Gender and age related differences in patients with ST-elevation Myocardial Infarction

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Voor Sander, mijn hartensteler

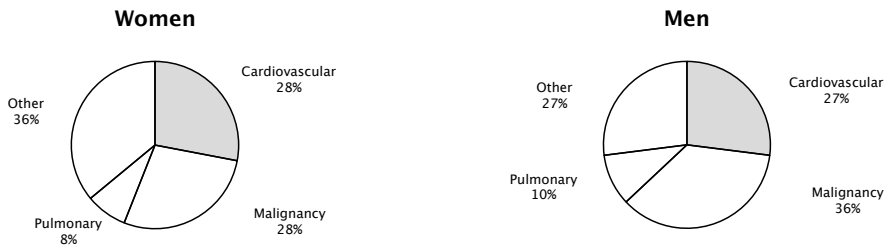
CONTENT

Chapter 1

Introduction

Ischemic heart disease is traditionally seen as a men's disease and publications include predominantly male patients (1). This has resulted in extensive knowledge on traditional, mostly male dominated symptoms, insights in pathophysiology, response to treatment and outcomes in patients with ischemic heart disease. Although the prevalence of ischemic heart disease is lower in women than in men, the combined death rates from cardiovascular diseases (ischemic heart disease, heart failure and strokes) are equal among women and men (figure 1).

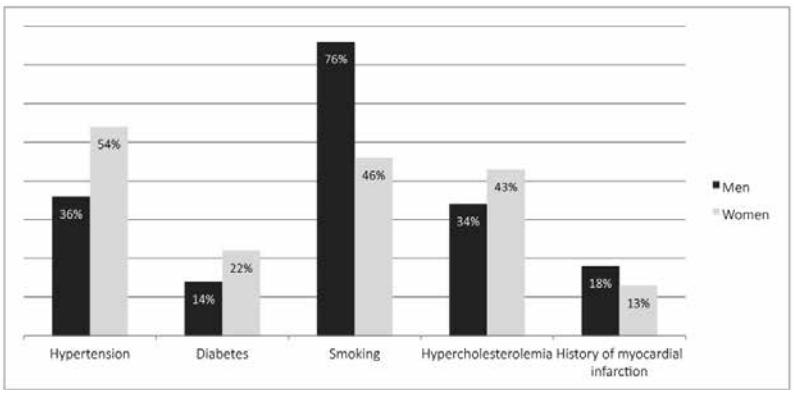
Figure 1
Percentage of causes of death in men and women in 2013 in the Netherlands.



Source: CBS (www.cbs.nl).

During the last decade, there is increasing evidence that there are many differences between men and women in ischemic heart disease, although female characteristics have not been extensively studied as male characteristics.
Myocardial infarction and particularly ST-Elevation Myocardial Infarction (STEMI), is among the most potentially dangerous presentations of ischemic heart disease. Differences between men and women regarding STEMI start already with the presentation. Next to the main symptoms of chest pain, women more often have symptoms of dyspnea, anxiety and vasovegetative signs that may be misleading for adequate and timely recognition among women themselves and medical workers (2,3). A third of the patients with STEMI present with atypical symptoms and patient delay in women is often longer due to later recognition (4-6). In general, women with STEMI are older with a higher clustering of cardiovascular risk factors than men. Also, the distribution of risk factors is different between both genders, with a higher risk factor burden in elderly women (figure 2).

Figure 2
Cardiovascular risk factors in 3134 men and 997 women presenting with STEMI.



Each risk factor between man and women had a p-value of 0.001 or less.
Source: Hochman JS, et al. N Engl J Med. 1999;341; 226–232.

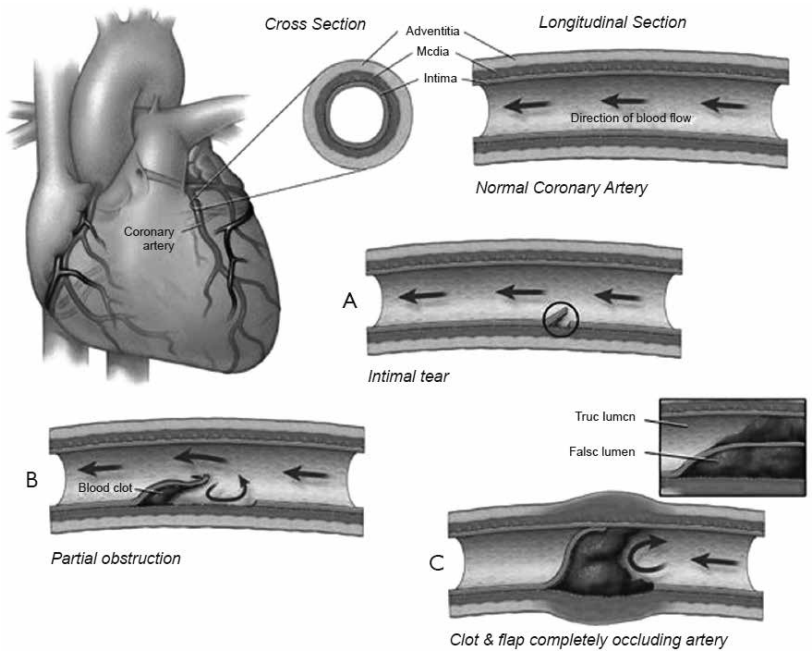
Women more often have hypertension, dyslipidemia and diabetes compared to similarly aged men (6,8). Furthermore, the impact of these risk factors on ischemic heart disease seems to be age-dependent. In the younger age groups (< 65 years) the contribution of smoking to the risk of myocardial infarction is relatively higher in women (9).
Also, there is increasing evidence that hormonal and reproductive status is important for the risk of ischemic heart disease in women (10,11). Early menopause is associated with a higher risk of ischemic heart disease (12). Age at menarche may also be a potential risk factor for ischemic heart disease, which is already revealed early in life. Although there is growing evidence that menarche is associated with cardiovascular morbidity and mortality, it is yet unclear whether women with early menarche are at increased risk of STEMI at younger age (13).

Besides different presentation and different risk profiles, men and women with STEMI may have a different pathophysiology. Men more often have a 'traditional' type I myocardial infarction with a preexisting plaque and acute thrombotic coronary obstruction as the cause of STEMI, whereas women at younger age more often have a type II STEMI with an open coronary artery with often erosive plaques, spasm and endothelial dysfunction (14-17). Other types of myocardial infarctions occurring

more often in women are spontaneous coronary artery dissection (SCAD) and Tako Tsubo cardiomyopathy (TTC) (18).

SCAD is a rare disease in which the coronary artery develops a tear, causing blood to flow between the different layers of the vascular wall. This flow forces the layers apart and could result in an obstructed coronary artery and STEMI (figure 3).

Figure 3
Spontaneous coronary artery dissection.

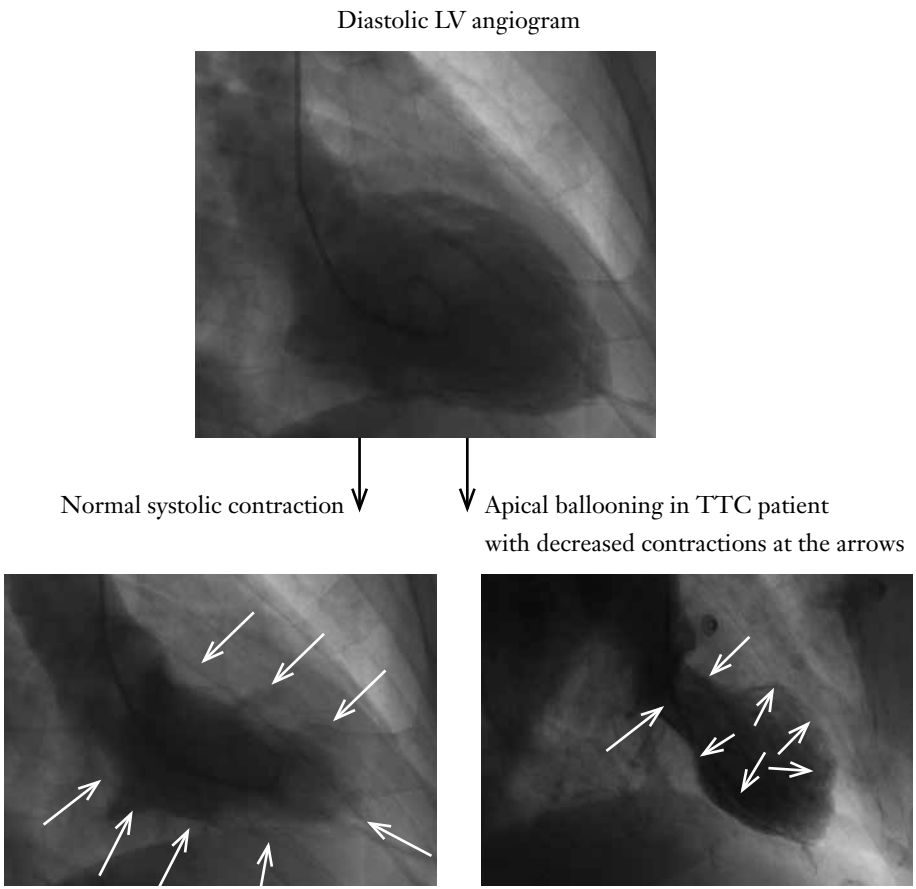


Source: Journal of thoracic disease.

Most patients with SCAD are younger women, leading to the hypothesis that SCAD is related to female associated diseases as fibromuscular dysplasia (14, 19). As the condition is rare, mostly small case series with lack of power are published about the characteristics and treatment of this disease (20,21).

Tako Tsubo cardiomyopathy is a sudden temporary failing of mostly the anteroapical muscular wall of the heart (figure 4). Because of the characteristic LV contractions, this is also called the apical ballooning syndrome.

Figure 4
Left ventricle "ballooning" in Tako Tsubo cardiomyopathy.



This acute failing can be triggered by severe emotional stress such as the sudden death of a loved one or it can be triggered by physical extremes as a bleeding in the brain. It occurs mostly in elderly women (> 60 yrs), suggesting a different mechanism between both genders in this STEMI mimicking disease. It is important to increase awareness for this diagnosis

in order to establish the correct diagnosis and treatment of these patients. Despite the fact that women more often have open coronary arteries than men when presenting with STEMI, (22-24) several reports have observed a higher in-hospital mortality after STEMI in women compared to similarly aged men, especially in younger age groups (14-16). This discrepancy has been called the "gender gap". There are conflicting results whether this difference in mortality is associated with age or with different risk profiles between men and women or with gender itself (25-27).
Women with STEMI may benefit from a more gender sensitive approach, not only during presentation and interventions, but also afterwards in relation to medical therapy, side –effects of medication and cardiac rehabilitation programs. More gender-based research is needed to optimize symptom recognition and to understand underlying pathophysiology and response to treatment.

Objectives
The main objective of this thesis is to investigate several gender related aspects of STEMI patients. Especially, we studied whether potential gender differences are age dependent. We investigated age and gender related differences in mortality in STEMI patients, as well as hormonal and metabolic factors that potentially influence this relationship. Further, we focused on the prevalence and diagnosis of several gender-specific subgroups of STEMI patients, related to spontaneous coronary artery dissections (SCAD) and Tako Tsubo cardiomyopathy (TTC).

Inclusion
All studies include data from the Zwolle ACS database since 1998 until as recent as possible at the time of publication except chapter 4 and 8. In chapter 4, we included data from 2004 onwards, since HbA1C was systematically registered at admittance from 2004 onwards. In chapter 8 we included data from 2002, since there was only one patient with a Tako Tsubo cardiomyopathy (TTC) registered before.

Outline of this thesis
In **chapter 2** we describe the general principles and diagnosis of myocardial infarction. The observed clinical differences between men and women are the basis for further research.

In **chapter 3** we investigated gender differences in outcomes in a large dataset of STEMI patients. In the literature, younger women with STEMI have a higher mortality than similarly aged men. The reason for this difference is unknown yet. We investigated whether age related differences and risk factors contribute to these mortality differences.

One important risk factor for ischemic heart disease that has a higher prevalence and mortality in women is diabetes. In **chapter 4** we investigated whether metabolic differences in STEMI patients with and without diabetes contribute to the gender related differences in mortality.

It is increasingly recognized that factors related to sex hormones are important in ischemic heart disease. We investigated whether early menarche is an independent risk factor for early STEMI in **chapter 5**.

Not all STEMI occur due to obstruction of a coronary artery by plaque rupture. Age and gender related differences in mortality in patients with STEMI may have an explanation in different mechanisms of STEMI between man and women. We investigated the characteristics, treatment assignment and angiographic outcome in patients with SCAD in **chapter 6**.

Tako Tsubo cardiomyopathy is a STEMI mimicking disease, predominantly prevalent in elderly women and rarely in men. We evaluated the occurrence of TTC in men and women in a large database of STEMI-patients in **chapter 7**.

The observed number of patients with TTC has changed over the past years since TTC was first described in 1991 and first cohorts approximately 10 years later. We investigate the occurrence of TTC and patient characteristics over the past 12 years in a large population of STEMI patients in **chapter 8**.

Chapter 9 contains the general discussion of the observed findings in perspective of our current knowledge on age and gender related differences in STEMI patients. Recommendations for future investigations are proposed.

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Chapter 2

Symptoms and diagnosis of myocardial infarction

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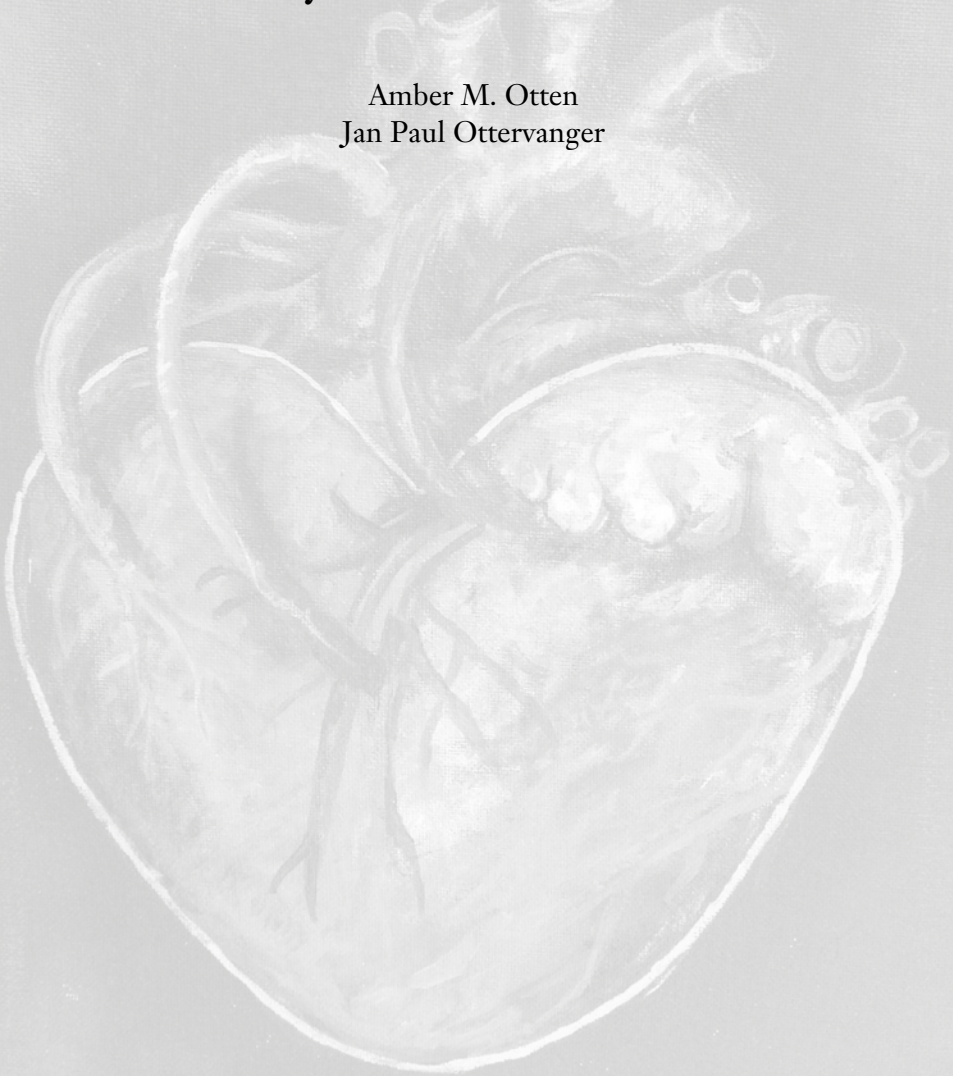

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Introduction

Fast and adequate treatment of myocardial infarction can make a change from an acute event with very high mortality and serious long-term morbidity into a condition with low mortality and a very good long-term prognosis. However, before treatment can be started, recognition and fast diagnosis of myocardial infarction is essential. A number of clinical, electrocardiographic, biochemical and imaging tools may be helpful in making the diagnosis. In some subgroups, including females, elderly and patients with diabetes, it is particularly challenging to the make fast and correct diagnosis.

Typical symptoms

Although patients with acute myocardial infarction may present with a variety of symptoms, the classic symptom is chest pain longer than twenty minutes in rest. Typical chest pain is a retrosternal heaviness or pressure radiating to the left arm, neck or the jaw. (1) Accompanying symptoms may be breathlessness, sweating, nausea and vomiting. Symptoms may be present at exertion or at rest and are usually longer than 20 minutes present and do not or only partially improve on sublingual nitroglycerine spray. To discriminate myocardial infarction from other causes of chest pain, identification of risk factors can be helpful. The presence of older age, diabetes, smoking, hypercholesterolemia, obesity positive family history, peripheral artery disease, renal insufficiency or previous coronary artery disease, increases the likelihood of myocardial infarction. (1) However, this can also be dangerous, and may be the cause that in young women the diagnosis is missed. The importance cannot enough be overstated, both for general population and all healthcare workers, that every patient with unexplained chest pain should be evaluated to exclude myocardial infarction.

Atypical symptoms

Recognizing atypical symptoms as signs of myocardial infarction is important, since one third of patients presenting with myocardial infarction do not have chest pain, and one fifth do not have ischemic symptoms at all. In this case myocardial infarction can be only diagnosed by ECG, laboratory results or imaging. (2) So called ‘silent’ myocardial infarctions are more common in women, diabetics and elderly patients. Also, these patients are less likely to be diagnosed with myocardial infarction at the

time of admission. (3) Atypical symptoms in patients presenting with myocardial infarction is common. A patient with atypical chest pain may present with a sharp or burning pain that is reducible with palpation or localizable with one finger in other areas of the upper body than the chest. Atypical chest pain is more prevalent in elderly, patients with diabetes and women.

Symptoms in women

Women are less likely than men to present with typical chest pain in myocardial infarction. They present more often with fatigue, sleep disturbance, weakness and shortness of breath, but these symptoms are of course not specific. (4,5) The higher prevalence of atypical symptoms in women compared to men presenting with myocardial infarction, is probably the most important reason for the longer patient delay in women. (3) Also, myocardial infarction may be unrecognized more often in women compared to men because of the more atypical presentation in women. Furthermore, awareness by both health care workers and patients may be less in symptomatic women, because in the general population and even healthcare workers it is still thought that myocardial infarction is a disease of men. This is difficult to "treat", the effects of national campaigns to increase awareness in women were not clear. (6) However, a local initiative was more successful, particularly decreasing door-to-table time delay in women. (7)

Key terms:

- Classic symptoms are retrosternal pressure radiating to the left arm, neck or the jaw.
- In every patient with unexplained chest pain, myocardial infarction should be excluded.
- Several subgroups, particularly women, may present with atypical symptoms.
- More efforts are necessary to decrease time delay in women.

Physical examination

Physical examination is almost normal in most patients with myocardial infarction, but is important to identify hemodynamic instability and sings of heart failure and to exclude other causes as pneumothorax, which can even be accompanied by transient ST-segment elevation on ECG. (8)

Other non-cardiac causes of chest pain that can be identified by physical examination include valvular heart disease, aortic dissection, thoracic muscle pain, pneumonia or a gastro intestinal origin. Body temperature, blood pressure differences in limbs, heart murmurs, abnormal lung auscultation and pain on palpation are therefore important to asses in every patient with suspected myocardial infarction.

Electrocardiography

Electrocardiography (ECG) has a key role in diagnosing myocardial infarction and to discriminate between ST elevation myocardial infarction (STEMI) and non ST elevation myocardial infarction (NSTEMI), and should be performed in every patient with chest discomfort.

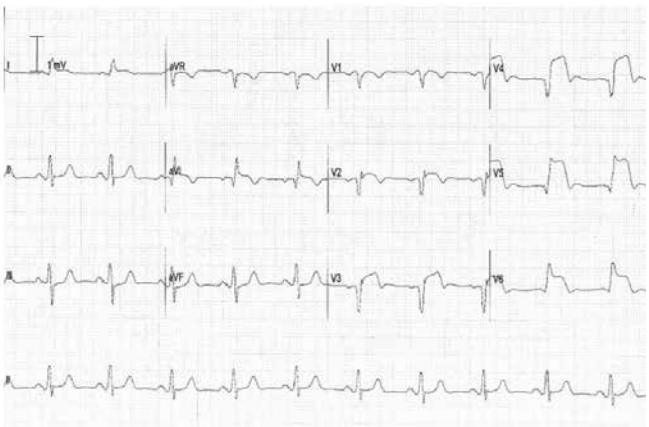
ECG changes in STEMI

ECG changes have prognostic importance, and can be used for risk stratification. ST-elevation myocardial infarction is defined as a new elevation, during at least 20 minutes, in two contiguous leads with ≥ 2 mV in men and ≥ 1.5 mV in women. In precordial leads (V2-V3) 1 mm ST-elevation is diagnostic for myocardial ischemia. (9) The localisation of ischemia can be diagnosed from which of the leads show ST-elevation. (Table 1) An anterolateral infarction is depicted in figure 1 as an example. In the first hours of myocardial infarction, T- tops become more positive followed by a ST-elevation. Reciprocal ECG ST depression in the other leads may be observed. After a few hours after initiation of myocardial ischemia, myocardial necrosis and therefore pathological Q-waves (defined as one third of the total QRS) occur and QS wave forms may be present. T waves become negative. In eighty to ninety percent of patients, pathological Q waves and negative T-waves stay present on the ECG. If ST-elevations are present six weeks after initiation of myocardial infarction, an aneurysm cordis might be present. (10) In case of a STEMI, also risk stratification can be made with an ECG: the higher the sum of the ST elevation the higher the mortality. (11)

Table 1
Localisation of myocardial ischaemia and ECG changes

Localisation myocardial ischemia	Leads of elevation	ST depression
Anterior	V2-V5	II, III, aVF
Septal	V1-V3	II, III, aVF
Lateral	I, aVL, V6	II, III, aVF
Inferior	II, III, aVF	I, aVL, V1-V4
Posterior	V7-V9	V1-V3 (mirrored)
Right ventricle (often in combination with inferior)	V4R, V1, V2	I, aVL

Figure 1
Electrocardiographic pattern of anterolateral myocardial infarction.



10mm/mV, 25mm/s

Left bundle branch block

Although it is difficult to make a diagnosis of myocardial infarction in patients with a left bundle branch block, a new left bundle branch block is a strong argument for ischemia. Furthermore, the criteria as defined by Sgarbossa can be used to diagnose myocardial infarction: ST elevation > 1mV concordant with the direction of the QRS complex (score 5), ST depression > 1mV in V1-V3 (concordant with the direction of the QRS complex) (score 3) or ST elevation > 5mV disconcordant with the direction of the QRS complex (score 2). With a sum of the scores of at

least 3, the diagnosis of myocardial infarction can be made with ninety percent specificity. (12)
Not all ST-elevations on the ECG are due to ischemic myocardium. In patients with peri(myo) carditis for instance, ST-elevation can be present diffusely in the ECG. In this case, an echocardiogram can aid to diagnose.

ECG changes in NSTEMI
A non ST-elevation myocardial infarction presents with ST segment depressions, T wave inversions or no ECG changes at all. These ST-T changes might be in one or two leads or be diffusely present on the ECG. It is an indication of myocardial ischemia, if there are dynamic changes in the ST-T segment. Unstable angina is distinguished from NSTEMI with cardiac biomarkers. If there are no ST-segment changes on the ECG, it is important to asses a right-sided and a posterior ECG, because myocardial ischemia in these locations is not well represented in the normal ECG and therefore, a STEMI in these locations might be missed. (13) In patients with a large area at risk, for instance a lesion of the left main artery or in all three main coronary arteries, ST elevations may only be present in V1 and ST depressions may be present in the other leads.

ECG indicating old myocardial infarction
Patients with previous STEMI's can have pathological changes such as Q waves on the ECG. NSTEMI patients usually do not have pathological Q waves on the ECG. The localisation of pathological Q waves is usually in the leads that the ST-elevation occurred in. However, not all pathological Q waves are specific for previous myocardial infarction. Examples of non ischemic pathological Q waves are wrongly placed ECG leads, a left bundle branch block, left and right ventricular hypertrophy, pulmonary embolism, hypertrofic cardiomyopathy and Wolf Parkinson White syndrome with an accessory electrical abnormal pathway.

Pre-hospital care
Most patients presenting with myocardial infarction are being transported by an ambulance. Not only fast transportation is important, but early diagnosing, triage and treatment of myocardial infarction have shown to reduce mortality in STEMI patients. (14) Therefore, ambulances should be fully equipped with ECG and defibrillators and ambulance teams should be trained to identify STEMI on the 12-lead ECG. (15) Once the

STEMI is identified, the nearest PCI hospital should be informed of the expected time of arrival.

Key terms:

- An ECG should be performed in all patients with chest discomfort and can differentiate between ST elevation and non-ST elevation myocardial infarction.
- With an ECG, the diagnosis can be made, but a normal ECG cannot exclude myocardial infarction.
- In case of left bundle branch block, diagnosis of myocardial infarction is more difficult, but should be considered if LBBB is new.
- Ambulance teams must be trained to diagnose electrocardiographic signs of infarction.

Biomarkers

There are several biomarkers indicating myocardial infarction. Troponin is the preferred biomarker to make a final diagnosis because the high sensitivity and specificity as compared to other biomarkers High sensitivity troponin is even more sensitive resulting in less false negative test results. Although cardiac biomarkers reflect myocardial necrosis, the aetiology of this necrosis might still be unknown. Stable elevated cardiac biomarkers might be present in patients with a tachycardia, bradycardia, renal failure, inflammatory diseases, extreme exertion and chronic heart failure. Therefore, myocardial infarction is only diagnosed in patients with a clinical setting of myocardial infarction in combination with elevated biomarkers.

A typical rise of the troponin value is a strong argument for myocardial ischemia and infarction. (9) Especially as previously described, when there are no ST-elevations on the ECG, elevation of cardiac biomarkers is the only parameter to distinguish patients with NSTEMI from a patient with an unstable angina. Troponin levels usually begin to rise two to three hours after onset of myocardial infarction. Therefore, in patients without ST-elevation on the ECG and a second troponin at least three hours apart should be assessed to detect myocardial ischemia. (16) If a patient have had symptoms for at least six hours prior to admission, only one troponin measurement suffices to detect myocardial ischemia.

CK and to minor extend, CK-MB, are less specific or sensitive than high sensitive troponins. These parameters however can be used to estimate the infarct size.
LDH is mostly used for the estimation of the onset of myocardial infarction. It is a cardiac biomarker that rises ten hours after the onset of a myocardial infarction and peaks at sixty-four to eighty hours. When LDH is elevated, it is generally accepted that the myocardial infarction is present for at least ten hours.

Key terms:
- Cardiac biomarkers can exclude acute myocardial infarction, but should be followed for hours.
- Cardiac biomarkers have a key role in diagnosing non-ST elevation myocardial infarction
- High sensitive troponin is the first choice biomarker

Non-invasive imaging
In the acute setting in patients with suspected myocardial infarction but without electrocardiographic evidence of infarction, echocardiography should be strongly considered to aid the diagnosis of myocardial infarction. It can differentiate between cardiac and non-cardiac, ischemic and non-ischemic (as pericarditis) heart disease, and may give information about the ischemic region, the extend of ischemia and whether there is an old myocardial infarction. If wall motion abnormalities are present in a regional segment and the myocardial thickness is reduced, an old myocardial scar may be present. (17) Furthermore, if there are wall regional wall motion abnormalities without reduction of the wall thickness, myocardial ischemia should be considered. Echocardiography is an important diagnostic tool to assess alternative diagnosis of the symptoms like peri(myo)carditis, cardiomyopathy, pulmonary embolism, aortic dissection and valvular stenosis or insufficiency. (18) If a patient is or become hemodynamically instable, complications from a myocardial infarction like pericardial effusion due to ventricular rupture or massive mitral insufficiency after papillary muscle rupture can be diagnosed adequately with echocardiography (19). Echocardiography is not validated to detect myocardial ischemia. A direct method to observe myocardial ischemia is radionuclide imaging. Several tracers allow viable myocardium to be imaged and differentiated from ischemic myocardium. However, small areas of infarction may be

undetected. Furthermore, ischemia is detected in relation to non-ischemic myocardial infarction, so if almost all of the myocardium is ischemic, the result can be false negative.
Magnetic resonance imaging has in theory the same application as echocardiography with a high spatial resolution. In clinical practice however, MRI is quite cumbersome and not practical in the acute setting.

Key terms:
- In the acute phase of patients with chest discomfort, echocardiography is important in patients with a non-diagnostic ECG, particularly if complaints sustain.
- Other modalities of non-invasive imaging, including radionuclide imaging and MRI can be used in the chronic phase.

Coronary angiography
In STEMI, coronary angiography is in many patients obtained urgently, shows the infarct related vessel, the presence of multivessel disease and is often combined with primary percutaneous coronary intervention. Also in patients with persisting chest pain despite optimal medical treatment or patients with complications (unstable arythmia's, acute mitral regurgitation, cardiogenic shock and ventricular septal defect) coronary angiogram is performed urgently if possible. The timing of coronary angiography for patients with NSTEMI less clear. (20)

Key terms:
- In STEMI, invasive coronary angiography can confirm the diagnosis and preferably is followed by primary PCI if indicated.
- In non-STEMI an invasive approach should be considered in most patients, although the timing of angiography is less clear.

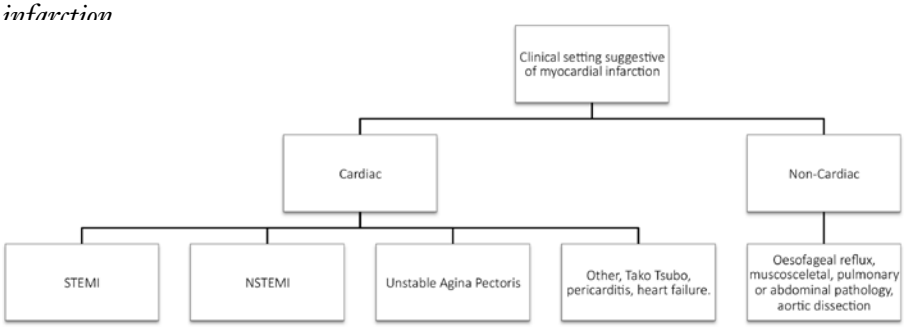
Differential diagnosis of myocardial infarction CARDIAC
In patients with a clinical suspicion of myocardial infarction, other differential diagnosis should also be considered. Patients with pericarditis can present with sharp chest pain, increasing with sitting up or leaning forward and pericardial friction rub with auscultation. The ECG can present with diffuse ST-elevation in all ECG leads, mimicking a STEMI with involvement of all coronary arteries, which rarely happens. Also, PR-segment depression on the ECG might be present. Echocardiography

can be used to visualise pericardial effusion, which is present in 60% of pericarditis patients. (21) Or visualise wall motion abnormalities, to improve the probability of myocardial infarction.
Tako Tsubo or apical ballooning syndrome is a cardiomyopathy induced by emotional stress. An acute and reversible ventricular dysfunction can be observed and ECG changes are mostly similar of an anterior myocardial infarction. Notably with Tako Tsubo, there are no coronary abnormalities. Mostly post menopausal women are affected by this cardiomyopathy. (22)

NON CARDIAC

Chest pain can be induced by other organs or tissue in the chest. Muscosceletal chest pain is a vast proportion of patients presenting with chest pain to the emergency ward. (23) Muscosceletal pain might be induced by palpation on the sternum or movement of the upper limbs. Oesofageal reflux is another cause of acute chest pain in patients. (24)
Pulmonary embolism is another important differential diagnosis in patients with a clinical suspicion of myocardial infarction. Patients might present with chest pain, increasing with respiration. The ECG changes in pulmonary embolism may be a right bundle branch block, Q waves (pseudo infarction pattern) ST-elevations or depression in the precordial leads. (25) Also in this situation, echocardiography might be very valuable to visualise elevated right sided pressures and dilatated right ventricle, sometimes present in pulmonary embolism or wall motion abnormalities in myocardial infarction.
In case of abdominal pathology for instance with an ileus or pancreatitis, ECG and even clinical presentation might mimick a STEMI. (26)

Figure 2
Differential diagnosis in patients with a clinical suspicion of myocardial infarction



Key terms:

- In the differential diagnosis of myocardial infarction, a structured approach should be performed.
- First step in the differential diagnosis is to differentiate between cardiac and non-cardiac causes.

DEFINITIONS OF DIAGNOSES

STEMI

In patients in the clinical setting of myocardial infarction and ST-elevation on the ECG suggestive of myocardial infarction or (presumed) new left bundle branch block.

NSTEMI

- Typical rise and fall of cardiac biomarkers (Troponin, CK, CK-MB, LDH) with at least one of the following:
  - Symptoms of ischemic symptoms
  - Development of pathological Q waves on the ECG
  - ECG changes indicative of new ischemia (negative ST elevation or depression, LBTB)
  - Imaging evidence of new regional wall motion abnormality or new loss of viable myocardium
- Evidence of fresh thrombus at coronary angiography or autopsy
- Pathological findings of a acute myocardial infarction

Prior myocardial infarction is defines as:

- development of new pathological Q waves on the ECG with or without symptoms. Biochemical markers may have normalized.
- Imaging evidence of a thin and a regional loss of myocardium that fails to contract in the absence of non-ischemic cause.
- Pathological findings of a prior myocardial infarction. (9)

When diagnosing a patient without ST-elevation the ECG the, it is important to asses possible rise and fall of the troponin, because NSTEMI should be differentiated from unstable angina pectoris by a relative or absolute increase in troponin values. (27) Other causes of elevated cardiac biomarkers not caused by coronary artery disease include: tachycardia, bradycardia, myocarditis, chronic heart failure, impaired kidney function.

(15) In some of these cases, even a rise and fall of the troponins can be observed. Therefore, careful anamnesis is essential.

Chapter summary

- As treatment can dramatically change prognosis of myocardial infarction (MI), fast and accurate diagnosis is essential.
- There are several tools in diagnosing MI, but everything starts with recognizing suspected symptoms.
- Women, the elderly and diabetics more often have atypical symptoms.
- Clinical examination is important to diagnose heart failure and exclude noncardiac causes.
- Electrocardiographic changes play a key role in diagnosing myocardial infarction and in differentiating between ST-segment elevation MI and non-ST-segment elevation MI.
- Elevated cardiac biomarkers are particularly essential in those without ECG changes and may have prognostic importance.

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Chapter 3

Is the difference in outcome between men and women related by primary percutaneous coronary intervention age dependent?

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Abstract

Aim: Poorer outcomes in women with ST-elevation myocardial infarction (STEMI) are often attributed to gender differences in baseline characteristics. However, these may be age dependent. We examined the importance of gender in separate age groups of patients with STEMI undergoing primary percutaneous coronary intervention (PPCI).

Methods and results: Data of 6746 consecutive patients with STEMI admitted for PPCI between 1998 and 2008 in our hospital were evaluated. Age was stratified into two groups, <65 years (young group) and ≥65 years (elderly). Endpoints were enzymic infarct size as well as 30-day and 1 year mortality. We studied a total of 4991 (74.0%) men and 1755 (26.0%) women; 40% of women were <65 years and 60% of men were <65 years of age. In the elderly group (≥65 years), women had more frequently diabetes and hypertension while they smoked less frequently than men. Younger women smoked more often than similarly aged men and had more hypertension. At angiography, single-vessel disease and TIMI 3 flow before PPCI was more present in younger women than men, whereas these differences were not found in the older age group. Patient delay before admission was shorter in men at all ages, while women had lower creatine kinase levels. Younger women had a higher mortality after 30 days (HR 2.1, 95% CI 1.3–3.4) and at 1 year (HR 1.7, 95% CI 1.2–2.6), whereas in the older age group women mortality rates were higher at 30 days (HR 1.5, 95% CI 1.1–2.0) but not at 1 year (HR 1.2, 95% CI 0.9–1.5). After multivariate analysis, 1-year mortality remained significantly higher in women at younger age (HR 1.7, 95% CI 1.1–2.5). Patient delay before admission was shorter in men in both age groups. Creatine kinase levels were in both age groups higher in men.

Conclusions: Differences in mortality between men and women with STEMI treated with PPCI are age dependent. Although young women have less obstructive coronary artery disease and more often TIMI 3 flow before PCI (suggesting a lower risk), survival was worse compared to similarly aged men. Women had a longer patient delay compared to men, but this was not related to gender-specific mortality.

Keywords

Acute coronary syndrome, age, gender, STEMI, women

Introduction

Over the past decade, several reports on gender differences in prognosis after primary percutaneous coronary intervention (PPCI) in ST-segment elevation acute myocardial infarction (STEMI) have revealed conflicting results (1–6). Higher in-hospital mortality in women was often attributed to a longer patient delay before admission, older age, a higher clustering of cardiovascular risk factors, lower use of invasive and medical treatment, and more bleeding com-plications after interventions (6–13). Remarkably, especially in the younger age groups, women had a worse outcome compared with age-matched men (14–18). This may be related to a variety of factors such as gender differences in plaque composition, differences in thrombotic activity, and a higher prevalence of microvascular disease in younger women (19–22). However, as most previous studies did not stratify into age groups, it is less clear whether these gender differences in prognosis after STEMI are age dependent. Some studies did stratify on age but included patients with both STEMI and non-STEMI, representing a heterogenous population with acute coronary syndrome (6,23). In our present study from the Zwolle Myocardial Infarction Study Registry, we compare outcomes between women and men with STEMI, all referred for PPCI, within two different age groups.

Methods

Population

From January 1998 to January 2008, individual data from all STEMI patients who were considered for PPCI at our centre, were prospectively recorded in a dedicated database. Patients were diagnosed with STEMI if they had chest pain longer than 30 minutes and ECG changes with ST elevation greater than 2 mm in at least two precordial leads or greater than 1 mm in the limb leads. Cardiac biomarkers were elevated in all patients. According to the protocol, all patients received 500 mg aspirin and 5000 IU heparin intravenously before the PPCI procedure. Primary PCI was performed using standard techniques, if the coronary anatomy was suitable for intervention. Success rate of the procedure was assessed according to TIMI (24) classification, in which a grade 3 blood flow within the infarct related artery and a myocardial blush grade (25) 2 or 3 were considered to be adequate. The classification for bleeding (major and minor) was used according to the definition of the TIMI study group. Where appropriate, patients were treated with drug therapy, including

aspirin, clopidogrel, heparin, beta-blockers, ACE, angiotensin-converting enzyme (ACE) inhibitors, and lipid-lowering medication. Glycoprotein IIb/IIIa inhibitors were used according to the discretion of the treating cardiologist.

Laboratory measurements

According to the hospital protocol, blood sampling for creatine kinase (CK) and CK-MB levels was done at baseline and 8, 16, and 24 hours after PPCI. Infarct size was also estimated according to measurements of cumulative enzyme activities using lactate dehydrogenase (LDH) as the reference enzyme, as we have previously described in detail (26).

Data collection

Data were divided into four groups according to gender and age <65 years and ≥65 years. Information on demographic parameters, risk factors, laboratory values, angiographic variables, and medication was derived from the patient files. Follow-up information was obtained from the outpatient files, the general physicians, or by direct telephone interview with the patients and was prospectively obtained using pre-defined time intervals of 30 days and 1 year with telephone interviews performed by independent research nurses, who were not involved in patient treatment. MACE was defined as the combination of death, myocardial infarction (MI), percutaneous coronary intervention (PCI), and/or coronary artery bypass surgery (CABG). Recurrent MI was diagnosed when there was 50% increase of CKMB from a previous peak value, followed by a subsequent rise to a level exceeding the upper limit during hospital stay or recurrent hospitalization with the diagnosis MI. Bleeding was defined as intracranial or overt bleeding with a decrease of haemoglobin ≥3 g/dl (≥1.9 mmol/l) or >10% decrease in haematocrit within 48 hours, and, if a bleeding site was not identified >4 g/dl decrease in haemoglobin or >12% decrease in haematocrit within 48 hours.

Statistical analysis

Statistical analysis was performed using SPSS version 18.0 (SPSS, Chicago, IL, USA). Continuous data were expressed as median and interquartile range and categorical data as number and percentage, unless otherwise indicated. Tests for significance were two-sided, with an α of 0.05. Cox proportional hazard regression was performed to estimate hazard ratios for

mortality. Proportional hazard assumption was evaluated both graphically as with the Schoenfeld residual (27). As proportional hazard assumption was not respected for gender, Killip class >1 and multivessel disease in the older age group, we therefore employed a time-dependent covariate. Mortality was reported with hazard ratio (HR) and 95% confidence intervals (CI). Baseline characteristics with a p-value of <0.1 and significantly values in the different age and gender groups with univariate analysis were analysed with stepwise regression and included in the final multivariate model. We limited the variables to four per group to prevent overfitting. Variables in the multivariate model were age, multivessel disease, Killip class, and hypertension. Medication use was analysed using landmark analysis at discharge and 30 days. Gray's test was used for analysis of competing risks to analyse re-PCI, re-CABG, and re-MI with mortality as a competing event (28).

Results

Data from 6746 patients with STEMI who underwent a PPCI between 1998 and 2008 in our hospital were evaluated, consisting of 4991 (74%) men and 1755 (26%) women. Baseline characteristics for men and women in age groups of <65 years (young) and ≥65 years (elderly) are presented in Table 1; 40% of the women were <65 years old and 60% of the men were <65 years old.

Hypertension was more prevalent in women within both age groups than in men. In younger women, a positive family history and current smoking were significantly more present, while at older age women had more hypertension and diabetes. In both age groups, total ischaemic time and patient delay before hospital admission were significantly longer in women, whereas there was no gender difference in in-hospital delay from admission to first balloon inflation. Angiographic data showed less obstructive coronary artery disease in younger women compared with younger men, with a higher TIMI 3 flow at angiography and a lower CK release (Table 2). In the older age group, the occurrence of multivessel disease and TIMI-3 flow before PPCI were not significantly different between men and women. The TIMI flow and blush grade 3 post PPCI was not significantly different between men and women.

Overall, mortality at 30 days (HR 2.1, 95% CI 1.6–2.5) and at 1 year (HR 1.6, 95% CI 1.3–1.9) was higher in women than in men. The median

duration of follow up in the younger group was 403 (396–409) days and in the older group 395 (389–400) days. The missing patients at 1 year in the younger group were 36 women and 187 men and in the older group 73 women and 146 men. At 1 year, 454 patients deceased in the total population. In the younger group 36 women and 87 men died and in the older group 124 women and 207 men died. At univariate analyses, women compared to men in the younger age group had a significantly increased risk of mortality both 30 days (HR 2.1, 95% CI 1.3–3.4) and at 1 year (HR 1.7, 95% CI 1.2–2.6). Mortality at 30 days was also higher in women in the older age group (HR 1.5, 95% CI 1.1–2.0). There was no difference, however, in mortality between both genders at 1 year (HR 1.2, 95% CI 0.9–1.5) (Table 3, Figure 1). At univariate analysis common predictors for mortality in elderly men and woman were age, Killip class, and previous history of cerebrovascular accident. In the younger age group, adverse predictors were age, Killip class, and the presence of multivessel disease. Hypertension was a common predictor for mortality in elderly women and in young men. Multivariate analyses, adjusting for multivessel disease, Killip class, age, and hypertension confirmed these findings in the younger age group (HR 1.7, 95% CI1.1–2.6). In the older age group, the hazard ratio for 1-year mortality was comparable in women and men (HR 1.0, 95% CI 0.8–1.4) (Figure 2). In the model with age and gender as an interaction term, 1-year mortality remained significant (HR 0.97, 95% CI 0.95–0.99). Re-MI, re-PCI, and re-CABG were analysed with the Gray's test for comparison of cumulative incidence curves between men and women for 30-day and 1-year mortality. Mortality remained significant between men and women in both age groups at 30 days and in the younger group at 1 year.

Medication use at various time intervals is depicted in Table 4. Women were using more often insulin and diuretics at discharge, except in the younger age group. The use of aspirin, beta-blockers, statins, and ACE inhibitors was comparable in all 12 subgroups, except for higher rates of ACE inhibitors use at discharge in elderly men. Clopidogrel has been routinely used in our hospital since 2004. Its use in the acute phase was comparable between women and men in both age groups. Also glycoprotein IIb/IIIa inhibitor use in the acute phase was comparable between women and men in both age groups (Table 4). Of the 367 patients in our study who initially received conservative treatment, 102 patients had non-obstructive

coronary artery disease and 23 patients were treated with PCI during the same hospitalization. In two patients it was not possible to pass the wire through the stenosis whereas in three patients, the PCI was performed after several days, after an initially conservative approach. One patient had an older infarction and PCI was performed after demonstrating residual ischaemia by non-invasive testing. Two patients were referred from other hospitals after conservative treatment for unknown reasons. In 10 patients no culprit vessel was treatable due to too small vessel size and in the remaining five patients no details were available, and 243 patients were treated conservatively because PCI was not indicated.

Discussion

In our present study in patients with STEMI, treated with PPCI, we found that 1-year mortality was higher in women than in men in the age group <65 years. Whereas in the older age group mortality was higher at 30 days in women, there was no gender difference at 1 year. Several other single-centre and multicentre studies have shown higher in-hospital mortality rates in women compared to men. These differences are often attributed to their higher age and clustering of more CV risk factors (9–11). In some studies, gender differences in treatment and higher rates of in-hospital complications in women are considered as possible causes for their higher mortality rates (5,10). In our study, we found that differences in mortality between women and men persisted after correction for confounders by multivariate analysis. Treatment strategies in the acute setting were standardized and therefore comparable between both genders. It is alarming, however, that, although younger women had a lower risk profile at baseline, with more TIMI 3 flow before PCI and less multivessel disease, they had a higher mortality than similarly aged men. There may be several explanations for this adverse prognosis in women. First, despite their increased mortality rates at 30 days and at 1 year, younger women undergo less often a re-PCI than men (Table 3). Almost half of all re-PCI procedures were performed within the first 30 days, in which time most gender-related mortality differences are also seen. With our data, we cannot demonstrate whether the lower number of re-PCIs in younger women has had prognostic importance, and this should be examined carefully in future studies.

The total enzymatic infarct size (as measured by CK) was lower in young women compared to similarly aged men. We found no gender differences

in LDH values within both age groups. This may partly be related to the usually smaller body weight in women, although detailed information on body mass index is lacking in our study. Further, since women have a longer patient delay in both age groups compared to men and therefore hypothetically present more often after the peak of the CK levels (2–12 hours), this may possibly have resulted in lower CK levels. Secondly, because men have a shorter patient delay, they are more likely to be discharged before the peak LDH levels (24–48 hours) as most patients were discharged shortly after the CK peak. It is noteworthy that longer patient delay in women may be related to the absence of chest pain. However, patient delay was not a strong predictor for gender-specific mortality neither in a recent large study (29) nor in our study. In our study cohort, we have no data on type of chest pain/discomfort.

Our present findings confirm the existence of the so called 'gender paradox' in young women with STEMI (13,14,30). Several mechanisms may be involved to explain this phenomenon. First, we found important gender differences in baseline characteristics within the younger age group with a higher percentage of current smokers in women (67%) in comparison with men (60%). Smoking increases the risk of an acute MI relatively more in young women than in young men (31,32). Cigarette smoking increases oxidative stress and promotes the release of vascular inflammatory markers leading to a decrease in endothelial function (33). This counteracts the protective vasodilating effects of endogenous oestrogens in women before menopause (34) Although data are lacking in our cohort on the percentage of women that were using oral contraceptives, its use is common in premenopausal women in the Netherlands and also enhances the risk of arterial thrombosis and MI (35,36) In contrast, the use of hormone replacement therapy after menopause is rare in our country. In addition, data on previous gynaecology operations, endogenous oestrogen status, or menopausal status are lacking in our patients while this has shown to be relevant in women (37). Evidence is increasing that hysterectomy, especially before the age of 50 years, interferes with an increased risk of cardiovascular disease (38).

Gender-related differences in the pathophysiology of STEMI in women at younger age may also increase mortality. At younger age, the occurrence of plaque rupture with subsequent thrombosis is more common in men, while plaque erosions with microvascular embolization are relatively more frequently reported in women (19–21). In pathology studies, it is

shown that erosive plaques have a lower degree of critical stenosis with a greater maturation of thrombus material compared to ruptured plaques, especially in younger women (19,39). Furthermore, if plaque ruptures occur, they are more related to thrombus formation in women than in men.40 Women exhibit acute coronary syndrome with open coronary arteries more frequently than men (41,42). Non-obstructive coronary artery disease with microvascular dysfunction and abnormal coronary reactivity may also be relatively more important in women with STEMI and affect prognosis negatively (43).
In our study, TIMI–flow post PPCI and myocardial blush grades, as indicators of reperfusion, were comparable between women and men in both age groups. This is in concordance with data from previous studies (44).

We found that main gender differences in medication use after STEMI were higher rates of insulin and diuretics use in women. This can be explained by the higher prevalence of hypertension and diabetes mellitus. Limitations are that our patients were included during a 10-year time period in which PPCI procedures and medication given during this procedure were due to some changes. Also, although clopidogrel was prescribed for 1 year in all patients, we do not have detailed information about eventually discontinuation of clopidogrel, and we can not exclude that discontinuation may have affected late stent thrombosis and re-MI (45,46). In conclusion, in our single-centre cohort with STEMI patients, we found that younger women have a higher mortality than similarly aged men, despite the presence of less obstructive coronary artery disease and better TIMI 3 flow before PCI. More data are needed to explain these differences to improve prognosis in younger women.

Table 1
Baseline characteristics according to gender and age.

	Women <65 years n=708	Men <65 years n=3006	p-value	Women ≥65 years n=1047	Men ≥65 years n=1985	p-value
Age (years)	55 (48–61)	54 (48–60)	0.25	75 (70–80)	72 (68–77)	<0.001
History of:						
MI	38 (5)	224 (8)	0.05	77 (7)	301 (15)	<0.001
CABG	11 (3)	56 (2)	0.58	35 (3)	115 (6)	0.003
PCI	19 (3)	162 (5)	0.003	57 (6)	195 (10)	<0.001
Stroke	17 (2)	50 (2)	0.18	33 (3)	110 (6)	0.003
Risk factors						
History of hypertension	245 (35)	799 (27)	<0.001	495 (48)	690 (35)	<0.001
History of DM	70 (10)	235 (8)	0.069	214 (21)	251 (13)	<0.001
Hyper-lipidaemia	137 (20)	701 (25)	0.023	204 (21)	372 (20)	0.69
Positive family history	375 (55)	1400 (48)	0.001	314 (32)	554 (29)	0.22
Current smoking	468 (67)	1766 (60)	<0.001	236 (23)	565 (30)	<0.001
Admission data						
Killip class >1	49 (7)	162 (5)	0.10	116 (11)	179 (9)	0.068
Ischaemic time (min)	218 (160–339)	200 (148–296)	0.001	237 (178–364)	220 (164–315)	<0.001
Patient delay (min)	165 (110–285)	150 (100–240)	<0.001	180 (120–291)	165 (110–254)	<0.001
Door-to-balloon time (min)	45 (30–64)	44 (30–66)	0.32	48 (33–73)	46 (33–73)	0.12

Values are median (IQR) or n (%).
CABG, coronary artery bypass surgery; DM, diabetes mellitus; MI, myocardial infarction; PCI, percutaneous coronary intervention.

Table 2
Angiographic findings and treatment strategies according to gender and age.

	Women <65 years n=708	Men <65 years n=3006	p-value	Women ≥65 years n=1047	Men ≥65 years n=1985	p-value
Multi-vessel disease	33.2	44.7	<0.001	59.7	61.6	0.31
Initial treatment			0.36			0.24
Conser-vative	5.6	5.4		6.5	5.3	
PPCI	91.9	91.1		89.0	89.4	
CABG	2.5	3.5		4.5	5.3	
Stent placement	75.2	74.8	0.85	66.4	69.7	0.07
Infarct related vessel						
Left main	1.2	0.8	0.34	0.9	1.3	0.58
Graft	0.7	0.8	0.76	1.8	3.3	0.02
LAD	43.9	43.9	0.97	45.2	45.4	0.91
RCA	41.3	38.9	0.25	40.7	36.7	0.04
Cx	12.9	15.6	0.07	11.4	13.4	0.12
TIMI-3 before PPCI	24.6	19.9	0.008	19.7	18.4	0.42
TIMI-3 after PPCI	92.1	91.7	0.72	87.3	87.8	0.73
TIMI 0–1 after PPCI	3.7	3.2	0.48	4.9	4.3	0.51
Blush grade 3 post PPCI	51.9	49.7	0.38	40.8	41.3	0.85
CK max.	1400, (581–2854)	1691, (685–3398)	0.001	1268, (549–2500)	1514, (640–3008)	0.001
LDH max.	489, (297–827)	485 (272–837)	0.80	503 (305–872)	491 (299–792)	0.24

Values are median (IQR) or %.

CK, creatine kinase; Cx, circumflex; LAD, left anterior descending; LDH, lactate dehydrogenase; PPCI, primary percutaneous coronary intervention; RCA, right coronary artery; TIMI, Thrombolysis in Myocardial Infarction.

Table 3
Clinical outcomes according to gender and age.

	Women <65 years n=708	Men <65 years n=3006	p-value	Women ≥65 years n=1047	Men ≥65 years n=1985	p-value
Bleeding (<48 hour)	5.0	3.8	0.125	6.6	9.3	0.008
At 30 days						
Death	3.6	1.7	0.002	9.6	6.4	0.005
Re-MI	1.3	2.1	0.18	2.0	2.8	0.16
Re-PCI	4.3	6.7	0.02	4.3	6.4	0.02
Re-CABG	2.3	3.1	0.25	3.6	4.6	0.23
Death and/ or re-MI	4.6	3.7	0.25	20.3	8.7	0.05
MACE	11.8	3.7	0.10	20.3	8.7	0.41
At 1 year						
Death	5.3	3.1	0.004	12.7	11.2	0.24
Re-MI	2.8	3.5	0.38	3.3	5.0	0.04
Re-PCI	12.7	13.6	0.55	10.1	12.2	0.12
Re-CABG	2.3	2.9	0.40	3.9	4.7	0.39
Death and/ or re-MI	7.6	6.4	0.26	15.4	15.0	0.81
MACE	23.9	24.8	0.64	33	35.2	0.27

Values are %. Death is depicted as cumulative mortality.
MACE, combination of death, myocardial infarction, PCI, and/or CABG; MI, myocardial infarction.

Table 4
Medication use at discharge by gender and age.

	Women <65 years n=708	Men <65 years n=3006	p-value	Women ≥65 years n=1047	Men ≥65 years n=1985	p-value
In the acute phase (since 2004)						
Clopido-grel	75	77	0.48	71	70	0.56
GP IIbIIIa inhibitor	27	28	0.69	25	25	0.79
At discharge						
Aspirin	92	94	0.09	91	92	0.43
Beta-blocker	93	90	0.06	88	87	0.43
Statins	85	84	0.44	76	77	0.23
ACE inhibitor	55	57	0.36	54	59	0.01
Diuretics	8	8	0.87	21	16	<0.001
Insulin	5	3	0.02	6	4	<0.001
At 30 days						
Aspirin	91	91	0.53	87	87	0.98
Beta-blocker	93	90	0.08	89	88	0.29
Statins	88	89	0.51	81	82	0.36
ACE inhibitor	60	61	0.64	59	63	0.06
Diuretics	8	5	0.002	17	12	<0.001
Insulin	2	4	0.006	6	3	<0.001
Oral anti-diabetics	3	3	0.50	6	3	0.003

Values are %, ACE, angiotensin-converting enzyme; GP, glycoprotein IIbIIIa inhibitor.

	Women <65 years n=708	Men <65 years n=3006	p-value	Women ≥65 years n=1047	Men ≥65 years n=1985	p-value
At 1 year						
Aspirin	90	89	0.51	83	82	0.35
Beta-blocker	83	79	0.05	81	81	0.70
Statins	91	90	0.37	83	83	0.70
ACE inhibitor	49	53	0.05	53	56	0.31
Diuretics	10	5	<0.001	19	13	<0.001
Insulin	4	2	0.014	6	3	0.004
Oral anti-diabetics	4	3	0.33	7	5	0.09

Values are %, ACE, angiotensin-converting enzyme; GP, glycoprotein IIbIIIa inhibitor.

Figure 1
Kaplan–Meier curves for gender and age groups in patients with ST-elevation myocardial infarction.

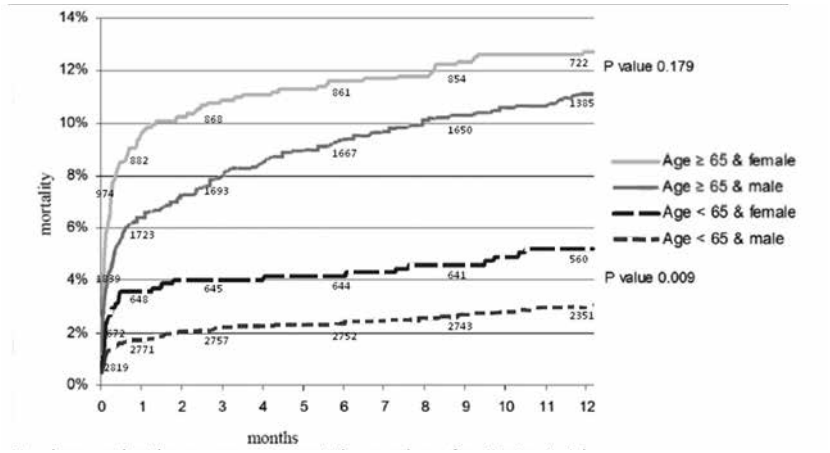
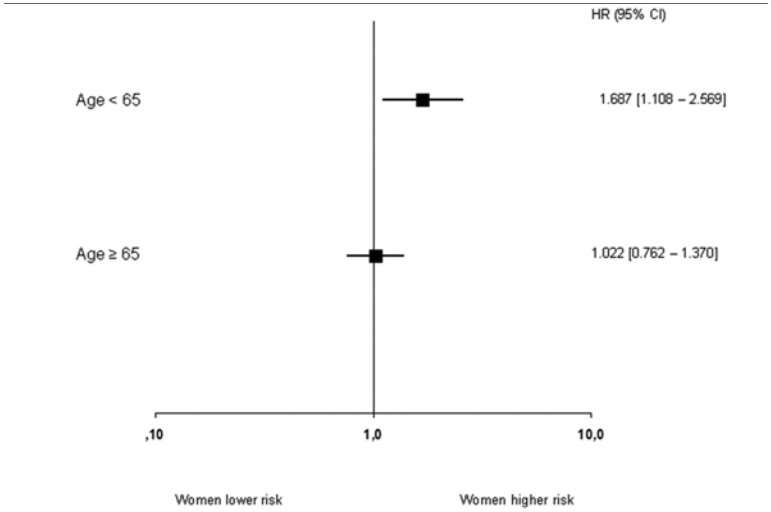


Figure 2
Multivariate analysis of 1-year mortality in women as compared to men, stratified to age.



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Chapter 4

Age-dependent differences in diabetes and acute hyperglycemia between men and women with ST-elevation myocardial infarction

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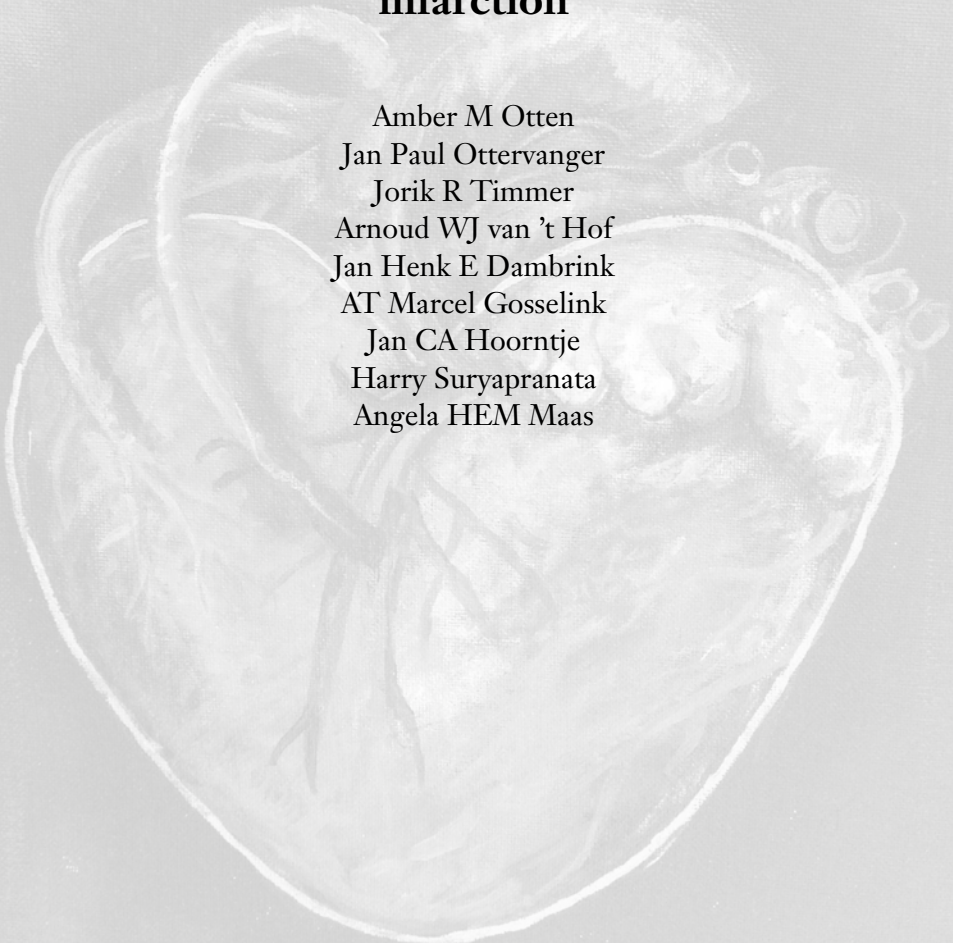

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Abstract

Background: Both acute hyperglycemia as diabetes results in an impaired prognosis in ST-elevation myocardial infarction (STEMI) patients. It is unknown whether there is a different prevalence of diabetes and acute hyperglycemia in men and women within age-groups.

Methods: Between 2004 and 2010, 4640 consecutive patients (28% women) with STEMI, were referred for primary PCI. Patients were stratified into two age groups, < 65 years (2447 patients) and ≥65 years (2193 patients). Separate analyses were performed in 3901 patients without diabetes. Diabetes was defined as known diabetes or HbA1c ≥6.5 mmol/l at admission.

Results: The prevalence of diabetes was comparable between women and men in the younger age group (14% vs 12%, p = 0.52), whereas in the older age group diabetes was more prevalent in women (25% vs 17% p < 0.001). In patients without diabetes, admission glucose was comparable between both genders in younger patients (8.1 ± 2.0 mmol/l vs 8.0 ± 2.2 mmol/l p = 0.36), but in older patients admission glucose was higher in women than in men (8.7 ± 2.1 mmol/l vs 8.4 ± 2.1 mmol/l p = 0.028). After multivariable analyses, the occurrence of increased admission glucose was comparable between men and women in the younger age group (OR 1.1, 95%CI 0.9-1.5), but increased in women in the older age group (OR 1.3, 95% CI 1.1-1.7). Both diabetes and hyperglycemia were associated with a higher oneyear mortality in both men and women.

Conclusions: The differences between men and women in hyperglycemia and diabetes in patients with STEMI are age dependent and can only be observed in older patients. This may have implications for medical treatment and should be investigated further.

Keywords

STEMI, Gender, Diabetes, Acute hyperglycemia

Background

Both hyperglycemia and diabetes are independent predictors of impaired prognosis after ST elevation myocardial infarction (STEMI) (1-4). Prevalences of both hyperglycemia and diabetes in STEMI are increased in women, which in part may explain their higher mortality rates (1,5,6). Moreover, diabetes has been associated with a higher cardiovascular mortality in women compared to men (7-9). In the general population

however, only in elderly people diabetes is more often present in women than in men (10). Until now, data with regard to the impact of age on the difference in prevalence of hyperglycemia and diabetes between men and women with STEMI are lacking. We investigated whether the differences in both hyperglycemia and diabetes are age-dependent within a large registry of patients with STEMI, treated with primary percutaneous coronary intervention (PCI).

Methods

We performed an observational study including all consecutive patients admitted with STEMI, referred for primary PCI to our hospital between 2004 and 2010. Within these time frames, HbA1c and glucose were routinely measured on admission in all STEMI patients. Patients were diagnosed with STEMI if they had chest pain longer than 30 minutes and ECG changes with ST elevation greater than 2 mm in at least two precordial leads or greater than 1 mm in the limb leads. All patients were directly transported to the catheterization laboratory on arrival, and acute coronary angiography was performed with subsequent PCI when indicated as part of the routine treatment for all STEMI patients. The interventional strategy was at the operator's discretion. All patients were pretreated with aspirin, heparin, and clopidogrel during transportation to the hospital according to protocol, or these drugs were administered at the emergency ward. Cardiac biomarkers were elevated in all patients. Diabetes was defined as known diabetes or a HbA1c $\geq$ 6.5 at admission. This HbA1c value was identified by the American Diabetes Association as diagnostic for diabetes mellitus (11). We performed additional analysis on a group without diabetes in order to concentrate on acute hyperglycemia due to stress. We conducted a multivariate analysis with gender as a predictor of a higher than median glucose levels. We corrected for confounders based on previously described variables in the literature (1,8). Therefore, the multivariate model consisted of gender, TIMI flow, Killip class and age.

Data collection

Patient characteristics were registered into a dedicated database. Thrombolysis in Myocardial Infarction (TIMI) (12) flow was scored according to the TIMI flow grading system before and after PCI. Follow-up information was obtained with pre-defined time intervals of 30 days and one year using the outpatient files or by direct telephone interview

by independent research nurses not involved in patient treatment, The HbA1c levels were measured on the Primus Ultra 2 affinity chromatography-HPLC (Primus Diagnostics, Kansas City, MO) with a within run coefficient of variation of < 0.5%. The reference normal values in non diabetics were 4.0% to 6.5%. Glucose levels were measures with a Modular device (Roche Diagnostics). The reference values did not change during the study period and yearly numeric quality control data revealed that the coefficient of variation remained < 2%.

Statistical analysis

Statistical analysis was performed using SPSS version 17.0 (SPSS Inc, Chicago, IL). Continuous data were expressed as median and inter quartile range and categorical data as percentages. In order to examinate differences in women and men, we performed the Chi2 test for categorical variables and one-way Anova for continuous variables. The test for significance were two-sided with an α of < 0.5%. Multivariate analyses were performed using binary logistic regression. Predictors were identified using forward, stepwise logistic regression with the likelihood ratio test of all baseline variables with an $\alpha \geq 0.1$. The three most significant values and gender were entered into the final multivariate model. Kaplan Meier was performed with the log rank test for the p-values.

Results

A total of 4640 patients with STEMI were admitted between 2004 and 2010. Mean age of the total population was 64 ± 13 years, including 1291 women (28%). In the total population, the prevalence of hypertension was 36%, smoking 41% and hypercholesterolemia 21%. A total of 464 (10%) patients had a previous myocardial infarction.

Effect of age

In older women, a higher killip class was observed compared to men.
This difference was not present in the younger age group. The prevalence of known diabetes was 10% in men en 16% in women in the total study group ($p < 0.001$). Undetected diabetes was observed in 4% of men and in 5% of women ($p = 0.80$), resulting in a significantly different prevalence of diabetes between both genders ($p < 0.001$). Diabetes was associated with an increased one-year mortality in both men (OR 1.9, 1.4-2.8 95% CI) and women (OR 2.1, 1.4-3.2 95% CI). In the older age group the prevalence

of diabetes was higher in women, while in the younger age group the prevalence was comparable (Table 1 and Figure 1). Hyperglycemia in patients without diabetes A total of 3901 patients had no diabetes, consisting of 1029 women (26%). Of the total group, 1761 patients (45%) were aged ≥65 years. Mean admission glucose was associated with both age and gender. Mean admission glucose was 8.2 ± 2.2 mmol/l in men and 8.5 ± 2.1 in women (p = 0.001). The mean admission glucose was 8.3 ± 2.6 mmol/l in younger patients and 8.9 ± 2.6 mmol/l in older patients (p < 0.001). Baseline characteristics of the 3901 patients, stratified to age group and gender are summarized in Table 2. Besides differences in history of hypertension and smoking there were no significant differences in risk factors between men and women in the patient group below 65 years of age. In the older patient group however, men had more often a previous history of cardiovascular disease (prior PCI, CABG, myocardial infarction or stroke) while women were more often known with hypertension. Glucose level at admission was comparable between men and women in the younger age group, but higher in women at older age (Table 2) Also, the prevalence of admission glucose above the median was comparable within both genders at younger age in the multivariate model (OR 1.1, 0.9-1.5 95% CI) while in the older age group, admission glucose above the median was more frequent in women. (OR 1.3, 1.1-1.7 95% CI) This age-related difference remained after multivariate analyses. In patients without diabetes, acute hyperglycemia was associated with an increased one-year mortality in both men (OR 2.2, 1.5-3.4 95% CI) and women (OR 2.9, 1.6- 5.4 95% CI). Mortality curves for patients without a history of diabetes are dichotomized into higher and lower than median glucose in women (8.1 mmol/l) and men (7.8 mmol/l) are depicted in Figure 2.

Discussion

In our present study of patients treated with primary PCI for STEMI the prevalence of diabetes was higher in older women compared to similarly aged men. In younger patients, however, we found no differences between men and women. Also, in patients without diabetes, a higher admission glucose could only be demonstrated in older women as compared to older men. Both diabetes and increased admission glucose in patients without diabetes, were associated with a higher one-year mortality in both women and men. Our study confirmed the increased prevalence of diabetes and acute hyperglycemia in women compared to men (5-7). A new finding

however in STEMI patients is that this association is age-dependent and only present in the older age-group. Diabetes (both known and unknown) confers to a greater risk for adverse cardiovascular events in women than in men (6,7). Therefore, the increased risk induced by diabetes in patients presenting with STEMI is predominantly observed in older women. In assessing the risk of adverse events in patients presenting with STEMI, both age and gender are important factors to consider. Importantly, the increased prevalence of diabetes in older women compared to older man is part of a different risk profile. Consistent with the literature, we found that men more frequently had ischemic heart disease in the medical history (6,7). Hypertension however was more common in both older and younger women, and this is interesting because hypertension has been associated with the development of diabetes (13-15). Hypertension may be an early sign of microvascular disease and increased risk of pre-diabetes and STEMI in (aging) women. The association between hypertension and diabetes is also important, since both risk factors induce microvascular and more diffuse coronary artery disease, which is more prevalent in older women (16-19). Our findings may have implications for medical treatment for patients with STEMI, since it has been shown that some antiplatelet drugs are more effective in patients with diabetes (20,21). Particularly since older women with abnormal glucose metabolism have a worse prognosis, optimal medical treatment is mandatory in this subgroup. It is important to discriminate diabetes from acute hyperglycemia at admission (1,22). High admission glucose in patients with diabetes is mainly due to glucose intolerance in the setting of diabetes. Whereas in patients without diabetes, hyperglycemia is probably associated with acute stress, induced by abnormal hemodynamics (1,23,24). There are several explanations for the increased prevalence of acute hyperglycemia in older women without diabetes. Firstly, although we excluded patients with increased HbA1c, several older women may have had abnormal chronic glucose metabolism. Therefore, women are more susceptible for hyperglycemia in response to a stressor, as compared to patients with completely normal glucose metabolism. Secondly, older women with STEMI may have had more acute stress as there is evidence that women more often present with cardiogenic shock compared to men (25). Also, in our study population older women had more often signs of heart failure on admission as compared to older men, whereas in the younger age group there was no difference in heart failure between men and women. However, after

adjustment for the observed differences in heart failure, we found that older women still had increased admission glucose levels. Finally, gender-differences to stress in STEMI patients may be more present in elderly woman than in similarly aged men. Our study has several limitations. The number of patients in some subgroups were small, and the study was not powered to detect small differences between these subgroups. Also, the sample size was too small to demonstrate survival differences between men and women within the different age groups. Information regarding renal failure, liver failure, obesity, physical activity, inflammatory markers and socioeconomic status were lacking. Therefore, we were unable to adjust for these potential confounders. Finally, our data cannot be extrapolated to non-STEMI patients,non-cardiac patients admitted to intensive care wards, or unstable patients since our study included only STEMI patients and only 8% of these patients had a killip class higher than 1.

Conclusion

In STEMI, diabetes and hyperglycemia on admission is more prevalent in older women compared to similarly aged men. This association was not prevalent in younger patients. We observed an independent increased risk of acute hyperglycemia in older women without diabetes and therefore, older women may have an increased stress response. Both acute hyperglycemia and diabetes are associated with a worse prognosis in both women and men. More research is needed to elucidate these age-dependent gender differences and to explore whether tailored treatment can improve prognosis.

Table 1
Prevalence of diabetes in the total study population (n = 4640) according to gender and age group

	Women <65 n=508	Men <65 n=1939	p-value	Women ≥65 n=783	Men ≥65 n=1410	p-value
History of diabetes	54 (11%)	157 (8%)	0.15	155 (20%)	184 (13%)	<0.001
Newly detected diabetes *	13 (3%)	77 (4%)	0.16	35 (4%)	51 (4%)	0.17
Total without chronic diabetes	439 (86%)	1701 (88%)	0.52	590 (75%)	1171 (83%)	<0.001
Missing	2	4		3	4	

* Patients without previously known diabetes and HbA1c ≥ 6.5% mmol/L

Table 2
Baseline Characteristics according to gender and age groups <65 and ≥65 years in 3901 patients admitted for primary angioplasty for ST-segment elevation myocardial infarction (STEMI) without diabetes.

	Women <65 N=439	**Men <65 N=1701**	**p-value**	**Women ≥65 N=590**	**Men ≥65 N=1171**	**p-value**
Age (year)	55 (48-60)	54 (49-59)	0.41	75 (70-81)	73 (69-78)	<0.001
History of, n (%)						
MI	19 (4%)	113 (7%)	0.07	39 (7%)	176 (15%)	<0.001
CABG	5 (1%)	30 (2%)	0.36	13 (2%)	67 (6%)	0.001
PCI	21 (5%)	117 (7%)	0.11	36 (6%)	141 (12%)	<0.001
Stroke	5 (1%)	21 (1%)	0.87	17 (3%)	57 (5%)	0.05
Risk factors						
History of hypertension	142 (32%)	431 (26%)	0.004	267 (45%)	432 (37%)	0.001
Positive family history	227 (53%)	841 (51%)	0.43	170 (30%)	310 (27%)	0.34
Current smoking	280 (65%)	963 (57%)	0.004	123 (21%)	263 (23%)	0.41
Hyper-cholesterolemia	65(15%)	320 (19%)	0.06	99 (17%)	205 (18%)	0.66
Admission data						
Glucose (mmol/l)	8.2 ± 2.2	8.0±2.2	0.36	8.7±2.1	8.4±2.1	0.03
Killip class = 1	412 (94%)	1619 (96%)	0.22	519 (88%)	1066 (91%)	0.05
TIMI-3 before PCI	105 (27%)	335 (22%)	0.06	116 (24%)	219 (22%)	0.36

Continuous variables are displayed as median and interquartile range.

Figure 1
Prevalence diabetes in STEMI patients according to age and gender.

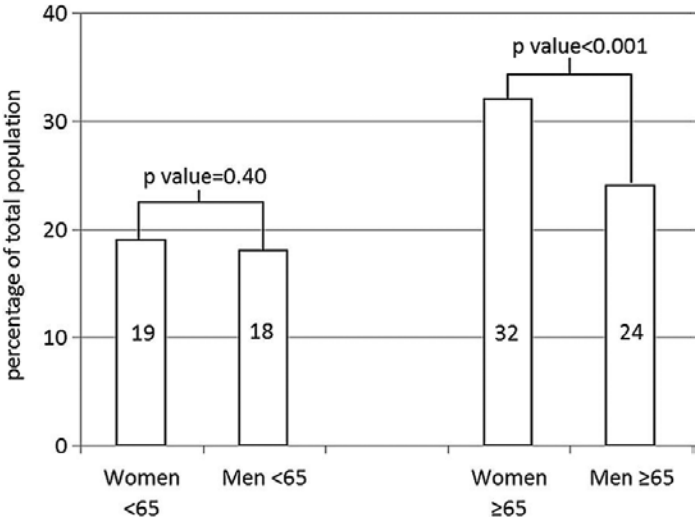
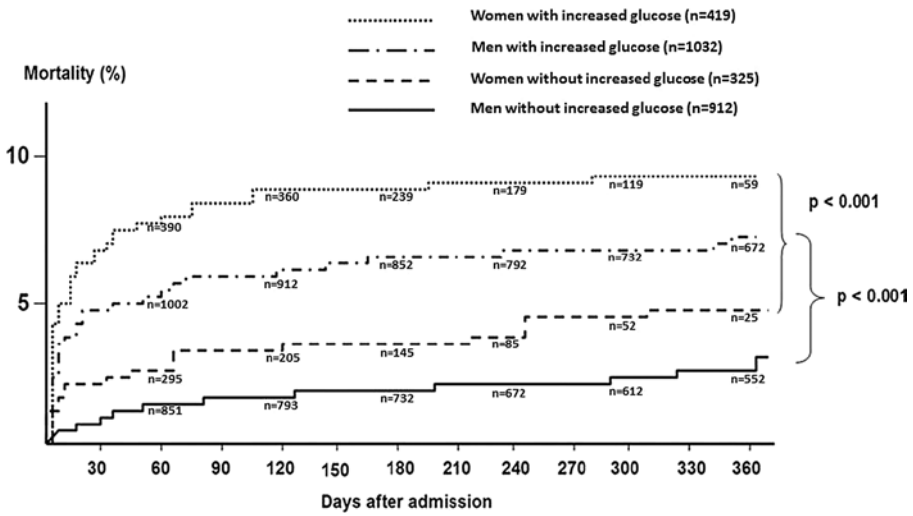


Figure 2
Kaplan Meier mortality curves for patients without a history of diabetes, dichotomized into higher and lower than median glucose and stratified to gender (n = 3901).



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Chapter 5

Early menarche is associated with Myocardial Infarction at younger age

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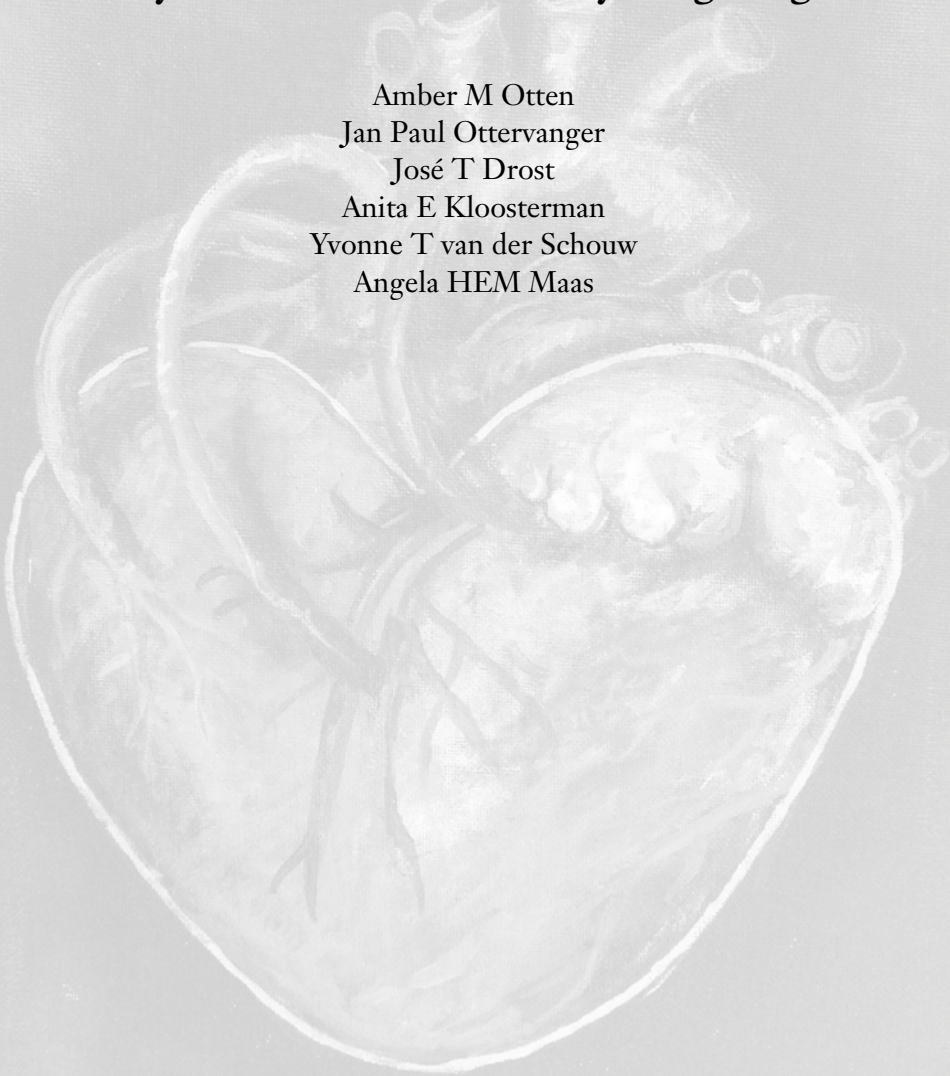


Submitted

Abstract

Objective: There is increasing evidence that reproductive factors are important in ischemic heart disease in women. We assessed the association between age at menarche and age of ST Elevation Myocardial Infarction (STEMI).

Methods: From 1998 until 2010 data from all women with STEMI were collected in Zwolle. Reproductive information was obtained in 688 women with age at STEMI <75 years. Younger age of STEMI was defined as STEMI below 60 years. Age at menarche was categorized as ≤12 years, 13 years, 14 years and ≥15 years.

Results: STEMI at younger age was observed in 50%. In 20% of the patients, age at menarche was ≥15 years Younger age at menarche was associated with a higher prevalence of smoking, all other classical risk factors for cardiovascular disease were comparable between the 4 groups. After both unadjusted and multivariable analysis, women with a lower age at menarche had a higher probability of STEMI at younger age, with the adjusted OR 1.6 (95% CI 1.0-2.6) for age <12 years as compared to ≥15 years.

Conclusions: In a group with STEMI, women with early menarche have an independently increased risk of STEMI at younger age. More insights into the underlying mechanisms is warranted.

Keywords

Menarche, STEMI, age, women

Introduction

Ischemic heart disease (IHD) is an important cause of morbidity and mortality in women. In women, hormonal or reproductive factors during various stages of life can influence the risk of IHD (as1,2). For example, women with a late menopause have a lower cardiovascular risk compared to women with an early menopause (3-6). Whether other reproductive risk factors including age at menarche may be relevant in risk prediction of IHD is important to determine, since this can provide an additional opportunity for prevention. However, it is still unclear whether age of menarche is independently associated with cardiovascular mortality and morbidity. Several previous studies have shown conflicting results (7-16). Most of these studies were performed in Asian women (7-10) or were performed with data more than 10 years ago (9-15). Furthermore,

most of the population-based studies did not have clinical information on IHD as the occurrence of myocardial infarction was diagnosed from death certificates, admission diagnosis and national or death registries (7-9,13,17). Recently, a large cohort has been published revealing an u-shaped association for coronary heart disease deaths in early and late menarche (17). To assess the potential association between age at menarche and age at myocardial infarction, we performed a retrospective cohort study in women admitted with ST Elevation Myocardial Infarction (STEMI).

Materials and Methods

Population

From January 1998 to January 2010 individual data from all consecutive STEMI patients who were considered for primary Percutaneous Coronary Intervention (pPCI) at Isala Klinieken, Zwolle, were prospectively recorded in a dedicated database. Our institutional review board, METC (Medical Ethical Test Committee), was consulted and approval for this observational data collection was obtained. No questions were asked that need approval according to Dutch medical research involving human subjects act.

All patients were informed at admittance that patient parameters were recorded for scientifical purposes. Information on demographic parameters and risk factors was entered into this database at the time of admission for STEMI. A positive family history was defined as a cardiovascular event in a relative ≤65 years.

Questionnaires

A total of 1351 women aged <75 years presenting in our hospital between 1998 and 2010 were included in the study and sent a questionnaire. The estimated response rate and recall bias in women >75 years at the time of STEMI would cause inaccurate data to be included and therefore, this was an exclusion criterion. The questionnaire was sent twice to non-responders and all non-responders were contacted by telephone. A total of 771 women responded (57%) and of these patients, 688 patients (89%) provided information for age of menarche. We included all 688 patients in the statistical model for the association of age of STEMI and age of menarche. The questionnaire included questions on socioeconomic status, height (centimeters), weight (kilograms) and reproductive factors (age of

menarche, duration of oral contraceptive use, miscarriages, pregnancies, birth weight, gestational hypertension, preeclampsia, Hemolysis Elevates Liver enzymes and Low Platelets (HELLP) syndrome, gestational diabetes, hysterectomy, ovariectomy, age at menopause and perimenopausal symptoms). Miscarriage was defined as dead born foetus after pregnancy duration of <24 weeks and neonatal death was defined as death between birth and 28 days afterwards (18). The number of reproductive years was defined as age of natural menopause minus age at menarche. Hypertensive pregnancy disorders were defined as self-reported gestational hypertension or pre-eclampsia/HELLP in one or more pregnancies. A high level of education was defined as pre-university or university. BMI was calculated as weight in kilograms divided by square height at the time of STEMI. Late menarche was defined as ≥15 years and early menarche was defined as ≤14 years.

Outcome

Patients were diagnosed with STEMI according to the European Society of Cardiology guidelines if they had chest pain longer than 30 minutes and ECG changes with ST elevation greater than 2 mm in at least two precordial leads or greater than 1 mm in the limb leads. Cardiac biomarkers were elevated in all patients (19).

According to the protocol pPCI was performed using standard techniques, if the coronary anatomy was suitable for intervention. Success rate of the procedure was assessed with a classification for coronary flow according to Thrombolysis In Myocardial Infarction (TIMI) classification (20). Angiographic results were entered into the database at the time of angiogram. The mean age of first STEMI was 59 years and therefore, lower age of STEMI was defined as <60 years and higher age of STEMI was defined as ≥60 years.

Data analysis

Distributions of population characteristics for women with early and late menarche were expressed as means ± standard deviations for continuous data and as frequencies and percentages for categorical data, unless otherwise indicated. To compare characteristics between women with early and late menarche, we used chi-square tests with p-values for homogeneity for categorical variables and one-way ANOVA for continuous variables.

To evaluate differences between non-responders and responders,

admission data between these women were reported. To assess whether early menarche was independently associated with STEMI at younger age, we used a linear regression model with age at STEMI and age at menarche as continuous variables, adjusted for confounders. Furthermore, a logistic regression model was performed in which we categorized age of STEMI in 2 groups according to the mean age, <60 years and ≥60 years. Age at menarche was categorized in quartiles, ≤12 years, 13 years, 14 years and ≥15 years, with ≥15 years as the reference group. The multivariate model also compromised smoking and BMI, since these are previously described in the literature as potential confounders for both early menarche and higher risk for IHD. Furthermore, we assessed which potential confounder deviated the beta-coefficient by more than 10%. This percentage was used, because it is most commonly used in the literature and this low value is known to best decide whether the confounder should be add into the model (21,22). All variables tested are displayed in table 1 and 2. Besides smoking and BMI, hypertension and number of miscarriages changed the coefficient by more than 0.1 and these variables were included into the final multivariate model.

In 46% of patients, data on body mass index (BMI) were missing and we decided to impute these missing values by multiple imputation (23). Assuming these data were missing at random, a multiple missing value imputation procedure with m=5 was applied in which the values of the BMI, pre-eclampsia, HELLP, gestational hypertension gestational diabetes, education level, smoking, age, hypercholesterolemia, hypertension and diabetes were imputed in case they were missing. To study the "missing at random" assumption we compared the prevalence of all traditional- and female-specific risk factors between the persons with any missing values and without missing values. When comparing persons without any missing values (i.e., 'complete cases') to persons with one or more missing values, differences are found in particular in age at STEMI, hypertension, >10 years of oral contraception and gestational hypertension. This indicates that missing values were not missing completely at random (MCAR) and using complete cases only would lead to biased estimates. Therefore in this situation with data being 'missing at random (MAR), (multiple) imputation is the preferable approach, even though there is no method to test missingness not at random (MNAR) and therefore we cannot fully exclude this.

Statistical analysis was performed using SPSS version 20.0 (SPSS Inc, Chicago, IL). Tests for significance were two-sided, with α=0.05.

Results

The mean age at the time of STEMI of the 663 non-responders was slightly higher than the 688 responders (62 vs. 60 years, p<0.005), diabetes and a history of myocardial infarction were more prevalent (14% vs. 11%, p=0.015 and 9% vs. 5%, p<0.001) and a positive family history was less often present (45% vs. 54%, p=0.007). Other general variables were comparable in both groups. Mean age at the time of STEMI was comparable between responders who contributed information about age of menarche or not (59 vs. 60, p=0.3).

Of the 688 patients completed the question about age of menarche, 41% had anterior location of infarction and 51% had TIMI 0 flow (or no flow) at the initial coronary angiography. Compared to women with late STEMI, a higher percentage of women with early STEMI were smokers, with a positive family history, while they had less often hypertension (table 1).

Furthermore, women with late STEMI had a lower prevalence of preeclampsia and HELLP, were more often multigravida, with a higher birth weight of their first child and a lower prevalence of surgical menopause.

Characteristics of early menarche

Women with an early menarche were more often smokers (p=0.02). Other classical cardiovascular risk factors as well as level of education were comparable between the 4 groups (table 2). Notably, women with early menarche did not have an earlier natural or surgical menopause compared to women with a late menarche. Duration of reproductive years was longer in women with early menarche (p<0.001). Miscarriages were more often observed in women with early menarche (p=0.02).

Association between age at menarche and age of STEMI

With linear regression, per year of increased age of menarche, the age at STEMI increased 0.79 years with a p-value of 0.001. Mean age of STEMI was different between the 4 menarche age groups. In bivariate logistic regression analysis, women with a lower age at menarche had a higher probability of having STEMI at younger age. Compared to women with highest menarcheal age ≥15 years, odds ratio (OR) and confidence intervals

(CI) were 1.8 (95%CI 1.2-2.8) for age-group <12 years, 1.2 (95%CI 0.8-1.9) at 13 years, and 0.8 (95%CI 0.5-1.3) at 14 years. This association remained significant in the multivariate model with BMI. The OR and CI was 1.6 (95%CI 1.0-2.6) for age at menarche <12 years , 1.0 (95%CI 0.6-1.6) at 13 years and 0.8 (95%CI 0.4-1.3) at 14 years, compared to women with menarcheal age ≥15 years (figure 1).
The multivariate model without BMI was comparable to the model with BMI. At <12 years the OR was 1.6 (95%CI 1.0-2.6), 1.0 (95%CI 0.6-1.6) at 13 years and 0.8 (95%CI 0.4-1.3) at 14 years, compared to women with menarcheal age ≥15 years.

Discussion

This study demonstrates that early menarche is independently associated with a lower age at myocardial infarction. Several population based studies in the literature have suggested an increased premature risk of IHD in women with early menarche (7-11,17). This earlier presentation of IHD is presumably only partly associated with the higher prevalence of traditional cardiovascular risk factors in these women. In our study, only smoking was associated with earlier menarche. This underlines that hormonal-related factors, such as early menarche, may also play an important role in the development of IHD in women.
After menarche, endogenous oestrogen levels increase in women. Both observational and experimental studies have shown an overall cardioprotective role of endogenous oestrogens during the reproductive years of life (24,25). However, oestrogen exposure may also have negative effects on atherothrombotic risk. There are conflicting results in the literature whether a more adverse risk profile in patients corresponds with a higher number of reproductive years or cumulative years of exposure to endogenous sex hormones (1,3). Furthermore, early exposure to oestrogens instead of later vascular (protective) exposure may be disadvantageous for the onset of (cardio) vascular diseases (7-11). Possibly, the timing of oestrogen exposure in the reproductive years may be more important rather than the total number of years, as late menopause is protective for cardiovascular diseases and early menarche is not.
Confounders and intermediary factors influencing the age of menarche may also affect cardiovascular risk. There is evidence that in more than fifty percent of women the onset of menarche is caused by a combination of environmental and genetic factors (26-29) and up to date, more than

30 genetic loci have been identified to be related to age of menarche (30). In IHD, it is estimated that genetic predisposition accounts for 40 to 60% of the disease risk (31,32). Although family history is an important cardiovascular risk factor in women with STEMI at younger age (33,34), we found no differences in family risk in women with early and late menarche.

In concordance with the literature, we found that early menarche is associated with a higher prevalence of smoking and this reinforces the need to discourage young women to start smoking (35). One possible explanation for this association is that girls with an early menarche are physically more mature than their counterparts with a later menarche and this may contribute to earlier engagement in tobacco use than their peers (36-38). In line with this hypothesis, smoking is an intermediary factor in the association of age of menarche and age of STEMI. A recent large study, showing a u-shaped association between age of menarche and cardiovascular heart disease deaths irrespective of smoking, past smoking or non-smoking women, supporting the theory that smoking is an intermediate (17).

Another traditional risk factor and confounder for the relation with IHD possibly linked with age of menarche is BMI. An increased BMI is a risk factor for both early menarche as well as IHD (39-41). Although data in the literature are inconsistent about this correlation, the association between early menarche and STEMI at younger age did not change after correcting for BMI at STEMI in our present study.

We found a different prevalence of traditional risk factors between younger and older women with STEMI. In agreement with earlier observations, we observed a higher prevalence of hypertension and diabetes in older women with STEMI while smoking and a positive family history were more prevalent in younger women (42,43). This may facilitate a matched (secondary) prevention program since smoking, hypertension and diabetes are modifiable risk factors. Although we did not specifically investigate it, timing of menarche might be a valuable addition to long term cardiovascular risk prediction in women. Individual risk algorithms may be improved if reproductive risk factors are incorporated (44). Currently, age of menarche seems to be a relatively more accurate risk factor than age at menopause, since many women use oral contraceptives during menopause transition, hiding their true age of menopause.(45) More studies are needed to further investigate whether age of menarche may be

a valuable addition in risk algorithms.
Worldwide, a decline in age of menarche is observed presumably due to several factors as increased obesity or exposure to environmental toxicants (46). Combined with an increase in adverse life-style factors in younger generations, this may be a signal for a higher cardiovascular disease risk profile in future generations.

Limitations:
An important limitation of our study was the low response-rate at the questionnaire (57% responders), and the fact that several baseline variables (as age at STEMI, diabetes) were different between responders and non-responders. Furthermore, the non-survivors only were present in the non-responder group. This may influence both internal and external validity of the study.
We do not have information about hormonal use during menopausal transition, birth weight, detailed subsequent menstrual cycles, hypoandrogenic state or PCOS, although it is likely that hormonal use during menopause is 5% (47). Future studies should include these data and focus more on women specific risk factors.
Although age at menarche is an occurrence that is mostly well remembered by women, a modest recall bias may be present (48). This is likely independent of age at STEMI and may therefore lead to an underestimation of the association between menarcheal age and outcome in this study. Self reported pre-eclampsia could not be validated with medical records and may be moderately valid, although misclassification may be not different between higher and lower age of STEMI and not influence the results (49).
Although general variables are prospectively entered into this database and most variables therefore had a relatively low percentage of missing data (<2%) we had 46% missing data on BMI at admission. Therefore, we used multiple imputation of the missing BMI variables on order to enhance statistical power in the multivariate analysis. We also have no detailed information about various ethnic groups, although it is ascertained that this STEMI population is mainly of white origin, since our hospital is located in a rural area in the Netherlands.

Conclusions

Early menarche is independently associated with STEMI at a younger age and this is not mediated through classical cardiovascular risk factors. A better understanding of the underlying mechanisms is needed.

Table 1
Traditional ischemic heart disease risk factors and reproductive factors in 688 women with STEMI < 75 years, stratified to age at STEMI.

	Menarche ≤ 12 years n=254	Menarche = 13 years n=166	Menarche = 14 years n=131	Menarche ≥ 15 years n=137	p-value
Age at STEMI (years)	57±10	59±10	61±10	59±10	0.01
BMI (kg/cm²)	27±5	26±4	27±5	26±4	0.08
Previous MI	4%	4%	2%	8%	0.08
Previous CABG	1%	2%	1%	3%	0.32
Previous PCI	4%	2%	2%	4%	0.51
Previous Stroke	2%	2%	1%	2%	0.71
Diabetes	12%	9%	10%	14%	0.53
Hypertension	39%	31%	32%	36%	0.12
Hyper-cholesterolemia	18%	22%	22%	29%	0.13
Positive family history	53%	52%	54%	55%	0.95
Smoking (ever)	60%	54%	50%	45%	0.02
High level of education	11%	10%	9%	12%	0.82
≥ 10 years of oral contraception	48%	45%	51%	42%	0.66
Intra uterine device (ever)	21%	18%	15%	20%	0.64
One or more pregnancies	93%	90%	92%	93%	0.48
Multigravity (≥ 4)	19%	24%	18%	22%	0.58
Birth weight first child (gram)	3156±804	3259±800	3277±865	3290±942	0.51

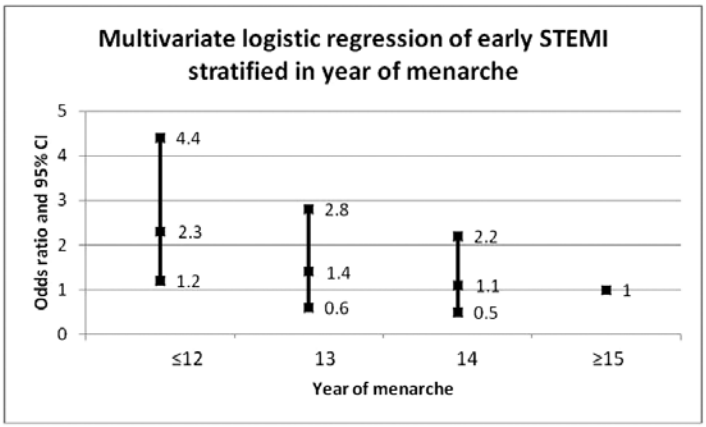
	Menarche ≤ 12 years n=254	Menarche = 13 years n=166	Menarche = 14 years n=131	Menarche ≥ 15 years n=137	p-value
Gestational hypertension	23%	24%	27%	19%	0.65
Pre-eclampsia/ HELLP	5%	4%	7%	3%	0.5
Gestational diabetes	4%	2%	6%	8%	0.07
Miscarriage	32%	26%	16%	28%	0.02
Neonatal death	6%	2%	2%	7%	0.1
Surgical menopause < 50 years	16%	8%	14%	13%	0.25
Age at menopause (years)	46±5	47±5	47±5	46±6	0.71
Number of reproductive years	35±7	35±5	33±6	32±6	<0.001
Perimenopausal complains	98%	96%	97%	98%	0.76

HELLP = Hemolysis Elevates Liver enzymes and Low Platelets.

Table 2
General characteristics of women with a STEMI < 75 years, stratified by age of menarche.

Variable (sample size)	Women <60 year n=350	Women ≥ 60 year n=338	p-value
Age at STEMI (years) (n=688)	50±6	67±4	<0.001
BMI (kg/cm²) (n=370)	27±5	26±4	0.56
Previous MI (n=684)	5%	4%	0.51
Previous CABG (n=684)	0%	3%	0.009
Previous PCI (n=684)	10%	11%	0.76
Previous Stroke (n=683)	2%	2%	0.95
Diabetes (n=681)	8%	14%	0.009
Hypertension (n=674)	31%	42%	0.002
Hypercholesterolemia (n=659)	20%	25%	0.13
Positive family history (n=671)	63%	43%	<0.001
Smoking, ever (n=686)	71%	35%	<0.001
High level of education (n=652)	11%	10%	0.45
≥ 10 years oral contraception (n=475)	56%	32%	<0.001
Intra uterine device, ever (n=686)	28%	10%	<0.001
One or more pregnancies (n=652)	89%	94%	0.07
Multigravity, > 4 births (n=575)	12%	25%	<0.001
Birth weight first child, gram (n=686)	3152±845	3385±951	<0.001
Gestational hypertension (n=686)	23%	23%	0.91
Pre-eclampsia/HELLP (n=686)	7%	3%	0.03
Gestational diabetes (n=686)	4%	2%	0.14
Miscarriage (n=585)	25%	20%	0.10
Neonatal death (n=597)	5%	6%	0.74
Surgical menopause < 50 years (n=680)	17%	10%	0.023
Age at menopause, years (n=540)	47±6	47±6	0.91
Number of reproductive years (n=540)	34±6	34±6	0.25
Perimenopausal complains (n=597)	92%	92%	0.89

Figure 1
Multivariate logistic regression of early menarche as a risk factor for early STEMI in a population of STEMI patients <75 years.



≤ 12 years; n= 254, 13 years; n= 166, 14 years; n= 131, ≥15 years; n= 137

Corrected for: smoking, BMI, hypertension and number of miscarriages.

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Chapter 6

Treatment assignment in young women with spontaneous coronary artery dissection

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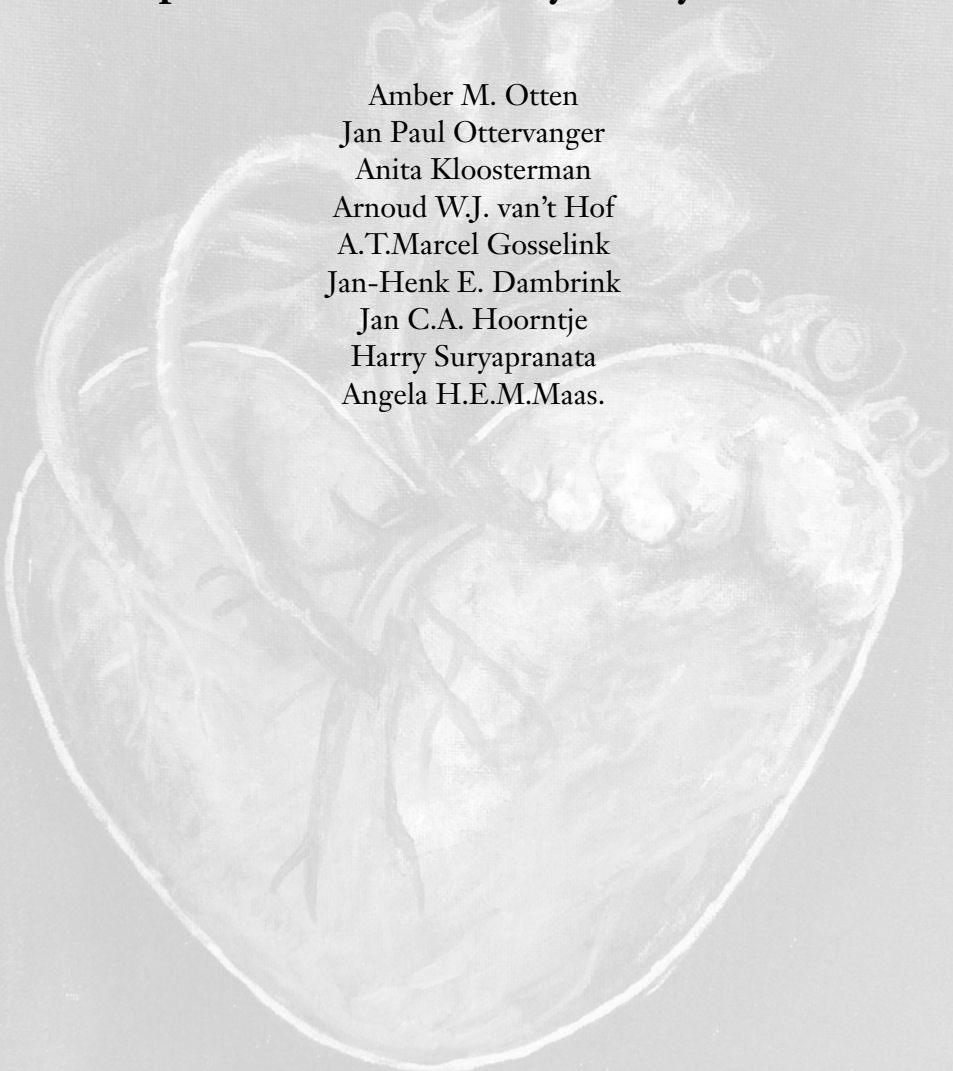

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Spontaneous coronary artery dissection (SCAD) is a rare and poorly understood cause of myocardial infarction and sudden cardiac death (1–5). In ST elevation myocardial infarction (STEMI), SCAD is more common in young women than men (2). There are currently no guidelines for acute and chronic management of these patients. According to previous reports, about half of SCAD patients with STEMI are treated with percutaneous coronary intervention (PCI), but it is debatable whether this treatment is beneficial (2,4,5). Moreover, it is unclear yet which secondary prevention strategy after SCAD is effective. In order to investigate the initial treatment assignment and angiographic success in a larger cohort, we evaluated all women <50 years with STEMI admitted in our hospital between January 1998 and December 2010. During the study period, 263 women <50 years with STEMI were admitted. All angiographies were retrospectively reviewed by two experienced interventional cardiologists, without knowledge of the general characteristics. The presence of SCAD was suspected if there was an angiographic characteristic finding suggesting the presence of coronary artery dissection (3,6,7). A definite diagnosis of SCAD was given if there was an agreement between both reviewers.

SCAD was observed in 26 patients (10%). Differences in the general characteristics between women with and without SCAD are presented in Table 1. Though not statistically different, hypercholesterolemia was less present in women with SCAD (20% vs. 8%, $p = 0.12$). Other general variables, including duration of ischemic time were not different between women with and without SCAD. In both groups the prevalence of smoking was high (80% and 73%). TIMI 3 flow was comparable between women with and without SCAD at the start of the angiography (30% vs. 48%, $p = 0.62$). However, in women treated conservatively or with PCI, at the end of angiography, TIMI 3 flow was less prevalent in women with SCAD than in women without SCAD (73% vs. 95%, $p < 0.001$). Especially in women treated with PCI (n = 236), TIMI 3 flow was less often reached in patients with SCAD than in women without SCAD (61% vs 96%, $p < 0.001$). A worse prognosis should be expected in patients with SCAD since an impaired coronary flow is established as an important endpoint in STEMI patients, associated with a higher mortality (8). There were important differences in treatment assignment between patients with and without SCAD (Fig. 1). Patients with SCAD were significantly more often treated conservatively compared to non-SCAD

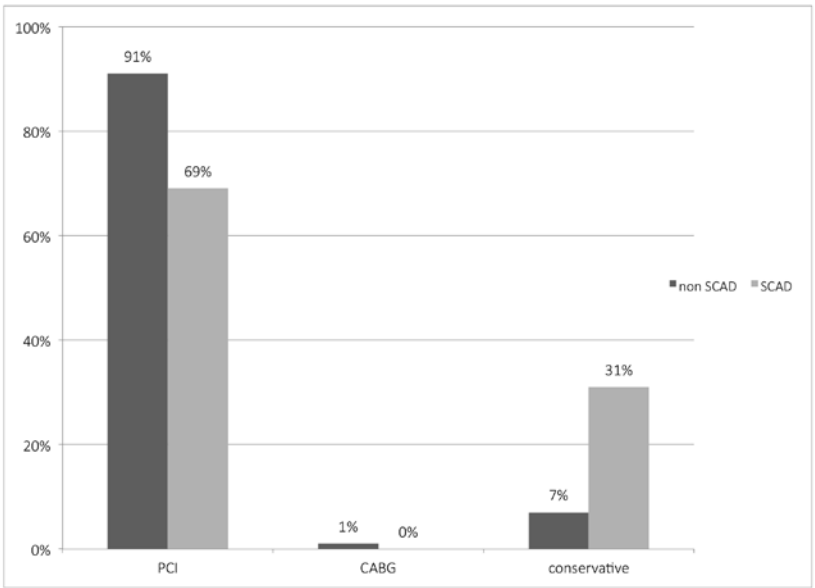
patients. Conservatively treated women with SCAD more often had TIMI 3 flow at the start of the procedure compared to women with SCAD treated with PCI (88% vs 29%, p = 0.007). Furthermore, conservatively treated SCAD patients had a smaller enzymatic infarction compared to SCAD patients treated invasively or with PCI. It is therefore likely that these conservatively treated patients were at lower risk for adverse events or impaired coronary flow at the end of the procedure. Unfortunately, OCT or IVUS was not routinely performed in our patients to provide additional information on the length and type of dissection (9). Concluding, SCAD can be observed in 10% of women <50 years presenting with STEMI. Women with SCAD were treated more often conservatively. PCI in women with SCAD was more often unsuccessful. More research should be encouraged to clarify mechanisms and optimal treatment.

Table 1
Patient characteristics of 263 women <50 years with ST Elevation Myocardial Infarction.

	237 women without SCAD	**26 women with SCAD**	**p-value**
Age (years) mean ± SD	44 ± 5	45 ± 4	0.15
BMI (kg/cm²) mean ± SD	26 ± 4	26 ± 5	0.96
Previous MI	8 (3%)	0 (0%)	0.34
Previous CABG	0 (0%)	0 (0%)	-
Previous PCI	9 (4%)	0 (0%)	0.31
Previous Stroke	1 (0%)	0 (0%)	0.74
History of diabetes	14 (6%)	0 (0%)	0.20
History of hypertension	50 (22%)	8 (31%)	0.29
Positive family history	142 (62%)	13 (52%)	0.36
Current smoking	187 (80%)	19 (73%)	0.42
Hypercholesterolemia	44 (20%)	2 (8%)	0.14
Killip class = 1 on admission	221(95%)	25(96%)	0.77
Total ischemic time (min) mean ± SD	260 ± 168	287 ±239	0.66

SD: standard deviation
BMI: Body Mass Index
MI: Myocardial Infarction

Figure 1
Treatment assignment in women <50 years referred for ST elevation myocardial infarction.



SCAD: Spontaneous Coronary Artery Dissection

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Chapter 7

Tako tsubo cardiomyopathy is age-dependent in men, but not in women presenting with ST Elevation Myocardial Infarction

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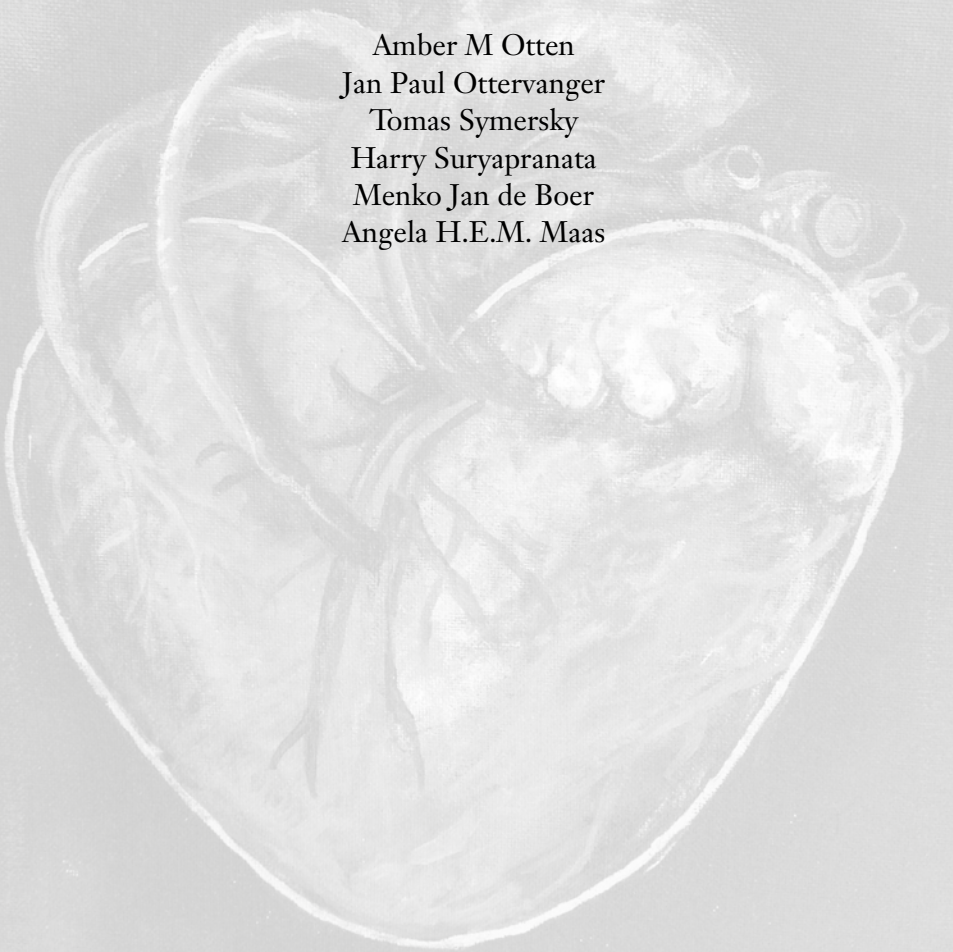

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Initial clinical presentation of tako-tsubo cardiomyopathy (TTC) often mimics ST-elevation Myocardial Infarction (STEMI), including acute chest pain, ST-segment elevation and raised cardiac biomarkers(1). TTC mostly occurs in post-menopausal women, and has been associated with acute stress, smoking, alcohol abuse and hypercholesterolemia(2). It is yet unclear why TTC is more often observed in women and whether increasing age is a predictor of TTC in both men and women. Possibly, cardiovascular risk factors for STEMI may also be associated with an increased risk of TTC(3). Since men and women with STEMI have a different, age-related risk profile, there may also be an age-related difference between genders in TTC(4). Although case series are available regarding predictors of TTC, only few studies focus on gender differences(5). Furthermore, no studies report a control group of STEMI patients, which is important to differentiate ischemic cause of STEMI and TTC in order to investigate the pathophysiological mechanisms(1,5). We investigated whether there is an independent age-related difference in TTC in both men and women who present with STEMI. We included all 10166 STEMI patients admitted between January 1998 and December 2013. Patients were diagnosed with TTC according to Mayo Clinics diagnostic criteria(1). All patients with TTC had transient hypokinesis, dyskinesis or akinesis of the left ventricular mid segments with or without apical involvement. Patients with myocarditis or pheochomocytoma were excluded.

Furthermore, organic stenosis or spasm of a coronary artery perfusing the territory of hypo- or akinesis of the myocardium is an exclusion criteria for TTC. Therefore, we examined all patients not treated with pPCI or coronary artery bypass grafting(1). Patients with a myocarditis or pheochromocytoma were excluded. We retrospectively examined all angiograms and echocardiograms of the remaining 685 STEMI patients to identify whether TTC was present. Chi2 test was used for categorical variables and one-way ANOVA for continuous variables. To analyse whether there was an independent association in men and women with and without TTC according to age, binary logistic multivariate regression was performed. The multivariate model consisted of all baseline variables between men and women with $\alpha < 0.1$ and all baseline variables in patients with and without TTC with $\alpha < 0.1$. The final multivariate model consisted of age, previous myocardial infarction, previous PCI, previous CABG, diabetes, hypertension and current smoking.

TTC was observed in 43 patients (0.4% of the total population, 5.6% of the patients treated conservatively). Differences in the general characteristics and hemodynamic parameters between women and men with and without TTC are presented in the table. In both men and women, patients with TTC were less often current smokers. Men with TTC were significantly younger than men without TTC (figure). However, women with and without TTC had comparable age. Women with TTC, were older than men with TTC (70 vs. 50 years, p<0.001). Women without TTC were older than men without TTC (67 vs. 62 years, p <0.001) and except one women of 40 years, all women were above 50 years of age at the time of TTC.

Although in men with STEMI the observed amount of TTC is low (0.12%), TTC is more often observed in younger men. In women with STEMI, the observed amount of TTC is higher (1.3%), but not associated with age. This novel finding may give new insights in the aetiology of TTC.

The main hypothesis on the pathophysiological mechanism of TTC is the combination of an increased sympathetic stress reaction with excess release of catecholamines, followed by an abnormal response to this catecholamine release(6). An important explanation for the age related difference in prevalence of TTC in men, but not in women, may be differences in stress hormones that are also related to estrogen status during life. In animal models, an age related decrease in noradrenergic nerve fibres and increase of catecholamine levels with ageing is observed(7). This means that theoretically both younger men and women may have an increased risk of a TTC. The elevated levels of premenopausal estrogen however may compensate for high levels of catecholamine release in younger women, but not in men. Women have an increased response to adrenergic stress after menopause, which may add to their increased risk of TTC(8,9). Low estrogen status in the postmenopausal years, leads to an impairment in vasodilating and vasoconstrictive reactivity, resulting in an increased responsiveness to sympathetic activity (10). In postmenopausal women, the epicardium is relatively unprotected against an adrenergic storm, resulting in a predisposition for TTC when a severe stress event occurs. Another explanation of the higher prevalence of TTC in older women, but not in older men may be that the acute excess of catecholamine in TTC leads to an impaired vascular reactivity through endothelial dysfunction(11), especially in the microcirculation. As microvascular coronary dysfunction is often present in elderly (hypertensive) postmenopausal women, they

may be at increased risk to develop TTC (12). Since similarly aged elderly men have a lower prevalence of hypertension and microvascular dysfunction, (13) this may also explain the lower incidence of TTC compared to women. Finally, another reason for a higher prevalence of TTC in men at younger age, may be more misdiagnosis of TTC in older men. As significant coronary artery disease is often present in ageing men, it is more likely that an occurring TTC remains unrecognized, and is assigned to a coronary lesion that is considered as the culprit lesion. For the same reason, TTC may be more often misdiagnosed in men as in women, since there is a higher prevalence of obstructive coronary artery disease in men compared to women(4).

Concluding, in patients presenting with STEMI, we observed that younger men have an increased risk of TTC compared to older men. The age of women with TTC was comparable to women without TTC and women with TTC were older than men with TTC. This suggests a different mechanism of TTC patients between men and women with a possibly hormonal protection in younger women.

Figure

Age at admittance with women and men presenting with a ST-Elevation Myocardial Infarction.

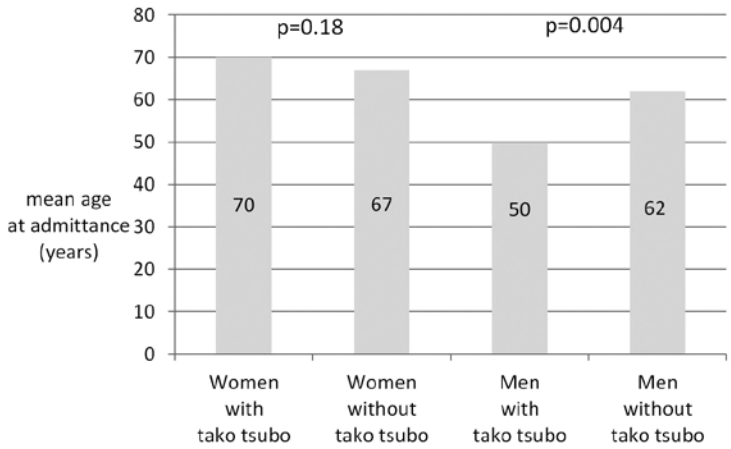

Table
Women and men presenting with STEMI stratified into with and without tako tsubo cardiomyopathy

	Women with TTC (n=34)	Women without TTC (n=2671)	p-value	Men with TTC (n=9)	Men without TTC (n=7381)	p-value
Risk Factors, n(%)						
History of MI	2 (6%)	199 (7%)	0.73	1 (11%)	850 (12%)	0.97
History of CABG	1 (4%)	69 (3%)	0.41	0(0%)	269 (4%)	1
History of PCI	0 (0%)	156 (6%)	0.26	1 (11%)	695 (9%)	0.86
History of Stroke	2 (6%)	90 (3%)	0.32	0 (0%)	228 (3%)	1
History of hypertension	12 (35%)	1186 (45%)	0.11	0 (0%)	2327 (32%)	0.065
History of DM	3 (9%)	432 (16%)	0.25	0 (0%)	726 (10%)	1
Hyperlipidemia	6 (18%)	551 (21%)	0.60	1 (11%)	1606 (23%)	0.41
Pos Family	7 (21%)	989 (38%)	0.05	3 (33%)	2841 (40%)	0.71
Current smoking	5(15%)	1031 (39%)	0.004	1 (11%)	3301 (45%)	0.05
Admission data						
Killip class > 1	1 (4%)	242 (11%)	0.33	0 (0%)	465 (7%)	1
Systolic blood pressure (mmHg)	136±29	134±29	0.38	123±31	132±26	0.37
Diastolic blood pressure (mmHg)	82±14	79±20	0.45	75±19	80±17	0.51
Heart rate (per minute)	84±15	78±19	0.042	73±16	76±19	0.70

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Chapter 8

Diagnosis of Tako Tsubo cardiomyopathy is increasing over time in patients presenting as ST-Elevation Myocardial Infarction

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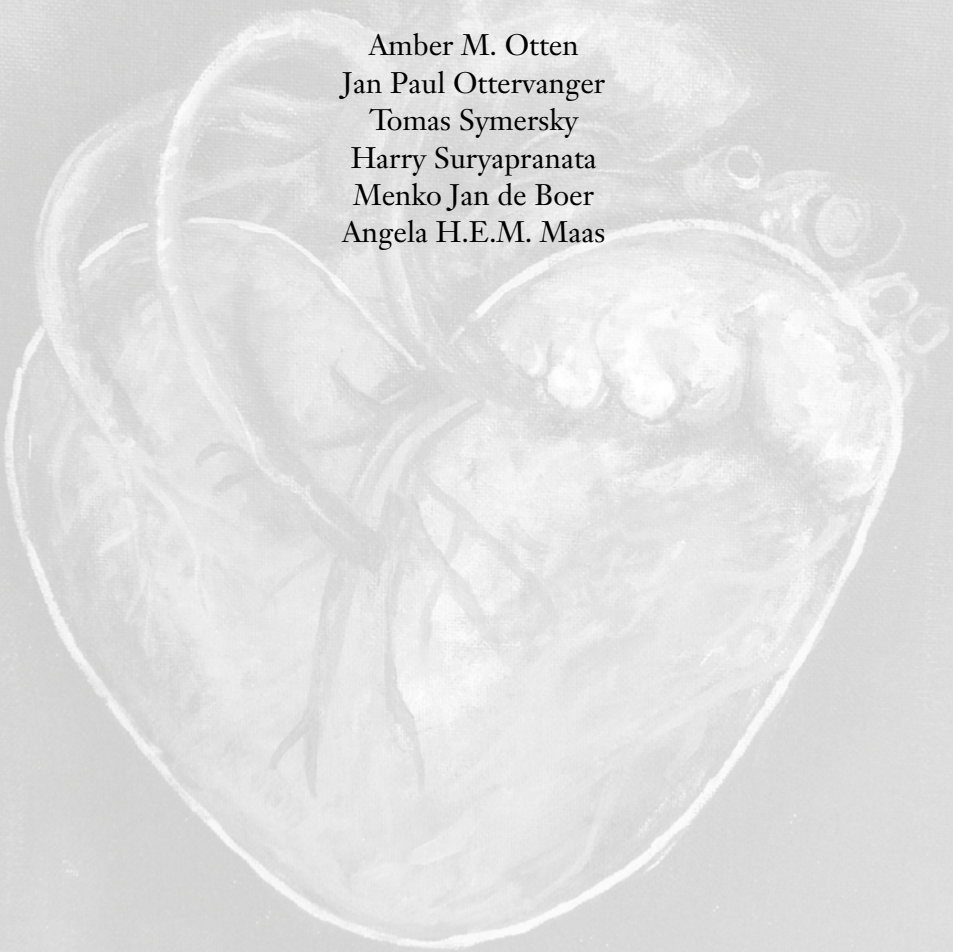

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Abstract

Background: Tako Tsubo cardiomyopathy(TTC) often presents with the clinical signs of ST-elevation myocardial infarction(STEMI). The increase in scientific publications addressing this relatively rare condition may result in higher awareness and diagnosis of TTC.

Aim: To assess the observed prevalence/year of TTC in a large registry of patients with STEMI, during a 12 year inclusion period.

Method: All patients presenting with STEMI at a large regional cardiology clinic were entered into a database(N=8413, mean age=63±13 years). TTC was diagnosed in 42 patients(0.5%). Years of evaluation were defined as "early years"(January 2002 until December 2007; N=4350) and "later years"(January 2008 until December 2013). Multivariable analyses were performed to adjust for differences in demographic and clinical variables.

Results: In later years, the age of STEMI patients was slightly higher(64±13 vs. 63±13 years,$p<0.001$), with more patients with clinical symptoms of shock(10% vs. 7%,$p<0.001$) or a history of PCI or hypertension(10% vs. 8%,$p=0.001$ and 37% vs. 34%,$p<0.001$). Smoking and a positive family history were less often observed during later years(39% vs. 46%,$p<0.001$ and 37% vs. 42% $p<0.001$). Patients with TTC were more often female(81% vs 27%, $p=0.001$). TTC was more often diagnosed in later years(0.7% vs. 0.3%, OR2.4, 95% CI 1.2-4.6,$p=0.009$). The higher prevalence of TTC in recent years remained significant after adjustment for differences in patient characteristics (OR2.1, 95% CI 1.1-4.3).

Conclusion: TTC is currently more often diagnosed in patients with STEMI compared to earlier years. This is probably due to the increased scientific and clinical awareness among doctors, but the prevalence is still low.

Introduction

Tako Tsubo cardiomyopathy (TTC) is characterized by transient wall motion abnormalities mimicking ST-elevation myocardial infarction (STEMI). It was first described in 1991 in Japan (1). At that time, TTC was completely unrecognized in Europe and North America and it was thought only to occur in Asia, where the first cohorts were published approximately 10 years later (2,3). The first observation of TTC in Caucasian patients was published in 2003 (4). Since then, awareness of TTC in Europe and North America among cardiologists has increased, with more patients initial presenting as STEMI being diagnosed as TTC.

However, it is also likely that a distinctly different population of patients are referred for STEMI over time due to improved therapy, logistics and modifications in referral (5,6). This may contribute to a shift in observed numbers of TTC. For instance, as currently more elderly women with STEMI are referred for immediate PCI, the number of observed TTC may have increased, since it is more prevalent in post-menopausal women (7,8). To assess alterations of the observed prevalence of TTC in patients with STEMI, adjustments should be made for these potential confounding factors (3,9,10). In the current study, we investigated whether the observed number of patients with TTC changed over a 12 years time period and if this is related with alterations in patient characteristics.

Methods

From January 2002 to December 2013 individual data from all STEMI patients who were considered for primary PCI (Percutaneous Coronary Intervention) and who underwent early coronary angiography at our centre, were prospectively recorded in a dedicated database. Early years were defined as January 2002 until December 2007 and later years were defined as January 2008 until December 2013. Patients were diagnosed with STEMI if they had chest pain longer than 30 minutes and ECG changes with ST elevation greater than 2 mm in at least two precordial leads or greater than 1 mm in the limb leads. Cardiac biomarkers were elevated in all patients. Information on demographic variables was directly registered at first contact with the patient, including age, sex, medical history, family history and traditional cardiovascular risk factors. In patients in whom echocardiography during admittance or after one month for assessing the left ventricle function was performed, the echocardiography was reviewed by an expert cardiologist or a resident cardiology supervised by an expert cardiologist. In order to investigate the number of publications concerning TTC, we sought in the PubMed database with the following search strategy per year: ("2002/01/01"[Date-Publication] : "2002/12/31"[Date - Publication]) AND ((tako AND tsubo) OR takotsubo). Although TTC is sometimes mentioned as 'ampulla cardiomyopathy', 'apical ballooning syndrome', 'broken heart' or 'stress induced cardiomyopathy' in the literature, almost all articles were still revealed with the search strategy because Takotsubo or Tako Tsubo was mentioned in the article (11-13).

TTC definition

ECG changes (either ST-segment elevation and/or T wave inversion) are major diagnostic criteria for TTC. Since all patients in our database had ST-elevation, this criterium was fulfilled for all patients. The presence of an epicardial stenosis or spasm of a coronary artery perfusing the territory of hypo- or akinesia of the myocardium are exclusion criteria for TTC (7, 14). Patients with TTC had transient hypokinesia, dyskinesia or akinesia of the left ventricular mid segments with or without apical involvement according to the Mayo Clinics diagnostic criteria (10).

Statistical analysis

Statistical analysis was performed using SPSS version 20 (SPSS Inc, Chicago, IL). Continuous data were expressed as mean and standard deviation and categorical data as percentages. Tests for significance were two-sided and values with an α of 0.05 were considered significant. In order to analyse whether an independent association was present of the frequency of observed TTC patients over time and the number of publications, we used binary logistic regression comparing early years to later years. The multivariate model consisted of all baseline variables with a $p \leq 0.1$ (gender, age, previous PCI, hypertension, smoking, hypercholesterolemia, positive family history and Killip class ≥ 2).

Results

In total, 8413 patients with a STEMI were referred to our centre during a 12 year time period. The mean age was 63 ± 13 years. During the study period, 685 (8%) patients had no identifiable stenosis or spasm of a coronary artery at angiography. These patients may have had a diagnosis of TTC according to the Mayo Clinics diagnostic criteria (10). All patients had complete resolution of the myocardial segments on echocardiography or angiography within a month. Two patients with myocarditis were excluded and there were no patients with a pheochomocytoma. Of these 685 patients, 1 month follow-up data on left ventricular function were missing in 2 patients from 2002, therefore these were excluded from further analysis. In total, 42 patients (0.5%) were diagnosed with TTC according to the criteria as described in the methods.

The 643 patients who were treated conservatively and did not have TTC, were older than invasively treated patients (65±16 vs. 63±12 years, p=0.002). They were also more often female (31% vs. 27%, p=0.01), more

often had a history of myocardial infarction (15% vs. 10%, p<0.001), a history of CABG (9% vs. 3%, P<0.001), a history of PCI (12% vs. 9%, p0.02), a history of CVA (6% vs. 3%, p<0.001).
hypertension (41% vs. 36%, p=0.007) and diabetes (14% vs. 11%, p=0.03). Patients treated conservatively less often had a positive family history (31% vs. 40%, p<0.001) and were less often smokers (30% vs. 44%, p<0.001).

Trends over the years in patients referred for STEMI
Compared to earlier years, patients referred for STEMI during 2008-2013 were older and more often had a history of previous PCI, hypertension, and a higher Killip class at admission. Current smoking and a positive family history were less often present in later years. Furthermore, the duration of hospital stay was slightly longer in later years. The other clinical characteristics including gender did not change over time (table 1).

Difference in patients with and without Tako Tsubo
Patients with TTC were more often older, female, less often current smokers and had a higher heart rate at admission compared to usual STEMI patients (table 2). All other cardiovascular risk factors and hemodynamic parameters were comparable between patients with and without TTC.

Trends over the years in prevalence of TTC
The annual observed prevalence of TTC in patients with STEMI ranged from 0% in 2002 to 1.05% in 2009 and significantly increased over time (Figure 1). Compared to the number of patients with TTC in the early years, TTC was more often observed in the later years (OR 2.4, 95% CI 1.2-4.6). In the multivariate model, this difference remained significant (OR 2.1, 95% CI 1.1-4.3).
The literature search showed that in the early years, Tako Tsubo was less often mentioned in the literature compared to later years (figure 2).

Discussion
In this large cohort of patients with STEMI, we found a significant increase in the number of patients observed with TTC over time, independent from patient characteristics. However, the prevalence of TTC among STEMI patients is still low.

The prevalence of TTC in the literature ranges from 0.02% in general population to 1-2% in populations with acute coronary syndromes (14,7). However, these prevalences cannot be compared with our study because we present a cohort of patients with STEMI. To our knowledge, this is the first STEMI population being studied for TTC.

The increased number of observed TTC-patients over the years may have different explanations. Firstly, since patients with STEMI are currently older and TTC is associated with increasing age, TTC may be more often diagnosed (15-17). However, this cannot be the entire explanation for the increased frequency of observed TTC patients, because after correcting for age in the multivariate model there was still a relationship between later years and an increase of observed TTC in our study. Another explanation for an increase of TTC may be changed risk profiles of admitted STEMI patients over the years, what was also observed in other studies (18,19). These changes in risk factors only partly explain the difference of observed frequency of TTC patients in our study, since after multivariable analyses the frequency of TTC was still higher in the recent years. A third, and probably most important reason for the increased frequency of TTC may be due to improved network and facilities in the treatment of acute STEMI patients. In fact, almost all STEMI patients are currently referred to a tertiary centre with primary PCI facilities. Furthermore, improved recognition of TTC may also play an important role, which may be related to a higher awareness of cardiologists and other medical personnel due to an increasing number of scientific studies on TTC in the literature and communication at conferences (figure 2). Large systemic registries or multicentre trials (20-22) do not only increase awareness, they also result in a better understanding of the demographics and ultimately also the (medical) therapy of TTC. Furthermore, case reports concerning a new clinical presentation of TTC are more often published (23,24).

In our study, left ventricle (LV) function was assessed with an echo or LV angiogram primarily in the acute situation after STEMI. Therefore, we used only the LV function assessment in the acute setting. However, standard evaluation of the LV function both in the acute moment and after one month can avoid misdiagnosis of TTC. The ESC guidelines also recommend evaluation of resting LV function both in the acute moment and after more than two weeks after STEMI (25). If the outpatient LV assessment is performed after 4 weeks from STEMI, most TTC patients can be diagnosed with more certainty, because LV function due to TTC

should be normalised within 4 weeks according to the TTC definition (26).
Although we evaluated every STEMI patient without coronary intervention for possible TTC, only 0.5 % of all patients with STEMI admitted in our hospital were diagnosed as TTC. Our observed prevalence of TTC is lower than estimates in the literature and therefore it is likely that we may have underdiagnosed TTC in our database (9,27,28). Particularly in patient groups with a high prevalence of coronary artery disease, TTC may be underdiagnosed. As both coronary artery disease and TTC might be present in these patients and TTC can only be diagnosed in absence of a significant coronary artery stenosis, a TTC may not be recognized (27).

Discriminating TTC with heart failure from STEMI with heart failure, is of importance because it may have important implications for treatment.
Firstly, although it has not been properly studied, medical treatment for systolic heart failure can be considered in TTC patients in order to relieve acute symptoms (e.g. oedema) (29). Three important drugs to administer to these patients are mineralocorticoid receptor antagonists, beta blockers and angiotensin-converting enzyme (ACE)- inhibitors (or angiotensin receptor blocker) (30). When LV function normalises in TTC patients after one month, it could be considered to stop the ACE-inhibitor and the mineralocorticoid –receptor antagonist to avoid adverse events associated with these drugs (31). Although evidence is limited, the continuation of beta blockers can be considered in patients with TTC, because of the theory that TTC is caused by sympathetic hyperactivity (32).
Secondly, temporal aggressive heart failure treatment as LV assist devices may be considered in TTC patients if needed, even if the patient is not a heart transplant candidate (33). Misdiagnosing a TTC patient for a patient with a type 1 myocardial infarction, may result in unnecessary long-term treatment with dual anti platelet therapy. Without a plaque rupture, only long term prescription of acetylsalicylic acid is indicated and without coronary artery disease no anti platelet therapy at all should be given in TTC patients. This will potentially diminish bleeding complications (34). Finally, since TTC in most patients has a good prognosis, especially after 4 weeks, when LV function normalises, patients may receive more adequate information about their prognosis.

There are several opportunities to improve diagnosing TTC. First of all, increased awareness in doctors and (possibly) patients is necessary. Moreover, a history of emotional trigger(s) must prompt the doctor to put TTC in the differential diagnosis. This is especially so in elderly women presenting with STEMI, because the prevalence of TTC is highest in this patient group (10). The evaluation of possibly emotional triggers should be routinely done in every patient with STEMI. Furthermore, when a coronary stenosis, but not a coronary occlusion is observed with invasive angiography, fractional flow reserve could be considered to evaluate whether the stenosis is hemodynamically significant in a later phase. If no epicardial coronary stenosis is found as the cause for the STEMI at coronary angiography, apart from routine echocardiography, a LV angiography can visualize an apical ballooning pattern of the LV.

Study limitations

This study was performed retrospectively in the beginning years not all patients received sequential imaging of the left ventricular function. Therefore, it is likely that especially patients with TTC were underdiagnosed.

Conclusions

We observed an increased frequency of observed TTC over the years. Since this difference remained irrespective of classical cardiovascular risk factors, and since TTC received more attention in the literature in the course of this study, it is likely that increased awareness contributed to this increase. National registries for patients with TTC may further increase awareness and stimulate scientific research about aetiology and (medical) treatment of TTC.

Conflict of interest: none declared

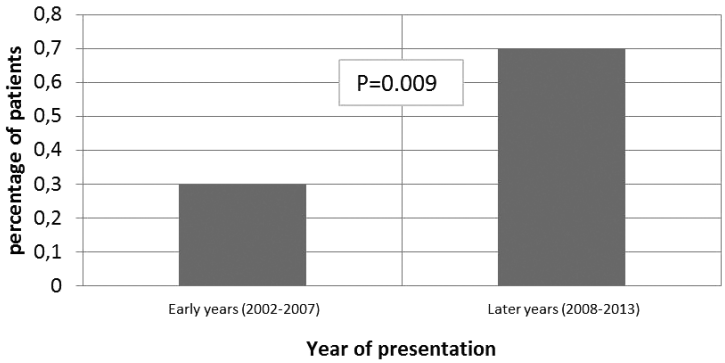
Table 1
Clinical characteristics of patients referred for STEMI in early (2002-2008) and later (2008-2013) years.

	Early years (n=4350)	Later years (n=4063)	P-value
Age	63±13	64±13	0.001
Gender (women)	1165 (27%)	1154 (28%)	0.10
Observed Tako Tsubo cardiomyopathy	13 (0.3%)	27 (0.7%)	0.007
BMI (kg/m^2)	27±5	28±8	0.20
History of			
MI	441 (10%)	412 (10%)	0.88
CABG	156 (4%)	135 (3%)	0.56
PCI	356 (8%)	414 (10%)	0.001
Stroke	129 (3%)	134 (3%)	0.36
Diabetes	508 (12%)	458 (11%)	0.59
Hypertension	1454 (34%)	1557 (37%)	<0.001
Positive family history	1710 (42%)	1413 (37%)	<0.001
Smoking (ever)	1925 (46%)	1557 (39%)	<0.001
Hypercholesterolemia	958 (23%)	840 (22%)	0.07
Killip class >2 on admission	302 (7%)	283 (10%)	<0.001
Hospital stay (days)	4±6	5±8	<0.001
Heart frequency (min)	76±18	76±19	0.023
Systolic blood pressure at admittance (mmHg)	133±25	132±27	0.70
Diastolic blood pressure at admittance (mmHg)	80±16	80±23	0.78

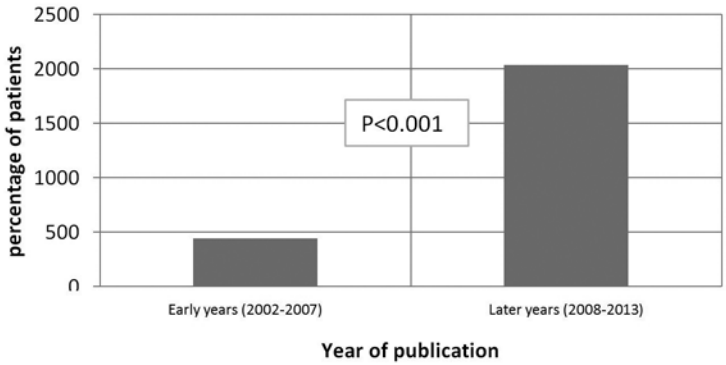
Table 2
Comparison of clinical characteristics between patients with and without Tako Tsubo cardiomyopathy in 8413 patients admitted with STEMI.

	Patients without Tako Tsubo cardiomyopathy n=8371	Patients with Tako Tsubo cardiomyopathy n=42	p-value
Age	63±13	66±13	0.13
Gender (women)	2285 (27%)	34 (81%)	<0.001
BMI (kg/m²)	28±13	25±4	0.22
History of			
MI	850 (10%)	3 (7%)	0.54
CABG	291 (4%)	0 (0%)	0.23
PCI	769 (9%)	1 (2%)	0.13
Stroke	261 (3%)	2 (5%)	0.53
Diabetes	963 (12%)	3 (7%)	0.40
Hypertension	2999 (36%)	12 (29%)	0.35
Pos family history	3113 (39%)	10 (25%)	0.08
Smoking (ever)	3477 (43%)	5 (12%)	<0.001
Hypercholesterolemia	1792 (22%)	6 (15%)	0.24
Killip class ≥ 2 on admission	582 (8%)	3 (9%)	0.80
Hospital stay (days)	4±7	3±3	0.21
Heart frequency (min)	76±21	83±15	0.04
Systolic blood pressure at admittance (mmHg)	133±27	135±29	0.47
Diastolic blood pressure at admittance (mmHg)	76±19	80±15	0.90

Figuur 1
Percentage of observed Tako Tsubo presenting as STEMI.



Figuur 2
Amounth of publications in pubmed with Tako Tsubo in the title.



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Chapter 9

Discussion and future perspectives

The findings of the studies presented in this thesis give some answers about gender and age related features in patients with STEMI, but there are also many things still unclear. The incidence of STEMI in women is still high, even after decades of anti-smoke and lifestyle campaigns with better treatment of hypertension, diabetes and hypercholesterolemia. Myocardial infarction rates have not declined over the last decade in young patients, especially not in women (1). Furthermore, even after nationwide performing of primary PCI, with improvements in both stent techniques and antithrombotic medication, there is ample evidence that prognosis improved remarkably in older patients, but not in younger patients (2). So, research in STEMI should and must be continued, particularly for younger women with STEMI.

Presentation of women with STEMI

Women with STEMI more often present with 'atypical' symptoms compared to men and this may be an important reason for the observed longer patient delay in women (3). An important reason for the atypical symptom presentation is most likely related to the lower prevalence of acute epicardial coronary occlusion in women compared to men (4). National campaigns have been performed to increase awareness, both for patients and health care workers, but unfortunately, with insufficient results (5). Symptoms of atypical chest pain are often present in (young) women and only a minority will have a STEMI. Since many women present their complaints first to their general practitioner, improvements in objective diagnostic tests to rule out STEMI should be encouraged. There is evidence that high sensitive cardiac troponin increases diagnosis of myocardial infarction in women, whereas it has minimal additional effect on diagnosing type II myocardial infarction in men (4). Possibly, even more sensitive laboratory tests than troponin may be helpful in the near future (6). Besides this, primary prevention in (young) women should have much more attention, since also in our study the prevalence of untreated and modifiable risk factors, especially smoking, in young women was high.

Increased mortality in younger women after STEMI

Our finding that, despite an initial more favorable risk profile, younger women have increased mortality after STEMI is alarming. Regarding the possible different etiology of STEMI between men and women, we found

that younger women with STEMI more often have a myocardial infarction with non-obstructive coronary artery disease (MINOCA) compared to similarly aged men. Recently it has been studied that in MINOCA, still 20% of patients had signs of myocardial necrosis (7). So an open coronary artery at STEMI, does not implicate a benign course of STEMI. In patients with MINOCA, a delayed flow of the coronary arteries has been shown at angiography (8), which may be associated with microvascular coronary dysfunction (9). Another manifestation of a MINOCA is Tako Tsubo Cardiomyopathy (TTC), which is also increasingly acknowledged to be associated with microvascular coronary dysfunction. We will discuss TTC further in another paragraph. Another proportion of patients with MINOCA had signs of myocarditis (7).

So it is essential to consider multiple potential causes if a patient presents with MINOCA. These patients require optimal evaluation, so that specific therapies can be considered and prognosis improved (10,11). Future studies should be performed using more often advanced intravascular diagnostic techniques such as intravascular ultrasound (IVUS) or optical coherence tomography (OCT), in these STEMI patients to evaluate the optimal individual management.

Also, young women may have a less favorable response to medication. This is of importance, because in many large trials, only a minority of young women was included and the knowledge about myocardial infarction in young women has been largely extrapolated from studies primarily focused on (older) men (12,13). Furthermore, young women may withdraw medication more frequently because of side effects and repulsion to lifelong treatment (14).

Another possible reason for the worse prognosis in young women with STEMI may be the higher incidence of spontaneous coronary dissections (SCAD). We will discuss this in a separate section. However, the occurrence of SCAD cannot entirely explain the higher mortality of STEMI in young women.

Smoking is particularly in young women a major risk factor for STEMI. It has been demonstrated that cessation of smoking results in an improved prognosis after STEMI (15,16). We had no data whether in our study cessation of smoking was comparable between young women and men. Possibly, in the future, cessation of smoking should be an outcome indicator for patients with STEMI.

Gender differences in hyperglycemia and diabetes

An important risk factor in STEMI in men and women is diabetes. Although many previous studies demonstrated a higher prevalence of diabetes in elderly women with STEMI with a worse prognosis in women, we demonstrated that particularly in younger patients (< 65 years) there are no gender differences in the prevalence of diabetes. The occurrence of diabetes does not seem to contribute to the increased mortality among younger women with STEMI.

We did observe that both diabetes and hyperglycemia were more prevalent in older women with STEMI compared to similarly aged men. Since hyperglycemia and diabetes are associated with an increased mortality after STEMI, this is important for the treatment of older women.

When a STEMI patient presents with hyperglycemia, it is important to distinguish hyperglycemia due to a higher abnormal chronic glucose metabolism in (not-yet known) diabetics from hyperglycemia due to increased stress, particularly induced by abnormal hemodynamics (17,18). Hemodynamic deterioration is sometimes difficult to observe, but has major prognostic implications. Particularly in patients with concomitant hypertension, use of only blood pressure as sign of hemodynamic deterioration has its limitations. So, in women with hyperglycemia there should be an increased awareness on abnormal hemodynamics and possible causes, such as re-occlusion of an infarct related vessel and mechanic complications. In those with hemodynamic deterioration treatment should be initiated and medication that can worsen hemodynamics (such as calcium channel blockers) should be discontinued.

Although the increased prevalence of diabetes in (older) women with STEMI as compared to (older) men with STEMI has been observed in many previous studies, it is remarkable. In the general elderly population the prevalence of diabetes is comparable or even higher in men (19). Possibly, women with diabetes have a higher risk of myocardial infarction than men with diabetes, although this is debated in the literature (20-22). However, there is increasing evidence that the impact of vascular and myocardial damage of diabetes differs between women and men (23). In diabetic women with STEMI, there should be a more aggressive treatment of risk factors to prevent recurrence of MI. Future studies have to assess whether treatment strategies between men and women with diabetes should be different.

Early menarche as a risk factor for STEMI

We observed that hormonal factors influence the risk of STEMI, as women with lower age at menarche had a STEMI at a younger age. As a first step, early menarche should be evaluated more often in women presenting with a STEMI, to evaluate its importance as a potential female-specific risk factor.

In a population-based study, the incidence of cardiovascular disease was increased in women with early menarche (24). Early menarche is an important clinical characteristic occurring early in life, which may reveal a higher risk of STEMI in later life. It is important to note that current Western populations are at higher CVD risk than those decades ago, with a shift towards an earlier age at menarche (25). This provides an opportunity to use early menarche as an additional risk factor in women in combination with other indicators for an increased risk for ischemic heart disease. Ultimately, future studies should investigate whether more aggressively monitoring and treating risk factors such as smoking, diabetes, hypertension and hypercholesterolemia in women with early menarche is cost effective.

Apart from the clinical importance of our findings, more basic research should be performed on the mechanisms involved in early menarche and myocardial infarction at young age.

Treatment of Spontaneous Coronary Artery Dissection

Spontaneous Coronary Artery Dissection (SCAD) is a relative rare observation in patients with STEMI (26,27). However, in young women with STEMI the prevalence is much higher than in men, with a prevalence rate up to 10% (28).

There are various studies investigating the etiology of SCAD, suggesting that connective tissue disorders such as fibromuscular dysplasia or Ehlers-Danlos syndrome are associated with SCAD (29). It should be further investigated whether all patients with SCAD should be screened for genetic factors related to connective tissue disorders. Furthermore, it is the question whether this has therapeutic consequences.

We observed that primary PCI in SCAD was more often unsuccessful. Although intracoronary visualization with OCT or IVUS can better visualize the characteristics of the culprit coronary lesion and may identify the type and extend of SCAD (24), these techniques have also risks. It is therefore recommended to concentrate these invasive procedures in

experienced invasive cardiology centers. It is not known whether these techniques will lead to improved treatment choices in SCAD patients and if this possible benefit justifies the risk of inserting a bulky catheter in a dissected artery. This should be the aim of future research.
Because of the relative low incidence of SCAD, multi-center prospective studies are needed. After the acute event, it is unclear if either continued conservative treatment, or PCI with stenting or bypass surgery (if appropriate) are optimal strategies for this patient group, resulting in the best long-term prognosis.

Most SCAD patients receive statins, acetylsalicylic acid, beta blockers and ACE-inhibitors, but it is unknown whether these drugs are beneficial. Moreover, signs of atherosclerosis are only present in a minority of these young patients. Particularly in young women, it is the question whether life-long use of standard ACS medication improves their prognosis. This should be another topic of future research.

Increased awareness and gender differences in Tako Tsubo Cardiomyopathy

Since the first report of TTC was published in the literature in 1991, TTC has gained much awareness (30). This was probably augmented by an increased number of scientific studies on TTC in the literature (31). Furthermore, TTC is increasingly diagnosed, since left ventricular imaging in/direct after STEMI is much more customary (32). While in the early years predominantly case reports on TCC were published (33), in the last decade several national registries with a large number of patients have been published (34,35). Dutch hospitals can and should also participate in the international registry (36).
There are still many uncertainties regarding the different mechanisms involved in TTC in men and women. They respond differently to stress and this may importantly contribute to the observed gender differences in TTC. Men more often present with physical triggers while women more often present with emotional triggers for TTC (37,38).
Furthermore, an important hypothesis for the mechanism of TTC is that microvascular dysfunction and subsequently myocardial stunning causes TTC (36, 39). Microvascular dysfunction is more often seen in elderly women with ACS than in men (40,41) and possibly, women have a predisposition for TTC because of the higher prevalence of micovascular

dysfunction. Prospective studies should focus on differences in mechanism of TTC between genders and on techniques to enhance microvascular perfusion in TTC patients.

Concluding, women with STEMI differ in many aspects from their male counterparts, related to differences in presentation, etiology, risk factors and outcome. They may even respond differently to (medical) treatment. Prospective, sex-specific studies should be performed to elucidate these differences. The current thesis is a small step in our better understanding of myocardial infarction in women.

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Chapter 10

Summary

Myocardial infarction and particularly ST-Elevation Myocardial Infarction (STEMI), is among the most serious presentations of ischemic heart disease. Although there are many similarities between women and men with STEMI, they have different cardiovascular risk profiles, different clinical and angiographic presentation and different outcomes after STEMI. Therefore, treatment strategies vary between women and men. So, gender differences are important to acknowledge, with ultimately consequences for a gender specific management of STEMI. In this thesis, several aspects of the difference between women and men with STEMI are investigated.

In **Chapter 2** we described that the presentation of STEMI in men and women often is different. Women present more often with less typical symptoms. This atypical presentation is probably the most important reason for the longer patient delay in women compared to men with a STEMI. This may contribute to a significantly worse prognosis in women. However, it has been still unclear whether the potential different prognosis between men and women is age dependent.

To assess whether prognosis in patients with STEMI is different between men and women and whether this is age-dependent, we studied in **Chapter 3**, 6746 STEMI patients. Age was stratified into 2 groups, < 65 years (young group) and ≥ 65 years (elderly). At angiography, single vessel disease and normal coronary flow before Percutaneous Coronary Intervention (PCI) were more present in younger women than in younger men, whereas these differences were not found in the older age group. Compared to younger men, younger women had a higher mortality at both 30-days (HR 2.1, 95%CI 1.3-3.4) and at 1-year (HR 1.7, 95%CI 1.2-2.6), whereas in the older age group women had a higher mortality at 30-days (HR 1.5, 95%CI 1.1-2.0) but not at 1-year (HR 1.2, 95%CI 0.9-1.5). We concluded that differences in mortality between men and women with STEMI are age-dependent. This may be surprising, since younger women had less obstructive coronary artery disease and more often normal coronary flow before PCI, suggesting a lower risk STEMI. Women had a longer patient delay compared to men, but this was not associated to gender-specific mortality.

Diabetes is not only a risk factor for developing STEMI, but diabetic STEMI patients also have a worse prognosis. Many studies have reported gender differences in the prevalence of diabetes in patients with STEMI. However, it has not been studied whether these differences can be observed in both younger and older patients with STEMI. In **Chapter 4**, we studied 4640 patients (28% women) with STEMI and examined whether the prevalence of either diabetes or hyperglycemia on admission was different between various age groups of men and women. The prevalence of diabetes was comparable between women and men in the younger (<65 years) age group (14% vs 12%, p=0.52), whereas in the older age group diabetes was more prevalent in women (25% vs 17% p<0.001). In patients without diabetes, admission glucose was comparable between both genders in younger patients (8.1±2.0mmol/l vs 8.0±2.2mmol/l p=0.36), but in older patients admission glucose was higher in women than in men (8.7±2.1mmol/l vs 8.4±2.1mmol/l p=0.028). This difference remained after multivariable analyses. Both diabetes and hyperglycemia were associated with a higher one-year mortality in both men and women. In conclusion, we observed differences in the occurrence of both hyperglycemia and diabetes between men and women in older patients, with a higher prevalence in older women.

Next to the traditional cardiovascular risk factors, reproductive risk factors may be associated with the risk of ischemic heart disease. Thus far the association of these reproductive risk factors with STEMI have been poorly investigated. In **Chapter 5**, we investigated whether early menarche is associated with the occurrence of STEMI at younger age. Reproductive information was obtained in 688 women with age at STEMI <75 years. Younger age of STEMI was defined as STEMI below 60 years and was observed in 50% of the patients who returned the questionnaire. Age at menarche was categorized as ≤12 years, 13 years, 14 years and ≥15 years. Younger age at menarche was associated with a higher prevalence of smoking. All other classical risk factors for cardiovascular disease were comparable between the four groups. After both unadjusted and multivariable analysis, women with a lower age at menarche had a higher probability of STEMI at younger age, with the adjusted OR 1.6 (95% CI 1.0-2.6) for age <12 years compared to age ≥15 years. These results suggest that younger age at menarche is a risk factor for STEMI at a younger age.

Spontaneous coronary artery dissection (SCAD) is a relative rare cause of myocardial infarction, although it is more common in younger women. Since treatment may be more difficult in SCAD as cause of STEMI, and there are limited data available in the literature about outcome of primary PCI in patients with SCAD, we investigated treatment strategies in SCAD in young women. In **Chapter 6**, we described 263 women < 50 years with STEMI. In this group, SCAD was observed in 26 patients (10%). Baseline characteristics, including smoking were comparable between women with and without SCAD. Women with SCAD were more often conservatively treated than women without SCAD (31% vs. 7%, p<0.001). Probably the most important finding was that primary PCI in patients with SCAD is less effective to restore normal coronary flow. This resulted in less common normal coronary flow after the procedure in women with SCAD (73% vs. 95%, p<0.001).

Although it is well known that Tako Tsubo cardiomyopathy (TTC) is more prevalent in women, it was not yet known in the literature whether this gender difference can be observed in both younger and older age groups. In **Chapter 7** 10166 STEMI patients were studied, of whom a total of 43 patients (0.4 %) had TTC. In the total cohort, women were older, women had less frequently a history of myocardial infarction, CABG or PCI, and women were less often smokers. Women had a higher prevalence of diabetes and hypertension. In the TTC group, there were more women than men (74% vs 26%, adjusted OR 10.7, 95% CI 5.1-22.4). The prevalence of smoking was lower in both men and women with TTC, the prevalence of hypertension was only lower in men with TTC compared to men without TTC. All other risk factors between patients with and without TTC were comparable in both men and women. The most interesting finding of our analysis was that men with TTC were younger than men without TTC (50 vs. 62 years, p=0.004), but that this age difference was not observed in women (70 vs. 67 years, p=0.18).

Tako Tsubo cardiomyopathy is a relative new diagnosis, since it was first described in 1991. In **Chapter 8**, we studied potential changes in the incidences of TTC over time in patients presenting with STEMI in Zwolle. Early years were defined as January 2002 until December 2007 (n=4350) and later years were defined as January 2008 until December 2013 (n=4063). Although there were small differences between the two

time periods regarding baseline characteristics, in general the two cohorts were comparable. Tako Tsubo was more often diagnosed in later years (0.7% vs 0.3%, p=0.009), also after correcting for differences in baseline characteristics (OR 2.1, 95% CI 1.1-4.3). Probably, the increased incidence of TTC in patients with STEMI is due to increased awareness among doctors.

Chapter 11

Samenvatting

Het myocardinfarct en in het bijzonder het ST-Elevatie Myocard Infarct (STEMI), is één van de meest ernstige presentaties van ischemische hartziekte. Hoewel er veel overeenkomsten zijn tussen vrouwen en mannen met een STEMI, bestaan er ook veel verschillen, zoals verschillende cardiovasculaire risicoprofielen, verschillende klinische- en angiografische bevindingen en verschillende uitkomsten na STEMI. Daarom zouden er wellicht ook verschillende behandelingsstrategieën voor vrouwen en mannen moeten zijn. Kennis van de verschillen tussen mannen en vrouwen met STEMI is echter nog beperkt. Meer inzicht in de verschillen tussen mannen en vrouwen met een STEMI is daarom van belang, voor het uiteindelijk ontwikkelen van sekse specifieke behandeling van STEMI. In dit proefschrift worden enkele studies beschreven omtrent verschillen tussen vrouwen en mannen met STEMI.

In **Hoofdstuk 2** wordt beschreven dat de klinische presentatie van STEMI bij mannen en vrouwen vaak verschillend is. Vrouwen presenteren zich vaker met minder typische symptomen. Deze atypische presentatie is waarschijnlijk de belangrijkste reden dat vrouwen een langere tijd nodig hebben om medische hulp te zoeken vergeleken met mannen. Dit kan bijdragen aan een significant slechtere prognose bij vrouwen. Het is echter nog steeds onduidelijk of de verschillende prognose tussen mannen en vrouwen afhankelijk is van de leeftijd.

Om te beoordelen of de prognose bij patiënten met STEMI verschillend is tussen mannen en vrouwen en of dit afhankelijk is van de leeftijd, werden in **Hoofdstuk 3** 6746 STEMI patiënten bestudeerd. De leeftijd werd gestratificeerd in 2 groepen, <65 jaar (jonge groep) en ≥ 65 jaar (ouderen). Bij angiografie was één vatslijden en normale coronaire doorstroming vóór eventuele Percutane Coronaire Interventie (PCI) vaker aanwezig bij jongere vrouwen dan bij jongere mannen. Deze verschillen tussen mannen en vrouwen werden niet gevonden in de oudere leeftijdsgroep. In vergelijking met jongere mannen, hadden jongere vrouwen een hogere mortaliteit na zowel 30-dagen (HR 2,1, 95% BI 1,3-3,4) als na 1 jaar (HR 1,7, 95% BI 1,2-2,6), terwijl in de oudere leeftijdsgroep vrouwen een hogere mortaliteit hadden na 30 dagen (HR 1,5, 95% BI 1,1-2,0), maar niet na 1 jaar (HR 1,2, 95% BI 0,9-1,5). We concludeerden dat de verschillen in sterfte tussen mannen en vrouwen met STEMI leeftijdsafhankelijk zijn. Dit is een verrassend resultaat, omdat jongere vrouwen minder

obstructieve coronaire hartziekte hadden met vaker normale coronaire doorstroming voor PCI. Deze kenmerken duiden op een lager risico STEMI. Vrouwen hadden wel een langere tijd nodig om medische hulp te zoeken in vergelijking met mannen, maar dit verschil kon de hogere sterfte bij vrouwen niet volledig verklaren.

Diabetes is niet alleen een risicofactor voor het ontwikkelen van STEMI, diabetische STEMI patiënten hebben tevens een slechtere prognose. Veel studies hebben sekseverschillen in de prevalentie van diabetes bij patiënten met STEMI genoemd. Er is echter niet onderzocht of deze verschillen kunnen worden waargenomen bij zowel jongere als oudere patiënten met STEMI. In **Hoofdstuk 4** onderzochten we 4640 patiënten (28% vrouwen) met STEMI, waarbij we keken of de prevalentie van diabetes en hyperglykemie bij opname varieerde tussen mannen en vrouwen in verschillende leeftijdsgroepen. De prevalentie van diabetes was vergelijkbaar tussen vrouwen en mannen in de jongere (<65 jaar) leeftijdsgroep (14% vs 12%, p=0,52), terwijl in de oudere leeftijdsgroep diabetes vaker voorkwam bij vrouwen (25% versus 17%, p<0,001). Bij patiënten zonder diabetes, was het glucose bij opname vergelijkbaar tussen beide geslachten bij jongere patiënten (8,1 ± 2,0 mmol/l vs 8,0±2,2 mmol/l, p=0,36), terwijl bij oudere patiënten het glucose bij opname hoger was bij vrouwen dan bij mannen (8,7±2,1 mmol/l vs 8,4±2,1 mmol/l, p=0,028). Dit verschil bleef aanwezig na multivariate analyse. Zowel diabetes als hyperglykemie waren geassocieerd met een hogere één-jaar mortaliteit bij zowel mannen als vrouwen. Concluderend, toonden we verschillen aan in het voorkomen van zowel hyperglykemie en diabetes tussen mannen en vrouwen bij oudere patiënten (met een hogere prevalentie bij oudere vrouwen geobserveerd), terwijl bij jongere patiënten er geen verschil kon worden aangetoond tussen mannen en vrouwen.

Naast de traditionele cardiovasculaire risicofactoren, kunnen reproductieve risicofactoren geassocieerd zijn met het risico op ischemische hartziekte. Deze reproductieve risicofactoren zijn in relatie tot STEMI weinig onderzocht. In **Hoofdstuk 5** hebben we onderzocht of een eerste menstruatie (menarche) op jongere leeftijd geassocieerd is met het optreden van STEMI op jongere leeftijd. Reproductieve informatie werd verkregen van 688 vrouwen, die ten tijden van STEMI jonger waren dan 75 jaar. Jongere leeftijd bij STEMI werd gedefinieerd als STEMI onder

60 jaar en werd bij 50% van de patiënten vastgesteld. De leeftijd bij menarche werd ingedeeld als ≤12 jaar, 13 jaar, 14 jaar en ≥15 jaar. Jongere leeftijd bij menarche was geassocieerd met een hogere prevalentie van roken ten tijde van het STEMI. Alle andere klassieke risicofactoren voor hart- en vaatziekten waren vergelijkbaar tussen de vier groepen. Na zowel uni- en multivariaat analyse, hadden vrouwen met een lagere leeftijd bij menarche een hogere kans op STEMI op jongere leeftijd, (multivariaat OR 1,6 95% BI 1,0-2,6) voor de leeftijd <12 jaar in vergelijking met de leeftijd ≥15 jaar. Deze resultaten suggereren dat jongere leeftijd van de menarche een risicofactor is voor STEMI op jongere leeftijd.

Spontane coronaire arteriële dissectie (SCAD) is een relatief zeldzame oorzaak van een hartinfarct, het komt echter het vaker voor bij jongere vrouwen. Aangezien de behandeling in SCAD als oorzaak van STEMI moeilijker kan zijn en er slechts beperkte gegevens beschikbaar zijn in de literatuur over de uitkomst van de primaire PCI bij patiënten met SCAD, onderzochten we behandelingsstrategieën in SCAD bij jonge vrouwen. In **Hoofdstuk 6**, beschreven we 263 vrouwen < 50 jaar met een STEMI. In deze groep werd SCAD geobserveerd bij 26 patiënten (10%). Kenmerken zoals roken waren vergelijkbaar tussen vrouwen met en zonder SCAD. Vrouwen met SCAD werden vaker conservatief behandeld dan vrouwen zonder SCAD (31% vs 7%, p < 0,001). De belangrijkste bevinding was dat primaire PCI bij patiënten met SCAD minder vaak een normale coronaire doorstroming herstelde. Normale doorstroming na de procedure van vrouwen met SCAD kwam daardoor minder vaak voor (73% vs 95%, p<0,001).

Hoewel het algemeen bekend is dat Tako Tsubo Cardiomyopathie (TTC) vaker voorkomt bij vrouwen, is het nog niet in de literatuur bekend of dit sekse verschil kan worden waargenomen op zowel jongere als oudere leeftijd. In **Hoofdstuk 7** werden 10166 STEMI patiënten onderzocht, waarvan in totaal 43 patiënten (0,4%) TTC hadden. In het totale cohort waren vrouwen ouder, rookten minder vaak en hadden minder vaak een voorgeschiedenis van myocardinfarct, CABG of PCI. Vrouwen hadden een hogere prevalentie van diabetes en hypertensie. De TTC groep, bestond uit meer vrouwen dan mannen (74% vs 26%, multivariaat OR 10.7, 95% BI 5,1-22,4). De prevalentie van het roken was lager bij zowel mannen als vrouwen met TTC, de prevalentie van hypertensie was alleen

lager bij mannen met TTC in vergelijking met mannen zonder TTC. Alle andere risicofactoren tussen patiënten met en zonder TTC waren vergelijkbaar in zowel mannen als vrouwen. De meest interessante bevinding van onze analyse was dat mannen met TTC jonger zijn dan mannen zonder TTC (50 vs 62 jaar, p=0,004), maar dit leeftijdsverschil niet werd waargenomen bij vrouwen (70 vs 67 jaar, p = 0,18).

Tako Tsubo Cardiomyopathie is een relatief nieuwe diagnose, die voor het eerst werd beschreven in 1991. In **Hoofdstuk 8** onderzochten we potentiële veranderingen in de incidentie van TTC in de tijd bij patiënten met een STEMI in Zwolle. De vroege jaren werden gedefinieerd als januari 2002 tot december 2007 (n=4350) en late jaren werden gedefinieerd als januari 2008 tot december 2013 (n=4063). Hoewel er kleine verschillen waren tussen de twee periodes met betrekking tot algemene patiënten kenmerken, waren in het algemeen de twee cohorten vergelijkbaar. Tako Tsubo werd vaker gediagnosticeerd in de late jaren (0,7% vs 0,3%, p=0,009), ook na correctie voor verschillen in de patiënten karakteristieken (OR 2.1, 95% BI 1,1-4,3). Waarschijnlijk is de verhoogde incidentie van TTC bij patiënten met STEMI veroorzaakt doordat dat artsen zich meer bewust zijn van de diagnose TTC en deze daardoor vaker stellen.

Chapter 12

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Amber M. Otten

Chapter 13

Overview of (scientific) career

Personal details

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Nationality:	Dutch
Date of birth:	18-09-1986
Place of birth:	Woudenberg
Marital status:	Married

Overview of diploma's

(1997-2004)	Christelijk lyceum Veenendaal	
(2004-2005)	Propedeuse Geneeskunde Erasmus MC	Rotterdam
(2005-2009)	Doctoral Geneeskunde Erasmus MC	Rotterdam
(2005-2009)	Master of Science in Clinical Research	Rotterdam
(July 2007)	Johns Hopkins school of public health, research courses	Baltimore
(March 2011)	Doctor of medicine	Rotterdam

Clinical experience

(February 2009-February 2011)	various internships various hospitals in the Netherlands
(March 2011-March 2013)	resident cardiology Zwolle
(April 2013-May 2014)	resident internal medicine (as a part of cardiology recidency) Amersfoort
(June 2014-March 2015)	resident internal medicine (as a part of cardiology recidency) University Medical Centre Utrecht
(April 2015-present)	resident cardiology Zwolle

Research experience
Master of Science in Clinical Research

Netherlands Institute for Health Sciences
Postgraduate Research Training (international degree programme Erasmus MC)

Overview MSc:
Theoretical phase

(2005-2008)	Summer research programme n i h e s / Erasmus MC
(2006-2008)	Winter research programme n i h e s / Erasmus MC
(2007-2009)	Advances research courses Erasmus MC
(2006-2008)	Methodologische training in ststistiek programma's SPSS, Stata, SAS, R.
(2007)	Internationale programma's in epidemiologie en clinical research in gezondheidszorginstellingen. (Harvard University, Boston USA en Johns Hopkins University, Baltimore USA.)

Research phase

(2008-2009)	Design and implementation of a research project.

(2009-2015) thesis: age and gender related differences in STEMI patients at Isala klinieken in Zwolle.

Scientific publications

1. **Otten A**, van Domburg RT, van Gameren M, Kappetein AP, Takkenberg JJ, Bogers AJ, Serruys PW, de Jaegere PP. Population characteristics, treatment assignment and survival of patients with aortic stenosis referred for percutaneous valve replacement. Eurointervention, 2008;4:2:250-255.
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Scientific presentations

Poster presentations

- Otten A, van Domburg R, van Gameren M, Kappetein AP, Takkenberg J, Bogers A, Serruys PW, de Jaegere P. Population characteristics, treatment assignment and survival of patients with aortic stenosis referred for percutaneous valve replacement.
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- Brugts JJ, Otten AM, Mercado N, Ix J, Shlipak MG, Dixon SR, Gersh BJ, Serruys PW, Lamos P, Guarneri M, Terstein P, Wijns W, O'Neill WW, and Boersma E. The need for blood transfusion is

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- Otten AM, Ottervanger JPO, Kloosterman A, van't Hof AWJ, Dambrink JHE, Gosselink M, Hoorntje JCA, Suryapranata H, Maas AHEM. Predictors and prognosis of spontaneous coronary artery dissection in young women presenting with STEMI.
    - American College of Cardiology 2013, JACC, 2013;61(10_S): doi:10.1016/S0735-1097(13)60074-1
- Otten AM, Ottervanger JP, Maas AHEM. Early menarche is associated with Myocardial Infarction at younger age.
    - ESC 2013

Oral presentations:

- Otten A, van Domburg R, van Gameren M, Kappetein AP, Takkenberg J, Bogers A, Serruys PW, de Jaegere P. Population characteristics, treatment assignment and survival of patients with aortic stenosis referred for percutaneous valve replacement.
    - AHA 2008. Circulation. Oct 2008; 118: S_806 - S_807
- Otten AM, Ottervanger JPO, Kloosterman A, van't Hof AWJ, Dambrink JHE, Gosselink M, Hoorntje JCA, Suryapranata H, Maas AHEM. Predictors and prognosis of spontaneous coronary artery dissection in young women presenting with STEMI.
    - NVVC 2012. Netherlands heart journal

Appendix

Courses followed

Summer and winter programmes Erasmus MC	
Principles of Research in Medicine and Epidemiology	2006
Methods of Clinical Research	2006
Pharmaco-epidemiology	2006
Introduction to Decision-making in Medicine	2006
Topics in Evidence-based Medicine	2006
Clinical Trials	2006
Regression Analysis	2007
Topics in Meta-analysis	2007
Survival Analysis	2008
Case-control Studies	2008
Introduction to Data-analysis	2008
Demography of Ageing	2008
Core courses	
Study Design	2006
Elective courses	
Modern Statistical Methods	2007
Broad orientation - 2nd year elective	2009
Advanced Courses	
Introduction to Clinical Research	2007
Advanced Topics in Decision-making in Medicine	2007
Intervention Research and Clinical Trial	2007
Prognosis Research	2007
Research Themes and Methodologies	2007
Diagnostic Research	2007
Repeated Measurements in Clinical Studies	2009
Advanced Topics in Clinical Trials	2009
Analysis of Time-varying Exposures	2009
Advanced Analysis of Prognosis Studies	2009

Skill oriented courses

A First Glance at SPSS for Windows	2007
Working with SPSS for Windows	2007

International courses at Johns Hopkins University

Genetic epidemiology in populations	2008
Nutritional epidemiology	2008
Public health dimensions of global tuberculosis control	2008
Topics in infectious disease epidemiology	2008

ACS masterclass 8-9 september 2011 at Geneve.

Chapter 14

Curriculum vitae

The author was born on September 18th 1986 in Woudenberg, the Netherlands. In 2004, she graduated from the Christelijk Lyceum in Veenendaal. Since she was tenfold Dutch swimming champion during high school, she was allowed to start her medical training at the Erasmus University of Rotterdam as a direct entry student. In her second year of medical training in 2005, she started a master of clinical research alongside her medical study and made an early start in what was then considered experimental project of transcatheter aortic valve implantation. She designed the database and wrote articles under the leadership of prof. dr. P.P.T. de Jaegere during her medical study. She obtained her master of clinical research in 2009 and became doctor of medicine in 2011. She started working as a resident cardiology in the Isala Klinieken in Zwolle. That same year she started a research project alongside her residency with prof. dr. A.H.E.M. Maas and dr. J.P. Ottervanger about age and gender related differences in ST-Elevation Myocardial Infarction which resulted in this thesis.