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Management and Outcome in ST-Elevation Myocardial Infarction from a Gender Perspective

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Life is what happens to you while you're busy making other plans

John Lennon (1940-1980)

To
Linnea, Albin and Dan

CONTENTS

Abstract

The aim of this thesis was to evaluate baseline characteristics, management and outcome in real life ST-elevation myocardial infarction [STEMI] cohorts from a gender perspective. We aimed to evaluate the total STEMI population as well as certain subgroups, such as the youngest. Moreover we aimed to analyse gender differences in renal function, and the prognostic impact of reduced renal function in men and women with STEMI.

In **Paper I** all STEMI patients registered in RIKS-HIA between 1st Jan 1995 and 31st Dec 2006 were included, in total 54 146 patients, 35% women. Women were 7 years older than men, with 30 min longer median symptom-to-door time. They had higher prevalence of co-morbidities such as diabetes, hypertension and heart failure whereas men were more often smokers, had a previous myocardial infarction [MI] or were previously revascularised. During hospital care, fewer women than men, 63% vs. 72%, p<0.001, received acute reperfusion therapy, odds ratio [OR] 0.83 (95% confidence interval [CI] 0.79 – 0.88) after multivariable adjustment. In-hospital mortality was 13% vs. 7%, women vs. men, p<0.001. After multivariable adjustments women had 22% higher risk of in-hospital death, OR 1.22 (95% CI 1.11 – 1.33). Adding reperfusion therapy to the adjustment model did not change the odds of death, OR 1.21 (1.11 – 1.32). Stratifying the cohort into four age-groups revealed increased mortality with increasing age as well as higher mortality in women than in men in all groups. The multivariable adjusted risk in women relative to men was highest amongst the youngest, OR 1.45 (95% CI 0.98 – 2.14). The long term prognosis was assessed in women vs. men with Cox proportional regression analyses, follow-up time 1 to 13 years. Women had 8% lower risk of long term mortality after multivariable adjustments, and after age-stratifying, women had better long term survival in all age-groups, except the youngest.

Previous studies based on mixed MI cohorts had found a gender-age interaction with higher risk of death women relative to men in the youngest group. In **Paper II** we included all STEMI patients <46 years old registered in RIKS-HIA between 1st Jan 1995 and 31st Dec 2006, 1748 men and 384 women. Cardiovascular risk factors were common, and women had more often clustering of risk factors compared to men. The most prevalent risk factor was smoking, 64% of the women compared to 58% of the men were current smokers. There was no gender difference in delay times or in rate of reperfusion. Almost 60% of both women and men underwent coronary angiography within one week. There was no gender difference in prevalence of non-obstructive disease, (p=0.64), but men had had multi-vessel/left main disease much more often than women (33.6% vs. 19.2%; p<0.001). In-hospital mortality was low, 3% in women vs. 1% in men, crude OR women vs. men 2.83 (95% CI 1.32 – 6.03). Female gender appeared as an independent predictor in the multivariable model of in-hospital mortality, OR 2.85 (95% CI 1.31– 6.19). When the cohort was followed up to 10 years (mean 5.4 years) the risk of mortality was not higher in women (hazard ratio [HR] 0.93, 95% CI 0.60 – 1.45; p=0.75), and men had significantly higher risk of a second new MI during the following 10 years, HR 1.82 (95% CI 1.25 – 2.65; p=0.002).

In the beginning of the 21st century there was a shift in reperfusion strategy with a decline in use of fibrinolytic therapy and an increase in use of primary PCI. We hypothesised that the gender differences noticed during the fibrinolytic era with lower chance of receiving reperfusion therapy and higher risk of early mortality in women, would have diminished during the new primary PCI era, as this is a better reperfusion strategy, especially for women. In **Paper III** we included STEMI patients from two time periods with different dominating reperfusion strategies in order to compare management and outcome between genders in both periods. Patients in the early period (n=15 697, 35% women) were registered in RIKS-HIA between 1st Jan 1998 and 31st Dec 2000 and those in the late period (n=14 380, 35% women) between 1st Jan 2004 and 31st Dec 2006. Among patients treated with reperfusion therapy 9% in the early compared to 68% in the late period were treated with primary PCI. The use of reperfusion therapy increased between the two periods, in men from 70.9% to 75.3%, in women from 63.1% to 63.6%. After multivariable adjustment, women were 14% and 20% less likely than men to receive reperfusion therapy, early and late periods, respectively. Heart failure, cardiogenic chock and major bleedings were more common in women compared to men. Evidence-based secondary preventive therapies were prescribed more often in the late compared to the early period in both genders, but more seldom to women in both periods. After multivariable adjustments women still had less chance of receiving ACE-inhibitors/ARBs but higher chance of receiving statins in the early period. In the late period women had 14 – 25% less chance of receiving any of the evidence-based secondary preventive therapies.

In **Paper IV** all consecutive patients who fulfilled the criteria for ST-elevation or bundle branch block on admission ECG and who were planned to undergo immediate coronary angiography with the intention to perform primary PCI at the Department of Cardiology in Linköping were included, 98 women and 176 men. Estimated glomerular filtration rate [eGFR] according to Modification of Diet in Renal Disease study [MDRD]

was calculated for all patients and they were staged into CKD stages 1-5. Estimated GFR was lower in women than in men, mean eGFR 54 vs. 68 mL/min/1.73m^2, p<0.001. Ten men but no woman were classified belonging to the best CKD stage 1(eGFR >90 mL/min/1.73m^2). In total 67% of women compared to 27% of men were classified as having renal insufficiency [RI] (eGFR <60 mL/min/1.73m^2) and female sex was a strong independent factor associated with RI, OR 5.06 (95% CI 2.66 – 9.59). Reduced eGFR per 10 mL/min decline was independently associated to higher risk of death and MACE (death, new MI or stroke) within one year in women whereas we found no such associations in men. There was a borderline significant interaction between gender and eGFR regarding one year mortality (p=0.08) but not regarding MACE (p=0.11).

As we found a remarkable gender difference in RI prevalence in Paper IV, we analysed an updated SWEDEHEART database including the years since S-creatinine became a mandatory variable to register. In **Paper V** all STEMI patients registered between 1st of Jan 2003 and 31st of Dec 2009 were included, in total 37 991 patients (36% women). RI was present in 38% in women vs. 19% in men according to MDRD and in 50% of men vs. 22% of men according to Cockcroft Gault [CG] (p<0.001 for both comparisons). Female gender was independently associated with RI regardless of used formula. In both genders, RI patients were older, had higher co-morbidity, suffered from more complications and had lower chance of receiving reperfusion therapy and evidence-based therapy at discharge compared to non RI patients. Among both RI and non RI patients, men had significantly higher chance than women of getting these therapies. In-hospital mortality was four to five times higher in RI vs. non RI patients. RI compared to non RI patients had approximately doubled risk of in-hospital mortality in women and 2.5 times higher risk in men after multivariable adjustment. Regardless of used formula, the risk of dying at hospital increased with approximately 30% and the risk of long term mortality with approximately 10% in both genders per 10 mL/min decline of eGFR. There was no significant interaction between gender and eGFR regarding short- or long term outcome according to any of the formulas. Women had twice as high in-hospital and also higher cumulative long term mortality than men. After multivariable adjustments including all confounders except kidney function women had 7% lower risk of long term mortality but still 11% higher risk of in-hospital mortality. If eGFR according to any of the formulas was also included, there was no longer a gender difference regarding in-hospital mortality and women had lower risk of long term mortality. This was also the case if only adjusting for eGFR according to CG.

Conclusion: In the real life STEMI setting, women were older with higher co-morbidity, longer delay, more complications and twice as high in-hospital mortality. They had significantly less chance of receiving acute reperfusion therapy, also after adjusting for possible confounders. During the fibrinolytic era women had higher risk of severe bleedings. We hypothesised that the gap in management would have decreased during the new primary PCI era, with a less time-dependent regime with less risk of fatal complications. Our hypothesis failed, and future studies ought to further scrutinise this gender difference in management. The less chance of reperfusion therapy did anyhow not explain the higher in-hospital mortality in women, which was 10-20% higher after multivariable adjustments, consistent with previous findings. Moderate to severe chronic kidney disease was very common in women with STEMI, 50% according to the Cockcroft Gault formula. Estimated GFR has seldom been taken into account in studies evaluating gender differences in outcome. If adjustment for eGFR was done, alone or added to the all other co-variates, women had no longer higher risk of in-hospital mortality. Adjusted long term outcome was better in women than in men, which was also the case in the youngest cohort when studied separately.

List of publications

Paper I.
Sederholm Lawesson S, Alfredsson J, Fredrikson M, Swahn E
A gender perspective on short- and long term mortality in ST-elevation myocardial infarction – a report from the SWEDEHEART register
Submitted

Paper II.
Lawesson SS, Stenestrand U, Lagerqvist B, Wallentin L, Swahn E
Gender perspective on risk factors, coronary lesions and long-term outcome in young patients with ST-elevation myocardial infarction
Heart. 2010 Mar;96(6):453-9.

Paper III.
Sederholm Lawesson S, Alfredsson J, Fredrikson M, Swahn E
Time trends in STEMI - improved treatment and outcome but still a gender gap
A prospective, observational cohort study from the SWEDEHEART register
Submitted

Paper IV.
Sederholm Lawesson S, Tödt T, Alfredsson J, Janzon M, Stenestrand U, Swahn E
Gender difference in prevalence and prognostic impact of renal insufficiency in patients with ST-elevation myocardial infarction treated with primary percutaneous coronary intervention
Heart. 2011 Feb;97(4):308-14.

Paper V.
Sederholm Lawesson S, Alfredsson J, Szummer K, Fredrikson M, Swahn E
Prevalence and prognostic impact of renal insufficiency in STEMI from a gender perspective - data from a large prospective cohort
Submitted

Abbreviations

ACC	American College of Cardiology
ACE	Angiotensin Converting Enzyme
ACS	Acute Coronary Syndrome
AHA	American Heart Association
ARB	Angiotensin Receptor Blocker
BMI	Body Mass Index
BSA	Body Surface Area
CAD	Coronary Artery Disease
CCB	Calcium Channel Blocker
CCS	Canadian Cardiovascular Society class
CCU	Coronary Care Unit
CHF	Congestive Heart Failure
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CrCl	Creatinine Clearance
CRP	C-Reactive Protein
CVD	Cardiovascular Disease
CG	Cockcroft Gault
DAT	Dual Antiplatelet Therapy
DM	Diabetes Mellitus
ECG	ElectroCardioGram
eGFR	estimated Glomerular Filtration Rate
EACT	European Association for Cardio-Thoracic Surgery
EF	Ejection Fraction
ESC	European Society of Cardiology
ESRD	End-Stage Renal Disease
EBM	Evidence-Based Medicine
GFR	Glomerular Filtration Rate
GP IIb/IIIa	GlycoProtein IIb/IIIa
HDL	High Density Lipoprotein
HF	Heart Failure
HR	Hazard Ratio
IHD	Ischemic Heart Disease
IQR	InterQuartile Range
LDL	Low Density Lipoprotein
LM	Left Main
LMWH	Low Molecular Weight Heparin
MDRD	Modification of Diet in Renal Disease
MI	Myocardial Infarction
NKF K/DOQI	National Kidney Foundation Kidney/Disease Outcome Quality Initiative
NSTE ACS	Non ST-Elevation Acute Coronary Syndrome
NSTEMI	Non ST-Elevation Myocardial Infarction
OR	Odds Ratio
PAD	Peripheral Artery Disease
PAR	Population Attributable Risk
PCI	Percutaneous Coronary Intervention
RCT	Randomised Controlled Trial
RAAS	Renin-Angiotensin-Aldosterone System
RIKS-HIA	Register of Information and Knowledge about Swedish Heart Intensive care Admissions
RR	Relative Risk
SEPHIA	the National Registry of Secondary Prevention
SCAAR	the Swedish Coronary Angiography and Angioplasty Registry
SCr	Serum Creatinine
STEMI	ST-Elevation Myocardial Infarction
SWEDEHEART	Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies
UAP	Unstable Angina Pectoris
UFH	UnFractionated Heparin

I. Introduction

Cardiovascular diseases are currently the leading cause of death in industrialized countries[1] and were the cause of death in 41% of women and 39% of men in Sweden 2010.[2] Ischemic heart disease [IHD] is the most prevalent manifestation of these including silent ischemia, stable angina pectoris and acute coronary syndromes, ACS.[2] IHD is caused by atherosclerosis affecting the coronary arteries. In stable angina, blood and oxygen supply to the myocardial tissue is diminished because of obstructive atherosclerosis and ischemia occurs when the demand increases, such as upon exercise. The acute manifestation of IHD is ACS, subdivided into sudden cardiac death, non ST-elevation ACS [NSTE ACS] and ST-elevation myocardial infarction [STEMI]. The non ST-elevation acute coronary syndrome is further subdivided into non ST-elevation myocardial infarction [NSTEMI] and unstable angina [UAP].

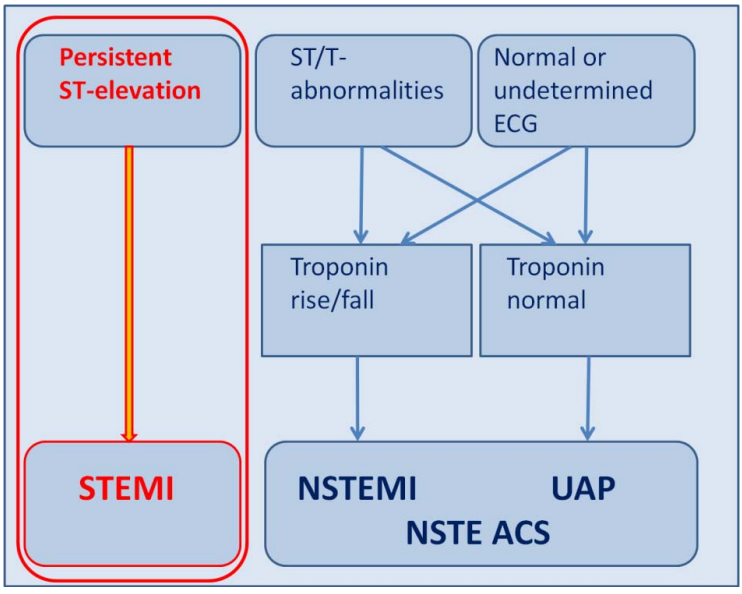
The leading symptom that initiates the diagnostic and therapeutic cascade is chest pain, but the classification of patients is based on the electrocardiogram [ECG]. The chest pain patients can be subdivided from the ECG in two main categories:[3, 4]

1. Patients with acute chest pain and persistent (>20 min) ST-segment elevation. This is termed ST-elevation ACS and generally reflects an acute total coronary occlusion. Most of these patients will ultimately develop STEMI.

2. Patients with acute chest pain without persistent ST-segment elevation. These patients could have persistent or transient ST-segment depression, T-wave inversion, pseudo-normalisation of T-waves or flat T waves but they could also have a normal ECG at presentation. The working diagnosis will be NSTE ACS based on symptoms and ECG. In a certain number of patients, ACS will subsequently be excluded as the cause of symptoms.

This thesis focuses on ST-elevation myocardial infarction, STEMI.

Figure 1. The spectrum of acute coronary syndromes[3, 4]



II. Background

Epidemiology

The incidence of myocardial infarction declines in the Western world as well as the case fatality.[1, 5] In Sweden 42 257 cases of acute MI were diagnosed 1987. Year 2010 this number had declined to 33 712 cases,[5] in spite of new MI diagnostic criteria implemented in 2001[6] with the use of more sensitive cardiac markers, thus identifying a higher number of small MI. In total, the incidence in 2010 was 25 percent lower among both men and women compared to year 2001.[5] The MI incidence is strongly related to sex and age and is the same in women in one age-group as for men five to ten years younger.[5] The MI incidence has been four times higher in men than women under the age of 60 years until the mid-1990[s].[5] This proportion changed the last decade and was year 2010 three to one. In the ages 70-84 years, men have almost twice as high MI incidence.[5]

On average the age standardized MI mortality has decreased with almost five percent per year in the years 1998-2010. Also the case fatality has fallen considerably in the last decades. In 1990, 42% of the men and 46% of the women died within 28 days post MI. By 2010, corresponding numbers were 27% and 31%, men and women respectively.[5]

During the last 16 years, the proportion of STEMI among all MI has diminished from 46% year 1995 to 26% year 2010. One explanation is the use of more sensitive cardiac markers, identifying more patients with very small NSTEMI. Another explanation is better primary and secondary preventive care. In Sweden, during recent years, approximately 5000 patients/year are diagnosed with STEMI.[7] A reduced age-adjusted prevalence of STEMI has also been observed in other countries.[8 9, 10]

Pathogenesis

Atherosclerotic plaque rupture or erosion with thrombus formation and distal embolisation resulting in myocardial ischemia is the basic pathophysiological mechanisms in most conditions of ACS.[11, 12] The evolution of atherosclerotic plaque is a slow process, evolving over years and decades. High levels of lipoproteins in the blood cause LDL particles to accumulate in the extracellular matrix in the artery vessel wall. They become targets for oxidative and enzymatic processes and release phospholipids that activate endothelial cells to express leukocyte adhesion molecules and to release chemokines.[13, 14] Leukocytes adhere to the vessel wall and migrate into the intima. Monocytes differentiate into macrophages that incorporate oxidized LDL with the help of scavenger receptors and transform into foam-cells.[15, 16] In addition T-cells migrate into the vessel wall and recognise local antigens and secrete pro-inflammatory cytokines, contributing to local inflammation and growth of so called atherosclerotic plaques.

The risk of plaque disruption depends on plaque composition and vulnerability (plaque type) and degree of stenosis (plaque size).[17] Around three-quarters of all infarct-related thrombi appear to evolve over plaques causing only mild to moderate stenosis. The proportion of activated T cells is particularly high in culprit lesions causing acute coronary syndromes. Intensified inflammatory activation may lead to local proteolysis, plaque rupture, and thrombus formation, triggering an acute event – the acute coronary syndrome.[11, 18] In most cases, if the thrombus is completely occluding a main coronary artery, a STEMI occurs but if

occlusion is partial or non persistent, NSTE ACS occurs. Concomitant coronary vasoconstriction and microembolisation may be involved to some extent.

Gender difference in pathogenesis

Instead of plaque rupture, endothelial erosion could lead to thrombus formation and ACS in rare cases. This is more common in women than in men, mainly young women.[19, 20] Young women have been found to have ACS without obstructive disease more often than men.[21, 22] A study from the CASS register on young MI patients found non-obstructive disease in one third of women compared to one fifth of men.[21] An Italian multicentre study found similar results with non-obstructive disease in 29% of the women compared to 15% of the men.[22] Thus, especially in young MI cohorts, a higher incidence of non-atherosclerotic causes of MI in women have been discussed [23] such as vasospastic syndromes,[24, 25] coronary artery dissection [26] and hypercoagulable states due to oral contraceptives [27] or hereditary coagulation disorders.[28, 29] Also, there are some conditions unique for the premenopausal women in the peripartum period, such as preeclampsia, eclampsia, gestational diabetes and giving preterm birth, which are all linked to higher risk of cardiovascular diseases.[30, 31]

A gender difference in platelet reactivity was found already more than 30 years ago[32] and this observation has been confirmed in several recent studies.[33-36] In MI survivors women have increased platelet reactivity compared to men.[37] Women have also been found to have microvascular, endothelial and vascular smooth muscle dysfunction [38-40] more often than men, all possible reasons to non-obstructive CAD. Also in fatal cases of IHD, women have more often non-obstructive CAD.[41] In case of STEMI with non-obstructive disease, spontaneous endogenous fibrinolysis or Takutsubo syndrome could be possible explanations. The latter is a relatively newly discovered form of cardiomyopathy predominantly affecting postmenopausal women and can mimic a STEMI.[42, 43] Whether there exists a gender difference in extent of coronary disease in young STEMI patients is not previously studied.

Diagnosis

The diagnosis of MI in clinical practice depends on three cornerstones, symptoms, ECG and measurement of cardiac biomarkers. Since year 2007, myocardial infarction is divided into 5 sub-types where Type 1 is the typical acute coronary syndrome due to plaque rupture and in rare cases endothelial erosion. Type 2 is different as this sub-type is not included in the acute coronary syndromes but is instead due to an imbalance between myocardial oxygen demand and delivery. Type 3 is MI leading to sudden cardiac death, and types 4-5 are periprocedural myocardial infarctions.[44]

Table 1. Myocardial infarction subtypes[44]

Myocardial infarction subtype	Aetiology
Type 1	Due to primary coronary event such as plaque erosion and/or rupture, fissuring or dissection
Type 2	Secondary to ischemia due to either increased oxygen demand or decreased supply, e.g. coronary artery spasm, coronary embolism, anaemia, arrhythmias, hypertension or hypotension.
Type 3	Sudden unexpected cardiac death, including cardiac arrest. Accompanied with myocardial ischemia symptoms and ECG-changes such as new persistent ST elevation or new LBBB and/or evidence of fresh thrombus in a coronary artery by angiography and/or at autopsy.
Type 4a	Myocardial infarction associated with PCI
Type 4b	Myocardial infarction associated with stent thrombosis as documented by angiography or at autopsy
Type 5	Myocardial infarction associated with CABG

STEMI vs. NSTEMI

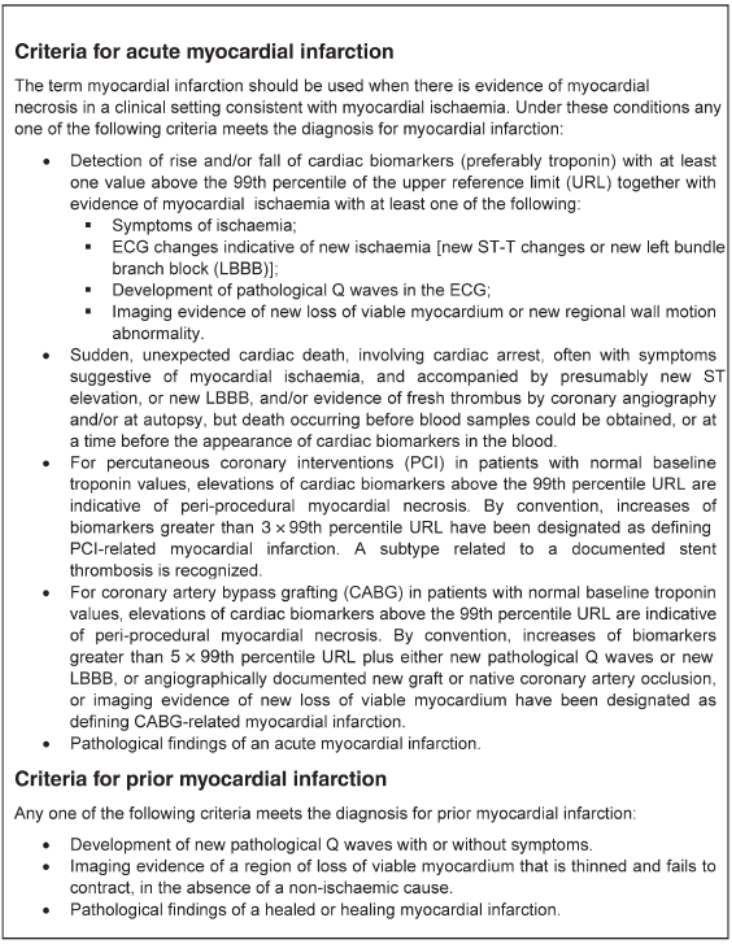
STEMI is suspected in case of typical symptoms (lasting more than 10-20 min not responding fully to nitroglycerine) and significant persistent ST-elevation (V1-V2; 2 mm in men or 1.5 mm in women, all other leads; 1 mm in both genders)[44] or new left bundle branch block [LBBB] on ECG. As rapid reperfusion is the key stone treatment, cardiac biomarkers have no place in the initial diagnosis of STE ACS but a final diagnosis of STEMI is dependent upon cardiac biomarkers (Figure 2).[3]

The clinical presentation of NSTE ACS encompasses a variety of symptoms but prolonged pain is present in 80% of patients and 20% have de novo or accelerate angina. Three clinical presentations can be distinguished:

- Prolonged (at least 20 min) typical chest pain at rest
- New onset of angina (CCS class II-III)
- Recent destabilisation of previously stable angina (CCS class III) or angina post-MI.[4]

The further classification into NSTEMI or UAP is based on the measurement of troponin. If the troponin tests are positive, the patient is classified as having NSTEMI, otherwise the patient is classified as having UAP (UAP patients may have minimally elevated troponins, i.e. under the MI diagnosis level). The diagnostic cut-off for MI is defined as a cardiac troponin measurement exceeding the 99th percentile of a normal reference population (upper reference limit) using an assay with an imprecision (coefficient of variation) of ≤10% at the upper reference limit.[3, 4, 45]

Figure 2. Global criteria for the diagnosis of myocardial infarction[44]



Criteria for acute myocardial infarction

The term myocardial infarction should be used when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischaemia. Under these conditions any one of the following criteria meets the diagnosis for myocardial infarction:

- Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile of the upper reference limit (URL) together with evidence of myocardial ischaemia with at least one of the following:
  - Symptoms of ischaemia;
  - ECG changes indicative of new ischaemia [new ST-T changes or new left bundle branch block (LBBB)];
  - Development of pathological Q waves in the ECG;
  - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
- Sudden, unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischaemia, and accompanied by presumably new ST elevation, or new LBBB, and/or evidence of fresh thrombus by coronary angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood.
- For percutaneous coronary interventions (PCI) in patients with normal baseline troponin values, elevations of cardiac biomarkers above the 99th percentile URL are indicative of peri-procedural myocardial necrosis. By convention, increases of biomarkers greater than 3 × 99th percentile URL have been designated as defining PCI-related myocardial infarction. A subtype related to a documented stent thrombosis is recognized.
- For coronary artery bypass grafting (CABG) in patients with normal baseline troponin values, elevations of cardiac biomarkers above the 99th percentile URL are indicative of peri-procedural myocardial necrosis. By convention, increases of biomarkers greater than 5 × 99th percentile URL plus either new pathological Q waves or new LBBB, or angiographically documented new graft or native coronary artery occlusion, or imaging evidence of new loss of viable myocardium have been designated as defining CABG-related myocardial infarction.
- Pathological findings of an acute myocardial infarction.

Criteria for prior myocardial infarction

Any one of the following criteria meets the diagnosis for prior myocardial infarction:

- Development of new pathological Q waves with or without symptoms.
- Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a non-ischaemic cause.
- Pathological findings of a healed or healing myocardial infarction.

Gender differences in diagnosis

Women are more likely to present with UAP and are less likely to present with MI than men among ACS patients.[46, 47] In the setting of acute MI, women more seldom present with STEMI/Q-wave MI compared to men[47, 48] and also have less marked ST-elevations.[49]

Symptoms and physical findings

In STEMI (and NSTEMI) chest pain or chest discomfort lasting for 10–20 min or more is the typical symptom and is often associated with radiation of pain to the neck, jaw or left arm.[3] Although older studies found absence of chest pain/discomfort one third to on forth of MI patients depending on research methods,[50] recent studies show that 80-90% of both men and women with MI do have chest pain/chest discomfort [51-54] which is the most common MI symptom in both genders.[55] The pain may not be severe and in the elderly other presentations such as fatigue, dyspnoea, faintness or syncope could instead be the major symptom making

the patient to seek medical care.[56] Thus, as among MI patients women are older than men, a clinical presentation without chest pain/discomfort is somewhat more common in women.[50, 54, 57] Also after multivariate adjustments including adjustment for age chest pain/discomfort is somewhat more common in men according to some[58] but not all studies.[54] Women are more likely to report additional symptoms including left arm pain, nausea/vomiting, dizziness, dyspnoea, palpitations and jaw/ back pain and also report a larger number of symptoms according to most studies.[50-52, 55]

Whether there are gender differences in symptoms in pure STEMI cohorts is not well studied, as the mentioned studies included mixed ACS or MI patients.[51-54, 57-59] A small study on 256 ASC patients found similar gender differences in the different ACS diagnostic groups with more indigestion, palpitations, unusual fatigue in women but no difference in rate of chest pain.[60] A very recent prospective study found no gender difference when ECG-confirmed ischemia was provoked by prolonged balloon inflation during elective PCI.[61] Patients with STEMI compared to NSTEMI have been showed having more frequent associated symptoms such as nausea/vomiting, vertigo/near syncope or diaphoresis, and higher intensity of chest pain.[56]

There are no individual physical signs diagnostic of STEMI. Many patients have evidence of autonomic nervous system activation with pallor and profuse sweating. The blood pressure can be high but also hypotension could be evident especially in case of cardiogenic shock. Features may also include bradycardia or tachycardia or signs of acute heart failure such as rales and a third heart sound.[3]

Risk factors

Classical CAD risk factors including gender differences

The classical modifiable CAD risk factors are the same in both genders; diabetes, hypertension, hypercholesterolemia, obesity, physical inactivity, alcohol, diet and psychosocial stress. These have been evaluated both in case-control and prospective observational cohort studies. It is important to differ relative risks [RR] from population attributable risks [PAR]. A very uncommon risk factor (low prevalence) with a strong impact on outcome will lead to a high RR but a low PAR. Vice versa, a very common risk factor (high prevalence) with only a modest impact on the risk of the adverse outcome will lead to a low RR but high PAR.

INTERHEART was a global case-control study of acute MI with cases and controls enrolled 1999-2003. Nine risk factors were shown to account for more than 95% of the PAR in both men and women; high ApoB/ApoA ratio, current smoker, abdominal obesity (high waist to hip ratio), hypertension, diabetes, physical inactivity, no regular use of alcohol, low consumption of fruit and vegetables and psychosocial stress.[62] There were some differences in PAR in the female compared to in the male population. Hypertension, diabetes, alcohol intake and physical activity were more strongly associated with MI in women whereas former smoking was more strongly associated with MI in men than in women. The metabolic syndrome-related risk factors contributed more to the PAR in women than in men (73% vs. 68%). In INTERHEART women experienced their first MI around 9 years later than men all over the world. More than 80% of the earlier age of first MI in men was explained by gender differences in distribution of these nine risk factors.[63]

Prospective cohort studies have also shown gender differences in the impact of CAD risk factors. The Copenhagen City Heart Study studied ten possible CAD risk factors; smoking, hypertension, diabetes, hypercholesterolemia, hypertriglyceridemia, obesity (BMI), no daily alcohol intake, physical inactivity, low or middle income and lower school education. Relative risks and PAR for both genders were presented. After stratifying for sex, diabetes mellitus, smoking, and hypertriglyceridemia were associated with higher RR in women than in men, whereas no daily alcohol intake was associated with a higher RR in men. PAR ranged from 3-22% in men and 3-37% in women, with the highest PAR for smoking and hypertension in both genders. The largest gender difference in PAR were noticed as regards smoking , 22% and 37%, men and women respectively, and for no daily alcohol intake, 12% in men, no contribution in women. Also in the Copenhagen City Heart Study the authors concluded that it is plausible that the gender difference in CAD incidence can be explained by the differences in frequencies and relative risks of these ten classical CAD risk factors.[64]

Kidney function

Reduced kidney function has got increased attention as an important risk factor of developing CAD but also for adverse outcome in case of ACS. According to the National Kidney Foundation Kidney/Disease Outcome Quality Initiative [NKF K/DOQI] chronic kidney diseases [CKD] is defined as kidney damage persisting for $\geq$ 3 months.[65] Patients with reduced kidney function should be staged into five CKD stages based on estimated glomerular filtration rate [eGFR].[65] Patients in stage 1-2 have normal to mildly reduced eGFR in addition to other signs of kidney damage. Patients in stage 3-5 have moderatly or severely reduced eGFR or are in end-stage renal failure [ESRD]. (Table 2) In this thesis, renal insufficiency [RI] is defined as CKD stage 3-5, i.e. eGFR less than 60 mL/min/1.73 m^2.[65]

Kidney function is best evaluated by measuring GFR. This could be done by using an endogenous or exogenous substance that is freely filtrated by the glomerular apparatus, neither actively secreted, nor absorbed. The classical endogenous substance used is creatinine, with measurement of S-creatinine as well as the creatinine concentration in urine sampled during a specified time interval (24 hours), creatinine clearance. Exogenous substances used are inulin, iohexol and Crom-EDTA. The blood concentration of an exogenous substance could be measured with predefined time intervals and the filtration rate could be calculated. Direct measure of GFR is cumbersome and time-dependent and usually not routine praxis in most clinical settings. This is especially not a feasible method in the case of acute STEMI. Instead estimating GFR has become routine praxis. The most commonly used formulas are the Cockcroft Gault [CG][66] and the simplified Modification of Diet in Renal Disease [MDRD][67, 68] formulas. The formulas differ in several aspects. The simplified MDRD equation exists in two forms, depending on the S-creatinine assay used (IDMS-traceable or not), but differ only in the multiplication constant, either 186 (original equation)[67, 68] or 175 (re-expressed equation).[69] The CG formula was developed in the 1970^s from a cohort of 249 men treated for a variety of diseases at medical wards[66] and the MDRD formula was developed in the 1990^s from a cohort of 1628 CKD patients of both genders.[67] MDRD estimates eGFR in mL/min/1.73m^2 whereas CG estimates absolute CrCl in mL/min. To allow comparison of results between people of different sizes, the CrCl is often corrected for the body surface area [BSA] and expressed compared to the average sized man as mL/min/1.73 m^2. While most adults have a BSA that approaches 1.7, extremely obese or slim patients should have their CrCl corrected for their actual BSA.The formulas also differ somewhat in their estimations in populations with varying sex, age and weight[70-72] and are recommended for different purposes, CG for dose adjustments,[73-75] MDRD for detection and classification of

renal dysfunction.[75, 76] CG has been shown to be somewhat more predictive of mortality than MDRD after MI.[77] In spite of that MDRD was developed on both genders but CG in only men, it is has been shown that the relative error (bias) of CG predictions is associated with age and BMI but not with gender whereas MDRD has been found to underestimate GFR in women. Equations for prediction of kidney function include a sex correction factor that compensates for the sex-dependent difference in muscular mass. This difference in muscular mass between men and women was found to be adequately predicted by the CG but overestimated by MDRD.[70]

Table 2. CKD stages according to the National Kidney Foundation. Kidney Disease Outcome Quality Initiative[65]

CKD stage	Estimated GFR	Definition
1	≥90 mL/min/1.73m^2	Normal kidney function*
2	60-89 mL/min/1.73m^2	Mild CKD*
3	30-59 mL/min/1.73m^2	Moderate CKD
4	15-29 mL/min/1.73m^2	Severe CKD
5	Dialysis or <15 mL/min/1.73m^2	ESRD

***In order to be staged into CKD stage 1-2 signs of kidney damage such as albuminuria or pathological imaging is required.**

Patients with ESRD are at high risk for cardiovascular events and over 50% of deaths among these patients are due to cardiovascular events.[78, 79] Two year mortality rate post MI is twice as high in patients with ESRD compared to MI patients without ESRD, approximately 50%.[80] In-hospital mortality ranges from 1-20% with increasing CKD stage from 1 to 5.[79, 81] The last decade also mild to moderate CKD have been proven to be associated with worse prognosis post MI.[82-84] The prevalence of RI has been shown to be much higher among ACS patients than among a normal population of same age. In a mixed MI cohort, 45% patients over 70 years had RI compared to 19-26% in people of the same age in the normal population.[85-88] Several studies have suggested that a cut-off value for eGFR less than 60 mL/min/1.73m^2 is predictive of adverse cardiovascular outcome.[67, 89, 90] As regards STEMI Sadeghi et al. compared RI with non RI patients in the CADILLAC cohort, including primary PCI treated STEMI patients, and found 5.77 and 2.86 higher multivariable adjusted risks of 30 day and one year mortality, respectively, in RI compared to non RI patients.[91] Even higher eGFR cut-off levels have been found associated with an increased risk of adverse post-MI outcome. In a study based on the VALIANT cohort the risk of death and nonfatal cardiovascular complications increased already below the level of 81 mL/min/1.73 m^2.[82] The multivariate adjusted increased risk per 10 mL/min/1.73 m^2 of eGFR decline was 19% regarding early mortality and 16% regarding late mortality in a study by Gibson et al.[92]

There are many possible explanations to why reduced kidney function is associated with an increase cardiovascular risk. Firstly, the conditions CAD and CKD have several common risk factors such as hypertension, diabetes and age. It is previously shown that there is a stepwise increase in these co-morbidities and other cardiovascular risk factors among patients with increasing CKD stage.[92] Secondly, some of the factors associated with renal dysfunction are also associated with endothelial dysfunction and accelerated atherosclerosis such as anaemia, oxidative stress, and derangements in calcium–phosphate homeostasis, inflammation and pro-coagulant conditions.[93] Thirdly, in case of ACS, several studies have found less active management of CKD patients that could also contribute to their worse prognosis [94-96] as well as more adverse drug reactions and complications including increased bleeding risks but also

thrombotic complications.[82, 97]

Figure 3. Cockcroft Gault and (Simplified) Modification of Diet in Renal Disease formulas[66-69]

GFR estimated according to MDRD in mL/min/1.73 m² = 186 * (serum creatinine/88.4 [in µmol/L])$^{-1.154}$ * age [in years])$^{-0.203}$ If women multiply the equation with 0.742.
(The multiplication constant 186 is replaced by 175 if IDMS-traceable serum creatinine is used)

CrCl according to CG in mL/min = ((140 - age [in years]) * weight [in kilogram])/(serum creatinine [in µmol/L]) * (88.4/72) If women multiply the equation with 0.85

Gender differences in kidney function

It is evident from most of the mentioned studies that with higher CKD stage, the proportion of women increases.[81, 82, 94, 97, 98] Women are 5-10 years older than men in MI cohort which is an important explanation to the gender difference in CKD prevalence among MI patients.[81, 99] Another explanation is the higher proportion of women with risk factors associated with worse kidney function such as diabetes and hypertension. Female gender has been found to be associated with worse renal function in MI patients with heart failure[82] and in NSTE ACS patients.[92] Anyhow, it is not clear if female gender is independently associated with RI in case of STEMI. It is also not known whether there is a gender difference in prognostic impact of CKD as is the case for smoking and diabetes. According to a relatively small single-centre study on a mixed PCI cohort, there is a stronger association between increased CKD stage and adverse long term outcome in women than in men.[100] This is not studied in the setting of STEMI.

Treatment

Acute reperfusion therapy

Time-to-treatment

As ST-elevation implicates a complete occlusion of a main coronary artery, acute reperfusion therapy is the corner stone treatment in STEMI management. There is clear evidence from the thrombolytic era that this treatment should be started as soon as possible, at the latest 120 min from first medical contact, preferably within 60 min.[101] In a meta-analysis by Boersma et al, the proportional mortality reduction was significantly higher in patients treated within 2 hours compared to those treated later (44% vs. 20%).[101] Myocardial necrosis can be totally prevented if reperfusion is achieved very early as an occlusion persisting for 15–30 min generally does not lead to significant myocardial damage.[102] After 30-45 min of occlusion, necrosis usually occurs in the sub-endocardial myocardium.[102] Longer durations of coronary occlusion result in a wave-front of necrosis moving towards the epicardium and at 90 min of occlusion the extent of cell death involves approximately half of the transmural thickness.[102, 103] Six hours after the onset of continuous ischemia the area at risk is completely infarcted and the damage is transmural. Thus myocardial salvage upon reperfusion after this time point will be minimal. Anyhow, collaterals could be recruited and the thrombotic response to plaque rupture is dynamic. Thrombosis and lysis of the thrombosis occur simultaneously and in 25-30% of STEMI patients planned for primary PCI there is patency of the infarct-related artery.[104] Thus, in these patients, it is presumed that spontaneous endogenous lysis has

occurred. Persistent although reduced flow in the affected artery extends the time window for achieving myocardial salvage.

From the current primary PCI era, randomised studies and observational studies based on registers have indicated that long delay times to primary PCI are associated with a worse clinical outcome. Reperfusion treatment with primary PCI could not be started as quickly as fibrinolysis as the later can be given already in the ambulance and the former have to be performed at a cath lab. The PCI-related delay time is thus the difference between symptom-to-balloon time and symptom-to-needle time. Up to date, no specifically designed study has addressed the issue to which extent the PCI-related time delay diminishes the advantages of PCI over fibrinolysis, we do not have a clear answer what PCI-related delay time could be acceptable. From randomised control trial post hoc analyses it has been calculated that depending on the fibrinolytic used, PCI-related delay times of 60-120 min still favours primary PCI over fibrinolytic therapy.[105 106 107]

Gender differences in delay-times

Delay times in MI can be divided into three phases, 1) the patient decision phase, 2) the transportation phase and 3) the hospital phase.[108] The summary of phase 1 and 2 is often referred to as symptom-to-door time. In STEMI the hospital phase is referred to as door-to-needle time if in-hospital fibrinolytic therapy is used and door-to-balloon time if primary PCI is used. The most important reason for long patient delay time is incorrect interpretation of symptoms.[109 110 111] Other determinates to increased delay are expectations that the pain will disappear, not taking the symptoms seriously, unwillingness to worry the family and, first contacting the GP.[109 112] According to many studies, women have longer delay times compared to men, especially symptom-to-door time,[113] while others have not found such difference.[114 115 116] A Swedish study based on the MONICA register found gender differences in delay times only among older but not in younger patients[52] which also was found in a French register.[117] Both these studies contained mixed MI patients, and did not separate STEMI from NSTEMI.

Based on the American ARIC study, McGinn and colleagues described trends in patient delay.[118] They only found small changes in delay time over the period 1997 until 2000 despite considerable public and media attention with the National Heart Attack Alert Program. Certain subgroups with longer delay times were identified, among those women. These findings are consistent with the Swedish MONICA study where no trends in change of delay were seen in either men or women.[52] Other subgroups with longer delay times are patients with diabetes, elderly and certain ethnic groups.[119 118 113 120]

Reperfusion strategies

Two reperfusion strategies exist, primary PCI and fibrinolytic therapy.[3] Randomised clinical trials comparing timely performed primary PCI with in-hospital fibrinolysis in high-volume, experienced centres have shown more effective restoration of patency, less re-occlusion, improved left ventricular function and better clinical outcome with primary PCI.[121] Thus, if it is possible to transfer the patients to a cath lab within 120 min, primary PCI is recommended by the ESC guidelines as the first line therapy for STEMI. If the area at risk is big and the time from first medical contact [FMC] is less than 2 hours, the symptom-to-balloon time should be even shorter, <90 min. For patients with the clinical presentation of STEMI within 12 hours after symptom onset with persistent ST-elevation or new LBBB, reperfusion therapy

should be given.[3] There is also a general agreement to consider primary PCI even if more than 12 hours have past since symptom onset, if there is clinical evidence of on-going ischemia.[3] After 24 hours, the evidence is less clear that it is of gain instead of harm to open up the occluded artery. In the OAT trial PCI was performed 2-28 days after symptom onset. Opening up the occluded infarct-related arteries did not improve outcome, not even in the subgroup treated between 24-72 hours after symptom onset.[122, 123]

Fibrinolytic therapy is still an important reperfusion strategy where PCI facilities are not available or the transfer times are too long. The benefit of fibrinolysis is well established with approximately 30 early deaths prevented per 1000 patients treated.[124] Fibrin-specific agents have been proven superior of streptokinase.[125] Pre-hospital admission is proven to be superior of hospital admission with 17% relative risk reduction,[126] and the therapy should be given as fast as possible, preferably within 2 hours from symptom onset.[101] More recent studies have also confirmed the usefulness of pre-hospital fibrinolytic therapy with outcome data similar to primary PCI trials[127, 128] but the strategies has not been compared prospectively in early presenters in an adequately sized randomised clinical trial. Previous haemorrhagic stroke, bleeding disorders, recent ischemic stroke/trauma/surgery/head injury/GI bleeding, non-compressible punctures or presence of aortic dissection are the absolute contraindications of fibrinolytic therapy.[3]

Gender differences in reperfusion strategy

A review of the larger placebo-controlled trials of fibrinolytic therapy showed that the relative benefit of fibrinolytic treatment among STEMI patients is irrespective of gender.[124] The largest absolute benefit is found in high risk patients, and mortality reduction has also been found in the oldest subgroup.[129] Anyhow, an increased bleeding risk in women has been found in several STEMI studies from the fibrinolytic era.[47, 130 131 132]

Primary PCI is more effective in securing and maintaining coronary artery patency than fibrinolytic therapy and in addition avoids some of the bleeding risks associated with fibrinolysis. In patients with contraindications to fibrinolytic therapy primary PCI can be performed with success[133] and it is also the preferred treatment for patients in cardiogenic shock.[134] Women with MI are older with more co-morbidity and higher risk of mechanical complications as well as bleeding. In case of STEMI, the incidence of heart failure and cardiogenic shock is also higher in women than in men.[47, 48]

Since women with STEMI have a more severe risk profile than men, a similar relative risk reduction with primary PCI would translate to a larger absolute benefit. Several studies suggest that women compared with men derive a higher absolute benefit from primary PCI compared with fibrinolytic therapy.[135 136 137 138] The GUSTO II-B PTCA sub-study comparing primary PCI vs. fibrinolytic therapy found no interaction between gender and treatment effect as regards outcome, but as the absolute benefit in women was higher, more major events were prevented in women than in men (56 vs. 42 events per 1000).[136] According to one study, myocardial salvage after primary PCI was actually greater in women than in men. Scintigraphy was performed close to the primary PCI and at follow-up 7-10 days after intervention. Initial area at risk did not differ between the genders but the salvage index was 64% in women compared to 50% in men in spite of longer delay times in women.[135] Anyhow, as this is a single study, it has to be interpreted with caution until further studies have either confirmed or rejected these results.

A recent Dutch single-centre study on almost 3300 STEMI patients all treated with primary PCI and without any other gender differences in management, found no gender difference in crude mortality rates in 30 days (8.1% vs. 9.2%, men and women respectively) or in one year (10.5% vs. 12.2%, men and women respectively) in spite of longer delay, higher age and more severe risk profile in women. The authors concluded that their study probably reflected an increased awareness of potential treatment biases towards women, and thus an increased adherence to treatment guidelines resulting in better outcome.[139]

Thus there are several are rationales, including the longer patient delay time in women, to why the shift from fibrinolytic therapy to primary PCI might be even more advantageous in women than in men. Previous studies from the fibrinolytic era have found a lower rate of reperfusion therapy in women. Whether this is also true in Sweden is not known. Neither is it known whether the shift from fibrinolysis to primary PCI as reperfusion strategy has resulted in diminished gender gaps in management, particularly regarding rate of reperfusion therapy.

Anti-platelet therapy

Acetyl salicylic acid

Acetyl salisylic acid [ASA] acts mainly by irreversible inactivation of cyclooxygenase-1 [COX-1], thereby inhibiting platelet thromboxane A2 [TXA_2] synthesis and subsequent TXA_2-mediated platelet aggregation. The effect persists for the lifetime of the platelet. Upon suspicion of STEMI, ASA should be given as soon as possible if there are no contraindications, i.e. hypersensitivity, active gastrointestinal bleeding, known clotting disorders, or severe hepatic disease. According to the ESC guidelines, ASA should be started at a dose of 150–325 mg orally. The maintenance dose is thereafter 75–160 mg daily for life.[3]

In vitro data have found greater inhibition of platelet aggregation in men than in women[140] and female gender has been associated with higher platelet reactivity in ASA-treated CAD patients.[33] Incomplete ASA-mediated inhibition of TXA_2 mediates an increased risk of serious cardiovascular events shown in sub-studies from CHARISMA and HOPE[141, 142] and female gender was an independent predictor of reduced TXA_2 inhibition.[142]

As secondary prevention ASA therapy reduces the risk of serious vascular events by about a quarter, and the effect is well confirmed in both genders.[143, 144] The benefit of ASA in case of STEMI was proven in the ISIS-2 trial[145] where a 23% highly significant relative reduction in 5-week vascular mortality was found. In contrast, the significance of ASA as primary prevention has been debated after the Women's Health Study as only a reduction in stroke but not in MI/total cardiovascular risk was observed[146] which was the opposite of previous results on men.[147-150] In the latest meta-analysis on this topic, primary prevention with ASA was questioned in both genders as the current totality of evidence provides only modest support for a benefit in patients without cardiovascular disease, which is offset by its bleeding risk.[151]

Clopidogrel

Thienopyridins are irreversible inhibitors of the platelet adenosine diphosphate [ADP] $P2Y_{12}$-receptor. Clopidogrel is a second generation thienopyridine and inhibits binding of ADP to its platelet receptor and subsequent ADP-mediated activation of the glycoprotein IIb/IIIa complex required for platelet aggregation. Clopidogrel is a prodrug that needs oxidation by hepatic CYP-enzymes and subsequent hydrolysis to produce the active metabolite.

Pharmacokinetic studies have revealed no gender differences in plasma levels of the active metabolite.[152] Variability with regard to inhibition of platelet aggregation in clopidogrel treated subjects is today well recognized[153, 154] and no/low responders are at higher risk of new ischemic events.[155 154] Carriers of the loss-of-function variant allele on the CYP2C19 hepatic enzyme, mainly responsible for the prodrug conversion, have reduced clopidogrel-induced platelet inhibition[156] and are associated with an increased risk of ischemic events.[157 158]

The addition of clopidogrel on top of ASA in STEMI patients treated with fibrinolysis was assessed in the CLARITY-TIMI 28 trial. Women comprised only 20% of the study population. A 36% reduction in the composite endpoint (death, MI, stroke) was observed overall, with similar reduction for men and women.[159] In the PCI-treated subgroup (PCI-CLARITY) the relative risk reduction was higher in women than in men (59% compared to 41%).[160] In COMMIT (27.8% women) patients with suspected acute MI were treated with dual antiplatelet therapy including clopidogrel compared to ASA alone. Half of the patients underwent treatment with fibrinolysis; no one was treated with primary PCI. The absolute risk reduction for the composite endpoint (death, MI, stroke at 28 days) was the same in women and in men (0.7% vs. 0.9%) but did not reach statistical significance in women.[161]

A meta-analysis of all the most important randomised clinical trials on clopidogrel (CURE[162 163], CREDO[164], CLARITY-TIMI 28[159], COMMIT[161] and CHARISMA[165]) focused on the gender aspect.[166] Overall, clopidogrel was associated with a highly significant 14% proportional reduction in the composite endpoint (cardiovascular death, MI, or stroke) with no significant gender difference in treatment effect. In women, the overall effect of clopidogrel was driven by a reduction of MI whereas in men the effects of clopidogrel on MI, stroke, and all-cause mortality were separately significant. Clopidogrel increased the risk of major bleeding in both genders, OR 1.43 (95% CI: 1.15-1.79) in women and OR 1.22 (95% CI: 1.05-1.42) in men.[166]

Clopidogrel on top of ASA in STEMI patients planned for/treated with primary PCI has not been prospectively evaluated in a randomised controlled trial. However as the evidence for clopidogrel as adjunctive antiplatelet therapy on top on aspirin in patients treated with PCI is solid [167, 168] the ESC/EACT revascularisation guidelines recommend clopidogrel as soon as possible to all STEMI patients planned for primary PCI, but with a class I C recommendation. The loading dose should be at least 300 mg, but 600 mg gives a more rapid and stronger platelet inhibition. The recommended maintenance dose is thereafter 75 mg daily for 12 months.[45]

Prasugrel

Prasugrel is a third generation thienopyridine with a more favourable metabolic conversion compared to clopidogrel, and thus higher concentrations of the active metabolite and more potent inhibition of the platelet $P2Y_{12}$-receptor. Function CYP genetic variants does not seem to affect active metabolite levels, platelet inhibition or cardiovascular outcome in prasugrel treated patients.[169, 170] Prasugrel was tested against clopidogrel in ACS (NSTE ACS and STEMI) patients in the TRITON TIMI 38 trial, 26% were women.[171, 172] Therapy was started after diagnostic angiography in patients planned for PCI. Prasugrel was proved beneficial with respect to a combined ischemic endpoint. Severe bleeding complications increased with prasugrel use, specifically in patients with a history of stroke/TIA, in patients $\geq$75 years and in patients with body weight <60 kg.[171, 173] The relative risk reduction of the primary endpoint

was 19% (21% in men, 12% in women). Statistical significance was not obtained in women but no significant interactions between patient characteristics and treatment effect were found. In the STEMI subgroup (23% women) prasugrel was found superior to clopidogrel in reducing the combined ischemic endpoints as well as stent thrombosis without increasing the risk of severe bleeding.[174] No gender specific data were presented in this study. In the 2010 ESC/EACT revascularisation guidelines Prasugrel (60 mg loading dose, 10 mg maintenance dose) was given a class I B recommendation in STEMI patients treated with primary PCI. Prasugrel has not been evaluated in conjunction with fibrinolysis.[45]

Ticagrelor

Ticagrelor is a non-thienopyridine oral direct-acting $P2Y_{12}$-receptor receptor blocker inhibiting platelet function. It provides faster, greater and more consistent $P2Y_{12}$-receptor receptor blocking as compared to clopidogrel.[175] It has been compared with clopidogrel in the PLATO trial including STEMI patients intended for primary PCI as well as NSTE ACS patients intended for either invasive or medical approach.[176] A significant 16% relative reduction of the combined ischemic endpoints (cardiovascular death, MI or stroke) was found in favour of ticagrelor. Compared with men, women showed similar absolute (2.0% vs. 1.9%) and relative (17% vs. 15%) reduction of the primary endpoint within the ticagrelor arm, and similar effects were also seen in terms of major bleedings. A predefined subgroup analysis demonstrated that STEMI or NSTE ACS patients referred for PCI (25% women) significantly benefited from ticagrelor vs. clopidogrel, with similar bleeding rates.[177] In the 2010 ESC/EACT revascularisation guidelines ticagrelor (180 mg loading dose, 90 mg twice daily maintenance dose) was given a class I B recommendation in STEMI patients treated with primary PCI. Ticagrelor has not been evaluated in conjunction with fibrinolysis.[45]

GPIIb/IIIa antagonists

The glycoprotein [GP] IIb/IIIa antagonists block the final common pathway leading to platelet aggregation by inhibiting fibrinogen binding to its platelet. Most STEMI studies on GPIIb/IIIa antagonists have used abciximab. Abciximab is an antibody with irreversible platelet inhibition, whereas tirofiban and eptifibatide are small molecules with reversible platelet inhibition and thus fast recovery of platelet function after treatment discharge.
A systematic review of the randomised clinical trials using abciximab in STEMI including primary PCI studies[178-182] as well as fibrinolytic studies[183-185] showed a 32% relative risk reduction in 30 day mortality in the primary PCI subgroup, but no reduction of mortality in the fibrinolytic subgroup.[186] A later meta-analysis on primary PCI treated STEMI patients (including the BRAVE-3[187] and HORIZONS-AMI[188] trials, where no benefits of adjunctive GPIIb/IIIa antagonists on top of clopidogrel administration were found) found no reduction in 30-day mortality or re-infarction but a higher risk of bleeding with GPIIb/IIIa antagonist therapy although a significant relationship between risk profile and benefits of GPIIb/IIIa antagonists was noticed.[189] Upstream vs. cath lab treatment with abciximab was tested in the FINESSE trial without a net clinical benefit.[190] In the On-TIME 2 trail the GPIIb/IIIa antagonist tirofiban was compared to placebo in the prehospital phase on top on ASA, heparin and a 600 mg loading dose with clopidogrel. ST-resolution was improved but there was no significant net clinical benefit compared with placebo.[191]

According to a meta-analysis by Boersma et al, a highly significant interaction with respect to cardiac events was seen between gender and allocated treatment. In men, GPIIb/IIIa antagonists were associated with a 19% odds reduction of 30-day death or MI compared with

placebo or control. On the contrary, women had an increased risk if treated with GPIIb/IIIa antagonists. However, no gender difference in treatment effect was seen in a selected subgroup of patients with raised cardiac troponin concentrations.[192]

Whether the use of GPIIb/IIIa antagonists provides benefits on top on optimal dual antiplatelet therapy including the modern $P2Y_{12}$-receptor blockers prasugrel and ticagrelor has yet to be shown. Also whether bivalirudin combined with the new $P2Y_{12}$-receptor receptor blockers reduces the clinical benefit from adjunctive GPIIb/IIIa antagonists is tested in on-going trials.[193] Current ESC/EACT guidelines recommend GPIIb/IIIa antagonists in STEMI patients treated with primary PCI (with evidence of high intracoronary thrombus burden) as adjunctive to dual antiplatelet therapy with the highest class of recommendation for abciximab (IIa B) and lowest for eptifibatide (IIb B). Upstream therapy is not recommended. Abciximab should be given as i .v. bolus of 0.25 mg/kg followed by 0.125 µg/kg/min infusion for 12 hours. GPIIb/IIIa antagonists are not recommended in combination with fibrinolytic therapy.[3, 45]

Anticoagulants

Unfractionated and low-molecular-weight heparins

Unfractionated heparin [UFH] and low-molecular-weight heparins [LMWH] bind to antithrombin III and enhance inactivation of factors Xa and, to a less extent, thrombin. As compared to UFH, LMWH has a higher anti-factor Xa/IIa ratio, a longer duration of anti-factor Xa-effect and a more predictable dose-response. LMWH do not usually require laboratory monitoring of activity as opposed to UFH where activated partial thromboplastin time [APTT] has to be measured or activated clotting time guidance [ACT] in the setting of PCI.

Women are more likely to achieve higher APTT in response to UFH[194] whereas the pharmacokinetic and –dynamic effects of enoxaparin do not seem to differ between the genders.[195] In ASSENT-3 (23% women) abciximab and enoxaparin was compared to UFH as adjunctive therapy to tenecteplase as regards ischemic events and safety. Whereas the efficacy and combined efficacy+safety endpoints were reached in men, no net clinical benefit was seen in women, neither with enoxaparin, nor with abciximab compared to UFH.[183] In EXTRACT-TIMI 25 enoxaparin vs. UHF were compared in patients treated with fibrinolysis. Women derived a similar relative benefit (16% vs. 19%) and a greater absolute benefit (2.9% vs. 1.9%) than men when treated with enoxaparin.[196]

UFH is the standard anticoagulant therapy during primary PCI but there is a lack of randomised clinical trial comparing UFH and placebo in this setting. This is due to the strong belief that UFH is required during the procedure and such a study will probably never be performed. LMWH have been studied in a limited number of studies in primary PCI treated STEMI patients and is not recommended for use instead of UFH. In the 2010 ESC/EACT revascularisation guidelines UFH has a class I C recommendation in the setting of primary PCI with a start dose of 100 U/kg (60 U/kg if a GPIIb/IIIa antagonist is given) followed by ACT guided therapy during the PCI procedure (200-250 sec if co-treatment with GPIIb/IIIa antagonists, otherwise 250-350 sec). In case of fibrinolytic therapy (fibrin-specific agent), enoxaparin is recommended as adjunctive therapy.[45]

Bivalirudin

Bivalirudin is a direct thrombin inhibitor which blocks the interaction of thrombin to its substrates as well as inhibits thrombin-mediated activation of platelets. In the HORIZONS-AMI trial primary PCI treated STEMI patients received bivalirudin or UFH plus GPIIb/IIIa inhibitors (abciximab or ebtifibatide) on top of ASA and clopidogrel. Primary endpoints were major bleedings and a combined clinical event endpoint (death, re-infarction, target-vessel revascularisation and stroke). The two endpoints were achieved with 24% relative risk reduction as regards the combined adverse clinical event endpoint and 40% relative risk reduction as regards major bleeding.[188] In the three year follow-up results, the main results were still valid, and also a 25% relative risk reduction in all cause mortality was noticed for the bivalirudin group.[197] Seventy-seven % of the patients were male; no gender subgroup analyses were done in the original study or in the one- or three- year follow-up studies.[188, 197, 198] Bivalirudin is recommended (class I B) in the setting of primary PCI, especially in patients with high bleeding risks.[45]

Fondaparinux

Fondaparinux is a synthetic pentasaccharide that selectively binds antithrombin and rapidly inhibits factor Xa. It was compared with UFH or placebo in STEMI patients treated with fibrinolysis, primary PCI or no reperfusion therapy in the OASIS-6 trial.[199] Fondaparinux was inferior to UFH in the setting of primary PCI and is not recommended in these patients, whereas it can be given to STEMI patients not treated with reperfusion therapy.[3, 200 45]

Other adjunctive therapy

Beta-blockers

The use of beta-blockers is mainly based on old trials before the reperfusion era. Those found a 20-25% relative risk reduction of mortality and re-infarctions in MI patients treated with beta-blockers. A meta-analysis based on 82 randomised clinical trials found strong evidence that beta-blockers reduce the risk of mortality and morbidity after STEMI also in patients treated with ACE-inhibition.[201] The use of i.v. beta-blockers in the early phase of STEMI is less established. During the first few hours after STEMI onset, beta-blockers may diminish myocardial oxygen demand by reducing heart rate, blood pressure and contractility and prolongation of diastole can augment coronary perfusion. In the ISIS-1 trial MI patients received 5-10 mg of i.v. atenolol followed by 100 mg atenolol orally with reduced 7-day mortality.[202] Also in the TIMI-II trial the risk of re-infarctions and recurrent ischemia was reduced by early i.v. metoprolol in alteplase-treated patients.[203] However, later trials and a meta-analysis have challenged this concept.[201, 204, 205] In the COMMIT CCS 2 trial, i.v. metoprolol followed by oral administration of metoprolol did not improve survival in patients with suspected MI. The risk of re-infarction or ventricular fibrillation was diminished but the risk of cardiogenic shock was increased.[205] Randomised trials of beta-blocker therapy in patients with STEMI undergoing PCI without fibrinolytic therapy have not been performed.

Gender differences in pharmacokinetic properties have been described for beta-blockers.[152] Men have a greater activity of the CYP2D6 enzyme that is responsible for the metabolism of metoprolol, and thus a faster clearance.[206] This, together with the lower weight-adjusted distribution volume in women, leads to higher concentrations in women if the same doses are used as in men.[207] Major clinical endpoint studies of beta-blocker therapy after MI have found

contradictory findings with respect to gender.[152] However, too few women have been included to enable significant findings.[208, 209] A meta-analysis investigating effects of metoprolol on mortality after MI revealed a reduction in cardiovascular deaths comparable in both genders.[210] The more recent heart failure beta-blocker trials have found more favourable prognosis in men than in women upon beta-blocker therapy, but include considerable fewer women than men.[211-214] In both MERIT-HF[211] and COPERNICUS[213] the mortality reduction for women in the subgroup analysis failed to reach statistical significance but did so in CIBIS II.[214] The reasons could be too few women included, but also that they were older and sicker than their male counterparts. In a meta-analysis incorporating all these three studies, beta-blocker therapy was associated with a significant reduction in mortality also in women.[212]

According to the European guidelines, early use of beta-blockers should only be administrated in haemodynamically stable patients. The presence of acute heart failure in STEMI should preclude the early use of i.v. beta-blockers but is a strong indication for the oral use as secondary prevention when the patient is stable. Beta-blockers are recommended in all STEMI patients as secondary prevention, especially if the left ventricular function is reduced or if there have been signs of heart failure.[3]

RAAS inhibition

ACE-inhibitors have been proved to attenuate ventricular dilation and improve clinical outcomes among patients with LV dysfunction partly through their ability to interfere with ventricular remodelling after STEMI. A number of large randomised clinical trials have assessed the role of oral ACE-inhibition in the early course of MI, all demonstrating clinical benefits.[215-217] A meta-analysis of the major but also 11 smaller trials enrolling more than 100 000 patients revealed an absolute benefit of 4.6 fewer deaths per 1000 patients treated.[218] As secondary prevention after STEMI, ACE-inhibitors improve long term survival, especially in patients with anterior infarctions, LV-dysfunction or symptoms of heart failure.[219-222 223] Later studies support the more broad use of ACE-inhibitors, after positive results on high-risk patients in the HOPE and EUROPA trials.[224, 225] Thus given these results, ACE inhibitor therapy is recommended for all patients after STEMI in the ESC and ACC/AHA guidelines unless otherwise contraindicated.[3, 75, 226]

The use of ARBs has not been explore as thoroughly as ACE-inhibitors in STEMI although there are data supporting the shift from ACE-inhibitors to ARBs in case of ACE-inhibitor intolerance and signs of heart failure/depressed LV function.[227-230] Aldosterone blockade on top of ACE-inhibition has been shown valuable in MI patients in NYHA class III-IV in the RALES trial (spironolactone) where IHD was the cause of heart failure in 55% of patients.[231] In EPHESUS post-MI patients were included if EF was below 40%. Eplerenone was added to optimal post-infarction therapy and resulted in a reduction in overall and cardiovascular mortality as well as cardiac hospitalisation.[232]

In pre-menopausal women, ACE and renin activity as well as angiotensin II Type-1 receptor expression is lower than in men and post-menopausal women because of negative feedback loops from higher plasma levels of angiotensin II induced by oestrogens. The cardioprotective effect of oestrogens is thought to partly result from this RAAS inhibition.[233 234] The effect of ACE-inhibitors on blood pressure reduction seems to be comparable in both genders[235] whereas women have around two times higher risk of developing cough.[236] Women have been underrepresented in most of the ACE-inhibitor trials and data is thus less well founded for women.[152] Two meta-analyses on patients with chronic heart failure found benefits of ACE-

inhibition therapy for both genders but less for women than for men[237, 238] whereas a meta-analysis on post-MI patients found comparable effects in both genders.[239] Regarding ARB, these are evaluated in patients with heart failure [228, 240, 241] and post-MI.[227, 229] Fewer women than men were included in all these trials.[152] No gender-specific differences in effects have been found.[152] The aldosterone blockage trials RALES and EPHESUS did not shown any gender-specific differences in subgroup analyses.[231, 232]
The use of ACE-inhibitors in all STEMI patients has a class I A recommendation in the ESC guidelines. An ARB can be used instead in case of ACE-inhibitor intolerance. Aldosterone antagonist could be added in case of EF <40% and heart failure.[3]

Nitrates

Nitrates reduce preload and induce vasodilatation especially in the venous system and is effective in reducing symptoms in ACS and in case of pulmonary oedema. Anyhow, a routine use of nitrates has not been shown to reduce mortality or morbidity. In the GISSI-3 trial, ACS patients were treated with transdermal nitrates. No significant reduction in mortality was found.[216] In the ISIS-4 trial, oral nitrates were administrated one month from the acute event started immediately on arrival. No benefit was found.[215] Thus a routine use of nitrates is not recommended in STEMI patients.[3]

Statins

Several randomised clinical trials such as the 4S[242], CARE[243] and LIPID[244] trials have demonstrated benefits of long term use of statins in ACS reducing the risks of mortality and re-infarctions. Later trials have also evaluated early initiation of statins in STEMI, such as the MIRACL[245] trial where the primary endpoint of death, MI, cardiac arrest or recurrent ischemia was reduced from 17.4% to 14.8% after initiation of 80 mg Atorvastatin during the hospital phase. A meta-analysis including 7 trials compared different intensities of statin therapy and found the intensive statin regime to be superior to a more standard lipid-lowering regime with further reduction of re-infarction, stroke and all cause mortality.[246] Thus statins are recommended in all STEMI patients started as soon as possible with recommended targets in total cholesterol of 4 - 4.5 mmol/L and LDL of 2.0 - 2.5 mmol/L.[3]

Most of the statins undergo hepatic metabolism via the CYP-enzymes. In general, only small gender differences in pharmacokinetics have been found although women do have higher plasma concentrations when same dosages are used as in men. The risk of adverse drug reactions is also higher in women, such as myopathy.[152] The major secondary prevention trials have found comparable risk reductions of cardiovascular events in men and women. The percentage of women examined in these studies was however <25%. A meta-analysis revealed same relative risk reduction upon statin therapy in men and in women.[247]

Insulin

Among STEMI patients, 21-23% of women and 13-14% of men have a previous diagnosis of diabetes upon admission.[48, 132, 196] Studies have also found that in MI patients without previously known diabetes, one third has diabetes and one third has disturbed glucose metabolism.[248] The acute phase of STEMI is associated with increased levels of catecholamine, cortisol and glucagon in the blood as well as decreased insulin sensitivity, thus impaired glucose utilisation. High glucose levels are associated with increase mortality rates in STEMI.[249 250] Previous studies found support of strict glycaemia control by use of insulin

infusion in STEMI as well as in other critically ill patients[251, 252] The more recent DIGAMI-2 trial did not find any reduction in mortality in the group treated with infusion compared to standard management, probably reflecting lack of difference in glucose control between the groups.[253] Also the NICE-SUGAR trail on intensive care patients raises uncertainty regarding the optimal glucose level to target. The risk of death was increased in the intensive glucose control treatment group that had significantly more episodes of hypoglycaemia than the conventional glucose control treatment group.[254] Whether these data can be extrapolated to the STEMI group is uncertain as randomised clinical trials evaluating the optimal glucose target in case of STEMI is still lacking.

According to ESC guidelines target glucose levels in the acute phase should be 5-7.8 mmol/L but hypoglycaemia must be avoided. After the acute event, the aim is to achieve HbA1c levels < 6.6%.[3]

Gender differences in management

Several studies during the 1990s found less aggressive management of female than male MI patients.[255-262] Data from the NRMI register found less use of aspirin, heparin and beta-blockers in women compared to men during the hospital phase,[260] similar findings were done recently from a Swiss register [263], from the American Get With the Guidelines-Coronary Artery Register (GWTG-CAD),[264] and from an Italian register.[265] Invasive procedures have also been used less in women in mixed MI cohorts.[9, 263, 264, 266, 267]

More recent studies have also found less active secondary prevention such as use of aspirin, beta-blockers, statins and ACE-inhibitors.[263, 268, 269] but multivariable adjustments have not been done. The gender difference in age in MI cohorts has impact on management, and can thus explain part of the found gender management gap. One study on patients treated with primary PCI found more active management in women in the younger subgroup, and more active management in men in the older subgroup, after stratifying on age.[270]

Almost all of these studies have included both STEMI and NSTE ACS patients.[255-257, 260, 261, 268, 269] Pure STEMI cohorts have most often been extracted from randomised controlled trials, and thus do not represent real life management.[48, 196, 271-273]

During the fibrinolytic era there were several reports on gender differences in rate of reperfusion therapy [274-280] Some studies mixed STEMI and NSTEMI patients[117, 275, 279] which make the results hard to interpret as among MI patients, women have STEMI less often than men.[47, 264, 277] Also several studies have not performed multivariable adjustments regarding this particular endpoint,[263, 281] and thus gender differences in management could be due to confounders, such as higher age and co-morbidities in women.[280, 282] A study from the GRACE register on trends in acute reperfusion therapy concluded that female gender is one out of eight independent factor of not receiving reperfusion therapy among eligible STEMI patients.[283] Vaccarino et al studied difference in management in MI patients between genders but also races from the NRMI register. The chance of receiving reperfusion therapy in eligible patients was highest in white men, followed by white women, black men and finally black women. The differences in management between races were more pronounced than the differences between genders.[267]

Whether gender differences in management affect outcome has been debated for many years. There are studies that claim that at least part of the gender outcome gap is due to less

aggressive therapy in women[284] whereas others have found no or minor such associations.[274] A French study published a couple of year ago used nonparametric microsimulation models on almost 75 000 MI patients (NSTEMI and STEMI not separated) to estimate what the PCI and mortality rates would like be like if women had been "treated like men". The simulation models related 0.46% of the excess adjusted absolute mortality noticed in women to less active management.[285]

Whether there are gender disparities in management in-hospital as well as at discharge in real life STEMI patients after multivariable adjustments, and if this affects outcome, continues to be a matter of debate and has to be more thoroughly evaluated. To our knowledge, there is no comparison between the fibrinolytic era and the new primary PCI era as regards gender differences in management including use of reperfusion therapy in STEMI patients.

Complications

Bleeding

Bleeding complications in the setting of ACS are common because of the use of multiple antiplatelet and anticoagulant therapies combined with reperfusion and revascularisation procedures. Among STEMI patients, 2 - 12% suffers from a major bleeding.[286, 287] Especially fibrinolytic therapy has been associated with major bleeding complications both in randomised clinical trials as well as in registers with intracranial haemorrhage affecting around 1% of treated patients.[288-290] [124] For long time bleeding was seen as the price to pay for an improvement in outcome with the new modern therapy including reperfusion and revascularisation. However, it is now well-known that bleeding has a strong impact on the risk of death and other adverse clinical outcomes in ACS patients.[291, 292] The mechanisms are not totally understood but probably include hemodynamic instability, discontinuation of anti-platelet therapy, stimulation of an inflammatory process and high co-morbidity in bleeding patients. Also transfusions may have deleterious effect on outcome although it is not clear whether the transfusion themselves are harmful or if they are simply markers of increased risk.[293, 294]

It is now recommended that risk stratification for both ischemic and bleeding risk is undertaken in ACS patients. There are difficulties in comparing bleeding rates between studies as several bleeding definitions are used in the literature. The original TIMI criteria [295-297] and GUSTO criteria [125] were initially used to identify bleeding predictors in STEMI patients treated with different thrombolytic therapies. There are also several study-specific definitions of bleeding such used in CURE[162] , ACUITY[298] and REPLACE-2[299]. The Bleeding Academic Research Consortium (BARC), an independent multidisciplinary working group, has recently tried to define a standardized bleeding reporting system for clinical ACS investigators.[300]

Important independent risk factors of bleeding in ACS patients are age, low body weight, renal failure, anaemia, hypertension, bleeding history, invasive procedures, use of GP IIb/IIIa blockers, clopidogrel or fibrin-specific thrombolytic agents.[286, 287] Several ACS studies have found an increased risk of bleeding in women.[132, 301] Weight, haemoglobin level and glomerular filtration rate is lower in women and they are older and more often hypertensive compared to men. Even after multivariable adjustments, female gender has been found to be an independent risk marker for increased bleeding in ACS[286, 287] and female gender is

included in most of the bleeding risk scores.

The increased bleeding risk in women has particularly been found in STEMI studies during the fibrinolytic era.[47, 130-132] but also in PCI studies using abciximab [302] or bivalirudin [303] an increased bleeding risk in women has been found. However, in the REPLACE-2 study there was a similar reduction in the bleeding risk with bivalirudin compared to heparin + GPIIb/IIIa blockers in women (5.9% vs. 3.7%, P =0.04) and in men (3.5% vs. 1.9%, P = .001).[299] Several PCI studies have found increase site-related bleeding in women[304-306] but this has not been the case in some modern studies using radial approach.[307, 308]

Acute heart failure including cardiogenic shock

Signs of heart failure in the setting of STEMI are common and are associated with an adverse prognosis.[222] The cause is most often the myocardial damage but mechanical complications and malignant arrhythmias can also provoke heart failure in STEMI patient. The degree of heart failure may be categorized according to the Killip or the Forrester classification.[3] In case of cardiogenic shock the patient show signs of hypoperfusion because of low cardiac output and simultaneously high LV filling pressure. Cardiogenic shock is mainly associated with extensive LV damage but can also occur in case of right ventricular infarctions or mechanical complications as well. Thus an urgently performed echocardiography should be performed and emergency revascularisation has the potential of being life-saving. Ionotropic drugs should be considered and supportive treatment with intraaortic ballon pump is recommended.[134] The incidence of cardiogenic shock in case of STEMI has diminished during the latest years probably due to better prevention and fast reperfusion,[7] but it is higher in women than in men.[132, 309, 310]

Mechanical complications

In case of transmural MI the myocardium may not tolerate the wall stress and may rupture. Most often, these very dangerous complications does not occur the very first day but during the first week. The rupture affects the dead myocardium and could thus lead to free wall, ventricular septal [VSD] or papillary muscle rupture. In case of free wall rupture heamocardium immediately occurs leading to electromechanical dissociation and death within minutes. In a minority of cases a thrombus seals the lesion and the presentation is more subacute with signs of tamponade. In case of VSD the patient is suddenly severely clinically deteriorated and a load new systolic murmur is evident because of the left-to-right shunt. Papillary muscle rupture presents with acute MR with abrupt elevation of left atrial pressures, secondary pulmonary oedema and RV dysfunction. The treatment of choice for all mechanical complications is trying to stabilise the patient (intraaortic ballon pump, ionotropic drugs etc.) while preparing for acute surgery. There is no consensus about optimal timing for surgery for myocardial infarction VSD.[3] The incidence of mechanical complications has declined in the era of reperfusion therapy. Women are more often affected then men.[311]

Arrhythmias and conduction disturbances

Up to 20% of STEMI patients develop malignant arrhythmias such as sustained ventricular tachycardia [VT] or ventricular fibrillation [VF].[312] It may be the first manifestation of STEMI and cause sudden cardiac death. Use of beta-blockers in the acute phase is proven to reduce the incidence of VF/ sustained VT.[313] Also supraventricular arrhythmias could occur in

case of STEMI. Atrial fibrillation occurs in 10-20% of STEMI patients and an adequate heart rate must then be targeted as well as anticoagulation therapy.[3]

AV block occur in around 7% of STEMI patients.[314] It is usually transient if associated with inferior STEMI. In case of anterior STEMI, the block is often located below the AV node with more unstable ventricular escape rhythms and will most often need pacemaker therapy. A new LBBB usually indicates a STEMI with extensive anterior infarction with high likelihood for developing complete block. A temporary pacing electrode could be necessary.[3] There are gender differences in prevalence of these complications. Whereas ventricular arrhythmias are more common in men, bradycardia and AV block as well as new atrial fibrillation is more common in women.[47, 261, 280]

Outcome

The case fatality in STEMI is highest the first week and after that it successively declines until after 1-2 month when a more stable level of risk is reached.[7] In men and women, the case fatality as well as the long term mortality has declined during the last decades.[315, 316] An American study found significant decrease in age-adjusted mortality rates from STEMI regardless of gender between 1988 and 2004 but women had persistently double mortality rate in comparison to men over the years studied.[315] Short term mortality is higher in STEMI compared to NSTE ACS whereas the long term mortality is equal or even worse in NSTE ACS because these patients are older with higher co-morbidity compared to the STEMI patients.[10, 48, 317] There seems to be an interaction between gender and type of acute coronary syndrome regarding outcome where several studies based on randomised clinical trials and observational register cohorts have reported that the multivariable adjusted mortality is higher in women in STEMI but lower in women or gender equal in the setting of NSTE ACS.[47, 48, 281] Reported case fatality in studies depends on when the study is performed, if STEMI patients are mixed with NSTE ACS patients and if the cohort is extracted from a randomised clinical trial or if it is an observation study with consecutive including of STEMI patients. Most studies on gender differences in prognosis after STEMI have used cohorts from randomised clinical trials.[48, 132, 137, 196, 271-273, 318]

Fibrinolytic era

Short term outcome

The short term mortality after STEMI is about twice as high in women than in men, and range from 4.4-5.8% in men and 9.8-13.2% in women in STEMI studies based on randomised control trails from the fibrinolytic era such the ExTRACT-TIMI 25, ISIS-3, the GUSTO and the ASSENT trials.[48, 132, 196, 272] Case fatality figures from hospital MI registers are often higher as the patients are older and have higher co-morbidity, such as data from the American NRMI register,[281] 7.9% in men vs. 16.0% in women[281] or from a study on consecutive MI patients in 25 Israeli CCUs with predominantly STEMI/Q-wave infarctions, 9.6% vs. 17.6%.[319] Age-adjusted in-hospital mortality in STEMI has declined in both genders during the last decade.[315] More recent hospital STEMI register studies have revealed in-hospital mortality numbers around 5% vs. 10%, men and women respectively, concordant with the randomised clinical fibrinolytic trials.[264, 320] After multivariable adjustments, the risk of dying in the early phase after STEMI has been around 20% higher in women than in men during the fibrinolytic era,[48, 196, 271, 272] but even higher in studies selecting high risk subjects.[321]

Long term outcome

The cumulative one year mortality is around 7% in men and 13% in women in cohorts from randomised clinical trials[132] but much higher in hospital register studies including predominantly STEMI patients, 16% in men and 25% in women.[117] After multivariable adjustments, women have around 10% higher risk of dying within one year.[132]

There is very limited data on gender differences in STEMI prognosis beyond one year after the acute event. Older data, such as from the German MITRA register on STEMI patients registered 1994-1997, found worse 18 month prognosis in women but no gender difference after age-adjustment.[278] During the last decade, some small single centre studies are published; most of them without opportunity to properly adjust for confounders, and their results are conflicting.[320, 322-324] A Norwegian study on 396 women and 1,169 men found 37% increased relative risk in women (median follow-up 501 days) for long term mortality after age-adjustment.[320] In another single centre study, Nicolau et al. studied 686 STEMI patients treated with Streptokinas followed for up to 12 year (median follow-up 5.1 years) with no significant gender difference in long term prognosis after multivariable adjustments (a non-significant 5.5% higher survival rate for men was found).[323] If early deaths were excluded, women fared better than men. In a recent publication D'Ascenzo et al studied gender difference in long term outcome (median follow-up 60 months) in 833 patients treated with PCI. In the STEMI group (59 women and 181 men) women had worse crude long term mortality (20% vs. 7%). According to the authors a higher risk in women also persisted after multivariable adjustments but no hazard ratios were shown.[324]

Primary PCI era

Studies from the new primary PCI era have revealed less gender differences in both short and long term mortality after multivariable adjustments but results are conflicting.[137-139, 265, 301, 310, 318, 325-331] Most of these cohorts have mainly been small, consisting of 1000-2000 patients[137, 138, 318, 325-328, 331] and often single-centre.[138, 139, 265, 326 331] Possible explanations to the contradictory findings could be different selection criteria, differences in outcome definition (total mortality, cardiac mortality, short- or long term outcome) and differences in multivariable adjustments for confounders.

Short term outcome

The vast majority of the studies comparing the short term outcome in genders in STEMI cohorts treated mainly with primary PCI have not found an multivariable adjusted gender difference[137, 139, 265, 301, 318] especially if body surface area has been included in the multivariable adjustment. An increased risk of a small BSA has been recognized in both PCI and CABG revascularisation studies.[332, 333] On the contrary Vakili et al reported higher multivariable adjusted risk of in-hospital mortality in women in 1044 primary PCI treated STEMI patients.[325]

During the last couple of years gender analyses on short term outcome after primary PCI have been published from some multicentre registers such as from the French CARDIO-ARHIF Register, [329] a Polish register [310] and an Austrian register. [330] The crude in-hospital mortality figures in the registers are similar to the RCTs on fibrinolysis, around 5-7% in men and 10-15% in women. Data are still contrasting whether female gender is an independent predictor of in-hospital mortality according to those register reports.[329, 330]

Motovska et al performed gender analyses on the PRAGUE 1 and 2 studies which were a multicentre randomised controlled trials comparing fibrinolytic therapy vs. primary PCI in STEMI. Interestingly, the gender difference in 30-day mortality was more pronounced in the fibrinolytic group than in the primary PCI group. Among the patients treated with fibrinolysis, 30-day mortality was significantly higher in women than in men, (15% vs. 9%, p=0.04) There was no significant gender difference in mortality in the PCI group (8.2% of women vs. 6.2% of men, p=0.41). After multivariable adjustments, the relative risk reduction in mortality primary PCI compared to fibrinolytic therapy was better in women than in men, 45% compared to 31%.[137]

Long term outcome

In a single study by Antoniucci et al 230 women and 789 men treated with primary PCI were compared as regards 6-month mortality without a significant gender difference in risk after multivariable adjustments.[138] De Luca et al presented one year follow-up data from the EGYPT database on 1662 patients also without any significant gender difference[328] whereas Mehilli et al reported lower multivariable adjusted risk of one year mortality in women in 1937 patients.[326] In the study by Mehilli et al, only 64% were STEMI patients.

As regards outcome beyond one year post MI a single-centre study long term reported 7-year outcome (mean follow-up time 5.6 years) in 464 STEMI-patients treated with primary PCI who had survived the first 30 days. No gender difference in long term cardiac mortality was found.[322] In another single-centre study, female gender did not seem to be an independent predictor of adverse real long term outcome after primary PCI with 3 year follow-up.[139]

Gender-age interaction

STEMI in-hospital mortality is higher in old than in young patients and spans from a few percent in patients less than 50 year to around 25% in patients above 80 years.[281] The higher age in women compared to men in STEMI cohorts is the main explanatory factor to their higher mortality. Thus age-adjustment diminish a doubled risk of in-hospital mortality women (odds ratio=2) to around 20% increased risk (odds ratio=1.2) and adjustments for all other possible confounders only diminish that risk a few more percents.[48, 196, 271]
Several studies based on mixed MI cohorts have found a paradox interaction between age and gender as regards short term outcome. When analysing age subgroups the risk in women relative to men has been found much higher among the youngest, whereas the difference among the oldest has been very small or absent.[117, 261, 277, 334, 335] In the pioneer study on this matter by Vaccarino et al from 1999 based on the large American NRMI register including almost 400 000 mixed MI patients, the overall in-hospital mortality in women was 18% higher than in men. For every five year decrease in age, the odds of in-hospital death in women relative to men increased 11%.[261] The same group published a second report on this matter 2009 from the same register, then separating STEMI from NSTEMI. The same pattern was found in STEMI as in the whole MI group, i.e. the younger subgroup they studied the higher was the risk in women relative to men. In the youngest group with patient <50 yrs women had 68% higher risk whereas in the oldest subgroup with patients >80 years, there was no gender difference (odds ratio 1.03) in risk of early death.[277]

Also a Greek national register study has confirmed these findings with 29% higher risk of early death in all women but in the patients <55 years old, the adjusted risk of in-hospital death was almost 4 times as high as in men.[335] A French register study on mainly STEMI

patients found the same with 3 times adjusted risk of in-hospital mortality in women compared to men in the subgroup under 60 years but no significantly higher risk in the group aged over 60 years.[117]

A number of possible explanations have been suggested such as higher risk-burden in women compared to men in young cohorts,[261] a possible bigger gender gap in management in the youngest because of longer time delays, atypical symptoms and missed diagnoses in women,[261] as well as a survival advantage in women preadmission.[336]As women are protected from MI to a great extent before menopause, a greater number of risk factors can be expected in the young women who do get the disease.[261] There are studies suggesting a different pathophysiology in young women compared to men and older women with more plaque erosions and pure thrombotic lesions.[20, 28, 37, 337] Gender differences in young STEMI patients in angiographic data and long term outcome is not evaluated in the literature.

In conclusion there is a lack of STEMI studies evaluating gender differences in short term but especially in long term outcome based on larger real life cohorts. Gender differences in outcome in the youngest population needs further evaluation as there seems to be a gender-age interaction regarding mortality after MI, possible also in pure STEMI cohorts. Also, the question remains whether the gender differences in outcome will disappear in the new primary PCI era.

Pre-hospital mortality

Studies based on registers participating in the World Health Organization's Monitoring Trends and Determinants in Cardiovascular Disease (MONICA) Project have shown that a higher rate of pre-hospital death in men balance the higher death rate during hospitalisation in women. These studies included a limited number of younger women and no persons above the age of 64 years. No data on outcome were available beyond 28 days.[338-340] A Swedish study based on the National Hospital Discharge Register and the National Cause of Death Register also found a larger proportion of men compared to women that died outside hospital in all age subgroups except below 50 years.[334] On the contrary, a Scottish study, found greater odds of death women vs. men for every 10-year decrease in age consistence with Vaccarino et al., but concluded that also among the youngest this was due to a prehospital survival advantage in women.[336] A possible diagnostic bias could be present as regards out-of-hospital deaths with a higher tendency to diagnose men than women as dying of MI, if autopsy is not performed. All these studies included mixed MI patients.

III. Aims

In STEMI patients evaluate gender differences

- Regarding baseline characteristics
- In management regarding EBM, reperfusion strategies and changes over time
- In short- and long term outcome in different ages and changes over time
- In kidney function and its potential explanation for gender differences in outcome

IV. Hypotheses in the different papers

- Paper I. Our hypothesis was that women vs. men have higher risk of in-hospital mortality but lower risk of long-term mortality in a STEMI real life cohort. We hypothesised that the relative difference would be greatest among the youngest. We also hypothesised that women have longer delay times than men and lesser chance than men to get acute reperfusion therapy, and that this would affect their prognosis.

- Paper II. Our hypothesis was that in a young STEMI cohort, women have much worse short term prognosis than men. We also hypothesised that they have different angiographic findings than men, with non-obstructive disease more often. We aimed to evaluate the long term prognosis, but had not a specific hypothesis as previous reports were lacking.

- Paper III. Our hypothesis was that the last decades debate on gender differences in management and outcome in ACS, the focus on adherence to treatment guidelines and the reperfusion strategy shift to a strategy that might be more advantageous to women, would have led to a diminished gender gap in management and outcome in the STEMI group.

- Paper IV. Our hypotheses were that in the STEMI population women have higher prevalence of RI than men, that female gender is independently associated with RI and that RI has a higher prognostic impact in women than in men.

- Paper V. Our hypotheses were that in STEMI women have higher prevalence of RI than men, that female gender is independently associated with RI and that RI has a higher prognostic impact in women than in men and that this might be part of the explanation to why women fare worse after STEMI than men

V. Material and methods

The SWEDEHEART register

The Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies [SWEDEHEART][341] includes the former separate registers the Register of Information and Knowledge about Swedish Heart Intensive care Admissions [RIKS-HIA], the Swedish Coronary Angiography and Angioplasty Registry [SCAAR], the Swedish Heart Surgery Register and the National Register of Secondary Prevention [SEPHIA]. The registers were merged into one register, SWEDEHEART, in 2009. RIKS-HIA contains information about all patients admitted to coronary care units [CCU] of the participating hospitals in Sweden. RIKS-HIA was founded 1991 and it has been the national quality register of CCU care since 1995. Today all CCUs deliver data into RIKS-HIA/SWEDEHEART. During all years as RIKS-HIA has been the quality register of Sweden, the vast majority of CCUs have delivered data to RIKS-HIA.

The papers in this thesis are mainly based upon data from the RIKS-HIA part of SWEDEHEART. RIKS-HIA collects information prospectively with more than 100 variables including patient demographics, admission and discharge electrocardiography, risk factors, past medical history, medical treatment before admission, biochemical markers, complications, investigations, medical treatment and interventions during CCU care, hospital outcome, discharge diagnoses and discharge medications.

The register has a continuous internal and external validation of data. The internet-based program for data input has interactive instructions, manuals, definitions and help functions and a number of compulsory variables and inbuilt validity controls. To ensure the correctness of the data entered a monitor visits approximately 20 randomly selected hospitals each year and compares data entered into RIKS-HIA/SWEDEHEART with the information in the patients' records in 30 to 40 randomly chosen patients for each hospital. When 637 computer forms from 21 hospitals containing 38 121 variables were reviewed for RIKS-HIA in 2007, there was 96.1% (range 92.6 to 97.4%) agreement.

More information about RIKS-HIA/SWEDEHEART can be found at
http://www.ucr.uu.se/swedeheart

Other registers

In this thesis RIKS-HIA/SWEDEHEART has been merged with the National Patient Register and the Swedish National Death Register. Data on prior co-morbidities such as previous MI, diabetes mellitus, stroke, heart failure, dementia, chronic obstructive pulmonary disease, peripheral artery disease and cancer were obtained from the National Patient Registry, which collects all discharge diagnoses for patients admitted to a hospital in Sweden since 1987. Vital status and cause of death on all Swedish citizens is possible to obtain from the National Cause of Death Register.
Some variables were registered both in RIKS-HIA/SWEDEHEART and the National Patient Register, such as previous MI, previous heart failure, and diabetes. A patient was coded as having such a diagnosis if it appeared in any of these registers.

The STEMI 2005 database

On 1st January 2005 the Cardiology Department at Linköping University Hospital adopted a strategy to treat all STEMI patients in the county of Östergötland with primary PCI with direct transportation to the cath lab. The county of Östergötland covers a population of around 420 000 inhabitants. Between the 1st January and 31st December 2005 all STEMI patients were consecutively logged on a log sheet at the CCU regarding information about onset of symptoms and ECG findings. In addition they were entered into the quality registers RIKS-HIA and SCAAR. A database was created including all patients with;

1) Symptoms suggestive of acute coronary syndrome
2) A significant ST-elevation, an extensive ST depression or a bundle branch block on ambulance/admission ECG
3) An emergency angiography or primary because of STEMI registered in the SCAAR register. Patients planned to undergo angiography but dying before were also included.
4) Final diagnosis of myocardial infarction in RIKS-HIA

In the case the patient had more than one STEMI during the study period, only the first STEMI was included. Data about ECG on admission, cardiovascular risk factors, Killip class on arrival, medications, results of investigations, complications during hospital care, diagnoses at discharge and the occurrence of a new MI during the first year after the index STEMI were retrieved from RIKS-HIA. Key times were retrieved from the log sheet at the CCU. Angiographic data including data about complications after PCI and information about any new angiography or PCI within the first year after the index MI was retrieved from SCAAR.

Serum creatinine [SCr] on arrival was retrieved from patient files. Estimated GFR was calculated for each patient using MDRD formula. According to guidelines from the National Kidney Foundation we classified the patients in CKD stages 1 to 5. As SCr at arrival may be affected by the acute condition with possible acute heart failure, acute bleeding/dehydration, also SCr values from within one year before or after the acute event (the two first weeks after the acute event excluded) were included in the register. At least one more SCr was found in 249 of the 274 patients (91%).

Information about other co-morbidities was obtained from the National Patient Register which was also used to find hospitalisations for stroke within one year from index STEMI. The Cardiac Surgery database at the Heart Centre of Östergötland and the Swedish Heart Surgery Register were examined to find patients who had undergone Coronary Artery Bypass Grafting [CABG] after the index STEMI. From the National Cause of Death Register information was available about the vital status of all Swedish citizens. Patients were followed for one year regarding death, new MI, new revascularisation and rehospitalisation for stroke. A major adverse cardiac event [MACE] was defined as death, non-fatal MI, stroke or new revascularisation not planned at the index event within the first year after the index STEMI.

Definition of STEMI

STEMI was defined as significant ST-elevation on admission ECG and a diagnosis of acute MI at discharge. The criteria for the MI diagnosis were standardized and identical for all participating hospitals. [44, 340, 342]

Definition of RI

RI was defined as eGFR <60 mL/min/1.73 m^2 (≥ CKD stages 3).[65] MDRD was used in Paper IV and V (multiplication constant 186 used as the MDRD formula based on serum creatinine standardised to reference methods was published after the study period in Paper IV and in the end of the study period in Paper V).[69] In Paper V also CG was used, estimating absolute CrCl in mL/min. Anyhow, the term eGFR was used regarding both formulats in order to simplify. Correction of CG eGFR for BSA can be done to allow for a more accurate comparison of eGFR between subjects of different body sizes/weights.[71] This was not done as height was frequently missing in SWEDEHEART.

Study populations

In Paper I all STEMI patients registered in SWEDEHEART/RIKS-HIA between 1st January 1995 and 31st December 2006 were included. Patients with pacemaker/unknown /unspecified rhythm or bundle branch block on admission were excluded.

In Paper II we included all STEMI patients <46 years old registered in SWEDEHEART/RIKS-HIA between 1st January 1995 and 31st December 2006. Patients with other rhythm than sinus rhythm or atrial fibrillation/flutter were excluded.

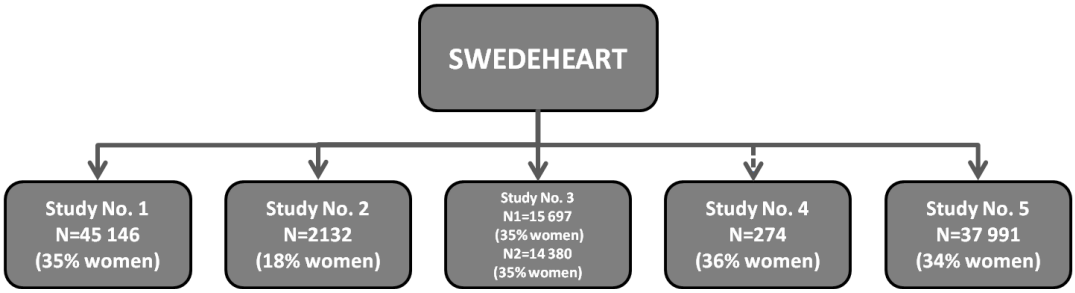
In Paper III we included all STEMI patients registered in SWEDEHEART/RIKS-HIA between 1st January 1998 and 31st December 2000 and between 1st January 2004 and 31st December 2006. Patients with pacemaker/unknown/unspecified rhythm or bundle branch block on admission were excluded.

In Paper IV all consecutive patients who fulfilled the criteria for ST-elevation or bundle branch block on admission ECG and who were planned to undergo immediate coronary angiography with the intention to perform primary PCI at the Department of Cardiology in Linköping between 1st January and 31st December 2005 were included.

In Paper V all consecutive STEMI patients registered in SWEDEHEART/RIKS-HIA between 1st January 2003 and 31st December 2009 were included. Patients with pacemaker rhythm or bundle branch block on admission were excluded.

Regarding all studies, if a patient was admitted several times with STEMI, only the first admission was included in the analyses.

Figure 4. Study populations in the different papers



Statistics

In all papers continuous variables were summarised by their mean and standard deviation or median and interquartile range as appropriate. Categorical variables were summarised by counts and percentages. Comparisons were performed by chi-square tests for categorical variables and by student t-test or Mann Whitney test for continuous variables, depending if they were normally distributed or not. P-values <0.05 were considered to indicate statistical significance.

As women and men with STEMI differed a lot in age and co-morbidity, different kinds of multivariable regression analyses in order to adjust for these and other confounding factors were done in all papers in order to conduct proper gender comparison as regards management, risk of reduced kidney function and outcome. As regards use of different therapies, risk of reduced kidney function and in-hospital mortality, logistic regression analyses were performed and odds ratios with 95% confidence intervals were presented. As regards long term outcome, Cox proportional regression analyses were performed with hazard ratios with 95% confidence intervals presented. Kaplan-Meier curves for long term survival and long term risk of re-infarction were presented in paper II, with log rank test used in order to compare the genders. In paper IV, Kaplan-Meier curves for one year outcome in different CKD stages, men and women separately, were presented. Log rank tests were used in order to compare the different CKD stages. In paper V Kaplan-Meier curves for long term outcome in 5 CKD stages according to MDRD or CG, the two genders separately were presented. Comparisons were done between CKD groups, each gender separately, with Wilcoxon (Gehan) Statistics. Statistical analyses were performed using SPSS versions 15.0 (Paper II and IV) and 18.0 (Paper I, III and V).

For further details please see statistical method sections for the individual papers.

VI. Results

Paper I

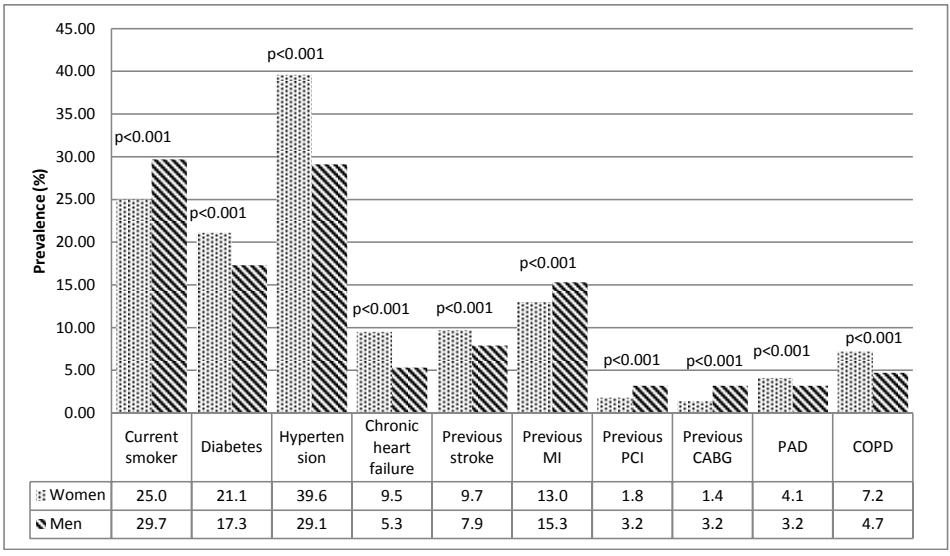
A gender perspective on short- and long term mortality in ST-elevation myocardial infarction – a report from the SWEDEHEART register

A real life population was used covering almost all Swedish STEMI patients hospitalised 1st January 1995 until 31st December 2006 using the SWEDEHEART register. In total 54 146 patients, 35% women, were included.

Baseline characteristics

Women were 7 years older than men, 73 yrs compared to 66 yrs, p<0.001. The median symptom-to-door time was 30 minutes longer in women than in men. They had higher cardiovascular co-morbidity with higher prevalence of diabetes, hypertension, chronic heart failure, previous stroke and peripheral arterial disease. (Figure 5)
Women also had higher prevalence of non-cardiovascular diseases such as chronic pulmonary obstructive disease and dementia. There was no gender difference in prevalence of previous cancer or chronic kidney disease. Men had more often suffered from a previous MI or had undergone previous revascularisation procedures. (Figure 5)
After age-adjustments most of these differences persisted, except of smoking (OR 1.32, 95% CI 1.26 – 1.38) and stroke (OR 0.86, 95% 0.80 – 0.91), odds ratios expressed as women vs. men.

Figure 5. Prevalence of co-morbidities



	Current smoker	Diabetes	Hypertension	Chronic heart failure	Previous stroke	Previous MI	Previous PCI	Previous CABG	PAD	COPD
Women	25.0	21.1	39.6	9.5	9.7	13.0	1.8	1.4	4.1	7.2
Men	29.7	17.3	29.1	5.3	7.9	15.3	3.2	3.2	3.2	4.7

Therapy on admission

Before admission, women were somewhat more often than men on treatment with platelet inhibitors, beta-blockers, ACE-inhibitors/ARBs or calcium-channel blockers and twice as often treated with diuretics or digitalis. Men were somewhat more often on treatment with statins. After adjustment for age, there where no gender differences left except 12% and 17% higher risk in women of being on treatment with a beta-blocker or digitalis, respectively. Women had almost twice as high possibility of being treated with diuretics, also after age-adjustment.

Complications

On admission, women had higher Killip class, including cardiogenic shock. In total 33% of the women showed sign of heart failure compared to 25% of men. Women had higher risk of heart failure also after age-adjustment. Among the 12 217 where data was available about ejection fraction (among the 67% of men and 60% of women who performed echocardiography during hospital care), women had lower age-adjusted risk of reduced LV-function (EF<50%) than men. Among the 31 349 who received reperfusion therapy, the incidence of major bleeding was 2.4% in women and 1.5% in men (p>0.001). Women had 37% higher age-adjusted risk of bleeding. In the fibrinolysis-treated group, women had 19% higher age-adjusted risk of bleeding with borderline significance (OR 1.19, 95% CI 0.98 – 1.45). In the PCI treated group the risk of bleeding was 2.3 times in women (OR 2.3, 95% CI 1.57 – 3.39), but there were only valid data for 61% in the PCI treated group compared to 96% of the fibrinolysis treated group.

Evidence-based therapy

Fewer women than men, 63% vs. 72%, p<0.001, were treated with acute reperfusion therapy defined as primary PCI, fibrinolytic therapy or acute CABG. Women had less chance of reperfusion therapy also after multivariable adjustments, odds ratio 0.83 (95% confidence interval 0.79 - 0.88). At discharge, women had somewhat lower chance of getting secondary prevention therapy such as aspirin, other platelet inhibitors, beta-blockers, ACE-inhibitors/ARBs or statins. Most of these differences persisted after age-adjustment. (Table 3)

Table 3. Use of evidence-based therapies in STEMI patients

	Women N=18876	Men N=35270	p-value	Age-adjusted odds ratio (95% confidence interval)
Pre or in-hospital therapy				
Acute reperfusion therapy	11788 (62.5)	25410 (72.1)	<0.001	0.83 (0.80 – 0.86)
Therapy at discharge				
Aspirin	14603 (82.5)	29183 (86.3)	<0.001	0.91 (0.87 – 0.96)
Other platelet-inhibitor	4895 (27.7)	11259 (33.3)	<0.001	0.93 (0.88 – 0.97)
Beta-blocker	13968 (79.0)	28708 (85.0)	<0.001	0.86 (0.82 – 0.91)
ACE-inhibitor/Angiotensin receptor blocker	8195 (46.5)	16842 (50.1)	<0.001	0.85 (0.82 – 0.88)
Statin	8326 (47.3)	18933 (56.3)	<0.001	0.99 (0.95 – 1.03)

Data is presented as numbers (percentages) if not otherwise indicated

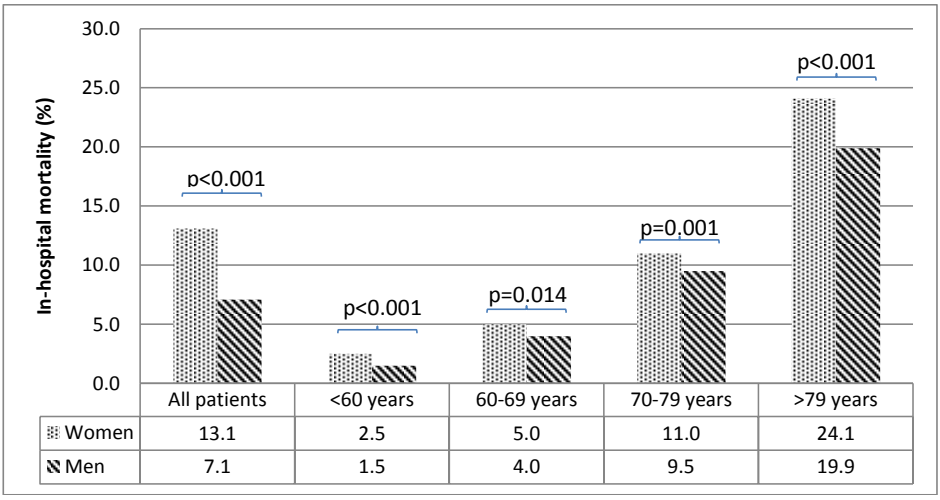
When analysing age-subroups the gender difference in rate of reperfusion therapy was largest among the oldest (56% of men vs. 48% of women, p<0.001) and least among the youngest (81% of men vs. 78% of women, p<0.001). After multivariable adjustments, the chance of reperfusion therapy was lowest among women in the oldest group and in the group 60-69 years old, odds ratios 0.78 (95% CI 0.69 – 0.87) and 0.77 (95% CI 0.69 – 0.87), respectively. In the youngest group the odds ratio was 0.89 (95% CI 0.78 – 1.01), and in the group 70-79

years old 0.89 (95% CI 0.81 – 0.98).

Outcome

In-hospital mortality was 13% and 7%, women and men respectively, p<0.001. (Figure 6) After multivariable-adjustments the women had 22% higher risk of in-hospital death, odds ratio 1.22 (95% CI 1.11 – 1.33). Hardly no change of the odds of death was seen after also adjusting for reperfusion therapy, OR 1.21 (1.11 – 1.32).The mortality increased with increasing age, but was higher in women compared to men in all age-groups. After age-stratifying, the multivariable adjusted risk in women relative to men was highest among the youngest, OR 1.45 (95% CI 0.98 – 2.14), followed by the oldest, OR 1.28 (95% CI 1.13 – 1.45). Women 60-69 years old did not have higher risk of in-hospital mortality after multivariable adjustment, OR 1.05 (0.82 – 1.36). Among patients 70-79 years old, the risk was 16% higher in women, OR 1.16 (95% CI 1.01 – 1.34). The risk of in-hospital death was the same whether or not reperfusion therapy was incorporated in the multivariable adjustment or not.

Figure 6. In-hospital mortality in all patients and in age subgroups



	All patients	<60 years	60-69 years	70-79 years	>79 years
Women	13.1	2.5	5.0	11.0	24.1
Men	7.1	1.5	4.0	9.5	19.9

Crude cumulative one year mortality was higher in women than in men, 22.6% vs. 14.0%, p<0.001. Women had 4% higher risk of one year mortality after multivariable adjustments, HR 1.04 (95% CI 1.00 – 1.10). After age-stratifying, multivariable adjusted risk was still higher among the oldest women, HR 1.06 (95% CI 1.00 – 1.14) but no difference was seen among the other three age-groups. After also adjusting for reperfusion therapy and evidence-based cardiovascular therapies at discharge, there was no difference in one year mortality in the whole group or in any of the age-groups. (Table 4)

Forty-six percent of women compared to 32% of men died during follow-up. The long term outcome was compared women vs. men with Cox proportional regression analyses, as follow-up time varied between at least one to maximum 13 years. Women had 59% higher risk of long term mortality after univariate adjustment but after multivariable adjustment, women had 8% lower risk of long term mortality. (Table 4) Age stratifying revealed minimal gender

differences all four age subgroups regarding long term outcome. (Figure 7) When multivariable adjustments were done within each age-group, women had better long term survival in all age-groups, except the youngest. (Table 4)

Figure 7. Long term mortality in all patients and in age-subgroups, univariate Cox-regression curves.

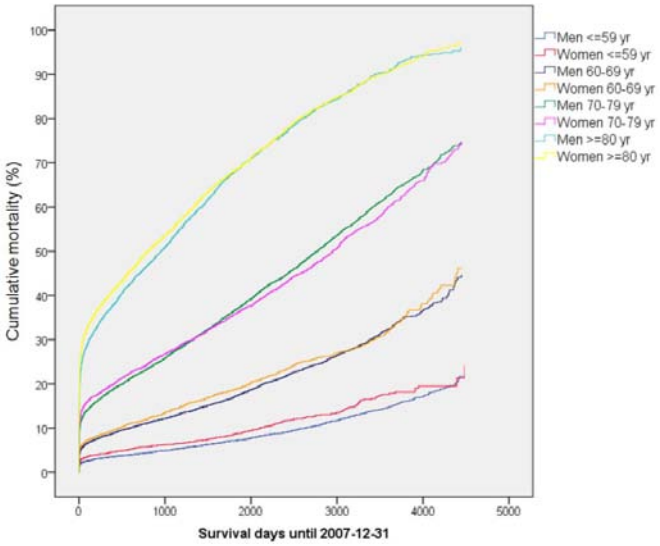


Table 4. Long term survival. Crude and multivariable adjusted hazard ratios women vs. men.

	Crude hazard ratios (95% confidence interval)	Multivariable adjusted hazard ratios (95% confidence interval)
Cumulative one year mortality		
All	1.71 (1.64 – 1.78)	0.97 (0.92 – 1.03)
<60 years old	1.31 (1.06 – 1.60)	0.93 (0.71 – 1.22)
60-69 years old	1.09 (0.96 – 1.24)	0.92 (0.78 – 1.08)
70-79 years old	1.08 (1.00 – 1.16)	0.99 (0.90 – 1.08)
>79 years old	1.32 (1.07 – 1.20)	0.99 (0.91 – 1.07)
Cumulative long term mortality		
All	1.59 (1.55 – 1.64)	0.92 (0.89 – 0.96)
<60 years old	1.20 (1.06 – 1.08)	0.91 (0.77 – 1.07)
60-69 years old	1.07 (0.98 – 1.15)	0.89 (0.86 – 0.98)
70-79 years old	0.97 (0.91 – 1.02)	0.92 (0.86 – 0.98)
>79 years old	1.05 (1.01 – 1.10)	0.93 (0.88 – 0.99)
Data presented in hazard ratios, women vs. men		

Paper II

Gender Perspective on Risk Factors, Coronary Lesions and Long-term Outcome in Young Patients with ST-Elevation Myocardial Infarction

Myocardial infarction was diagnosed in 5088 patients below 46 years of age (4018 men and 1070 women) 1st January 1995 until 31st December 2006. Of those, 1790 men and 401 women had a first register recorded diagnosis of STEMI, defined as ST-elevation on admission ECG, and a diagnosis of acute MI at discharge. Fifty-nine patients with other heart rhythm than sinus rhythm or atrial fibrillation/flutter were excluded and the final study population consisted of 1748 men and 384 women.

Baseline characteristics

Ischemic risk factors were defined as being a current smoker, having a diagnosis of diabetes mellitus or hypertension or being treated with statins already before admission. Among women 64% were current smokers compared to 58% among the men. Seventy-two percent of men compared to 79% of women had at least one risk factor and 17% of men and 25% of women had more than one risk factor. (Table 5)

Table 5: Baseline characteristics

	Women N=384	Men N=1748	p-value
Age, years (standard deviations)	40.4 (4.8)	40.8 (4.3)	0.14
At least one ischemic heart disease risk factor	289 (78.5)	1211 (71.8)	<0.01
More than one ischemic heart disease risk factor	93 (25.3)	290 (17.2)	<0.001
Current smoker	237 (63.9)	982 (58.0)	0.04
Hypertension	83 (21.7)	243 (13.9)	<0.001
Diabetes Mellitus	71 (18.5)	217 (12.4)	<0.01
Statin therapy before admission	23 (6.1)	147 (8.4)	0.12
Previous myocardial infarction	20 (5.2)	116 (6.6)	0.30
Previous percutaneous coronary intervention	7 (1.9)	43 (2.5)	0.46
Previous coronary artery bypass grafting	1 (0.3)	14 (0.8)	0.25

Data presented as numbers (percentages) if not otherwise indicated

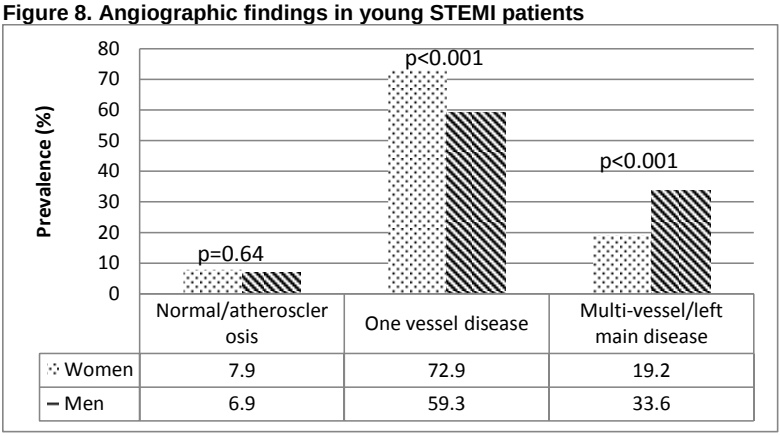
The symptom-to-door time did not differ between the genders, 1:52 (hours: minutes) in women vs. 1:45 in men, p=0.18. Cardiogenic shock on admission was almost twice as common in women as in men, 6.3% vs. 3.5%, p=0.01. The majority of patients received reperfusion therapy (78.1% of women vs. 80.5% of men, p=0.28).

Coronary angiography findings

Almost 60% of both women and men underwent coronary angiography within one week (59.6% vs. 58.8%, p=0.77). A sub-study of coronary angiographic findings was performed in the 1257 patients where angiograms were performed within 7 days of admission. Ninety-two percent of the women compared to 93% of the men had significant coronary artery disease (p=0.64). On the other hand there was a gender difference in the extent of coronary artery disease where men more often had multi-vessel or left main disease (33.6% vs. 19.2%; p<0.001), whereas one-vessel disease was more common in women (59.3% vs. 72.9%; p<0.001). (Figure 8) The validity of these findings was verified by comparisons of sub-cohorts based on admission year or day of investigation, respectively, as the SCAAR register was not complete in the beginning of the study period and as the dominating reperfusion

therapy has changed during the study period from fibrinolytic therapy to primary PCI in Sweden.
Women tended to have signs of heart failure during hospital care more often than men (19.4% vs. 15.4%, p=0.06) and to have more re-infarctions (2.4% vs. 1.2%, p=0.07). Other complications did not significantly differ between the genders.

Figure 8. Angiographic findings in young STEMI patients



	Normal/atherosclerosis	One vessel disease	Multi-vessel/left main disease
Women	7.9	72.9	19.2
Men	6.9	59.3	33.6

Therapy at discharge

Therapy at discharge in hospital survivors did not significantly differ between the genders as regards most of the cardiovascular drugs. Exceptions were beta-blockers and statins that were prescribed more often to men (91% vs. 87%, p=0.03 as regards beta-blockers, 71% vs. 62%, p<0.001 as regards statins) and calcium-channel blockers that were prescribed more often to women (8.2% vs. 4.6%, p=0.005).

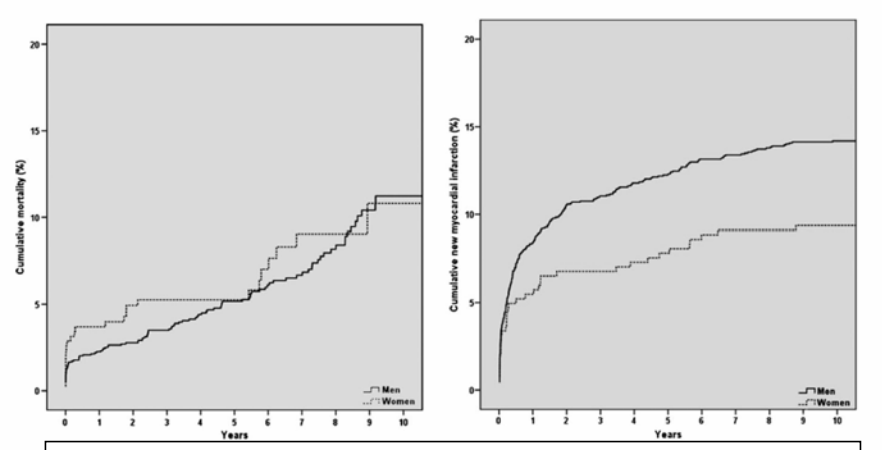
Short term outcome

In-hospital mortality was low, 3% in women vs. 1% in men, crude odds ratio women vs. men 2.83 (95% confidence interval [CI] 1.32 – 6.03). Female gender appeared as an independent predictor in the multivariable model of in-hospital mortality, OR 2.85 (95% CI 1.31 – 6.19). Diabetes mellitus more than doubled the in-hospital mortality risk (OR 2.42, 95% CI 1.03 – 5.66) while acute reperfusion therapy was associated with halved mortality risk (OR 0.48, 95% CI 0.22 – 1.06).

Long term outcome

When the cohort was followed up to 10 years (mean 5.4 years) the mortality rates were not different between genders. (Figure 9) Twenty-seven women (7%) compared to 108 men (6%) died during follow-up, p=0.54. There were no gender difference in risk after multivariable Cox regression (HR 0.93, 95% CI 0.60 – 1.45; p=0.75). Men had significantly higher risk of a second new MI during the following 10 years. (Figure 9) The risk of having a new MI was 82% higher in men after multivariable adjustments (HR 1.82, 95% CI 1.25 – 2.65; p=0.002).

Figure 9. Long-term outcome in young STEMI patients.



Kaplan-Meier curves for long term mortality and re-infarctions, respectively, in young men and women with STEMI. Log-ranks test comparing the genders; p=0.40 and 0.01, risk of mortality and re-infarctions, respectively

Paper III

Time trends in STEMI - improved treatment and outcome but still a gender gap
A prospective, observational cohort study from the SWEDEHEART register

In the beginning of the 21st century there was a shift in reperfusion strategy with a decline in use of fibrinolytic therapy and an increase in use of primary PCI. (Figure 10) As secondary prevention, the use of ACE-inhibitors/ARBs, clopidogrel and statins increased dramatically within the STEMI population the last decade (Figure 11). Mortality declined simultaneously, both in-hospital and cumulative long term mortality. (Figure 12) We included patients from two time periods with different dominating reperfusion strategy in order to compare management and outcome. In total 30 077 STEMI patients were admitted during the two inclusion periods, 15 697 (35% women) in 1998-2000 and 14 380 (35% women) in 2004-2006. Among patients treated with reperfusion therapy 9% in the early period compared to 68% in the late period were treated with primary PCI.

Figure 10. Reperfusion strategy in Swedish STEMI patients 1995-2006

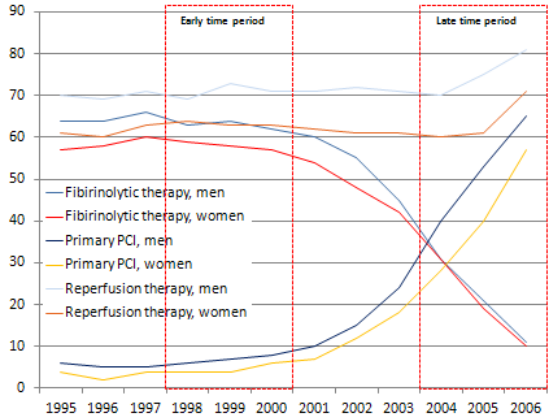


Figure 11. Use of evidence-based therapies at discharge in Swedish STEMI patients 1995-2006

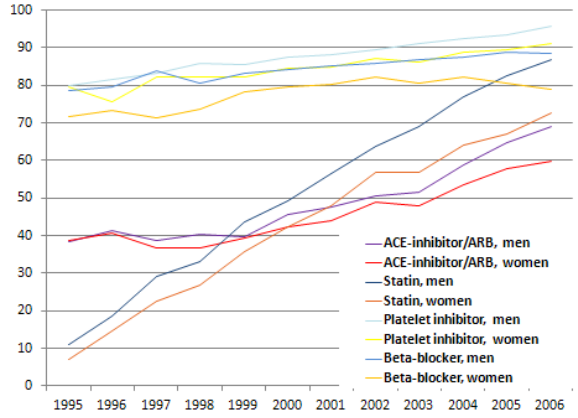
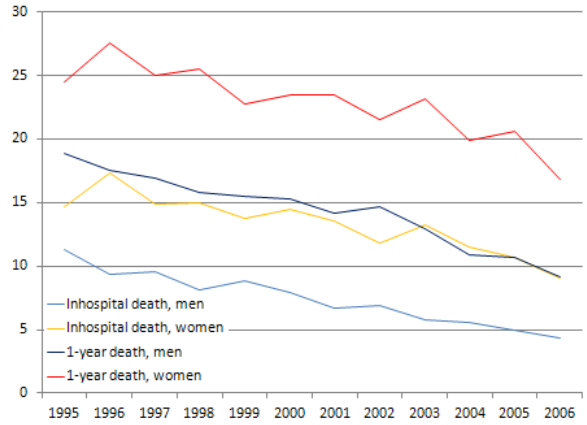


Figure 12. In-hospital and cumulative one-year mortality in Swedish STEMI patients 1995-2006



Baseline characteristics

In both time periods, women were 6.5 years older than men and arrived 30 minutes later from symptom onset to arrival to the hospital. They had higher prevalence of co-morbidities such as diabetes, hypertension and heart failure but were more seldom smokers or were previously revascularised. About a quarter of men and a third of women used aspirin before admission in both time periods and the figures regarding beta-blockers were similar. More patients used statins or ACE-inhibitors/ARBs in the late compared to the early period, but gender differences were small as regards these therapies before admission in both time periods. (Table 6)

Table 6. Baseline characteristics in the early and late period.

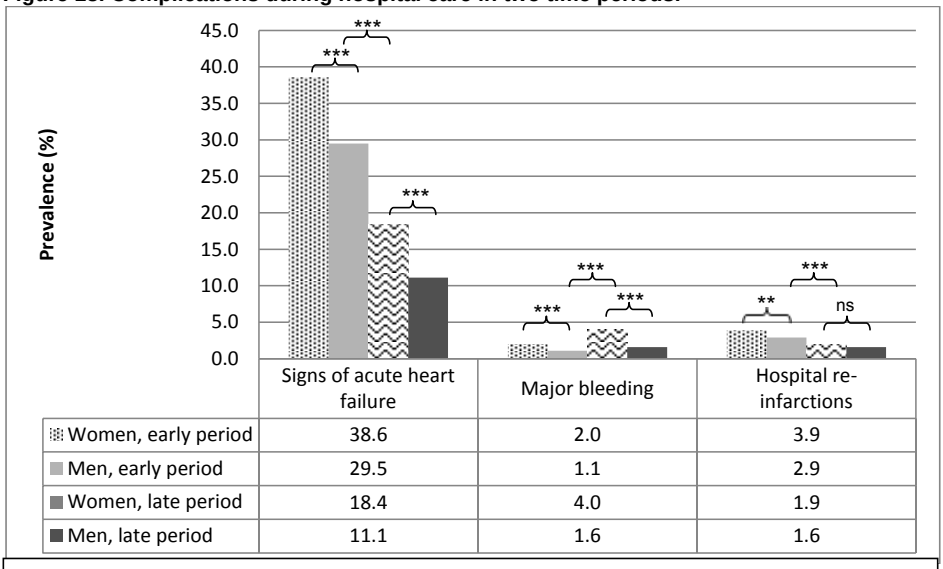
	EARLY PERIOD YEAR 1998-2000			LATE PERIOD YEAR 2004-2006			PERIODS COMPARED
	Men N=10151	**Women** N=5546	**p-value**	**Men** N=9386	**Women** N=4994	**p-value**	**p-value**
Age (SD)	66.4 (12.2)	72.9 (11.5)	<0.001	65.9 (12.2)	72.4 (12.1)	<0.001	0.11
Symptom-to-door time hours:min (IQR)	2:45 (1:39 – 5:10)	3:15 (1:54 – 6:15)	<0.001	3:00 (1:40 – 5:50)	3:30 (2:00 – 6:30)	<0.001	<0.001‡
Current smoker	2762 (28.9)	1220 (23.8)	<0.001	2680 (30.9)	1224 (27.6)	<0.001	<0.001‡
Co-morbidity							
Previous MI	1781 (17.5)	742 (13.4)	<0.001	1062 (11.3)	529 (10.6)	0.19	<0.001†
Previous PCI	287 (2.9)	87 (1.6)	<0.001	372 (4.0)	110 (2.2)	<0.001	<0.001‡
Previous CABG	307 (3.1)	58 (1.1)	<0.001	308 (3.3)	82 (1.7)	<0.001	0.05 ‡
Diabetes Mellitus	1758 (17.3)	1198 (21.6)	<0.001	1679 (17.9)	1014 (20.3)	<0.001	0.82
Hypertension	2736 (27.2)	1972 (36.0)	<0.001	3053 (32.8)	2195 (44.5)	<0.001	<0.001‡
Therapy on admission							
Aspirin	2680 (26.6)	1512 (27.5)	0.25	2127 (22.9)	1440 (29.2)	<0.001	<0.001†
Other platelet inhibitor	37 (0.4)	16 (0.3)	0.43	309 (3.3)	195 (3.9)	0.05	<0.001‡
Beta–blocker	2525 (25.1)	1544 (28.1)	<0.001	2194 (23.6)	1565 (31.8)	<0.001	0.57
ACE inhibitor/ARB	1081 (10.7)	586 (10.7)	0.89	1553 (16.7)	924 (18.7)	0.002	<0.001‡
Statin	750 (7.5)	318 (5.8)	<0.001	1249 (13.4)	621 (12.6)	0.16	<0.001‡

Data presented as numbers (percentages) if not otherwise indicated. † More in early period ‡ More in late period. SD, standard deviation; IQR, interquartile range; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker

Complications

Heart failure on admission, i.e. Killip class II-IV, and re-infarction during hospital stay were more common in the early compared to the late group. In both time periods women suffered from acute heart failure more often than men. They also suffered more often from re-infarctions, at least in the early period. The prevalence of major bleedings was higher in the late than in the early period, but higher in women in both time periods. (Figure 13)

Figure 13. Complications during hospital care in two time periods.



	Signs of acute heart failure	Major bleeding	Hospital re-infarctions
Women, early period	38.6	2.0	3.9
Men, early period	29.5	1.1	2.9
Women, late period	18.4	4.0	1.9
Men, late period	11.1	1.6	1.6

*** p<0.001 ** p<0.01 * p<0.05 ns, non-significant

Use of evidence-based therapies

Table 7. Use of evidence-based therapies in two time periods

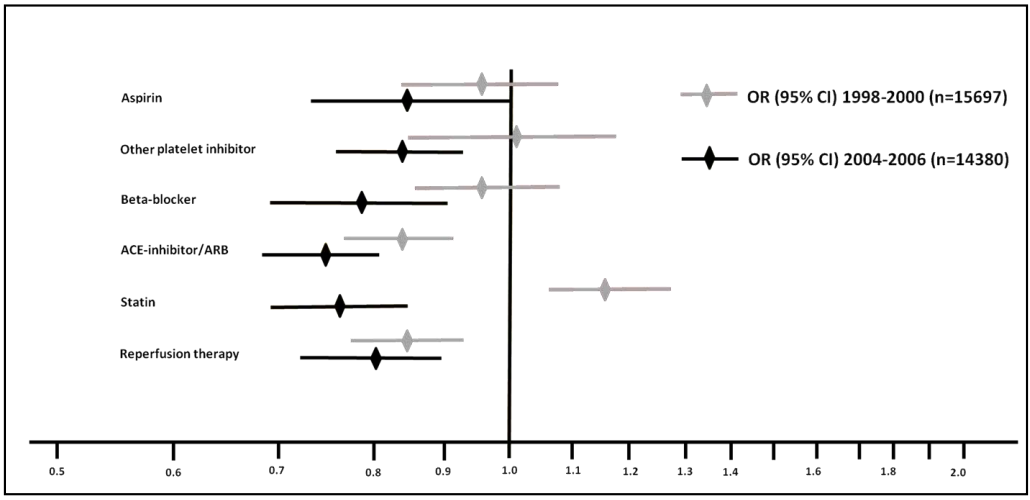
	Women N=18876	Men N=35270	p-value	Crude OR (95% CI)	Multivariable-adjusted OR (95% CI)
EARLY PERIOD					
Pre/in-hospital therapies and procedures					
Acute reperfusion therapy	3500 (63.1)	7194 (70.9)	<0.001	0.70 (0.66 – 0.75)	0.86 (0.78 – 0.94)
Coronary angiography	975 (17.6)	2539 (25.0)	<0.001	0.64 (0.59 – 0.69)	0.92 (0.83 – 1.02)
Therapy at discharge					
Aspirin	4004 (86.1)	7994 (87.5)	0.02	0.89 (0.80 – 0.98)	0.96 (0.85 – 1.08)
Other platelet-inhibitor	330 (7.1)	800 (8.8)	0.001	0.80 (0.70 – 0.91)	1.01 (0.86 – 1.18)
Beta-blocker	3812 (82.1)	7801 (85.4)	<0.001	0.78 (0.71 – 0.86)	0.96 (0.87 – 1.08)
ACE-inhibitor/ARB	1952 (42.4)	3934 (43.4)	0.25	0.96 (0.89 – 1.03)	0.85 (0.78 – 0.92)
Statin	1757 (38.1)	3991 (44.0)	<0.001	0.78 (0.73 – 0.84)	1.16 (1.06 – 1.27)
LATE PERIOD					
Pre/in-hospital therapies and procedures					
Acute reperfusion therapy	3174 (63.6)	7065 (75.3)	<0.001	0.57 (0.53 – 0.62)	0.80 (0.73 – 0.89)
Coronary angiography	3313 (66.4)	7686 (81.9)	<0.001	0.44 (0.40 – 0.47)	0.80 (0.73 – 0.89)
Therapy at discharge					
Aspirin	4062 (91.2)	8318 (93.6)	<0.001	0.71 (0.62 – 0.82)	0.86 (0.73 – 1.00)
Other platelet-inhibitor	3045 (68.4)	6978 (78.5)	<0.001	0.59 (0.55 – 0.64)	0.85 (0.77 – 0.94)
Beta-blocker	3895 (87.5)	8105 (91.2)	<0.001	0.68 (0.60 – 0.76)	0.79 (0.69 – 0.91)
ACE-inhibitor/ARB	2719 (61.1)	5894 (66.4)	<0.001	0.80 (0.74 – 0.86)	0.75 (0.68 – 0.81)
Statin	3279 (73.8)	7570 (85.2)	<0.001	0.49 (0.45 – 0.53)	0.77 (0.69 – 0.86)

Data presented as numbers (percentages) if not otherwise indicated. Odds ratios presented as women vs. men.
OR, odds ratio; CI, confidence interval; ARB, angiotensin receptor blocker

In the early period, 18% of women compared to 25% of women underwent coronary angiography. In the late period the numbers were higher in both genders (66% vs. 82%). After multivariable adjustments women had 8% vs. 20% less chance of angiography in early and late periods, respectively. The use of reperfusion therapy increased between the two time periods, in men from 70.9% to 75.3%, in women from 63.1% to 63.6%. After multivariable adjustment, women were 14% and 20% less likely to receive reperfusion therapy in the early and late periods compared to men, early and late periods respectively. (Table 7, figure 14)

Evidence-based treatment with statins, platelet inhibitors, beta-blockers and ACE-inhibitors/ARBs were prescribed more often in the late compared to the early period in both genders. All evidence-based therapies were prescribed more seldom to women in both periods. Women still had less chance of receiving ACE-inhibitors/ARBs but higher chance of receiving statins after multivariable adjustments in the early period. In the late period women had 14 – 25% less chance of receiving any of these therapies after multivariable adjustments. (Table 7, figure 14)

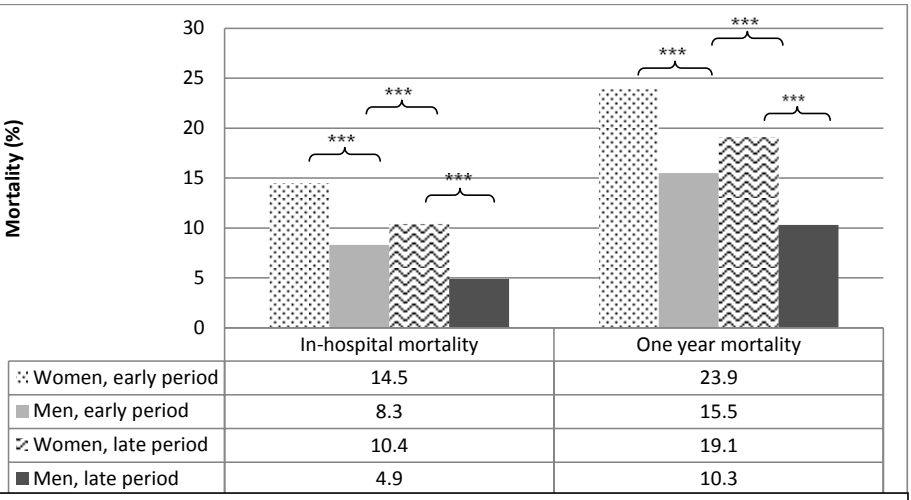
Figure 14. Evidence-based treatment in two time periods, women vs. men.



Outcome

In-hospital as well as cumulative one year mortality was higher in the early than in the late time period, in both genders. The absolute mortality numbers were about twice as high in women than in men in both time periods. (Figure 15)

Figure 15. In-hospital and cumulative one year mortality in the early and late time periods.

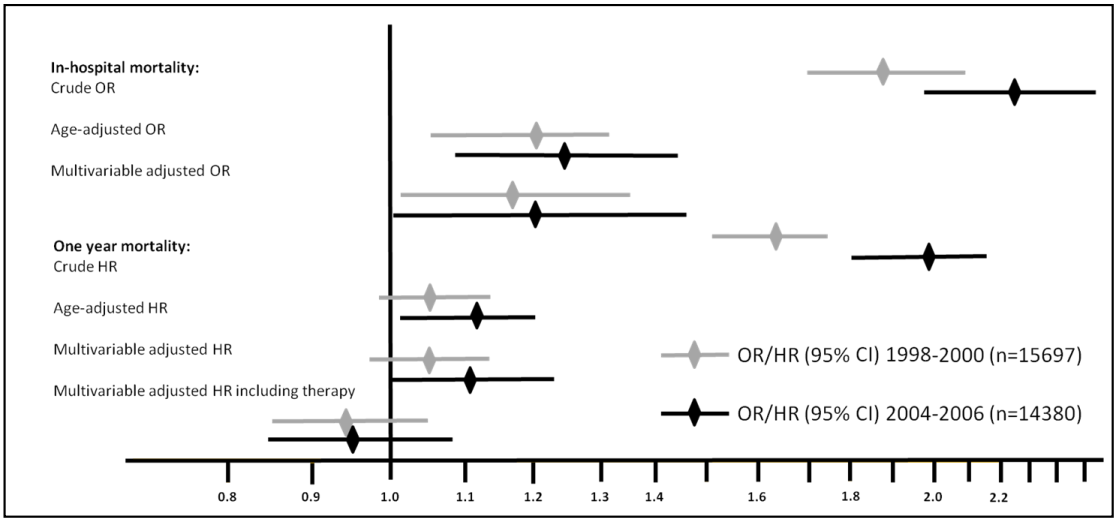


	In-hospital mortality	One year mortality
Women, early period	14.5	23.9
Men, early period	8.3	15.5
Women, late period	10.4	19.1
Men, late period	4.9	10.3

*** p<0.001 ** p<0.01 * p<0.05 ns, non-significant

After multivariable adjustments, the in-hospital mortality was about 20% higher in women than in men in both time periods (OR 1.18, 95% CI 1.02 – 1.36 vs. OR 1.21, 95% CI 1.00 – 1.46). One year mortality was 5% and 11% higher in women in the early and late periods, respectively, after multivariable adjustments (HR 1.05, 95% CI 0.97 – 1.14 vs. 1.11, 95% CI 1.00 – 1.24). After also adding adjustments for reperfusion therapy and evidence-based therapy at discharge, there was no longer any gender difference in cumulative one year mortality (HR 0.95, 95% CI 0.87 – 1.05 vs. HR 0.96, 95% 0.86 – 1.08).

Figure 16. In-hospital and cumulative mortality in two time periods



Paper IV.

Gender difference in prevalence and prognostic impact of renal insufficiency in patients with ST-elevation myocardial infarction treated with primary percutaneous coronary intervention

During 2005, 274 STEMI patients underwent immediate coronary angiography with the intention to do primary PCI at the Department of Cardiology, Linköping University Hospital, and were included in the study.

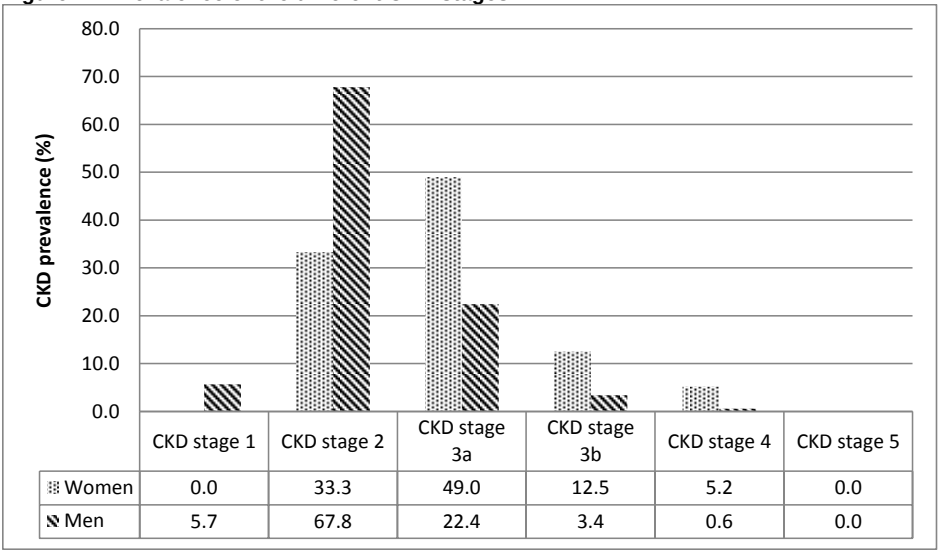
Baseline characteristics

The women were older, had higher prevalence of hypertension and chronic obstructive pulmonary disease but there was no significant gender difference in prevalence of diabetes, previous stroke or heart failure. Neither was there a difference in prevalence of smoking. On admission, women were on treatment with diuretics (37% vs. 13%, p<0.001) and/or digitalis (6% vs. 1%, p=0.05) more often than men. Seven percent of women and 4% of men were classified as having cardiogenic shock on admission (Killip class IV). There was no significant difference in time from symptom onset to first ECG (125 min vs. 117 min, p=0.64) or to beginning of PCI (221 min vs. 211 min, p=0.59).

Kidney function

Serum creatinine was higher in men compared to women, 105 vs. 99 µmol/L, p=0.03, but eGFR according to the MDRD formula was lower in women than in men, mean eGFR 54 vs. 68 mL/min/1.73m^2, p<0.001. Ten men but no woman were classified belonging to the best CKD stage, 32 women and 118 men were classified being in CKD stage 2, 59 women and 45 men in CKD stage 3 (3a=45-59 mL/min/1.73m^2, 3b=30-44 mL/min/1.73m^2) and finally 5 women and 1 man in CKD stage 4. No patient was staged as being in CKD stage 5, i.e. in ESRD. Thus, in total 67% of women compared to 27% of men were classified as having RI, i.e. eGFR less than 60 mL/min/1.73m^2. (Figure 17)

Figure 17. Prevalence of the different CKD stages



	CKD stage 1	CKD stage 2	CKD stage 3a	CKD stage 3b	CKD stage 4	CKD stage 5
Women	0.0	33.3	49.0	12.5	5.2	0.0
Men	5.7	67.8	22.4	3.4	0.6	0.0

Predictors of renal insufficiency

After multivariable adjustment, female gender was a very strong independent predictor of RI, with more than five time higher risk of RI than men. Other independent predictors of RI were age, previous PCI, previous heart failure, aspirin or statin on admission. (Table 8)

Table 8. Independent predictors of renal insufficiency in primary PCI treated STEMI patients

	Multivariable adjusted OR (95% CI)	p-value
Female vs. male gender	5.06 (2.66 – 9.59)	<0.001
Age in 10 year decrement	2.09 (1.53 – 2.85)	<0.001
Previous PCI	3.10 (1.07 – 8.97)	0.04
Previous heart failure	8.77 (1.47 – 52.19)	0.02
Aspirin on admission	2.78 (1.19 – 6.50)	0.02
Statin on admission	2.58 (1.12 – 5.93)	0.03

OR, odds ratio; CI, confidence interval; PCI, percutaneous coronary intervention

Prognostic impact of reduced eGFR

The independent effect of reduced eGFR on one year outcome was analysed in men and women separately. As the cohort was small, not only mortality but also a combined endpoint, MACE, consisting of death, non-fatal MI, stroke or new revascularisation procedure within one year after the index event was used. The cumulative one-year mortality was 15% (n=15) in women and 9% (n=16) in men whereas the cumulative one-year MACE was 32% (n=31) in women and 28% (n=50) in men. After multivariable adjustments, each 10 mL/min incline of eGFR was associated with a 63% relative risk reduction of one-year death and 39% relative risk reduction of one-year MACE in women. No such associations were found in men. (Table 9) Interaction test showed borderline significant interaction between gender and eGFR regarding one year mortality (p=0.08) but no significant interaction regarding one year MACE (p=0.11).

Table 9. Prognostic impact of eGFR per 10 mL incline

	Multivariable adjusted OR (95% CI)	p-value
One-year mortality, women	0.37 (0.15 – 0.89)	0.03
One-year mortality, men	1.05 (0.63 – 1.76)	0.85
One-year MACE, women	0.61 (0.40 – 0.92)	0.02
One-year MACE, men	1.05 (0.79 – 1.40)	0.73

OR, odds ratio; CI, confidence interval, MACE, major adverse cardiovascular event

Paper V.

Prevalence and prognostic impact of renal insufficiency in STEMI from a gender perspective – data from a large prospective cohort

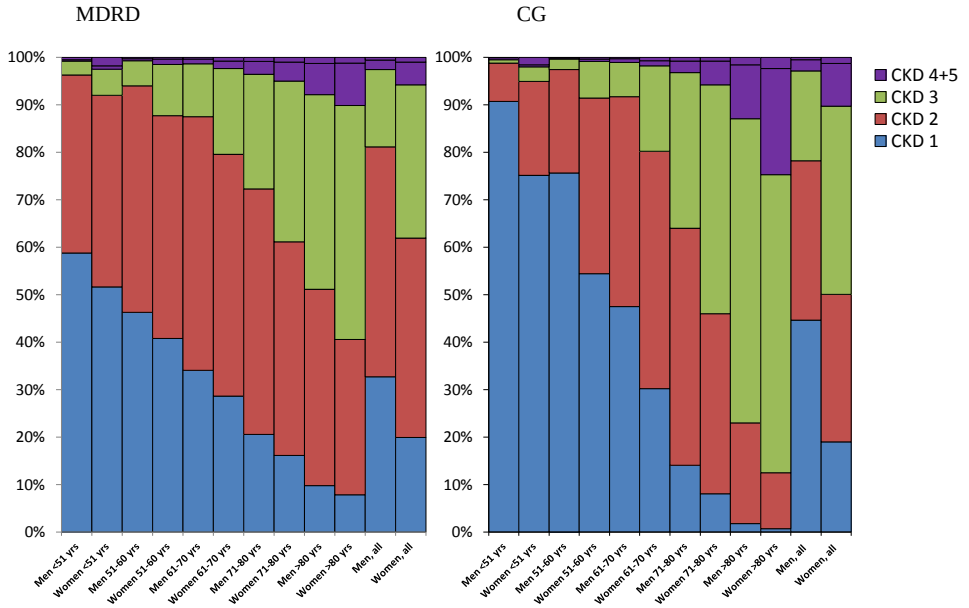
All STEMI patients registered in SWEDEHEART between 1st January 2003 and 31st December 2009 were included, in total 37 991 patients, 34% women. We had complete data in order to estimate GFR according to the MDRD formula for 93% of these patients. Regarding estimated CrCl according to the Cockcroft Gault formula (from now on referred to as eGFR according to CG), complete data was available for 70% of the patients.

Kidney function women vs. men

Mean creatinine was higher in men than in women whereas eGFR according to both formulas was lower in women than in men, 69 and 66 mL/min compared to 81 and 88 mL/min, MDRD and CG used, respectively. Renal insufficiency, defined as eGFR < 60 mL/min(/1.73m^2) was present in 38% in women vs. 19% in men according to MDRD and in 50% of men vs. 22% of men according to CG ($p<0.001$ for both comparisons). Among men 33% and 45% were staged as being in the best CKD stage, compared to 20% and 19% of women, MDRD and CG used, respectively. After stratifying upon age, more than 90% of men and 75% of women were in CKD stage 1 in the youngest age group whereas only a few percent among the oldest men and women were in the best CKD group, according to CG. The difference in CKD stage between age-groups was less pronounced if MDRD was used. (Figure 18)

After multivariable adjustments, female gender was associated with 58% higher risk of RI if MDRD was used (OR 1.58, 95% CI 1.48 – 1.68). If CG was used, women had more than twice as high risk of RI compared to men (OR 2.18, 95% CI 2.02 – 2.36). Women had also higher multivariable adjusted risk of severe CKD (<30 mL/min) according to both formulas (OR 1.30, 95% CI 1.11 – 1.47 according to MDRD, OR 1.85, 95% CI 1.61 – 2.12 according to CG, women vs. men)

Figure 18. Prevalence of the different CKD stages in age subgroups in each gender



Baseline characteristics, RI compared to non RI patients

Patients with RI were older than the non RI patients, 9 years in women, 11 years in men. They were leaner with higher heart rate and lower blood pressure on admission. In both men and women, they were half as often smokers compared to non RI patients but had twice as often suffered from a previous MI or a stroke and had previous heart failure four times as often. They had higher prevalence of diabetes, hypertension and peripheral artery disease. More than 40% were already on aspirin and beta-blockers on admission and more than 20% were on ACE-inhibitors or ARBs, which was twice as often as non RI patients, regarding both genders. (Table 10)

Among women with RI mean eGFR were 44 and 40 mL/min, MDRD and CG used respectively. In men with RI corresponding figures were 45 and 46 mL/min. Among women without RI, eGFR was 85 and 80 mL/min compared to 89 and 97 mL/min in men, MDRD and CG used, respectively. (Table 10)

In both genders, complications such as AV-block, re-infarctions and bleeding were about twice as common and cardiogenic shock three times as common among RI patients compared to non RI patients. (Table 10)

Evidence-based therapy in RI and non RI patients

Among RI patients, 65% of men vs. 54% of women received acute reperfusion therapy. Among non RI patients the corresponding figures were 89% vs. 80%, respectively. At discharge, in both genders, RI patients had significantly less chance of evidence-based treatment compared to non RI patients. Also, among both RI and non RI patients, men had significantly higher chance than women of getting these therapies. (Table 10)

Impact of reduced eGFR on outcome

Nineteen percent of women with RI compared 5% of women without RI died during hospital care. The corresponding figures in men were 15% vs. 3%. During follow-up, 52% of women with RI died compared to 20% of women without RI. Corresponding figures in men were 46% vs. 13%. For each incremental step of CKD stage, the long term mortality increased in both genders. (Figure 19)

After multivariable adjustments, the risk of in-hospital mortality per 10 mL/min decrease in eGFR increased with 29% and 33% in men vs. 22% and 28% in women, CG and MDRD used respectively. RI compared to non RI patients had approximately twice the risk of in-hospital mortality in women and 2.5 times higher risk in men after multivariable adjustments. The increased risk of long term mortality per 10 mL/min decline of eGFR was 16% and 11% in women vs. 11% and 9% in men, CG and MDRD used, respectively. The risk of long term mortality was about 1.5 higher in RI compared to non RI patients in both men and women, according to both formulas. (Table 11)

There was no significant interaction between gender and eGFR regarding short- or long term outcome according to any of the formulas.

Table 10. Baseline characteristics, hospital care and outcome in RI vs. non RI patients, each gender separately.

	WOMEN			*MEN*		
	RI (n=4585)	**Non RI (n=7454)**	**p-value**	**RI (n=4411)**	**Non RI (n=18902)**	**p-value**
Baseline characteristics						
Age in years, mean (SD)	79.4 (9.3)	70.2 (12.3)	<0.001	75.5 (10.2)	64.2 (11.6)	<0.001
Weight in kg, mean (SD)	67.8 (13.8)	68.8 (14.0)	0.001	80.1 (14.0)	83.3 (13.6)	<0.001
Systolic BP, mmHg, mean (SD)	135.8 (32.8)	142.1 (29.6)	<0.001	133.9 (31.2)	141.8 (28.2)	<0.001
Heart rate, beats/min, mean (SD)	80.8 824.9)	78.2 (20.5)	<0.001	79.2 (24.7)	75.1 (19.2)	<0.001
Current smoker	614 (15.4)	2376 (34.3)	<0.001	700 (18.0)	5979 (33.4)	<0.001
Co-morbidity						
Previous myocardial infarction	1133 (25.0)	865 (11.7)	<0.001	1339 (30.7)	2759 (14.7)	<0.001
Previous PCI	196 (4.3)	305 (4.1)	0.58	359 (8.3)	1347 (7.2)	0.01
Previous coronary artery bypass grafting	134 (2.9)	120 (1.6)	<0.001	320 (7.3)	691 (3.7)	<0.001
Diabetes Mellitus	1286 (28.2)	1326 (17.9)	<0.001	1132 (25.8)	3244 (17.2)	<0.001
Hypertension	2534 (56.3)	3061 (41.6)	<0.001	2112 (48.8)	5950 (31.9)	<0.001
Previous heart failure	933 (20.3)	398 (5.3)	<0.001	735 (16.7)	690 (3.7)	<0.001
Previous stroke	743 (16.2)	640 (8.6)	<0.001	764 (17.3)	1278 (6.8)	<0.001
Peripheral artery disease	305 (6.7)	214 (2.9)	<0.001	354 (8.0)	434 (2.3)	<0.001
Therapy on admission						
Aspirin	1965 (43.3)	1869 (25.3)	<0.001	1888 (43.4)	4336 (23.1)	<0.001
Other platelet inhibitor	234 (5.2)	259 (3.5)	<0.001	249 (5.7)	641 (3.4)	<0.001
Beta–blocker	2088 (46.3)	2087 (28.3)	<0.001	1849 (42.6)	4442 (23.7)	<0.001
Angiotensin converting enzyme inhibitor	942 (20.9)	845 (11.4)	<0.001	1001 (23.1)	2224 (11.9)	<0.001
Angiotensin receptor blocker	451 (12.9)	515 (8.3)	<0.001	442 (13.2)	1065 (6.8)	<0.001
Statin	828 (18.3)	1089 (14.8)	<0.001	1007 (23.3)	3118 (16.6)	<0.001
Therapy/procedures at CCU						
Coronary angiography	2419 (52.9)	5154 (69.2)	<0.001	2610 (59.3)	14938 (79.1)	<0.001
Reperfusion therapy	2464 (53.7)	5964 (80.0)	<0.001	2868 (65.0)	16852 (89.2)	<0.001
Kidney function						
Creatinine (umol/L)	125.3 (68.0)	66.4 (11.3)	<0.001	162.7 (98)	83.8 (14.2)	<0.001
eGFR, MDRD (mL/min/1.73m^2)	43.7 (12.3)	85.2 (23.3)	<0.001	45.0 (12.7)	89.0 (26.0)	<0.001
eGFR, CG (mL/min)	39.5 (15.4)	80.0 (30.7)	<0.001	45.5 (16.8)	97.0 (33.9)	<0.001
Complications during hospital care						
Killip class IV (cardiogenic shock)	320 (7.5)	185 (2.7)	<0.001	285 (7.0)	393 (2.2)	<0.001
Ejection fraction ≤50%	1638 (67.3)	2559 (51.2)	<0.001	7068 (52.3)	6439 (47.7)	<0.001
2nd-3rd degree atrioventricular block	237 (5.2)	169 (2.3)	<0.001	213 (4.9)	376 (2.0)	<0.001
Major bleeding	172 (4.5)	161 (2.4)	<0.001	133 (3.6)	202 (1.2)	<0.001
Re-infarction	120 (2.7)	106 (1.4)	<0.001	120 (2.8)	238 (1.3)	<0.001
Therapy at discharge						
Aspirin	3591 (79.9)	6740 (91.0)	<0.001	3565 (82.1)	17603 (93.6)	<0.001
Other platelet inhibitor	2351 (52.3)	5601 (75.7)	<0.001	2567 (59.2)	15338 (81.5)	<0.001
Beta-blockers	3473 (77.4)	6419 (86.7)	<0.001	3436 (79.2)	17001 (90.4)	<0.001
Angiotensin converting enzyme inhibitor	2089 (46.5)	4263 (57.7)	<0.001	2224 (51.3)	12123 (64.5)	<0.001
Angiotensin receptor blocker	427 (12.2)	572 (9.1)	<0.001	414 (12.3)	1198 (7.6)	<0.001
Statins	2521 (56.2)	5891 (79.6)	<0.001	280 (64.8)	16524 (87.9)	<0.001
Outcome						
In-hospital mortality	849 (18.5)	379 (5.1)	<0.001	675 (15.3)	494 (2.6)	<0.001
One year mortality	1419 (33.6)	773 (11.5)	<0.001	1226 (30.2)	1139 (6.7)	<0.001
Long term mortality	2368 (51.6)	1505 (20.2)	<0.001	2038 (46.2)	2501 (13.2)	<0.001

Data presented as numbers (percentages) if not otherwise indicated. RI, renal insufficiency; SD, standard deviation; BP, blood pressure; PCI, percutaneous coronary intervention; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease study; CG, Cockcroft Gault

Figure 19. Long term outcome in CKD stage 1-4 according to MDRD and CG formulas.

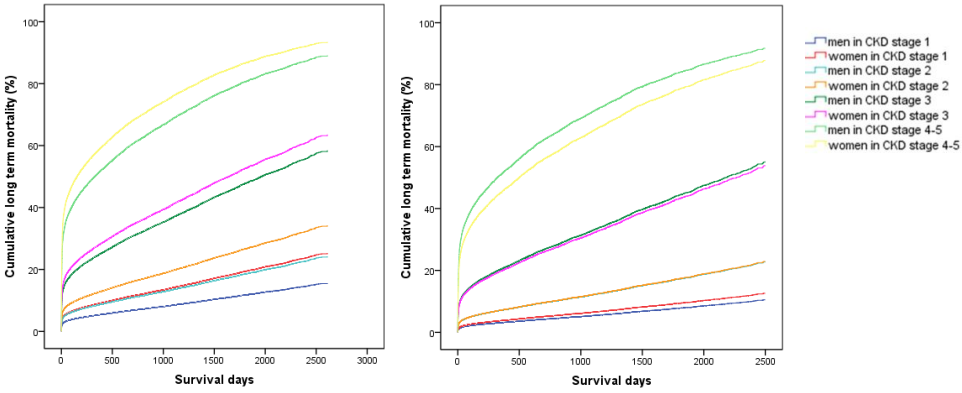


Table 11. Impact of reduced renal function on short and long term outcome in men and women.

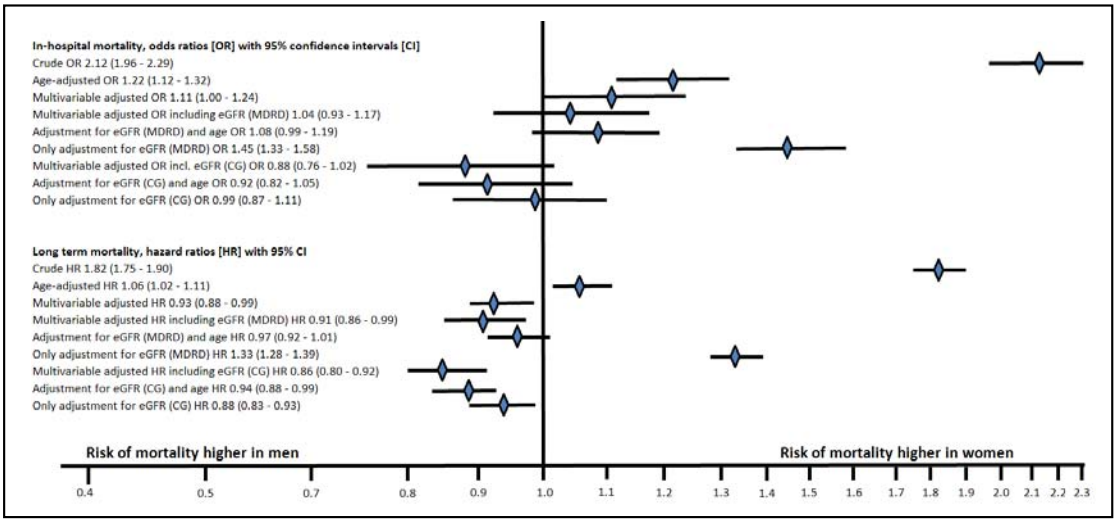
	Multivariable adjusted OR/HR (95% CI) MDRD used	Multivariable adjusted OR/HR (95% CI) CG used
In-hospital mortality		
Men (n=25062)		
Per 10 mL decline in eGFR	1.33 (1.18 – 1.28)	1.29 (1.23 – 1.36)
RI compared to non RI	2.59 (2.19 – 3.07)	2.49 (1.95 – 3.17)
Women (n=12929)		
Per 10 mL decline in eGFR	1.28 (1.23 – 1.33)	1.22 (1.14 – 1.30)
RI compared to non RI	2.01 (1.69 – 2.38)	1.87 (1.40 – 2.49)
Long term mortality		
Men (n=25062)		
Per 10 mL decline in eGFR	1.09 (1.07 – 1.11)	1.11 (1.08 – 1.13)
RI compared to non RI	1.57 (1.43 – 1.72)	1.43 (1.27 – 1.60)
Women (n=12929)		
Per 10 mL decline in eGFR	1.11 (1.09 – 1.14)	1.16 (1.12 – 1.19)
RI compared to non RI	1.47 (1.34 – 1.62)	1.71 (1.47 – 1.99)

OR, odds ratio; HR, hazard ratio; CI; confidence interval; MDRD, Modification of Diet in Renal Disease study; CG, Cockcroft Gault; RI, renal insufficiency

Gender differences in outcome and impact of eGFR

Women had more than twice as high in-hospital (11.0% vs. 5.5%) and higher cumulative long term mortality (33.4% vs. 20.1%) than men. After adjustment for age, women still had 22% higher risk of in-hospital and 6% higher risk of long-term mortality. After multivariable adjustments including all confounders except kidney function women had 7% lower risk of long term mortality but still 11% higher risk of in-hospital mortality. If eGFR according to any of the formulas was also included, there was no longer a gender difference regarding in-hospital mortality and women still had lower risk of long term mortality. In fact, after just adjusting for eGFR according to CG, there was no longer any gender difference in short term mortality and women had lower risk of long term mortality. (Figure 20)

Figure 20. Impact of eGFR on gender differences in short and long term mortality



VII. Discussion

Background characteristics

Age and co-morbidity

There is an old notion that myocardial infarction is a male disease. The fact is that almost half of all women as well as men will die of cardiovascular diseases in Sweden, dominated by IHD.[2] Although the incidence of IHD is markedly lower among women than men prior to the age of 50 years, it increases in women after menopause and approaches that seen among men in the highest ages.[1, 5] The number of deaths caused by MI per year in Sweden is approximately the same in women and men.[2] Among STEMI patients, women comprise a minority but they have higher case fatality.[47, 48] Around thirty-five percent in our cohorts (Paper I, III -V) were women, which is similar to other studies based on observational registers including consecutive STEMI patients.[281] This is considerably higher than in randomised clinical STEMI trial cohorts where the proportion of females has typically been around 25% [48, 196, 271, 273] because of exclusion of the oldest, patients with co-morbities such as CKD but also premenopausal women.[343, 344]

We found (paper I) in accordance with others[47, 48, 269, 271, 281, 310, 329] that women were older than men in the STEMI group. Women were on average 73 years old and men 66 years old, which are older than compared to cohorts derived from randomised clinical trials,[48, 132, 272] but similar to other observational register reports.[263] The major reason to the well-known 7-9 years age gender difference in age of first MI is probably the higher risk factor levels at younger ages in men compared to women.[63]

The women had higher prevalence of diabetes, hypertension, stroke, heart failure as well as COPD. On the other side, men were more often smokers, had a history of previous MI or had undergone previous revascularisation procedures. These are findings concordant with previous studies.[48, 269] The age difference is a major reason to the higher co-morbidity in women, but we found that age alone did not explain these gender differences as women had 16-42% higher age-adjusted risk of smoking, diabetes, hypertension, congestive heart failure and COPD.[9] Major IHD risk factors are the same in women and in men[62, 63] but particularly diabetes and smoking has been shown to interact with gender as regards risk of CAD, with higher relative risks in women than in men.[63, 64 345-348] The anti-oestrogenic effect has been proposed as an explanation for the higher relative risk associated with smoking in women than in men.[348]

Young STEMI patients

The younger the mean age of studied MI subjects, the higher is the male-to-female ratio.[349] According to INTERHEART data, it appears that this is largely explained by a lower risk factor burden in women than in men in young ages.[63] In our young STEMI cohort (Paper II) with patients aged 45 years old or less, only 18% were women, which is in accordance with previous reports (mixed MI cohorts).[349, 350] As women are relatively spared from IHD before menopause, there have been speculations that those who become affected have either a particularly aggressive disease driven by a load of traditional risk factors,[281] or have another pathophysiology,[261, 281] such as coronary vessel dissection,[26] vasospasm or pure thrombotic

disease.[28, 29] In agreement with the first hypothesis, we found at least one IHD risk factor (defined as current smoker, diabetes mellitus, hypertension and/or statin therapy before arrival) in the vast majority of these young women and one forth had two or more risk factors. In the young men the majority had at least one previously known IHD risk factor, although fewer than among women. The prevalence of diabetes and hypertension was 50% higher in young women than in young men. Compared to the whole (older) STEMI cohort (Paper I), the prevalence of diabetes was approximately the same in the young as in the older women (19% among the young, 21% among the older) whereas among men there was a difference in prevalence between the younger and the older (12% and 17%, respectively). A more marked gender difference in risk profile among younger than in older MI patients has been shown also by others in mixed MI cohorts,[9, 281] and support the hypothesis that premenopausal women needs a higher burden of risk factors in order to suffer from MI.

The most prevalent risk factor in this young cohort was smoking. As many as 64% of the women were smokers compared to 58% of the men, which were far higher numbers compared to what we found in the older cohort (25% of women, 30% of men in Paper I). This is although somewhat lower than in previous studied young mixed MI cohorts were the percentages of smokers have ranged between 70-90%.[21, 349, 351, 352] Smokers usually suffer their first MI earlier in life compared to non-smokers and it is shown before that this age difference seems to be greater in women than in men.[353, 354] Our data support previous epidemiological studies findings of smoking as the most important risk factor for developing MI in young age.[355] In contrast to studies on older cohorts, thus women were smokers more often than men in this young cohort. As already discussed, smoking has even more deleterious effects in women than in men,[63, 64, 345, 346, 348] including a stronger dose-response relationship,[346, 348] and thus it is particularly alarming that smoking is twice as common in girls than in boys according to the latest National Health report.[356]

Previous studies have also found that young MI patients often have positive family history of premature CAD, especially among the non-smokers,[357] but this risk factor was not mandatory to register in RIKS-HIA/SWEDEHEART and was therefore not included in our analyses. Other non-classical risk factors/MI causes, that we did not study, but which have been found more prevalent in younger than in older MI cohorts are cocaine use, congenital coronary artery anomalies, antiphosphlipide syndromes, certain lipid abnormalities and septic or paradoxical embolisations.[23]

Renal insufficiency

RI prevalence varies with age, race and gender and increases with advancing age according to both formulas, but most if CG is used.[358] [359] The most recent NHANES III survey found an increasing prevalence of RI in the American population, in total 8.1%, but 37.8% in people aged over 70 years.[88] More relevant for the Swedish situation is data from the HUNT II study, according to which 4.7% of the Norwegian population have RI, 18.6% in the subgroup aged over 70 years. RI was more prevalent in women than in men, even though gender specific data was not presented in age subgroups.[360, 361] End-stage renal failure is a well-known independent risk factor both regarding development of IHD as well as for poor outcome in case of MI,[78, 79] but already when eGFR according to MDRD goes below 60 mL/min/1.73m^2 there is an increased risk of morbidity and mortality.[90] The last decade mild to moderate renal impairment has been proven associated with adverse outcome also in ACS patients [82, 91, 97, 362] including STEMI.[81, 91, 94, 97, 98] Furthermore, Fox et al recently showed that the mortality gradient with increasing CKD stage was steeper in STEMI vs. in NSTE ACS patients.[94] The

eGFR is also important to know in order to adjust doses of several drugs commonly used in patients with ACS. Many drugs with exclusive or substantial renal elimination need to be down-titrated or might even be contraindicated in CKD patients, including enoxaparin, fondaparinux, bivalirudin, and small-molecule GP IIb/IIIa receptor antagonists.[45] The prevalence of CKD according to the National Patient Register in our studies was low and without a gender difference (Paper I and III). Only around 1% of the STEMI patient had a previous diagnose of CKD, which corresponds to numbers from other registers.[268] This is although a huge underestimation if all patients with at least moderate CKD (eGFR < 60 mL/min, RI) had been encountered and diagnosed. According to previous data, around 30% of all ACS patients have RI when this has been more thoroughly investigated, estimating eGFR for all patients.[81, 363] Starting in the mid 2000[s] to measure eGFR routinely we realised from daily practice that far more women than men had RI. This was also evident from studies exploring the relation between CKD stage and outcome in ACS, with increasing number of women as worse CKD stage studied.[81, 82, 97] This gender difference has been assumed explained by the higher age in women in several studies.[81, 99] The HERS study showed that even mild renal dysfunction (defined as CrCl 40-60 mL/min) in postmenopausal women with CAD was independently associated with a 20-30% increased risk for cardiovascular events such as MI, stroke and cardiovascular death.[364] According to our knowledge no-one had explored gender differences in a STEMI population with the aim to study if female gender per se is associated with RI in this setting.

In Paper IV we found a huge gender difference in RI prevalence, 67% of women compared to 26% of men and furthermore that women had more than 5 times multivariable adjusted risk of RI. There are very few related works in this area but a study on consecutive patients undergoing coronary angiography investigated the relation between gender and presence of CAD and long term outcome. They found an even higher prevalence of RI in their study subjects, 74% of women (mean age 63 years) compared to 45% of men (mean age 61 years), MDRD formula used. Their study was anyhow limited by missing values for SCr for 60% of the cohort[100] and our study by a very small population, from a limited geographic area.

Accordingly, as these findings were very interesting but more of hypotheses generating, we decided to continue with a bigger study using an updated SWEDEHEART database. A cohort of almost 38 000 STEMI patients admitted 2003-2009 was used (Paper V). Complete data for the MDRD formula was available for 93% of patients and for the CG formula for 70% of patients. According to MDRD, 38% of women and 19% of men had RI, which were considerably lower rates especially in women compared to our previous study, but still very high rates. The mean age and prevalence of diabetes was not higher in women in the smaller of the cohorts, rather the opposite. Thus the high prevalence of RI in women in our small cohort could be a matter of chance because of its small size, although other differences in risk profile between the cohorts or possible geographic differences cannot be excluded.

A previous study from the CRUSADE register including approximately 47 000 NSTE ACS patients, found that patients with moderate CKD according to CG but not MDRD had similar rates of major bleeding and of in-hospital mortality as when there was CKD agreement between the formulas. Patients with moderate CKD according to MDRD but not CG had lower rates of adverse events. In accordance, a Swedish study on 36 000 mixed MI patients found better prediction of one year mortality by CG compared to MDRD.[363] Accordingly, in paper V we also used the CG formula in addition to MDRD. When CG was used half of the women in our cohort had RI, as compared to one fifth of the men. In fact female gender was found to be independently associated with mild, moderate as well as severe CKD regardless

of used formula.

Thus, one of the most striking findings in both Paper IV and V was the high rate of CKD in women with STEMI regardless of used formula. The much higher risk of RI in women compared to men, especially according to CG, is a very important finding with many clinical implications both regarding dose adjustments and as a prognostic marker. Future studies ought to evaluate whether this gender difference in RI prevalence have impact on how we treat female and male STEMI patients, as previous studies have found not only gender differences in management[260, 261, 263, 274, 275, 279, 284, 285] but also a progressive underutilisation of cardioprotective therapies including reperfusion therapy with worsening CKD stage.[87, 94-96] Further which of the equations that better predict the underlying true renal function in female vs. male STEMI patients, is currently not known. There are conflicting data which of the two formulas better predict the true underlying renal function,[365] which probably is due to differences in distributions of age, sex, BMI and degree of renal dysfunction among studied cohorts.[70] The coefficient for gender differs between the two formulas, and they handle age differently mathematically as well. A coefficient derived in a given cohort may not adequately predict gender-associated difference in muscle mass (as source of creatinine) in another cohort (depending on differences in anthropometrics, age distribution etc).[70]

Therapy before arrival to hospital

There were some gender differences in therapy on admission. Women had more often ASA, beta-blockers, CCB, ACE-inhibitors or ARBs but these gender differences were small. (Paper I) The most marked gender difference was noticed regarding use of diuretics and digitalis, which was twice as common in women. This probably reflects their higher prevalence of hypertension and chronic heart failure, but then it is noteworthy that there was a much smaller gender difference in use of ACE-inhibitors and ARBs in spite of the higher prevalence also of diabetes and previous stroke in women. Also the use of statins was higher in men reflecting their higher LDL compared to women, except in the oldest ages[366] but also their higher prevalence of previous MI and revascularisation procedures. After age-adjustments, there were only small differences in therapy on admission, i.e. the main explanation to the higher use of these drugs in women was their higher age. Also after age-adjustments women had almost twice as high probability of treatment with diuretics.

Delay times

Delay-time was defined in our studies as from symptom onset until arrival to either CCU or cath lab, as this delay time was registered for the vast majority of patients. In accordance with previous studies, women had longer delay-times compared to their male counterparts. This was noticed in the total cohort (Paper I), and more disturbing, when studying an early and a late cohort (Paper III), the gender difference in delay did not diminish. A difference in median delay time from symptom-to-door time of 30 minutes was noticed in both time periods, as was exactly the same as in the analysis from ExTRACT-TIMI 25 study on STEMI patients treated with fibrinolysis, and in the fibrinolytic arm in the PRAGUE 1 and 2 studies.[137, 196] Longer patient delay times have also been found in primary PCI studies.[139, 310] In the late time period in Paper III, both men and women arrived later to CCU/cath lab compared to the early period. This is most probably due to the shift in reperfusion strategy from fibrinolysis to primary PCI. As many patients do not have a hospital with PCI facilities as their nearest hospital, transportation times will be longer compared to during the fibrinolytic era when they were treated at the nearest hospital or in the ambulance. Mechanisms to minimize delays to

definitive treatment (optimally <2 hours) can be expected to have beneficial impact on survival,[367] as every 30 min increased delay to primary PCI has been shown to increase mortality with 7.5%. Thus it is of great importance to reduce the delay times in all STEMI patients, especially in women.[310, 368]

A review revealed clinical, sociodemographic and psychosocial factors all contributing to the longer pre-hospital delay in women,[369] but reasons to the longer patient delay time in women within the STEMI population has to be further studied as well as methods in order to reduce it. Interestingly, and in contrast to speculations that young women do not recognize MI symptoms and thus delay,[281] we did not find any gender difference in patient delay time (7 min difference in median symptom-to-door time, p=0.18) in the young cohort (Paper II). In addition, the delay times in this young cohort were considerably shorter compared to in the old cohort (Paper I and III) which is consistent with previous findings that older MI patients delay more than younger, but also that the gender differences seems to be restricted to older MI patients.[52]

Hospital care

Reperfusion therapy

Reperfusion therapy has been shown to improve outcome after STEMI with reduced mortality [370] and should be provided as soon as possible and preferably as primary PCI[3, 75, 226, 371] as it has been proven superior of fibrinolysis.[107, 121] However fast admission of fibrinolysis, preferably pre-hospital, is also effective and the primary objective is to treat more STEMI patients with any type of reperfusion therapy.[372] In spite of this several previous studies have found that approximately 30% of STEMI patients do not receive reperfusion therapy [373] although with decreasing numbers over time.[283] In Paper I covering 1999-2006 63% of women compared to 72% of men received reperfusion therapy. In accordance, from the AMIS Plus Register in Switzerland, 55% of women compared to 69% of men received reperfusion therapy among STEMI patients registered 1997-2006.[263] Corresponding figures from the American Get With the Guidelines register (GWTG-CAD) with over 25 000 STEMI-patients registered 2001-2006, were 56% vs. 73%.[264] From the large American NRMI register a report including over 126 000 STEMI patients, an even larger difference was reported.[281] However, these data where not thoroughly evaluated, and no adjustments for confounders were done regarding this particular endpoint in any of these registers.[263, 264, 281] Thus, we wanted to evaluate if female gender was independently associated with not receiving reperfusion therapy. Also after adjustment for age, co-morbidities, therapy before arrival, type of hospital, year of inclusion, Killip class and delay-time women still had 17% less chance of receiving this therapy. (Paper I) In accordance, Eagle et al. found from the GRACE register that female sex was one of eight independent factors associated with not receiving reperfusion therapy among STEMI patients presenting within 12 hours of symptoms, together with previous heart failure, previous CABG, diabetes, previous MI, delay time, age and year of inclusion.[283]

In subgroup analyses the gender difference in receiving reperfusion was most pronounced among the elderly. There are previous findings that elderly patients have less chance to receive reperfusion therapy than younger even when eligible.[373, 374 375] Although there is general agreement that the risks of reperfusion therapy are greater in an elderly population, studies suggest that elderly people tend to derive a benefit equal to, if not greater than, that obtained by younger.[129, 375] In contrast to a report by Champney et al from the American

NRMI register,[281] in our young STEMI cohort, no gender difference in rate of reperfusion therapy was found, and the vast majority (78 and, 81%, women vs. men, p=0.28) received reperfusion therapy. (Paper II)

During the fibrinolytic era, many studies found gender differences in case fatality in STEMI patients, and fibrinolytic therapy was the dominating reperfusion strategy in Paper I. Several studies before us have shown an increased risk of bleeding, stroke and intracranial haemorrhage in women treated with fibrinolysis as compared to men, also in selected randomised clinical trial cohorts testing different fibrinolytic regimes.[132, 196] Female gender has been proven a powerful independent risk factor of bleeding after fibrinolytic therapy[130-132] together with high age, low body weight, renal failure and anaemia. Thus, in addition to higher age and co-morbidity, the higher risk of severe bleeding, together with the longer symptom-to-door time in women, could be major reasons for the noticed gender gap in rate of reperfusion therapy in spite of the proven net clinical benefit of fibrinolysis in both genders.[124]

Fibrinolytic therapy vs. primary PCI

As high risk subjects, several studies suggest that women compared with men would derive a higher absolute benefit from primary PCI compared with fibrinolytic therapy.[135-138] Primary PCI is also less time-dependant compared to fibrinolytic therapy. Thus, according to the DANAMI-2[376] and PRAGUE studies[377, 378], even after transportation, primary PCI was proven superior to on-site fibrinolysis.[107] Even though female gender has been shown to be an independent predictor of bleeding and vascular complications also in the setting of PCI [304, 318] several procedural improvements (radial approach, smaller sheaths, closer devices, improved antithrombotic therapies etc.) have led to an overall decline in complication rate post-PCI.[379-381] Accordingly, several modern studies have not found female gender to be independently associated with PCI failure or PCI complications.[137, 139] In paper III we compared two cohorts included during two time periods with different dominating reperfusion strategy (primary PCI in 9% vs. 68% among patients receiving reperfusion therapy, early vs. late period, respectively). A similar number of patients were registered during the two time periods, and the gender difference in mean age or in delay time did not differ. Surprisingly, we did not find a diminished gender treatment gap. After multivariable adjustments women had 14% and 20% less chance of receiving reperfusion therapy, early and late periods, respectively, and accordingly our hypothesis failed. In our Paper V we noticed a persistent gender treatment gap, where 69% of women compared to 84% of women received reperfusion therapy between 2006 until 2009 (almost exclusively as primary PCI). This was anyhow not further analysed as that was not the scope of that particular paper, but ought to be scrutinised in later work. In concordance others have shown a gender treatment gap, also regarding reperfusion therapy in form of primary PCI.[263]

There could be plenty of possible reasons to this persistent gender gap during the new primary PCI era. Firstly, a higher prevalence of TIMI III flow upon acute angiography in women would explain less primary PCI treatment. However, this cannot explain the gender difference in use of angiography (20% less chance during the late time period). Also, even though a higher prevalence of non-obstructive disease in women has been noticed in mixed MI and NSTE ACS cohorts[48, 268], there small gender differences in extent of coronary artery disease in pure STEMI cohorts[48, 137, 268, 329] which was also the case in the late time period in Paper III, where we had available data from 97% of investigated patients.

A second reason could be co-morbidities not adjusted for, such as kidney function, which was

not available during these years in RIKS-HIA/SWEDEHEART, as well as anaemia. Both these variables are strong predictors of bleeding in ACS patients besides age and female gender.[294, 382] The marked gender difference in prevalence of RI noticed in our studies Paper IV and V, added to its proven impact on management as well as outcome in previous works, makes it an important confounder that ought to be adjusted for in future studies examining gender differences in management and outcome in ACS.

A third reason could be a higher death rate before the opportunity of receiving reperfusion therapy. Even though the case fatality is highest the first 24 hours in STEMI, as well as the gender gap in outcome, this probably explains at most a minor part of the gender difference. Patients dying in the ambulance are not registered in RIKS-HIA/SWEDEHEART, and as reperfusion therapy should be given immediately after arrival (or before in case of prehospital fibrinolysis) the number of such cases ought to be few. Also, in case of cardiogenic shock (i.e. Killip IV) that was more prevalent in female than in male STEMI patients in accordance with others,[268] primary PCI is the first line treatment in order to save lives.[134]

A forth reason could be a fear of complications post-PCI. Although the overall complication risk post PCI have declined, the increased adjusted relative risk of bleeding (approximately 2-fold) in women vs. men has not diminished over time, at least not after femoral approach. Female gender was still an independent risk factor of both bleeding and vascular complications in a quit recent analysis on 200 000 ACS patients (40 000 STEMI) from the American national cardiac catherisation register.[268] If radial approach will abolish this increased risk in women is still not clear. From the EASY trial, with radial approach in ACS patients with maximal antiplatelet therapy, female gender was not associated with post-PCI complications except for local hematomas.[308] On the other side, in the bigger RIVIERA trial, female gender was still an independent risk factor of bleeding post-PCI also after adjusting for radial approach, which was associated with lower risk.[383] Very few STEMI patients were included in these trials. Thus STEMI patients undergoing primary PCI with a radial approach ought to be assessed with a gender perspective.

Finally a gender management bias cannot be excluded. Withholding a certain therapy from patients with high risk is a well-known phenomenon called the "treatment-risk paradox" for example shown in NSTE ACS patients regarding invasive treatment, [384-386] , but also shown in STEMI regarding reperfusion therapy.[387] Women with STEMI are probably not perceived as a high risk group, which they indeed are.[48, 310, 329] Thus, management including acute angiography and reperfusion therapy in a gender perspective should be further evaluated in future STEMI studies.

Angiographic data

Previous STEMI studies have found small or no differences between the genders in extent of coronary artery disease as opposed to studies on NSTE ACS cohorts, where women have non-obstructive disease or one vessel disease more often and multivessel disease more seldom than men.[48, 137, 268, 310, 329] According to recent studies, where all or the vast majority of consecutive STEMI patients underwent coronary angiography, approximately 2-3% of both women and men had zero vessel disease, about 45% had one vessel disease and close to 25% had multivessel disease.[310, 322, 329] As data from young mixed MI cohorts (i.e. including both NSTEMI and STEMI patients) have reported a high incidence of non-obstructive disease compared to older MI cohorts, especially in women,[21, 22] a higher prevalence of non-atherosclerotic causes of MI in young women such as hypercoagulable states or coronary

artery spasm has been assumed.[261, 281] Young women have been shown to have more active platelets [37] and more often plaque erosion instead of plaque ruptures compared to men and postmenopausal women.[20] Thus we aimed to analyse a young STEMI cohort as regards angiographic findings (Paper II) in order to evaluate if we could support those theories in a pure STEMI cohort. As compared to reports on older cohorts, the prevalence of non-obstructive disease was higher, but no gender difference was noticed (8% vs. 7%, women vs. men, p=0.64). On the other hand one vessel disease was much more prevalent in those young women compared to the young men (73% vs. 59%, women vs. men, p<0.001). Accordingly, multivessel/left main disease was more prevalent in men (19% vs. 34%, women vs. men, p<0.001). Whether we had more pure thrombotic lesions in women compared to men (i.e. without an underlying plaque rupture) cannot be answered by our study. Thus, we cannot confirm that these young women have another pathogenesis but they have a much less advanced atherosclerotic disease, which probably explains our finding of less re-infarctions during follow-up compared to their male counterparts.

Complications

Women with STEMI comprise a high risk subgroup. In spite of better EF, women had much higher incidence of symptoms of heart failure (Paper I).This was true also after age-adjustments (Paper I) and it was also seen in the young STEMI cohort (Paper II). Probably a higher prevalence of diastolic heart failure due to higher prevalence of hypertension and diabetes is the key explanation.[268] Cardiogenic shock on admission was more common in women than in men in Paper I, also after age-adjustment. The incidence of cardiogenic shock was lower in the late compared to in the early period (Paper III), but the gender difference persisted. The prevalence of bleedings was higher in women, both before and after adjustment for age (Paper I). Women had actually higher age-adjusted risk of bleeding after primary PCI compared to after fibrinolysis (times 2 compared to 19% higher risk, the latter with borderline significance). These finding must be interpreted with caution as we had valid data for 96% of patients treated with fibrinolysis but only for 61% of primary PCI treated patients, and thus a selection bias could have influenced these results. Anyhow the increased risk of bleeding in women (partly because of their high age and high prevalence of RI, but also as an inherent risk) needs further evaluation in future primary PCI studies, especially after the introduction of new even more effective antiplatelet drugs.

Discharge therapy

The continuous research and development in CVD influenced treatment guidelines in between the two studied periods in Paper III.[371] Accordingly, therapies such as clopidogrel, ACE-inhibitors/ARBs and statins were more used in the late compared to the early period as secondary prevention in hospital survivors. We analysed if female gender was an independent predictor of not receiving evidence-based therapies at discharge. In the late time period women had lower chance of receiving any of these evidence-based therapies in spite of higher prevalence of heart failure, diabetes and hypertension. In absolute numbers, the crude differences (men vs. women) were small (although significant depending on the high number of patients) as regards aspirin (94% vs. 91%), beta-blockers (91% vs. 88%) and ACE-inhibitors/ARBs (66% vs. 61%) but more marked regarding clopidogrel (79% vs. 68%) and statins (85% vs. 74%). Age can explain much of these differences, with higher risks of adverse drug effects as well as attempts to avoid polypharmacy. Anyhow, a higher crude rate of ACE-inhibitors/ARBs would have been expected in women than in men, depending on their higher prevalence of diabetes, heart failure and hypertension. Age alone did not explain

this gender difference as also after multivariable adjustments women had 14-25% lower chance of receiving those therapies with lowest odds ratios for beta-blockers (0.79, 95% CI 0.69 – 0.91), statins (OR 0.77, 95% CI 0.69 – 0.86), and ACE-inhibitors/ARBs (0.75, 95% CI 0.68 – 0.81).

There is conflicting evidence whether there are gender differences in evidence-based treatment at discharge in MI patient.[263, 269, 274, 275, 284, 326, 388] Reasons to diverging results could be differences in age-distribution, mix of NSTEMI and STEMI or whether the cohort was derived from a randomised clinical trial or not. Our study reflects real life clinical practice, with older patients with more co-morbidity compared to in RCTs. Possible reasons for the management gap could be confounders not adjusted for, such as reduced eGFR. Adverse drug effects are not reported in SWEDEHEART and are thus not accounted for in the multivariable analyses. It is plausible that women to a higher extent than men reported previous or current experiences of adverse drug effects.[152, 389] Apart from the higher risk of bleeding already discussed, women also have higher risk of developing cough on ACE-inhibitor treatment,[152, 236] but also adverse drug reactions of statins and beta-blockers.[152, 389] There are several gender differences that could affect basic pharmacology such as in lean/fat mass ratio, circulating plasma volume, amount of drug-binding plasma proteins, gastrointestinal motility, expression of drug-metabolizing enzymes etc.[152, 389] Thus, knowledge of correct dosage is important in order to avoid adverse drug-reactions. Trying to individualise and find a well tolerated class and dosage of the evidence-based drugs must be the goal in order to obtain well-being simultaneously as trying to avoid new future cardiovascular events.

Outcome

Short term outcome

Plenty of MI studies during the last two decades have found higher short-term mortality in women.[47, 117, 196, 257, 261, 264, 271, 272, 274, 275, 279-281, 284, 285] After adjustments for age and other confounders, female gender has still been an important predictor of adverse short term outcome in many[132, 196, 260, 261, 271, 274, 285, 329, 390] but not all studies.[263, 268, 273] Most of these have not separated STEMI from NSTE ACS,[117, 260, 261, 274, 275, 279, 280, 285] which has been proved important the last couple of years as there seems to be an interaction between gender and type of ACS regarding outcome, at least in the short term.[47, 48] During the fibrinolytic era, a relatively consistent 15-25% higher adjusted risk of early death in women was found in STEMI.[48, 196, 271, 272, 279 47] Studies on gender differences in STEMI have mainly used cohorts extracted from fibrinolytic trials[48, 132, 137, 196, 271, 272], thus with an inherent selection bias, and there are few studies based on consecutive STEMI cohorts evaluating gender differences. In paper I, where the majority of patients received fibrinolysis, we could confirm a 21% higher multivariable adjusted risk of short term mortality in the real life setting.

The longer delay, higher risk of bleeding and intracranial haemorrhage and thus also less reperfusion therapy in the fibrinolytic era were possible explanations to the gender difference in outcome at that time. Regarding the new primary PCI era, many studies have been published but when we planned our time trend study (Paper III) all these were relatively small[137, 138, 325, 326, 391], single-centre[138, 326] and some included both STEMI and NSTE ACS patients.[301, 326] The results were contrasting, but the majority of studies did not find female gender to be an independent risk factor of early death.[137-139, 328] Instead, several authors claimed that women would gain more than men with this reperfusion strategy shift.[135, 136] One more recent study even found similar crude event rates in women than in men, when treated

with same quality care and with same PCI success rate.[139] Thus, in paper III, we hypothesised that the gender difference in early outcome would have diminished in the late compared to in the early period, as primary PCI was dominating in the later period and fibrinolysis was dominating in the early period. As already discussed, we then hypothesised that the treatment gap would also have diminished.

We did not find a diminished gender gap regarding early mortality in the new primary PCI era (Paper III). The risk was 21% higher in women, consistent with the studies in the fibrinolytic era. This was however not due to less reperfusion therapy as this was adjusted for in the multivariable analysis, without a reduction of the odds ratio. Recently, a couple of other studies based on observational registers with multicentre consecutive inclusion have been published. In a study from the Polish PL-ACS register with more than 26 000 STEMI patients consecutively included June 2005-May 2006 (48% vs. 57% treated with primary PCI, women vs. men, respectively) female gender was independently associated with 12% higher mortality.[310] In another study, based on the French CARDIO-ARHIF register, almost 17 000 STEMI patients who between 2003 and 2007 underwent angiography during the first day were identified.[329] Female gender was associated with 38% higher multivariable adjusted risk of in-hospital mortality.

Many reasons have been postulated to explain this persistent higher early death in women with STEMI such as higher age,[47, 48, 263, 271] more co-morbidities[47, 48, 263] such as diabetes,[392, 393] longer delay,[263, 310] higher Killip class,[310] more bleedings[310, 394] and other complications[272, 278, 284], less intensive management including reperfusion therapy,[278, 284, 310] lower pre-hospital mortality[334, 336, 338, 339] as well as biological reasons such as smaller hearts and coronary vessels, less preconditioning because of less collateral flow[395] and a different autonomic nervous system response upon acute coronary vessel occlusion.[396] The answer is most certainly multifactorial.
We conclude from the latest trials,[310, 329] and our on data (Paper III) that women do still fare worse than men despite the reperfusion strategy shift. Whether an even higher use of primary PCI with more modern techniques, stents, and drugs could diminish this gender gap in early outcome is an interesting topic for future research.

Impact of reduced eGFR on outcome

Reduced eGFR has gained increased attention as an important independent prognostic marker in ACS.[81, 82, 91, 97, 362] Most often, eGFR has not been accounted for in the multivariable analyses looking for gender differences in outcome[48, 132, 196, 257, 271, 279, 285, 397] – neither in our analyses in paper I-III, as creatinine was not a mandatory variable to register at that time. Several traditional risk factors have been proven associated with higher risk in women compared to men, such as smoking and diabetes.[63, 64, 345, 346, 392] A previous study concluded that this was also the case regarding reduced eGFR, where an interaction between sex and eGFR regarding long term outcome was found in consecutive PCI patients.[100] Thus, we wanted to evaluate if reduced eGFR was a stronger prognostic marker in women than in men in case of STEMI, and if a higher prevalence of moderate to severe CKD in women could explain their worse outcome. In Paper IV we found a borderline significant interaction between sex and reduced eGFR regarding mortality. The cohort was small with few males within the worse CKD stages, and thus few events and the findings were therefore hypothesis generating.
In paper V, reduced eGFR was a strong prognostic factor but without a gender difference in

prognostic impact. As CG had been shown to predict adverse outcome better than MDRD in ACS patients [74, 77] we aimed to use both formulas. In both genders according to both formulas each 10 mL decline of eGFR was associated with about 30% increased multivariable adjusted risk of early and about 10% increased risk of late mortality. Female sex was still associated with twice as high crude early mortality concordant with Paper I and other STEMI studies.[48, 132, 196, 271, 272] After adding eGFR according to any of the formulas to the multivariable adjustments, there was no longer a significant gender difference in early outcome after STEMI. In fact, just adjusting for eGFR according to CG had an even greater impact than adjusting for age or even all other 27 variables, and reduced the odds ratio of in-hospital death women vs. men from 2.12 (95% CI 1.96-2.29) to 0.99 (95% CI 0.87-1.11). As eGFR co-varies with other important prognostic markers such as age and diabetes but also lower use of evidenced-based treatment, this is most certainly the explanation to why it was shown to have such strong influence on outcome. Age has a greater impact on the result in CG compared to the MDRD formula, which could maybe explain why CG had a stronger impact on prognosis compared to MDRD. However, even though prognosis following STEMI seems to be better described by CG compared to MDRD, it is still unknown which of the two formulas better describe the true underlying renal function as this has not been evaluated in a STEMI population.

Thus the high prevalence of RI in STEMI women had a major impact on outcome. The reason to why RI patient fare worse than non RI patients is multifactorial. Besides high prevalence of traditional risk factors such as diabetes and hypertension, undertreatment with evidence-based drugs and procedures, drug overdosing and higher bleeding risk, RI is also associated with specific metabolic abnormalities such as oxidative stress, hypoalbuminemia, hyperhomocysteinemia, hyperfibrinogenemia, insulin resistance, lipid abnormalities, inflammation and derangements in calcium-phosphate homeostasis that may all contribute to an excessive cardiovascular risk.[93]

Gender-age-interaction

Early mortality in STEMI was higher the higher age-group we studied consistent with previous studies, as age is a major predictor of MI case fatality.[398] In paper I, the difference between age groups was much more prominent than gender differences within each age group. In addition, in each age-group a significantly higher percentage of women died compared to men; 2.5% vs. 1.5% among patients less than 60 years, 5.0 vs. 4.0% in patients 60-69 years, 11.0% vs. 9.5% in patients 70-79 years and 24.1% vs. 19.9% in patients over 79 years. In concordance with studies on mixed MI cohorts[117, 261, 277] also in our pure STEMI cohort (Paper I) we found the highest multivariable adjusted relative risk in the youngest subgroup, although a significant sex-age interaction was not found. The odds of dying at hospital was 45% higher in women compared to men in the youngest cohort (Paper I) compared to 21% in the whole cohort.

When we studied the very youngest STEMI patients (Paper II) we wanted to include premenopausal women because of the theories of another MI pathophysiology. As time of menopause is not registered we used an arbitrary cut-off of 46 years. The percentage of women was much lower in this cohort, only 18%, compared to 35-36% in our other studies, where all consecutive STEMI patients were included (Paper I, III-IV) This is consistent with previous studies on young MI patients, although these have included mixed MI patients.[21, 22, 349, 350] In this very young cohort, case fatality during hospital care was low but the multivariable adjusted risk was 3 times higher in women compared to men, supporting

previous findings that the higher risk in women relative to men is particularly high in the very youngest. In our study, we did not find any difference in delay or in rate of reperfusion but we found major differences in extent of coronary disease as already mentioned. Thus, a possible explanation could be biological differences, where the young women had less collateral flow and thus less tolerance to a sudden coronary occlusion (less preconditioning). They had also twice as high prevalence of cardiogenic shock which could support this finding.

Long term outcome

The excess in cumulative one year mortality in women was to a great extent explained by their higher short term mortality but women did have higher crude mortality rates also among hospital survivors. This was mainly due to their higher age although the gender difference in management seemed to matter to a minor part. In paper III women had 5% and 11% higher adjusted one year mortality in the early and late periods, respectively. After adjustments for differences in reperfusion and discharge therapies, there was no longer any excess risk in women. Thus, even though there can be many valid explanations to the gender difference in evidence-based therapy, such as higher risk of bleeding or experiences of adverse effects, the gender management gap probably matters regarding outcome, although the impact was minor, confirming previous studies[284] such as the microsimulation study by Milcent et al.[285] High risk patients often benefit most from a certain treatment but we tend to treat low risk patients more aggressively.[285] Thus, a better adherence to treatment guidelines in women might reduce long term mortality even further.

There are very little data regarding real long term outcome after STEMI in a gender perspective, i.e. beyond one year after the acute event. In Paper I, with a follow-up time of up 1-13 years (mean 4.6 years), female sex was associated with better long term outcome as compared to men after multivariable adjustments. In the young STEMI cohort (paper II) the long term survival was the same in women as in men in spite of the higher prevalence of traditional risk factors in women. In this young cohort, men had more severe coronary artery disease and higher incidence of re-infarctions which probably explain the catch-up in long term mortality.

VIII. Conclusions

Age and co-morbidity

We found major gender differences in the STEMI group regarding background characteristics. Women were 7 years older than men and had higher prevalence of diabetes, hypertension, stroke, CHF and COPD whereas men had higher risk of smoking, previous MI and/or revascularisation. Most of these associations persisted after age-adjustments except of smoking and stroke.

In young STEMI patients the differences in risk factors and co-morbidities were even more pronounced with 50% higher prevalence of diabetes and hypertension in women. The vast majority of those patients were smokers, women more often than men.

STEMI patients had a very high prevalence of CKD. According to CG 50% of women compared to 22% of men had at least moderate CKD (RI). Corresponding figures when MDRD was used were 38% and 19%, respectively. Female gender was independently associated with mild, moderate and severe CKD even after multivariable adjustments, according to both formulas.

Hospital care

Women delayed 30 minutes longer than men from symptom onset to arrival to CCU/cath lab. The same delay was noticed in the early time period (1998-2000) as well as in the late time period (2000-2003). In young STEMI patients, women did not have longer symptom-to-door time compared to men.

In contrast to data on older STEMI patients, there were major differences in extent of coronary disease in the young STEMI patients as women much more often than men had one-vessel disease. There was no gender difference in prevalence of non-obstructive disease.

In two time periods with different reperfusion strategies, women had consistently lower chance than men to receive reperfusion therapy also after multivariable adjustments. They had also less often a coronary angiography performed. There are many plausible explanations such higher prevalence of cardiogenic shock, reduced kidney function, very early death and higher risk of bleeding.

Women had also lower multivariable adjusted chance of receiving evidence-based therapies such as platelet inhibitors, ACE-inhibitors/ARBs, statins and beta-blockers. A plausible explanation is a higher prevalence of previous or current adverse drug effects.
In the young STEMI cohort we found no gender difference in use of reperfusion therapy and minor differences in other management.

Outcome

Women had twice as high in-hospital mortality compared to men and approximately 10-20% higher risk of early death after extensive multivariable adjustments, which is a consistent finding in the literature. The huge gender difference in prevalence of moderate to severe CKD

could be an important explanation. After adjusting for eGFR according to CG, there was no longer any gender difference in early mortality. Further adjustment with adding of the other 27 variables did not change this result.

Reduced eGFR (per 10 mL decline of eGFR, RI compared to non RI or per increase in CKD stage) according to any of the formulas used was a strong independent prognostic factor both regarding short- and long term outcome in both genders. There seems to be no interaction between gender and eGFR regarding short- or long term outcome.

One-year mortality is also higher in women than in men. Age is the most important explanation but the gender difference in management seems to have a certain albeit small impact.

Long term mortality beyond one year after the acute event, is better in women than in men after multivariable adjustments.

IX. Clinical implications

Clinicians should be aware that women with STEMI comprise a high risk subgroup with higher risk of cardiogenic shock, bleeding, heart failure as well as early death. They are older, delay longer and have more co-morbidity. Especially their very high prevalence of RI, 50% according to CG, has to be taken into account during the PCI manoeuvre, when dosing drugs and as an important prognostic marker. Still we cannot conclude that primary PCI has the ability to abolish the gender difference in early outcome that was noticed before and during the fibrinolytic era. Anyhow, evidence is solid that women as well as men with STEMI benefit from acute reperfusion therapy which should be given promptly. Even though many cardiovascular randomised clinical trials included too few women to receive significant results for the female subgroup, there is no evidence today that women should be treated differently from men in case of STEMI. Thus, adherence to treatment guidelines in both men and women is important in order to reduce their risk of future cardiovascular events. Anyhow, in the unique doctor-patient consultation an individual approach taking all factors in to consideration is mandatory.

X. Future research

It remains to be evaluated if female gender is an independent predictor of adverse outcome in the setting of primary PCI with radial approach.

It remains to be evaluated if female gender is an independent predictor of adverse events such as bleeding, stroke and early mortality after introduction of new antiplatelet and anticoagulant drugs, in the STEMI setting, especially after primary PCI

It remains to be evaluated if the high prevalence of moderate to severe CKD in women (50% according to CG compared to 22% of men) with STEMI could explain the gender gap in use of invasive procedures as well as other evidence-based cardiovascular therapy.

It remains to be evaluated which of the two most commonly used formulas to calculate eGFR best correlate to measured GFR in women and men in the setting of STEMI.

The reason for the treatment gap both regarding reperfusion therapy and other evidence-based therapies needs to be more thoroughly investigated.

The reason to why women delay more than men in the setting of STEMI to be more thoroughly investigated, as well as methods in order to reduce it.

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