barrow S, Thompson D. A description of the characteristics of patients with non-ST elevation acute coronary syndromes admitted to different settings in the 1990s. Intensive Crit Care Nurs. 2008 Oct;24(5):286-94.
- 242. Scirica BM, Cannon CP, Antman EM, Murphy SA, Morrow DA, Sabatine MS, et al. Validation of the thrombolysis in myocardial infarction (TIMI) risk score for unstable angina pectoris and non-ST-elevation myocardial infarction in the TIMI III registry. Am J Cardiol. 2002 Aug 1:90(3):303-5.
- Douglas PS, Ginsburg GS. The evaluation of chest pain in women. N Engl J Med. 1996 May 16;334(20):1311-5.
- 244. Birdwell BG, Herbers JE, Kroenke K. Evaluating chest pain. The patient's presentation style alters the physician's diagnostic approach. Arch Intern Med. 1993 Sep 13:153(17):1991-5.
- 245. Heer T, Gitt AK, Juenger C, Schiele R, Wienbergen H, Towae F, et al. Gender differences in acute non-ST-segment elevation myocardial infarction. Am J Cardiol. 2006 Jul 15;98(2):160-6.
- 246. O'Donoghue M, Boden WE, Braunwald E, Cannon CP, Clayton TC, de Winter RJ, et al. Early invasive vs conservative treatment strategies in women and men with unstable angina and non-ST-segment elevation myocardial infarction: a meta-analysis. Jama. 2008 Jul 2;300(1):71-80.
- 247. Mueller C, Neumann FJ, Roskamm H, Buser P, Hodgson JM, Perruchoud AP, et al. Women do have an improved long-term outcome after non-ST-elevation acute coronary syndromes treated very early and predominantly with percutaneous coronary intervention: a prospective study in 1,450 consecutive patients. J Am Coll Cardiol 2002 Jul 17:40(2):245-50.
- 248. Lindahl B, Diderholm E, Lagerqvist B, Venge P, Wallentin L. Mechanisms behind the prognostic value of troponin T in unstable coronary artery disease: a FRISC II substudy. J Am Coll Cardiol 2001 Oct;38(4):979-86.
- 249. Mehta SR, Granger CB, Boden WE, Steg PG, Bassand JP, Faxon DP, et al. Early versus delayed invasive intervention in acute coronary syndromes. N Engl J Med. 2009 May 21;360(21):2165-75.