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FACULTY OF **MEDICINE AND HEALTH SCIENCES**

FEMALE GENDER

IN ACUTE CARDIAC CARE

Thesis submitted to fulfil the requirements

for the degree of Doctor in Medical Sciences

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Dankzij mijn ouders,

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Abbreviations

ACS:	Acute Coronary Syndrome(s)
ACE-I:	Angiotensin Converting Enzyme
AF:	Atrial Fibrillation
AHF:	Acute Heart Failure
AHT:	Arterial Hypertension
AMI:	Acute Myocardial Infarction
ARA:	Aldosterone Receptor Antagonist
ARB:	Angiotensin II Receptor Blocker
BP (SBP):	Systolic Blood Pressure
bpm:	beats per minute
CAD:	Coronary Artery Disease
CI:	Confidence Interval
CKD-EPI:	Chronic Kidney Disease Epidemiology Collaboration
CFR:	Case Fatality Rate
CPR:	Cardio Pulmonary Resuscitation
COPD:	Chronic Obstructive Pulmonary Disease
CVD:	CardioVascular Disease
DM:	Diabetes Mellitus
DTB:	Door-To-Balloon time
ECMO:	Extra Corporeal Membrane Oxygenation
eGFR:	estimated Glomerular Filtration Rate
FU:	Follow-Up
h:	hour
HF:	Heart Failure
HF-PEF:	Heart Failure with Preserved Ejection Fraction
HF-REF:	Heart Failure with Reduced Ejection Fraction

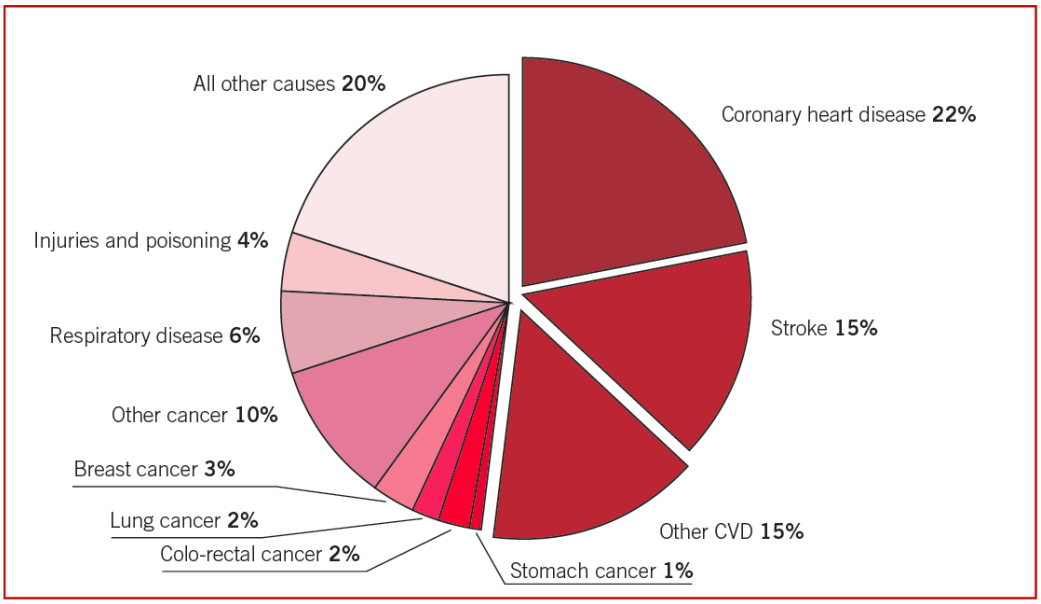
HR:	Heart Rate
HR:	Hazard Ratio
IABP:	Intra-Aortic Balloon Pump
IQR:	Inter Quartile Range
IV:	IntraVenous
kg:	kilogram
LBBB:	Left Bundle Branch Block
LVAD:	Left Ventricular Assist Device
LVEDD:	Left Ventricular End Diastolic Diameter
LVEF:	Left Ventricular Ejection Fraction
min:	minute
MR:	Mitral Regurgitation
NIV:	Non-Invasive Ventilation
NSTE-ACS:	Non ST-segment Elevation Acute Coronary Syndrome
NSTEMI:	Non ST-segment Elevation Myocardial Infarction
NYHA:	New York Heart Association
OR:	Odds Ratio
PAD:	Peripheral Artery Disease
pPCI:	primary Percutaneous Coronary Intervention
PPCM:	Peripartum Cardiomyopathy
RD:	Renal Dysfunction
ROC:	Receiver Operating Characteristic
SBP:	Systolic Blood Pressure
SD:	Standard Deviation
STEMI:	ST-segment Elevation Myocardial Infarction
TIMI :	Thrombolysis In Myocardial Infarction
UA	Unstable angina
VKA:	Vitamin K Antagonist
Y:	year

I. Introduction

I.1 Cardiac disease in women

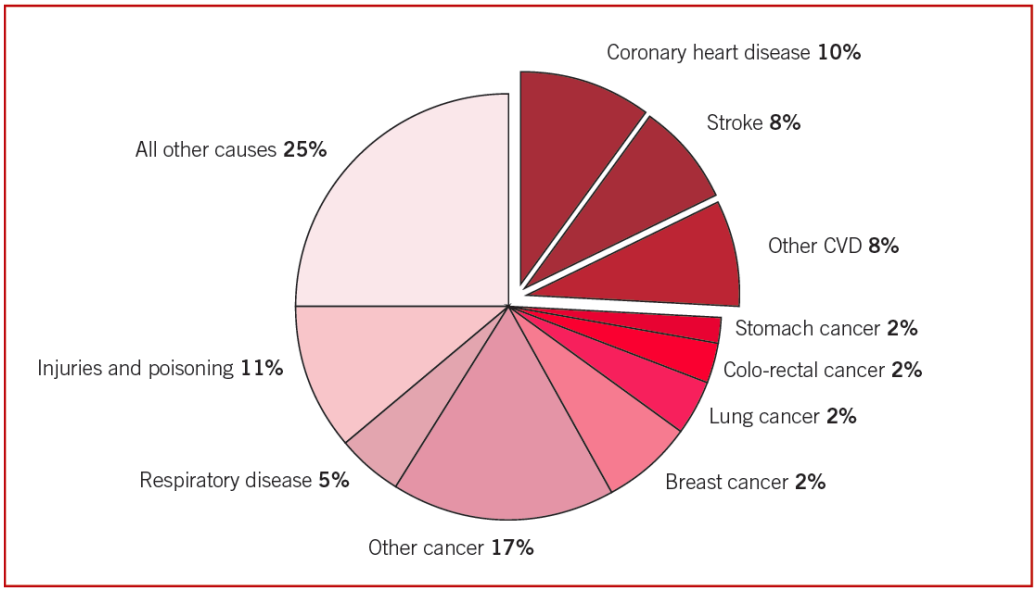
Cardiovascular disease (CVD: coronary artery disease [CAD], stroke and other CVD) is the leading killer of women at all ages. According to the latest European CVD statistics (2012) it accounts for 52% of the causes of death in European women (vs. 42% in men). **(Figure 1)**

Figure 1 Deaths by cause, women, Europe [1]



The longstanding disbelief that CAD does not occur in younger women was once again refuted by these statistics that point out CAD as the primary cause of death in 10% of the women <65 year of age in Europe (vs. 12% in men). **(Figure 2)** [1]

Figure 2 Deaths under 65 by cause, women, Europe [1]



CVD is also the leading cause of non-obstetric mortality during pregnancy while the number of women with pre-existing CVD or the development of cardiac problems during pregnancy is increasing and there is a lack of evidence-based data on the treatment of these patients. [2-5]

The interest for the female patient and gender differences in cardiac disease substantially increased during the last two decades [6,7], reflecting the need for more gender specific knowledge in order to reach better heart health care for women. More recently, strategies to improve the outcome of CVD in women were proposed during several international scientific symposia at both sides of the Atlantic. [8-10] Among these strategies was the encouragement of cardiovascular research in women with attention for gender-specific analysis and higher enrolment of women in clinical trials. There are many reasons why gender-specific basic and clinical research is valuable in cardiac disease: first there is the anatomical difference: a woman's heart is smaller and has a smaller vascular bed [11,12], second there are important gender differences in the pathophysiology of CVD [13-17], the impact of cardiovascular risk factors [18-20] and the effects of pharmacological therapy [21-23], third women tend to have more co-morbidities, especially at older age, fourth symptoms in women may be different [24-26] and sometimes misleading with the risk of under-recognition [27] and treatment-delay. Finally woman-specific cardiac disease exists such as pregnancy

related cardiac disease while Tako-Tsubo syndrome [28] and toxic cardiomyopathy following chemotherapy for breast cancer occur predominantly in women. [29]

Research on gender differences in cardiac disease initially focused on coronary heart disease but expanded to the different fields of cardiology including prevention [30], hypertension, heart failure (HF) [31-38], arrhythmia [39-41], valvular heart disease [42, 43] and complications of interventional cardiology. [44, 45]

This thesis focuses on gender differences in acute cardiology. Acute Coronary Syndromes (ACS) and Acute Heart Failure (AHF) are the major reasons for urgent hospital admission in this setting. Both are associated with high morbidity and mortality and require immediate risk stratification and initiation of evidence based and guideline recommended treatment strategies.

I.2 Acute Coronary Syndromes in women

'Acute Coronary Syndromes' (ACS) comprise unstable angina (UA), non ST-segment elevation myocardial infarction (NSTEMI) and ST-segment elevation myocardial infarction (STEMI). UA/NSTEMI and STEMI have a different clinical presentation but share a common pathophysiological substrate: atherosclerotic plaque rupture or erosion with different degrees of concomitant thrombosis. [46]

The INTERHEART study identified 9 modifiable risk factors associated with the risk for an ACS. These were the same for men and women: smoking, abnormal lipids, hypertension, diabetes, abdominal obesity and psychosocial stress were associated with increased risk while a healthy diet, moderate alcohol consumption and physical activity had a protective effect against myocardial infarction. [19] There are some gender differences in the impact and incidence of a risk factor: hypertension, diabetes, physical inactivity, lack of moderate alcohol intake and smoking (especially at young age) are more powerful risk factors in women. [18-20] Hypertension and diabetes are more prevalent among women with ACS while smoking is encountered more in men with ACS.

Women experience their first myocardial infarction on average 10 years later than men. Possible explanations for the later presentation in women are the protective effect of endogenous oestrogen before menopause and the higher risk factor burden in men at younger age. [47] In contrast, women who do develop an ACS at younger age often have a higher risk factor burden than men. [48]

Atherosclerotic lesions typically form over the course of years but the thrombotic complications that cause ACS occur suddenly. An occlusive thrombus arrests flow and causes STEMI while non-ST elevation ACS (NSTE-ACS) results from an incomplete or transient obstructive flow at the site of a critical stenosis. Rupture of the fibrous cap of a plaque causes most of the ACS. Plaque rupture is more often associated with thrombus formation in women as in men. [49] Plaque erosion through the intima of a calcified nodule triggers a small amount of ACS; autopsy studies demonstrated that this is encountered more in young female smokers. [14, 50] Spontaneous coronary artery dissection is another but very rare cause of ACS, occurring more in young women and often after emotional or physical stress. [51] About one third of spontaneous coronary artery dissections occur during or early after pregnancy, the true underlying mechanism is not clear but it is believed that

hormonal changes, haemodynamic stress and changes in auto-immune status play a role. [52]

An ACS is often the first presentation of CAD in men while angina predominates as the onset of CAD in women. [53] Within the ACS spectrum, women present more with UA/NSTEMI [13, 54-56] and exhibit fewer high-risk angiographic features on coronary angiography; 10-30% of women with ACS present without major coronary stenosis compared to 3-15% of the men. [56, 57] However, as demonstrated by the WISE investigators, non-obstructive CAD is also associated with adverse outcomes over the longer term among women with signs and symptoms of ischaemia and should be treated appropriately. [58, 59]

The diagnosis, risk stratification and management of ACS are based on:

1. Symptoms

   "*Chest pain, often described as a pressure or heaviness, often radiating to the left arm, neck or jaw, occurring at rest or with minimal exertion. This may be intermittent (>NSTE-ACS) or persistent (>STEMI) and can be accompanied by other symptoms such as diaphoresis, nausea and dyspnoea*"

There is on-going debate on gender differences in symptoms of ACS but the most important finding is that chest pain is the predominant symptom in both men and women but the absence of chest pain is more prevalent in women. However the majority of women without chest pain report at least 1 non-chest pain symptom, with more non-chest pain symptoms in women vs. men (back- neck or jaw pain, nausea and vomiting, shortness of breath, palpitations, dizziness, fatigue, …). Gender differences in the absence of chest pain are more pronounced among younger patients and become attenuated with age. [25, 26] The absence of chest pain or the atypical character of chest pain can lead to a delay in diagnosis and treatment.

2. ECG changes

   "No, new or presumed new significant ST segment-T wave changes or new left bundle branch block"

There are little data regarding gender differences in ECG in the setting of an ACS. For the diagnosis of STEMI: an ST-segment elevation at the J point should be present in 2 contiguous leads and be ≥0,25mV in men <40 years and ≥ 0,2mV in men over the age of 40. In women ST-elevation should be ≥0,15 in leads V2-3 and/or 0,1mV in

other leads. [60] In a mixed group of STEMI and NSTEMI patients, female gender was associated with lateral ST-depression, higher heart rate and longer QTc-interval whereas men had a longer QRS duration and a higher voltage of the QRS complex. Post MI ST-segment elevation in the anterior leads was associated with worse outcome in women while ST-depression in the lateral leads was associated with worse outcome in men in the same study population. [61]

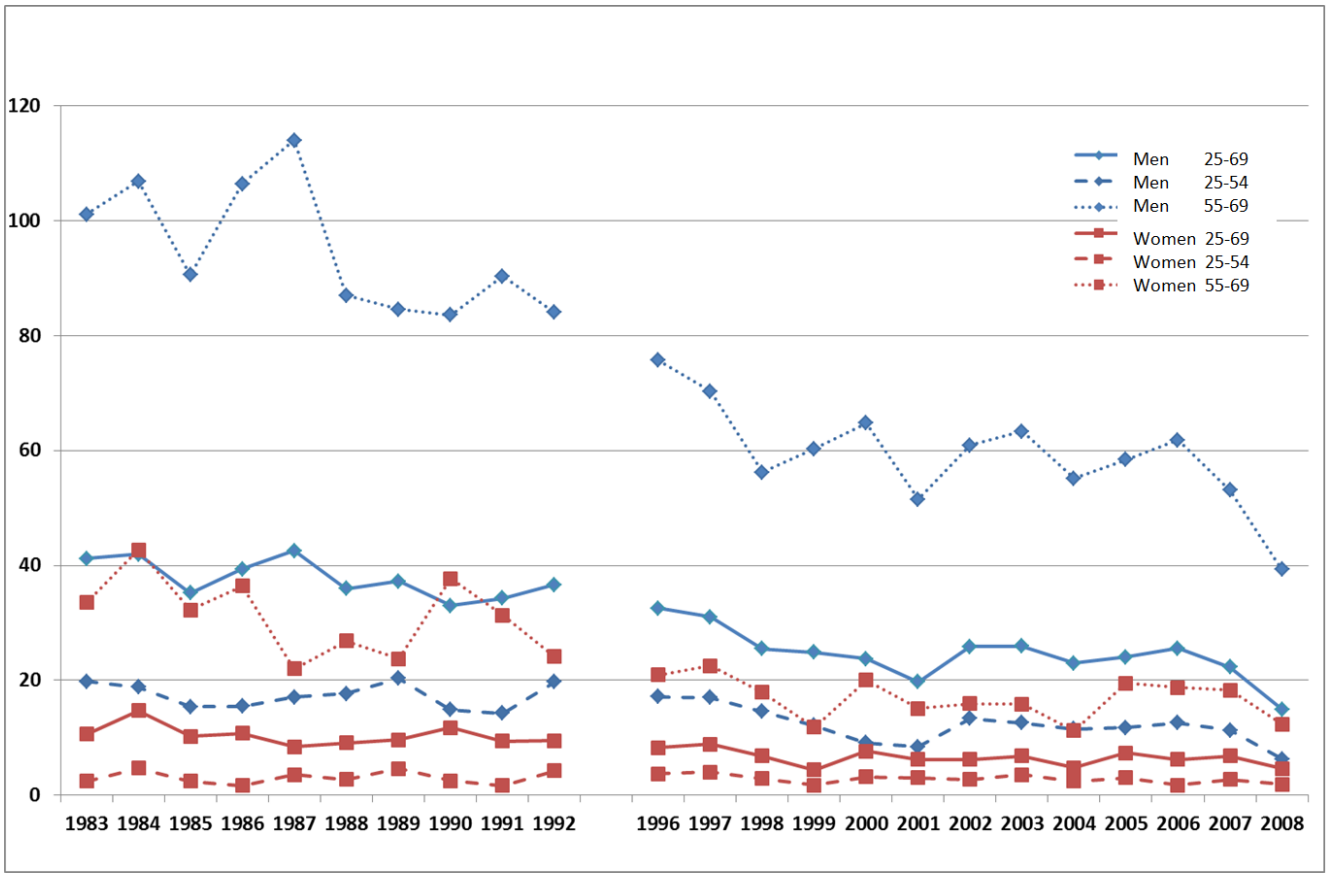
3. The detection of cardiac bio-markers :
   "Detection of a significant rise and/or fall in cardiac biomarkers (preferably cardiac troponin) with at least one value above the 99th percentile upper reference limit is necessary for the diagnosis of myocardial infarction"

Gender differences in the 99th percentile reference limit have been demonstrated for the old as well as for the new high sensitive troponin assays with higher 99th percentiles for males. 62, 63 For the moment male thresholds are used in clinical practice for both genders.

Men have higher attack rates of myocardial infarction. Overall, attack rates of STEMI declined in both men and women over the last 25 years but these declines were less pronounced among women. Despite the observed decline in case fatality rates for both sexes, women remained at higher risk for mortality and complications. [64-67] Local data from the Ghent Monica Registry (1983-2008) confirm the decline in attack rates, which is less pronounced in women than in men. During the same period a decline in 28-day case fatality rate is observed in Ghent, in both men and women (Unpublished data courtesy prof. dr. Koen Van Herck, **Figure 3**). Women however remain at higher risk but the gap is narrowing. (Unpublished data, courtesy prof. dr. Koen Van Herck, **Figure 4**)

Figure 3 **Evolution of attack rates*/10.000 men and women, aged 25-69**

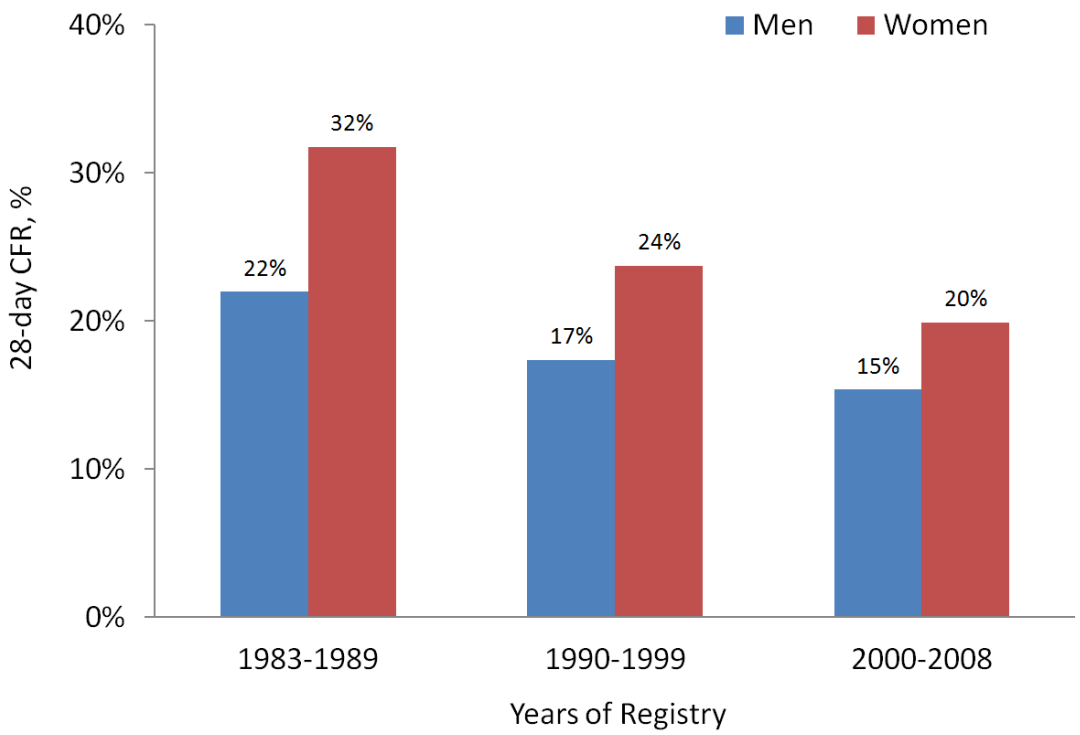
MONICA Registry Ghent , 1983-2008



* All cases included (fatal and non-fatal), ASR(E) standardised

Figure 4 **Evolution of in-hospital case fatality rates in men and women, aged 25-69**

Monica Registry Ghent, 1983-2008



CFR= case fatality rate

In the current guidelines on ST-segment elevation ACS and non ST-segment elevation ACS (NSTE-ACS) women are considered as 'a special patient' subset with the recommendation to treat both genders in a similar fashion (class I recommendation, level B in NSTE-ACS and level C in STEMI) and to dose antithrombotic therapies with close attention to bleeding risk. [60, 68]

Important advances in the acute treatment of STEMI have been made during the last three decades; in the eighties acute reperfusion with fibrinolytic agents was introduced followed by trials in the nineties that demonstrated the superiority of primary percutaneous intervention (pPCI) in opening the infarct related artery. [69]

Nowadays pPCI is the treatment of choice for STEMI, this treatment proved benefit in women and men as compared to thrombolytic therapy [70-73] and is increasingly used in Europe and Belgium. [74, 75] Further advances in the treatment of ACS include additional treatments such as beta-blocking agents, dual antiplatelet therapy, high dose statins and angiotensin-converting enzyme inhibitors (ACE-I) or angiotensin II receptor blockers (ARB).

Women constitute approximately one fourth of the patients admitted with STEMI. Different analyses demonstrated a worse short-term prognosis for women suffering a myocardial infarction [76], especially those below 60 years-of-age. [77, 78] The introduction of more sensitive assays for the diagnosis of ACS-subtypes, allowed to evaluate the outcomes per ACS-subtype: an analysis of Berger *et al.* showed that women with STEMI have a higher adjusted risk for 30 day mortality whereas this mortality risk was lower in women with UA and NSTEMI as compared to men. [56] Champney *et al.* demonstrated a worse outcome for younger women, irrespective of ACS type, while older women showed no mortality differences (in STEMI) or even a better survival (in NSTEMI). [79] Therefore, intensive research has been performed on the reasons behind the differences in short term outcome after STEMI; in general women present with less chest pain or other 'atypical' symptoms [25, 26], a worse risk profile [80] and are less likely to receive guideline based therapies [81] or to undergo coronary interventions. [82, 83] Furthermore women suffer more complications after percutaneous interventions. [84, 85] Recent reports demonstrate that the gender gap in access to early intervention is closing. [81, 86] In contrast men are at higher risk of malignant ventricular arrhythmia and sudden death in the pre-hospital phase [87], probably due to a higher parasympathetic autonomic tone in women which is thought to protect them against ventricular fibrillation. [88]

An overview of the main gender-differences and knowledge gaps in ACS is summarised in **Table 1.**

Table 1 Women vs. Men in ACS	
Age	Older, on average 10 years
Risk factors	More hypertension and more diabetes Less smoking Protective effect of oestrogen before menopause Higher burden of risk factors at younger age
Pathophysiology	Young and smoking: higher incidence of plaque erosion More thrombus formation in case of plaque rupture More coronary artery dissection (rare) Micro-vascular dysfunction, endothelial dysfunction
Co-morbidity	More: diabetes, hypertension, depression
Type	More NSTE-ACS, less STEMI
ECG	Lateral ST-depression, higher heart rate and longer QTc
Biomarkers	Lower 99th percentile upper reference limit
Anatomical	Less obstructive CAD, less atherosclerotic burden
Symptoms	Higher proportion: no chest pain More non-chest pain symptoms
Treatment	Delayed (patient and system related) Less invasive
Complications	More bleeding, vascular complications More contrast induced AKI
Outcome	Pre hospital phase: less sudden death NSTE-ACS: better outcome STEMI: worse outcome in young women
Knowledge gaps	• Reason for higher mortality in younger women with STEMI • Determinants for treatment delay in women • Best approach to assess chest pain and non chest pain symptoms suggestive of CAD in women • Sex differences in ECG in ACS • Could the use of sex-specific cut off values for troponin improve diagnosis?
ACS= acute coronary syndromes, NSTE-ACS: non ST segment elevation ACS, STEMI: ST-segment elevation myocardial infarction, CAD: coronary artery disease, AKI= acute kidney injury	

I.3 Acute Heart Failure in women

Heart failure (HF) is defined as the clinical syndrome that develops as a consequence of an abnormality of the heart with typical symptoms (e.g. breathlessness and fatigue) and clinical signs (e.g. peripheral oedema). Any abnormality of the heart can cause HF (structural: e.g. valvular heart disease, electrical: e.g. atrial fibrillation [AF], mechanical: e.g. systolic dysfunction). Left ventricular dysfunction caused by myocardial infarction or CAD is the commonest cause of HF in the Western world and is more prevalent among men. HF with preserved ejection fraction (HF-PEF) is more prevalent among women. [36]

The prevalence of chronic HF increases with age for both men and women with more women than men having HF after 79 years-of-age. [89] In general women with chronic HF have an improved survival as compared to men, despite the fact that they receive less evidence-based therapies for HF. The reason behind this better survival is not completely understood at this moment. [36]

The syndrome of AHF is defined as the rapid onset, or deterioration of the aforementioned symptoms and signs resulting in the need for urgent therapy. [90] Patients with AHF present with different clinical pictures ranging from a condition characterised by a gradual increase in peripheral oedema and dyspnoea due to fluid retention called 'acute decompensated heart failure' to the most severe form of AHF characterised by hypo-perfusion and tissue hypoxia called 'cardiogenic shock'. [91]

The commonest form of AHF is decompensated pre-existing chronic HF, often triggered by a precipitating factor such as infection, arrhythmia (especially AF), problems with compliance, renal dysfunction and many more. In the setting of ACS, AHF occurs in 20-30% of the cases and represents the most important cause of cardiogenic shock. Despite the fact that women show greater myocardial salvage after pPCI [92] and are believed to be protected against apoptosis and cell death [93] they are at higher risk for the development of HF during hospitalisation for ACS. [94]

Tako-Tsubo cardiomyopathy is an uncommon type of AHF that occurs predominantly in postmenopausal women after emotional and/or physical stress. [28] It can mimic a STEMI and is characterised by a transient and severe left ventricular dysfunction in the absence of significant CAD. Several possible mechanisms such as multi-vessel coronary artery spasm, micro-vascular dysfunction, myocarditis and catecholamine toxicity have been proposed but its pathophysiology remains not well understood. [95]

Peripartum cardiomyopathy (PPCM) is directly related to pregnancy and is defined as the development of HF during the last month of pregnancy or the months following pregnancy without any other identifiable cause of HF. [96] Women with PPCM usually present with typical signs and symptoms of HF. When PPCM occurs during pregnancy many of these symptoms are similar to those of normal pregnancy and the diagnosis is often delayed. [97] As a consequence many women with PPCM present in a later stage with de novo AHF requiring emergency admission and intensive cardiac care. The treatment is mainly supportive; when medical therapy is not sufficient mechanical support may be necessary. [98]

The prevalence of co-morbidities is high in patients with AHF: these can be of cardiac (CAD, arrhythmia [especially AF], valvular heart disease) and non-cardiac origin (hypertension, chronic kidney disease, chronic obstructive pulmonary disease [COPD], diabetes, peripheral vascular disease, anaemia…). [99] Both HF and AF are considered as the two epidemics of modern cardiovascular medicine. [100] These conditions may interact: a rapid ventricular rate can trigger AHF, and HF increases atrial stretch, which can make AF more resistant to therapy. The incidence of AF increases when HF severity worsens and AF is associated with worse outcome in HF patients. [101]

Due to improved survival after ACS and an ageing population, AHF has become the leading cause for urgent hospital admission in the population above 65 years-of-age. [102, 103] AHF is associated with increased mortality during and after discharge and a high risk (up to 30%) of hospital readmission making it a major public health challenge. [104-106]

Registry data show that women comprise half of the patients hospitalised for AHF but proportions of women in randomised controlled trials in this setting are far below 50%, illustrating that women are underrepresented in these trials. [38]

On average women with AHF are 5 years older (mean age women: 73.1 years, men: 67.8 years in the Euro Heart Failure Survey II), have other co-morbidities and present more with HF-PEF [32, 33] Ischaemic heart disease, COPD and peripheral artery disease occur more in men with AHF while hypertension, diabetes and chronic kidney disease occur more in women with AHF. Some AHF registries demonstrated small but non-consistent sex-differences in the prevalence of AF. [31-33, 35, 37]

Despite differences in age, comorbidities, aetiology and management most AHF registries found no gender differences in short-term outcome while a Danish group demonstrated a better adjusted long-term survival for women in patients hospitalised with congestive HF. [31-33, 37, 107, 108]

An overview of the main gender-differences and knowledge gaps in AHF is summarised in **Table 2.**

Table 2 Women vs. men in AHF	
Age	Older, on average 5 years
Pathophysiology	More HF-PEF Less ischaemic aetiology Higher proportion of HF complicating MI Tako Tsubo more prevalent among postmenopausal women Female specific: Peripartum cardiomyopathy
Co-morbidity	Less: COPD, peripheral artery disease, CAD More: hypertension, diabetes, chronic kidney disease Atrial Fibrillation?
Treatment	No significant differences in current registries
Prognosis	No significant differences in short-term outcome. Better long-term outcome.
Knowledge gaps	• Why do women develop more HF in the setting of ACS? • Have HF treatments the same effect in women or should we treat them differently? • Why is the long-term survival better in women?
AHF= acute heart failure, HF-PEF= heart failure with preserved ejection fraction, HF= heart failure, MI= myocardial infarction, COPD=chronic obstructive pulmonary disease, CAD=coronary artery disease, ACS= acute coronary syndrome	

II. Aims and outline of the thesis

The general aim of this thesis is to gain further insight into the clinical characteristics and outcomes of women with acute cardiac disease, more specifically STEMI and AHF.

Aims A-B-C

When starting this project the central question was: 'Are female patients presenting with acute cardiac disease equal or different to male patients in terms of prognosis'?

Aim A

The last 2 decades many investigators reported a worse outcome for women vs. men with STEMI. [54, 109, 110] Higher age, more advanced disease, the presence of comorbidity (especially hypertension and diabetes), longer ischaemic times (patient and system related), a worse clinical condition on presentation, the underuse of evidence-based therapy and invasive reperfusion strategies and a higher pre-hospital mortality for men were pointed out as confounding factors. [83, 109] Primary angioplasty is the treatment of choice in STEMI but there is conflicting evidence regarding gender-based differences in the short-term outcome after pPCI. [73, 111-118]

The Thrombolysis In Myocardial Infarction (TIMI) risk score for STEMI is a simple arithmetic score that predicts short-term mortality based on age and clinical data on admission, female gender is not included in this score. [119] There are no data on the predictive performance of the TIMI risk score for STEMI when applied to a community based cohort of men and women in the current era of pPCI, stenting and adjunctive antiplatelet therapy.

***Aim A**: To compare in-hospital mortality rate and the predictive performance of the TIMI risk score between male and female Belgian STEMI patients undergoing pPCI.*

Aim B

Chronic kidney disease, even mild, is independently associated with in-hospital mortality in STEMI patients treated with pPCI. [120, 121] Data on gender differences in prevalence of renal dysfunction at admission in pPCI treated STEMI patients are scarce and have seldom been accounted for when evaluating gender differences in outcome, furthermore different definitions (serum creatinine levels vs. estimated Glomerular Filtration Rate [eGFR] values) and different methods of estimating creatinine clearance have been applied. [112, 118, 122, 123] It is assumed that the newer Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation leads to a smaller average bias in a clinical population with a wide range of GFRs. [124]

***Aim B**: To investigate gender differences in prevalence and prognostic impact of renal dysfunction at admission (assessed by the CKD-EPI equation) on in-hospital mortality in STEMI patients undergoing pPCI.*

Aim C

The proportion of patients hospitalised with pre-existing AF and HF is increasing. [125, 126] There are little data regarding gender differences in treatment and prognostic impact of AF in AHF patients.

***Aim C**: To evaluate gender differences in the incidence, treatment and outcome of co-occurring AF in AHF.*

Accordingly we compared in-hospital mortality and the predictive performance of the TIMI risk score in STEMI between male and female patients undergoing pPCI and we evaluated gender differences in the setting of STEMI and AHF while focusing on the incidence and impact on prognosis of selected clinical variables (renal dysfunction in STEMI and AF in AHF). **(Aims A-B-C: chapters 1-2-3)**

Aims D-E

Women who are confronted with acute cardiac disease at a younger age present a major challenge.

Many authors have demonstrated a worse outcome for women with STEMI at younger age. [77,78] This was not yet reported among younger women admitted with AHF.

***Aim D**: To evaluate gender differences among younger men and women undergoing pPCI for STEMI (<65 years-of-age) or admitted with AHF and co-occurring AF (<75 years-of-age).*

We further evaluated the aforementioned gender differences of aims A and C in two age groups, a younger and older age group (< and ≥ 65 years in STEMI, < and ≥ 75 years in AHF complicated with AF). **(Aim D: chapter 1 and 3)**

Finally the number of pregnant women with pre-existing CVD or the development of cardiac problems such as PPCM during pregnancy is increasing. [4] Despite the low incidence of PPCM and potential reversibility or stabilisation with current medical therapy, some patients may evolve to severe haemodynamic compromise and death. [127] There are limited data on the use of mechanical support in PPCM patients.

***Aim E:** To evaluate the feasibility, efficacy and safety of mechanical support in patients with PPCM.*

Finally we evaluated the feasibility, efficacy and safety of mechanical support in critically ill patients presenting with PPCM refractory to medical supportive therapy. **(Aim E: chapter 4)**

III. Patients and methods

The research aims were explored in existing datasets, reflecting real world practice in unselected patients. These databases represent Belgian hospitals of various sizes and provide recent data regarding management of STEMI and AHF.

III.1 STEMI patients

Dataset

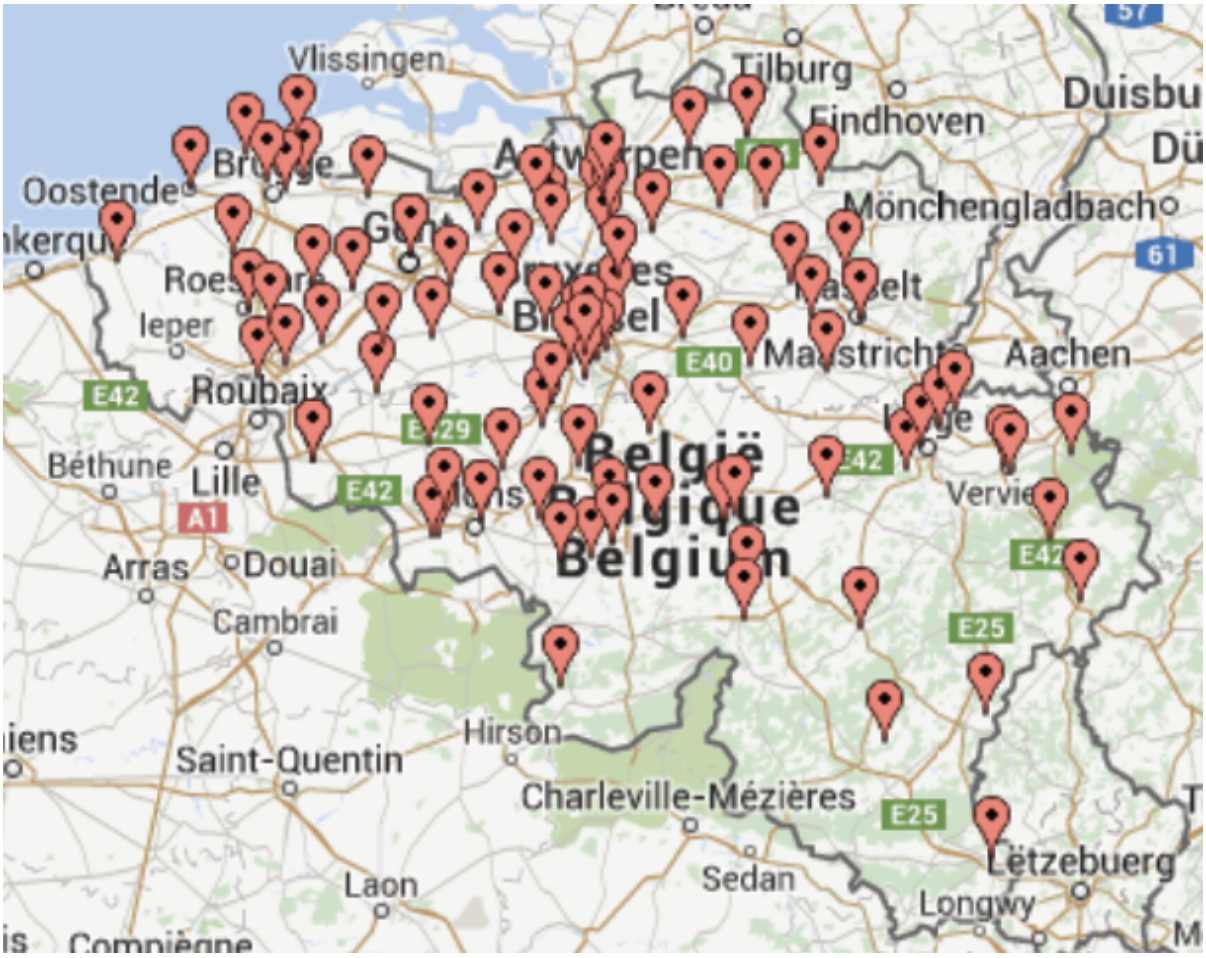
The Belgian STEMI registry is a prospective observational registry of unselected Belgian STEMI patients admitted in 113 hospitals and registered by 72 Belgian hospitals. [128] **(Figure 5)** The objective of this prospective registry is to collect real-life data on the clinical characteristics, the management and the in-hospital outcome of Belgian STEMI patients. The registry started in 2007 and contains demographics, previous history, clinical characteristics at admission, infarct localisation, practice patterns and in-hospital outcomes. The registry is an initiative of the Belgian Interdisciplinary Working Group on Acute Cardiology (BIWAC) and is supported by the Belgian government of Social Affairs and Public Health and the Belgian College of Cardiologists. All Belgian cardiologists working in hospitals with acute care facilities are required to prospectively collect data on all admitted STEMI patients starting from January 2007.

During the period January 2007-February 2011, a total of 9,535 STEMI patients were registered in the database. Out of these, all patients treated with pPCI <24 hours after hospital admission were selected (8,073 patients) to compare in-hospital mortality rate and predictive performance of the TIMI risk score between men and women. **(AimA)**

For **Aim B** we retrospectively collected admission values of serum creatinine of patients (N= 1,751) admitted in eight out of 28 tertiary care centres participating in the STEMI registry. Of these 1,638 patients, treated with pPCI <24 hours after hospital admission, were selected and included in the analysis. The eGFR was calculated using the CKD-EPI equation based on the admission value of serum creatinine. [124] The eGFR could not be calculated in 11.9% of the cases due to missing values.

The Belgian STEMI database was registered with clinicaltrials.gov (NCT00727623). [128] The study was approved by the central ethical committee of the Ghent University Hospital (2011/455). A yearly audit, conducted by an external commission, of 10% of all patients' files was performed to verify the validity of the data; 84% of the data were retrieved in the source documents and there was a 96% concordance rate between source documents and case report forms.

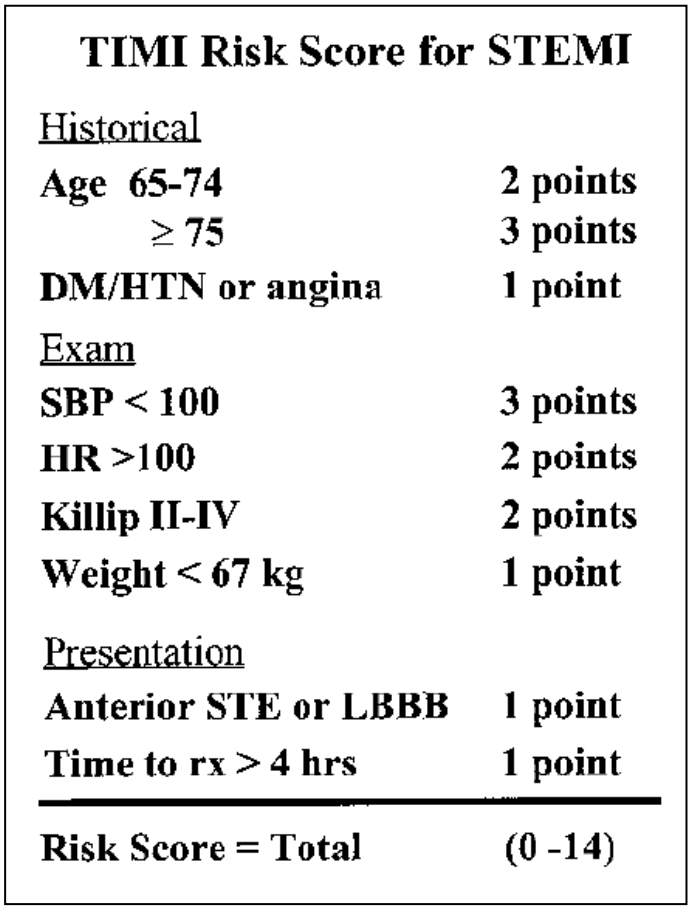
Figure 5 STEMI registration in Belgium: 2007-2011: admission hospitals



Statistical analysis

Aim A-D: A multivariable logistic regression model was created to evaluate the relationship between gender and in-hospital mortality, including all TIMI risk score variables (age group (< and ≥ 65 years old), history of hypertension, history of diabetes, previous CAD, Killip Class >I, ischaemic time >4 hours, admission systolic blood pressure (SBP) <100mmHg, admission heart rate >100 beats per minute (bpm), weight <67 kg, anterior myocardial infarction or LBBB). **(Figure 6)** [119]

Figure 6 Elements of the TIMI risk score [119]



TIMI Risk Score for STEMI	
Historical	
Age 65-74	2 points
≥ 75	3 points
DM/HTN or angina	1 point
Exam	
SBP < 100	3 points
HR >100	2 points
Killip II-IV	2 points
Weight < 67 kg	1 point
Presentation	
Anterior STE or LBBB	1 point
Time to rx > 4 hrs	1 point
Risk Score = Total	(0 -14)

(DM=diabetes mellitus, HTN= hypertension, SBP= systolic blood pressure, HR= heart rate, STE= ST-segment elevation, LBBB= left bundle branch block, rx= revascularisation, hrs= hours)

Female gender was added to this multivariable model. **(Aim A)** We further adjusted for age (continuous variable) in the subgroup of patients <65 and ≥65 years-of-age. **(Aim D)** The predictive discriminatory capacity of the TIMI risk score was expressed as the *c*-statistic, which represents the area under the Receiver Operating Characteristic (ROC), calibration was assessed by using the Hosmer-Lemeshow goodness-of-fit test. We established a logistic model for in-hospital mortality, including the TIMI risk score, gender and an interaction term between both. **(Aim A)**

Aim B: Multivariable logistic-regression analysis was used to determine the independent predictors of renal dysfunction (defined as an eGFR<60mL/min/1.73m^2) at admission including following covariates in the model: gender, age, bodyweight <67 kg, history of CAD, history of peripheral artery disease, hypertension and diabetes. Separate logistic regression analyses were performed regarding in-hospital mortality for each gender, including TIMI risk score as a continuous and renal dysfunction as a dichotomous variable in the model. Multivariable logistic regression analysis was also used to assess a possible interaction between gender and renal dysfunction regarding in-hospital mortality adding gender as a dichotomous variable and the product of gender and renal dysfunction as an interaction term to the previous model.

III.2 AHF patients

Dataset:

The BIO-HF registry is a prospective HF-registry evaluating all patients admitted with New York Heart Association (NYHA) class III-IV in 2 Belgian hospitals (AZ Maria-Middelares Ghent hospital and the UZ VUB Brussels). [129] The objective of the registry is to prospectively collect data regarding baseline characteristics, in-hospital treatment, therapy at discharge and outcome for consecutive patients with AHF treated in these hospitals. From November 2006 to May 2012 a total of 977 patients were included in the registry.

Data regarding AF on admission were missing in 20 patients. AF occurred in 432 of the remaining 957 patients. Clinical and echocardiographic data as well as data on therapy for HF and AF, before, during and at discharge were recorded in all patients. Risk factors and comorbidities were documented.

The central ethical committee of the UZ Brussels and the Maria Middelares Hospital Ghent approved the BIO-HF database. (2010/262). We received local Ethical Committee approval for this study as well as informed consent from the patients or their relatives.

Statistical analysis

Multivariable logistic regression analysis was used to determine the independent predictors of AF on admission, including the following covariates in the model: sex, age (continuous variable), hypertension, diabetes, anaemia, renal dysfunction, HF with reduced ejection fraction (HF-REF, defined as an EF<50%), left atrial diameter, CAD, peripheral artery disease, and mitral valve regurgitation (MR) > grade 2. To evaluate the composite of 1-year mortality and re-hospitalisation following covariates were included in the multivariable analysis: female gender, variables that were associated with the endpoint in a univariate analysis in this database (age, admission heart rate, renal dysfunction, β-blocker at discharge, vitamin K antagonists at discharge, angiotensin-converting enzyme inhibitor [ACE-I] or angiotensin receptor blocker [ARB] at discharge, aldosterone receptor antagonist [ARA] at discharge) and variables that were different between sexes in univariate

analysis in this database (age, hypertension, renal dysfunction, CAD, HF-REF, active smoking, COPD, and ARA at discharge). **(Aim C)**

The same analysis was done in the subgroup of patients < and ≥75 years-of-age. To assess a possible interaction between sex and age regarding the primary end point, the product of sex and age (continuous variable) was added as an interaction term to the previous model. **(Aim D)**

III.3 PPCM patients

We conducted a retrospective 10-year search (2000 to 2010) of the patient database of the department of Cardiology of the Ghent University Hospital for patients treated with mechanical support in the acute phase of PPCM. Diagnosis of PPCM was based upon development of symptoms of HF due to systolic dysfunction in the last month of pregnancy or within five months after delivery without any identifiable cause of HF or recognisable heart disease prior to the last month of pregnancy. Mechanical support was defined as 'intra-aortic balloon pump' (IABP), 'extra corporeal membrane oxygenation (ECMO) or 'left ventricular assist device' (LVAD).

During this period 6 PPCM patients were treated with mechanical support. Demographic, clinical, hemodynamic and echocardiographic data as well as data on serology were evaluated. The outcomes of the different treatment strategies as well as their complications were evaluated. **(Aim E)**

We received local ethical committee approval and informed consent from the patients or their relatives.

IV. Results

IV.1 Female gender in ST-segment Elevation Myocardial Infarction

IV.1.1 **Chapter 1:**

Gender, TIMI risk score and in-hospital mortality in STEMI patients undergoing primary PCI: results from the Belgian STEMI registry

EuroIntervention 2014;9(9):1095-1101

IV.1.2 **Chapter 2:**

Renal dysfunction in STEMI-patients undergoing primary angioplasty: higher prevalence but equal prognostic impact in female patients; an observational cohort study from the Belgian STEMI registry

BMC Nephrology 2013;14:62

IV.2 Female gender in Acute Heart Failure

IV.2.1 **Chapter 3:**

Gender differences in the management and outcome of atrial fibrillation complicating acute heart failure

Journal of Cardiac Failure 2014;20(6):431-7

IV.2.2 **Chapter 4**:

Acute and critically ill peripartum cardiomyopathy and **'**bridge to**'** therapeutic options: a single center experience with intra-aortic balloon pump, extracorporeal membrane oxygenation and continuous-flow left ventricular assist devices.

Critical Care 2011;15(2):R93

Chapter 1

Gender, TIMI risk score and in-hospital mortality in STEMI patients undergoing primary PCI: results from the Belgian STEMI registry

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EuroIntervention 2014,9(9):1095-1101

ABSTRACT

Background: The relationship between the predictive performance of the TIMI risk score for STEMI and gender has not been evaluated in the setting of primary PCI (pPCI). Here, we compared in-hospital mortality and predictive performance of the TIMI risk score between Belgian women and men undergoing pPCI.

Methods and Results: In-hospital mortality was analysed in 8,073 (1,920 [23.8%] female and 6,153 [76.2%] male) consecutive pPCI-treated STEMI patients, included in the prospective, observational Belgian STEMI registry (January 2007 to February 2011). A multivariable logistic regression model, including TIMI risk score variables and gender, evaluated differences in in-hospital mortality between men and women. The predictive performance of the TIMI risk score according to gender was evaluated in terms of discrimination and calibration. Mortality rates for TIMI scores in women and men were compared. Female patients were older, had more comorbidities and longer ischaemic times. Crude in-hospital mortality was 10.1% in women vs. 4.9% in men (OR 2.2 [95% CI 1.82-2.66], p<0.001). When adjusting for TIMI risk score variables, mortality remained higher in women (OR=1.47 [95% CI 1.15 to 1.87], p=0.002). The TIMI risk score provided a good predictive discrimination and calibration in women as well as in men (*c*-statistic= 0.84 [95% CI 0.809-0.866], goodness-of-fit p=0.53 and *c*-statistic = 0.89 [95% CI 0.873-0.907], goodness-of-fit p=0.13 respectively), but mortality prediction for TIMI scores was better in men (p=0.02 for TIMI score x gender interaction).

Conclusions: In the Belgian STEMI-registry, pPCI-treated women had a higher in-hospital mortality rate even after correcting for TIMI risk score variables. The TIMI risk score was effective in predicting in-hospital mortality but performed slightly better in men.

Clinical trial registration: The database was registered with clinicaltrials.gov (NCT00727623)

Key words: STEMI, gender, primary PCI, TIMI risk score, in-hospital mortality

INTRODUCTION

Cardiovascular disease is the major cause of death in women over the age of 65. Since the early nineties, higher mortality rates have been reported for women with ST-segment elevation myocardial infarction (STEMI) as compared to men. [54, 56, 70, 77, 109, 110, 130] The poorer outcome in women has been attributed to a higher age, more advanced disease, more comorbidities, longer ischaemic times, worse clinical condition on presentation and the underuse of evidence-based therapy and invasive reperfusion strategies. [83, 109] Several authors demonstrated that sex-related mortality differences are confined to younger patients, typically those younger than 50 years-of-age. [65, 77, 131] Despite the fact that pPCI improves outcome in STEMI in both men and women [132], as confirmed by the current guidelines [60], there is conflicting evidence regarding gender-based differences in the short-term outcome in women treated with pPCI. In 2001, Vakili et al. demonstrated that women treated with pPCI for a first STEMI still had a higher risk of death as compared to men. [111] This finding was confirmed in some studies [112, 113], while others found no significant sex-related differences in early mortality. [70, 114-118, 122]

The Thrombolysis In Myocardial Infarction (TIMI) risk score for STEMI is a simple arithmetic score that predicts short-term mortality based on age and clinical data on admission. [119] This score was initially developed and validated in a randomised controlled trial of patients treated with fibrinolysis but proved to be useful in patients treated with pPCI in an observational registry (*c*-statistic= 0.80 for patients treated with pPCI in the NRMI III registry [n=15,348]). [133] Ten baseline variables accounted for 97% of the predictive capacity and were constituted in the TIMI risk score. Female gender was not included in the TIMI risk score, as it was one of the 5 variables accounting for the remaining 3% of the predictive capacity for 30-day mortality (OR=1.2; 95% CI 1-1.2). There are no data on the predictive performance of the TIMI risk score when applied to a community-based cohort of men and women in the current era of pPCI, stenting and contemporary adjunctive antiplatelet therapy.

Accordingly, we compared the in-hospital mortality rate and predictive performance of the TIMI risk score between male and female Belgian STEMI patients undergoing pPCI.

METHODS

Belgian STEMI registry

The Belgian STEMI registry is a prospective observational registry of unselected Belgian STEMI patients from 72 Belgian hospitals. STEMI was defined as follows: symptoms suspicious of acute coronary syndrome, combined with ST-elevation (>1mm in 2 continuous leads) or new left bundle branch block (LBBB) on ECG. The registry contains demographics (zip code, PCI vs. no PCI centre), previous history (diabetes, hypertension, peripheral artery disease, coronary artery disease [CAD]), clinical characteristics at admission (weight < or ≥ 67 kg, admission blood pressure < or ≥ 100 mmHg, admission heart rate > or ≤ 100 bpm), infarct localisation (anterior, LBBB, non anterior), practice patterns (treatment, transfer, ischaemic and intervention times) and in-hospital outcomes. Ischaemic time is defined as the time between onset of symptoms and revascularisation therapy. The registry is an initiative from the Belgian Working Group on Acute Cardiology (BIWAC) and is supported by the Belgian government and the Belgian College of Cardiologists. All Belgian cardiologists working in hospitals with acute care facilities were required to prospectively collect data on all admitted STEMI patients starting from January 2007. Since a patient file can only be finalised when all required data are provided, there are no missing covariates in the registry. The database was registered with clinicaltrials.gov (NCT00727623). This study was approved by the central ethical committee of the Ghent University Hospital (2011/455). Informed consent was obtained from all patients or their legal representatives.

During the period between January 2007 and February 2011, a total of 9,535 STEMI patients from 72 hospitals (25 with PCI facilities and 47 without PCI facilities) were prospectively included. Of these, 8,073 (84.67%) patients were treated with pPCI <24 hours after hospital admission and included in the analysis. Patients receiving rescue PCI after failed thrombolysis (N=272, 2.85%) were not included in the PCI group, while patients who underwent facilitated PCI (N= 231, 2.42%) were included in the PCI group. A yearly audit, conducted by an external commission, of 10% of all patient files was performed to verify the validity of the data. Data were electronically collected via a protected eCRF. The database is managed by an independent electronic data-capture provider (Lambda Plus, SA, Gembloux, Belgium).

Clinical End Points

The primary endpoint of the study was in-hospital mortality.

TIMI risk score

The TIMI risk score was automatically calculated from 8 differentially weighted clinical indicators ascertained upon admission. The TIMI score ranges from 0 to 14 and is calculated as follows: age (2 points: 65-74, 3 points: 75 and older); history of angina, diabetes or hypertension (1 point); admission systolic blood pressure (BP) <100 mmHg (3 points); admission heart rate (HR) >100 beats/min (bpm) (2 points); admission Killip class >I (2 points); admission weight <67 kg (1 point); anterior infarction or LBBB (1 point); and time to reperfusion therapy > 4hours (1 point). [119]

Statistical Analysis

We compared the baseline characteristics and in-hospital outcomes of women with those of men. Categorical variables were compared with the Fisher's exact test. Continuous variables were evaluated for normality. The Student's *t* test was used for continuous variables with a normal distribution (presented as the mean ± SD), and Mann Whitney-U test was used for continuous variables (presented as the median and interquartile range [IQR]) without a normal distribution.

We created a multivariable logistic regression model to evaluate the relationship between gender and in-hospital mortality; including all TIMI risk score variables: age-group (< and ≥65 years-of-age), history of hypertension, history of diabetes, previous CAD, Killip Class >I, ischaemic time >4h, admission BP <100 mmHg, admission HR >100 bpm, weight <67 kg, anterior myocardial infarction or LBBB). Female gender was added to this multivariable model. Odds Ratios (OR) with 95% confidence intervals (CI) are reported. Statistical significance was defined as $p<0.05$ or CI for OR that did not include 1.0.

The predictive discriminatory capacity of the TIMI risk score was expressed as the *c*-statistic, which represents the area under the ROC (receiver operating characteristic: 0.50 indicating chance discrimination and 1.00 perfect discrimination) curve for predicting in-hospital mortality in both men and women. Calibration was assessed by using the Hosmer-Lemeshow goodness-of-fit test; a p-value > 0.05 was pre-specified as good calibration. We established a logistic model for in-hospital mortality, including the TIMI risk score, gender and an interaction term between both.

All statistical analyses were performed using the PASW 18 statistical software (SPSS Inc., Chicago, IL, USA).

RESULTS

Baseline characteristics

Baseline patient characteristics are shown in **Table 1**. During the period between January 2007 and February 2011, 8,073 patients were treated with pPCI: 1,920 (23.8 %) were female and 6,153 (76.2%) were male. TIMI risk scores at admission were higher in women vs. men (TIMI: median 5 [IQR 3-7] vs. 3 [IQR 2-5], p<0.001). As compared to men, the women were older (mean age 68.2 vs. 60.7 years, p<0.001) and more had diabetes (18.5% vs. 14.1%, p<0.001), hypertension (55% vs. 39.9%, p<0.001) and body weights <67 kg (42.6% vs. 8.9%, p<0.001). Furthermore, less of these women had previous CAD as compared to men (15.3% vs. 19.9%, p<0.001). Women had longer total ischaemic times (ischaemic time >4 h in 45.8% of the female patients vs. 36.5% of the male patients, p<0.001). The need for CPR was not different between women and men (11.5% vs. 10.8%, p=0.41). The Killip class at admission was higher in women vs. men (Killip >I: 28.3% vs. 19.9%, p<0.001). Women also experienced longer door to balloon times (DTB) as compared to men: DTB <60 min: 50.5% vs. 55%, DTB ≥120 min: 13.4% vs. 11.9 % (p=0.003).

Table 1 Baseline characteristics

Characteristic	Women, N=1,920 (28.3%)	Men, N=6,153 (76.2%)	p-value
TIMI score, median [IQR]	5 [IQR 3-7]	3 [IQR 2-5]	<0.001
Mean age, years (SD)	68.2 (13.6)	60.7 (12.5)	<0.001
Age <65 years	15.4	84.6	
Age 65-75 years	27.1	72.9	
Age >75 years	44.3	55.7	
Diabetes	18.5	14.1	<0.001
Hypertension	55	39.9	<0.001
Weight <67 kg	42.6	8.9	<0.001
Previous CAD	15.3	19.9	<0.001
Ischaemic time >4h	45.8	36.5	<0.001
CPR	11.5	10.8	0.41
HR >100bpm	16.8	13.1	<0.001
BP <100mmHg	23.7	18.7	<0.001
Ant. AMI or LBBB	46.3	44.4	0.10
Killip Class			<0.001
I	71.8	80.1	
II	13.3	10.1	
III	4.1	2.9	
IV	10.9	6.8	
Total Ischaemic time			<0.001
<2h	16.2	21.7	
2-4h	38.0	41.9	
4-8h	22.3	18.9	
8-12h	7.6	6.2	
12-24h	9.1	6.8	
>24h	6.8	4.6	
Door-to-balloon time			0.003
DTB <60min	50.5	55	
DTB ≥60 and <120min	36.1	33.1	
DTB ≥120min	13.4	11.9	

CAD= coronary artery disease , h= hour, CPR= cardiopulmonary resuscitation , HR= heart rate , bpm= beats per minute, BP= systolic blood pressure, Ant. AMI= anterior acute myocardial infarction , LBBB= left bundle branch block, DTB= door to balloon time, min= minutes.
Data are presented as percentage of patients unless otherwise specified

Gender and in-hospital mortality

The in-hospital mortality rate for the entire cohort of pPCI treated patients was 6.1 %. Crude mortality data show that mortality was double in invasively-managed Belgian women with STEMI as compared to men (10.1% vs. 4.9%; OR= 2.2 [95% CI 1.82-2.66], p<0.001). In a multivariable regression model, adjusting for TIMI risk score variables and gender, the disparity in the risk of death between men and women persisted (OR=1.47 [95% CI 1.15-1.87], p=0.002). Age ≥65 (OR=2.42 [95% CI 1.92- 3.06], p<0.001), HR >100 bpm at admission (OR=1.60 [95% CI 1.27-2.01], p<0.001), BP at admission <100 mmHg (OR=3.54 [95% CI 2.81-4.46], p<0.001), known CAD (OR=1.28 [95%CI 1.00-1.63], p=0.05) and a Killip class >1 (OR=9.63 [95% CI 7.33 to 12.64], p<0.001) were other independent predictors of in-hospital mortality, while hypertension (OR=1.00 [95% CI 0.80-1.25], p=0.98), diabetes (OR=1.16 [95% CI 0.88-1.51], p=0.29) and an ischaemic time> 4h (OR=1.17 [95% CI 0.95-1.45], p=0.14) were not. Interaction tests for each individual TIMI risk score variable and gender demonstrated that an admission heart rate >100 bpm, an admission systolic blood pressure <100 mmHg and a Killip class >I had more effect on mortality in male than in female patients. **(Table 2)**

Table 2 Odds Ratios for in-hospital mortality among patients undergoing pPCI for STEMI after multivariable adjustment

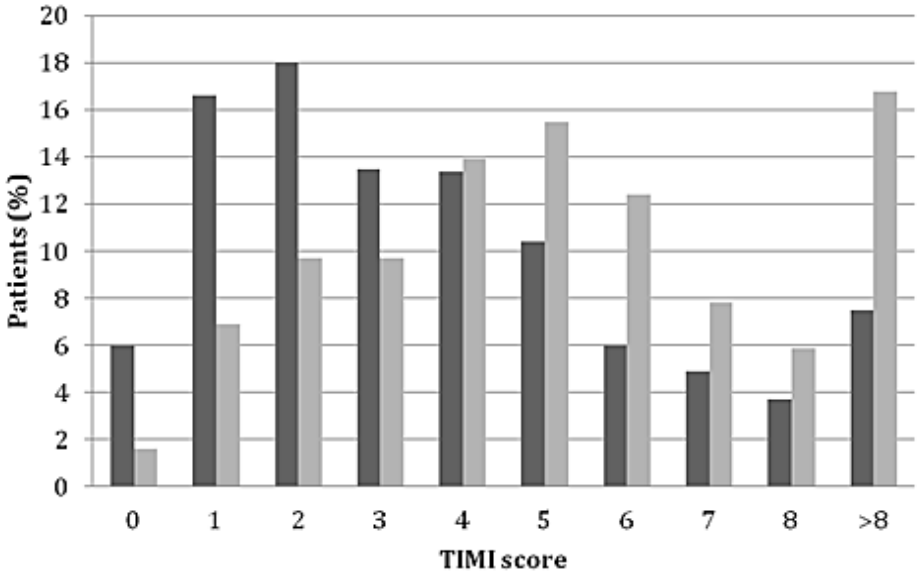
Variable	Women	Men	All	Interaction gender
	OR (95%CI), p-value	OR (95%CI), p-value	OR (95%CI), p-value	p-value
Female gender			1.47 (1.15-1.87), 0.002	
Age ≥65 y	2.32 (1.51-3.58), <0.001	2.46 (1.87-3.25), <0.001	2.42 (1.92-3.06), <0.001	0.72
Weight <67 kg	1.02 (0.72-1.45), 0.90	1.04 (0.69-1.56), 0.85	1.02 (0.78-1.33), 0.89	0.28
CAD	1.10 (0.72-1.68), 0.67	1.35 (1.00-1.82), 0.05	1.28 (1.00-1.63), 0.05	0.37
AHT	1.13 (0.78-1.64), 0.52	0.93 (0.70-1.23), 0.59	1.00 (0.80-1.25), 0.98	0.78
DM	1.10 (0.72-1.67), 0.67	1.24 (0.87-1.75), 0.23	1.16 (0.88-1.51), 0.29	0.90
HR >100 bpm	1.35 (0.93-1.98), 0.12	1.75 (1.31-2.34), <0.001	1.60 (1.27-2.01), <0.001	0.01
BP <100 mmHg	3.36 (2.32-4.88), <0.001	3.66 (2.72-4.92), <0.001	3.54 (2.81-4.46), <0.001	0.04
Ischemic time >4 h	1.01 (0.72-1.43), 0.95	1.28 (0.98-1.68), 0.07	1.17 (0.95-1.45), 0.14	0.79
Killip Class >1	8.14 (5.31-12.5), <0.001	10.70 (7.50-15.25), <0.001	9.63 (7.33-12.64), <0.001	0.04
Ant. AMI or LBBB	1.04 (0.73-1.47), 0.84	1.38 (1.05-1.81), 0.02	1.24 (1.00-1.54), 0.05	0.75

Y=year, kg= kilogram, CAD= coronary artery disease, AHT= arterial hypertension, DM=diabetes mellitus, HR= heart rate, bpm= beats per minute, BP= systolic blood pressure, h= hour, Ant. AMI= anterior myocardial infarction, LBBB= left bundle branch block

Gender and TIMI risk score performance

The median TIMI risk score for all patients treated with pPCI was 4; women had a higher median TIMI risk score than men (TIMI score 5 [IQR 3-7] vs. 3 [IQR 2-5]). More than half of the men, versus only a quarter of the women, had a TIMI risk score below 4 (54.1% vs. 27.6% of the women). Almost 17% of the women had a very high TIMI risk score (>8) as compared to only 7.5% of the men. **(Figure 1)**

Figure 1. TIMI risk score distribution in male and female patients



TIMI= The Thrombolysis In Myocardial Infarction (TIMI) risk score for STEMI

Calculation of TIMI score (0-14): age (2 points: 65-74, 3 points: 75 and older); history of angina, diabetes or hypertension (1 point); admission systolic blood pressure <100 mmHg (3 points); admission heart rate >100 beats/min (2 points); admission Killip class >I (2 points); admission weight <67 kg (1 point); anterior infarction or LBBB (1 point); time to reperfusion therapy > 4 hours (1 point).

Dark grey bars = men

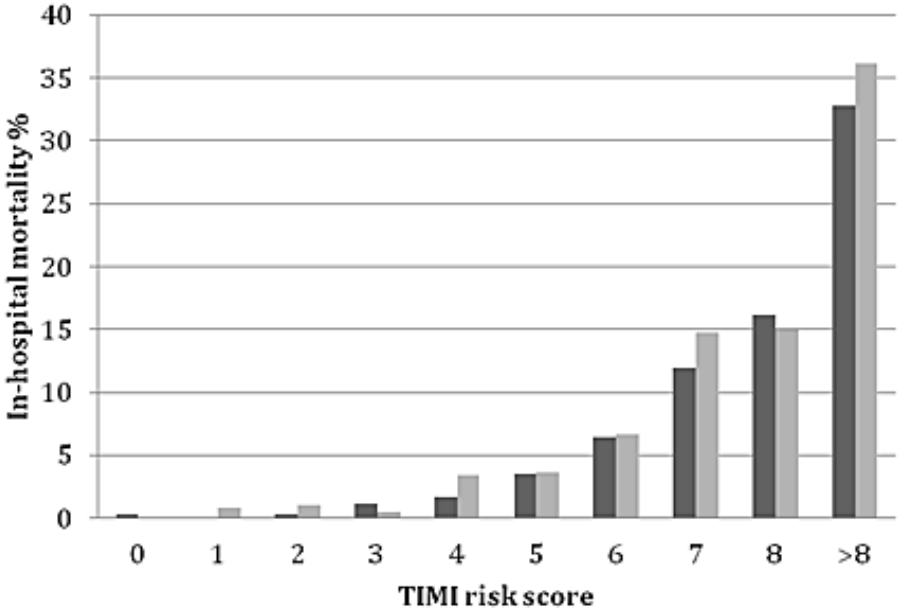
Light grey bars = women

The in-hospital mortality rate increased with increasing TIMI risk scores in both women and men. **(Figure 2)** The mortality rate difference between men and women was the highest for low TIMI risk scores (TIMI score ≤4) and in patients with TIMI scores >8. The mortality rate in women was higher for almost all TIMI risk scores.

The TIMI risk score provided a good prognostic discrimination of mortality among both women (*c-statistic* = 0.84 [95% CI 0.809-0.866]) and men (*c*-statistic = 0.89 [95% CI 0.873-0.907]). TIMI risk score calibration was good in both genders with a

Hosmer-Lemeshow goodness-of-fit of respectively p= 0.53 in women and p= 0.13 in men. When comparing mortality rates for TIMI risk scores between women and men, with an interaction term for TIMI score and gender, we found that mortality prediction for TIMI score was better in men compared to women (p=0.02 for TIMI score x gender interaction).

Figure 2. In-hospital mortality by TIMI risk score in male and female patients



TIMI= The Thrombolysis In Myocardial Infarction (TIMI) risk score for STEMI

Calculation of TIMI score (0-14): age (2 points: 65-74, 3 points: 75 and older); history of angina, diabetes or hypertension (1 point); admission systolic blood pressure <100 mmHg (3 points); admission heart rate >100 beats/min (2 points); admission Killip class >I (2 points); admission weight <67 kg (1 point); anterior infarction or LBBB (1 point); time to reperfusion therapy > 4 hours (1 point).

Dark grey bars = men

Light grey bars = women

Gender and age

The <65 years-of-age group (n= 4,605) comprised 708 (18.3%) female patients, as compared to 1,212 (34.9%) female patients in the ≥65 years-of-age group (n= 3,468). Adjusting for TIMI risk score variables (except age ≥65 year) and gender, demonstrated a sustained association between female gender and mortality in both age groups (<65 years-of-age: OR =1.71 [95% CI 1.05-2.77], p=0.03; ≥ 65 years-of-age: OR=1.39 [95% CI 1.05-1.83], p=0.02). After further adjustment for age in these age groups female gender remained a predictor for mortality in the <65 years-of-age group (<65 years: OR=1.73 [95% CI 1.07-2.82], p=0.03) but not in the ≥ 65 years-of-age group (≥ 65 years: OR=1.27 [95% CI 0.96-1.68], p=0.09).

Gender and body weight

Overall, 60% of the patients with body weights <67 kg and 16.4% of the patients with body weights ≥67 kg were women. The adjusted mortality difference between women and men remained significant in the subgroup with body weights ≥67 kg (OR=1.55 [95% CI 1.16-2.06], p=0.003) but not in the subgroup with body weights <67 kg (OR=1.29 [95% CI 0.82-2.01], p=0.27).

DISCUSSION

There is on-going debate whether gender itself is an independent predictor of in-hospital mortality in STEMI patients undergoing pPCI and the relationship between the predictive performance of the TIMI risk score for STEMI and gender has not been evaluated in this setting.

We demonstrated that female patients, from a nationally representative (Belgium) community-based registry of 8,073 consecutive STEMI patients reperfused with pPCI, had a higher in-hospital mortality rate than men. Even after adjusting for the baseline risk variables of the TIMI risk score for STEMI, the risk of dying remained almost 50% higher in women. We showed that the TIMI risk score for STEMI, which weighs these different risk factors, demonstrated a good prognostic discrimination and calibration in both men and women treated with pPCI, but the mortality prediction for TIMI risk score was better in men.

Several factors may contribute to the worse outcome of women experiencing a STEMI: first women are older and have more co-morbidities, including diabetes and hypertension and this has been observed consistently in different trials and registries. [56] Women seek treatment with later stage STEMI [134] and suffer longer door-to-balloon/-needle times [135], resulting in longer ischaemic times and more myocardium at risk. [136] Women generally have a lower body weight and hence a lower BSA, which is not only a risk factor for bleeding complications after PCI [137] but is also associated with a higher mortality. This is also known as the 'obesity paradox'. [138] Less frequent use of evidence-based management therapies, including invasive management, more extensive CAD and smaller coronary arteries, or a higher risk of peri-procedural complications may also contribute to their poorer outcome. [83, 135] In general, the question remains whether gender-related differences in outcome would persist if both men and women presenting with STEMI received the same evidence-based management, including pPCI as the current standard. Several investigators have addressed this question during the last two decades. However, sample sizes were often small, and these studies do not always reflect the current standards of stenting and adjunctive antiplatelet therapy.

We demonstrated that an age ≥ 65 years is an important predictor of mortality. A significant gender related mortality rate difference was observed in the <65 years-of-age group as well as in the ≥ 65 years-of-age group. After further adjustment for

age in these age groups, the mortality gap persisted in the <65 years-of-age suggesting that age alone does not fully explain the difference in outcomes between women and men, especially not in the patient group <65 years-of-age. Moreover the mortality gap in this group warrants close monitoring of these women in the acute phase.

Although diabetes and hypertension are two of the main risk factors for developing an ACS these conditions were no independent predictors of in-hospital mortality, not for the entire cohort or separately between women and men. The fact that diabetes was not associated with increased in-hospital mortality might be explained by a greater risk reduction with pPCI in diabetic patients as compared to non-diabetic patients [139] and is consistent with the findings of Meisinger *et al.* who showed only an association with long-term mortality, particularly in women. [140] There appeared to be no clear association between a history of hypertension and in-hospital mortality among STEMI patients. We presume that many patients with known hypertension already receive adequate treatment, including cardio-protective medication (ACE-inhibitors, statins, aspirin) while patients with unknown hypertension were classified in the registry as having no history of hypertension. [141, 142] Although more prevalent among women, diabetes and hypertension also did not account for the higher in-hospital mortality among women in our population.

We confirmed that women sought treatment with later stage STEMI as compared to men and experienced longer 'door to-balloon-times', which resulted in longer total ischaemic times. One of the reasons behind this later presentation is the lack of typical chest pain, especially in younger women suffering a myocardial infarction, as was recently demonstrated in the National Registry of Myocardial Infarction. [25] Another problem is the lack of awareness at the physician level: doctors can be misled by this atypical presentation and/or underestimate the possibility of an acute coronary syndrome, especially in young women. This may lead to delays in diagnosis and treatment as well as suboptimal treatment. Other reasons for the later stage presentation and longer door-to-balloon time remain unclear but are one of the reasons behind awareness campaigns addressing females around the world. After multivariable analysis, an ischaemic time >4 hours was not an independent predictor of in-hospital mortality, however an ischaemic time >4 hours may influence other TIMI variables such as Killip class and haemodynamic compromise.

Finally female Belgian STEMI patients more frequently had a body weight <67 kg and were sicker on admission, as reflected by their higher Killip class and prevalence of admission hypotension and tachycardia; correction for all of these differences, all included in the TIMI risk score, also failed to explain the differences in in-hospital mortality rates between men and women. However interaction tests for each predictor with gender demonstrated that a HR >100bpm, a BP <100mmHg and a Killip class >1 had more effect on mortality in men than in women.

After correction for all of the TIMI risk score variables, the mortality rate remained significantly higher in women as compared to men. On the other hand, our analysis showed that the TIMI risk score provides good predictive discrimination in both genders in a community-based population treated with primary angioplasty. The mortality prediction for TIMI risk score was slightly better in men. However, as pointed out by Vergouwe *et al*., comparing *c*-statistics between groups may be biased by the variation in patients risk profiles in these groups; the tighter interquartile range in the TIMI risk score distribution in men compared to women, seems rather inconsistent with this explanation. [143] There seemed to be a stronger impact of admission hypotension, admission tachycardia and a Killip class >I on mortality in men. **(Table 2)**

Despite the fact that the TIMI risk score was developed and validated in a randomised controlled trial of fibrinolysis, it is still a valuable tool to predict early mortality in currently treated male and female STEMI patients. It remains unclear whether the worse baseline haemodynamic profile in women (HR>100 bpm, BP<100mmHg and KILLIP >1), good for 7 points in the TIMI risk score, could be improved by reducing ischaemic times, and what impact this would have on gender differences in outcome after STEMI.

Strengths and limitations:

This relatively large registry offers a "real life" view of the men and women treated with pPCI. Several limitations need to be considered when interpreting the results. First, the data were examined using risk adjustment models; however, we cannot exclude other confounding factors that were not registered, such as renal function, lipid status, smoking habits, coronary anatomy, TIMI flow rates, success of PCI, peri-procedural complications, treatment (anti-coagulation, antiplatelet agents, β-blockers, ACE-inhibitors, statins) or other unrecognised differences. Second, the

characterisation of some continuous important characteristics (body weight < or ≥ 67 kg , ischaemic time, blood pressure and heart rate) into dichotomies was inherent to the registry and may have introduced residual confounding and hence biased our results to some extent. Third, we only collected data on in-hospital mortality rates; hence, it remains unclear whether our results can or cannot be extrapolated to long-term outcomes. Furthermore, a referral bias for invasive evaluation is not excluded; secondary care centres that do not routinely apply pPCI for STEMI may refer only the most severely ill patients for urgent PCI. We found no significant differences in the baseline characteristics in female patients admitted in PCI vs. non-PCI hospitals to support this possibility. Finally, underreporting cannot be excluded despite the fact that the registry design called for consecutive enrolment of all STEMI patients.

CONCLUSIONS

Analysis of the Belgian STEMI registry demonstrates that almost a quarter of all patients treated with pPCI for ST-segment elevation myocardial infarction comprised women. In-hospital mortality rates of PCI-treated female STEMI patients were higher as compared to their male counterparts, even after adjustment for TIMI risk score variables. The TIMI score for STEMI proved to have a good predictive performance in both women and men in predicting in-hospital mortality rates in currently pPCI treated patients, however this predictive performance was slightly better in men than in women. The TIMI risk score remains a reliable and simple bedside score suitable for early risk stratification in women as well as in men. Reducing the time delays remains one of the most important modifiable factors that could improve TIMI risk scores and outcomes in women. This stresses the need for continuous awareness campaigns, especially in younger women, but also in the physicians confronted with these patients.

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Chapter 2

Renal dysfunction in STEMI-patients undergoing primary angioplasty: higher prevalence but equal prognostic impact in female patients; an observational cohort study from the Belgian STEMI registry

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ABSTRACT

Background: Mortality in female patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary angioplasty (pPCI) is higher than in men. We examined gender differences in the prevalence and prognostic performance of renal dysfunction at admission in this setting.

Methods: A multicentre retrospective sub-analysis of the Belgian STEMI-registry identified 1,638 patients (20.6% women, 79.4% men) treated with pPCI in 8 tertiary care hospitals (January 2007-February 2011). The estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI equation. Main outcome measure was in-hospital mortality.

Results: More women than men suffered from renal dysfunction at admission (42.3% vs. 25.3%, p<0.001). Mortality in women was doubled as compared to men (9.5 vs. 4.7%, OR= 2.12 [95% CI 1.36-3.32], p<0.001]). In-hospital mortality for men and women with vs. without renal dysfunction was much higher (10.7 and 15.3 vs. 2.3 and 2.4%, p<0.001). In a multivariable regression analysis, adjusting for age, gender, peripheral artery disease (PAD), coronary artery disease (CAD), hypertension, diabetes and low body weight (<67 kg), female gender was associated with renal dysfunction at admission (OR=1.65 [95% CI 1.20-2.25], p=0.002). In a multivariable model including TIMI risk score and renal dysfunction, renal dysfunction was an independent predictor of in-hospital mortality in both men (OR = 2.39 [95% CI 1.27-4.51], p=0.007) and women (OR = 4.03 [95% CI 1.26-12.92], p=0.02), with a comparable impact for men and women (p for interaction=0.69).

Conclusions: Female gender was independently associated with renal dysfunction at admission in pPCI treated patients. Renal dysfunction was equally associated with higher in-hospital mortality in both men and women.

Keywords:

ST-segment elevation myocardial infarction (STEMI), estimated glomerular filtration rate (eGFR), CKD-EPI, renal dysfunction, gender, in-hospital mortality, primary angioplasty

BACKGROUND:

It has been demonstrated that women with STEMI undergoing primary PCI (pPCI) have higher odds for in-hospital mortality than men. Some authors demonstrated that this difference is likely explained by their older age and baseline comorbidities (especially hypertension and diabetes) [117, 118, 122, 144, 145], while other authors demonstrated a sustained mortality difference even after adjustment for appropriate confounders. [111-113] Chronic kidney disease, even mild, is associated with increased cardiovascular mortality. [146] More recently it was demonstrated that renal dysfunction is independently associated with in-hospital mortality in STEMI patients treated with pPCI. [120, 121, 147]

Data on gender differences in prevalence of renal dysfunction at admission in pPCI treated STEMI patients are scarce and have seldom been accounted for when evaluating gender differences in outcome, furthermore different definitions (serum creatinine levels vs. estimated Glomerular Filtration Rate [eGFR] values) and different methods of estimating creatinine clearance have been applied. [112, 118, 122, 123]

The GFR cannot be measured easily in clinical practice, instead it is estimated (eGFR) from equations, using variables such as serum creatinine level, age, body weight, race and sex. The most recent equation, the CKD-EPI equation (Chronic Kidney Disease Epidemiology Collaboration), published in 2009, is more precise and accurate than other equations such as the Cockroft-Gault, the MDRD (Modification of Diet in Renal Disease) and the re-expressed MDRD equation, especially at GFRs > 60 mL/min/1.73m^2. [124, 148] The CKD-EPI equation usually yields higher values for eGFR than the MDRD study equation, probably because it was developed in a more diverse study population, including participants with and without CKD. Therefore it is assumed that the CKD-EPI equation leads to smaller average bias in clinical populations with a wide range of GFRs, such as the STEMI population. [149] In a recent analysis of the PLATO trial, including 18,624 patients with an acute coronary syndrome, the CKD-EPI formula exhibited the highest prognostic value and produced a clinical relevant cut-off of 60 mL/min/1.73m^2. [150]

The Thrombolysis In Myocardial Infarction (TIMI) risk score for STEMI is a simple arithmetic score that predicts short-term mortality based on age and clinical data on admission. [119] This score was initially developed and validated in a randomised controlled trial of patients treated with fibrinolysis but proved to be

useful in patients treated with primary PCI in an observational registry (*c* -statistic= 0.80 for patients treated with primary PCI in the NRMI III registry [N=15,348]). [133]

Accordingly, we evaluated differences in prevalence of renal dysfunction at admission, defined as an eGFR<60mL/min/1.73m^2, in men and women presenting with STEMI and treated with pPCI, using the CKD-EPI equation for assessment of eGFR. We assessed the prognostic impact of renal dysfunction at admission, on top of the TIMI risk score, on in-hospital mortality in men and women and finally we evaluated whether there was an interaction between female gender and renal dysfunction regarding in-hospital mortality.

As far as we are aware this is the first study that investigates gender differences in prevalence and prognostic value of renal dysfunction, assessed by the CKD-EPI equation, in a subgroup of currently pPCI-treated STEMI patients included in a national STEMI-registry.

SUBJECTS AND METHODS

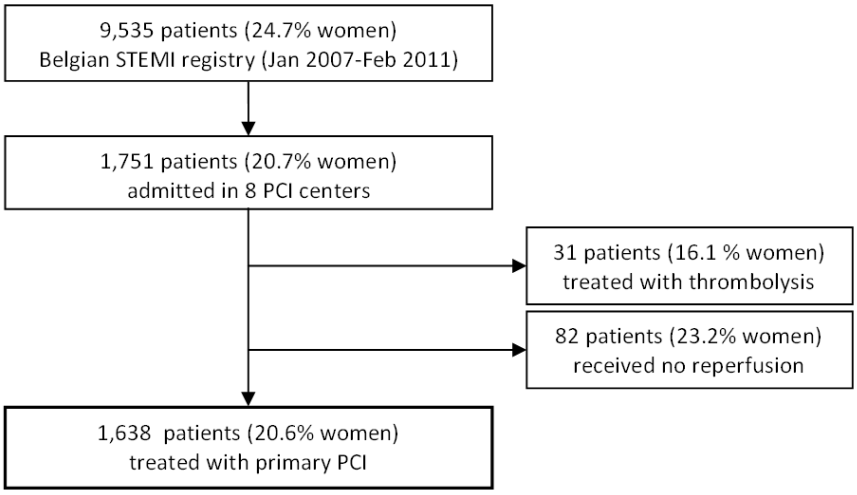
Study population:

The Belgian STEMI registry is a prospective observational registry of Belgian STEMI patients from 72 Belgian hospitals that contains demographics, clinical characteristics at admission, practice patterns and in-hospital outcomes. The registry is an initiative from the Belgian Working Group on Acute Cardiology (BIWAC) and is supported by the Belgian Government of Social Affairs and Public Health and the Belgian College of Cardiologists. Belgium constitutes a catchment area of 11.000.000 persons. All Belgian cardiologists working in hospitals with acute care facilities were required to prospectively collect data on all admitted STEMI patients (symptoms suspicious of acute coronary syndrome, combined with ST-segment elevation or new LBBB on ECG) starting from January 2007.

During the period January 2007 to February 2011, a total of 9,535 (24.7% women) patients from 72 hospitals (25 with PCI facilities and 47 without PCI facilities) were prospectively included in the STEMI registry. We retrospectively collected admission values of serum creatinine of patients (N= 1,751; 20.7% women) admitted in the eight tertiary care centres that participated in this sub-analysis. Of these 1,638 (20.6% women) were treated with primary PCI <24 hours after hospital admission and included in the analysis. **(Figure 1)**

A yearly audit, conducted by an external commission, of 10% of all patient files was performed to verify the validity of the data; the evaluation of these files demonstrated a 96% concordance rate between source documents and case report forms. Data were electronically collected via a protected eCRF. The database is managed by an independent electronic data-capture provider (Lambda Plus, SA, Gembloux, Belgium).

Figure 1 Study population, undergoing primary PCI in 8 (out of 25) selected centres



TIMI risk score

The TIMI risk score was automatically calculated from 8 differentially weighted clinical indicators ascertained upon admission. The TIMI score ranges from 0 to 14 and is calculated as follows: age (2 points: 65-74, 3 points: 75 and older); history of angina, diabetes or hypertension (1 point); admission systolic blood pressure (BP) <100 mmHg (3 points); admission heart rate (HR) >100 bpm (2 points); admission Killip class >I (2 points); admission weight <67 kg (1 point); anterior infarction or LBBB (1 point); and time to reperfusion therapy > 4hours (1 point). [119]

GFR measurement

We defined renal dysfunction as an eGFR< 60 mL/min/ 1.73m^2, corresponding to National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI) stages 3 to 5 of chronic kidney disease. The eGFR was calculated using the CKD-EPI equation based on the admission value of serum creatinine [124] as follows:

eGFR = 141 x min (Scr/k, 1)^a x max (Scr/k, 1)$^{-1.209}$ x 0.993^{age} [x 1.018 if female] [x 1.159 if black], where Scr is serum creatinine, k is 0.7 for females and 0.9 for males, a is -0.329

for females and -0.411 for males. The eGFR could not be calculated in 11.9% of the cases, due to missing values. We found no differences in proportions of women or baseline characteristics between patients with and without missing values, except for the incidence of Cardio Pulmonary Resuscitation (CPR) (19.5% vs. 10.1%, p<0.001) and in-hospital mortality (9.7 vs. 5.1%, p=0.009).

Outcome data:

The primary endpoint existed of in-hospital mortality

Statistical Analysis:

We compared the baseline characteristics, including renal dysfunction at admission, and in-hospital outcomes of women with those of men. Distributions of categorical variables were compared by using the Fisher exact test. Continuous variables were evaluated for normality. The Student's *t* test was used for continuous variables with a normal distribution (presented as the mean ± SD), and the Mann Whitney-U test was used for continuous variables (presented as the median and interquartile range [IQR]) without a normal distribution. Multivariable logistic-regression analysis was used to determine the independent predictors of renal dysfunction at admission including following covariates in the model: gender, age, bodyweight <67kg, history of coronary artery disease (CAD), history of peripheral artery disease (PAD), hypertension and diabetes. Separate logistic regression analyses were performed regarding in-hospital mortality for each gender, including TIMI risk score as a continuous and renal dysfunction as a dichotomous variable in the model. Multivariable logistic regression analysis was also used to assess a possible interaction between gender and renal dysfunction regarding in-hospital mortality adding gender as dichotomous variable and the product of gender and renal dysfunction as an interaction term to the previous model. All multivariable analyses were based on complete patient records.

Adjusted Odds Ratios (OR) with 95% confidence intervals (CI) are reported. Statistical significance was defined as p<0.05 or 95% confidence intervals (CI) for OR

that did not include 1.0. All statistical analyses were performed using the SPSS 19 statistical software.

Ethics approval:

This study was approved by the central ethical committee of the Ghent University Hospital (2011/455). Informed consent was obtained from all patients or their legal representatives.

RESULTS

Baseline characteristics:

During the period between January 2007 and February 2011, 1,638 patients were treated with primary PCI in eight participating centres. Of them 338 (20.6 %) were female and 1,300 (79,4%) were male. Baseline patient characteristics are shown in **Table 1**. As compared to men, women were on average 7 years older and more had diabetes, hypertension, and a body weight <67 kg. Furthermore, less women had previous CAD as compared to men. The history of PAD between women and men was not different. Women had longer total ischaemic times. The need for CPR was not different between women and men. The Killip class and TIMI risk score at admission were higher in women vs. men. Door to balloon times (DTB) were comparable among women and men.

Table 1 Baseline characteristics (N= 1,638)

Characteristic	Women (N=338, 20.6%)	Men (N=1,300, 79.4%)	p-value
Age, mean (SD), y	68.8 (12.7)	61.6 (12.0)	<0.001
Diabetes	21.3	13.8	<0.001
Hypertension	54.7	41.4	<0.001
Weight <67kg	42.3	9.8	<0.001
Previous CAD	16.9	22.4	0.03
Previous PAD	8.6	8.4	0.91
Ischemic Time >4h	47	35	<0.001
Door to Balloon >120min.	14.2	11.8	0.59
CPR	11.2	11.2	1.00
HR >100bpm	17.2	11.5	<0.001
BP <100mmHG	23.7	15.3	<0.001
Anterior AMI	49.4	45.1	0.16
Killip >I	26.6	14.3	<0.001
TIMI score, med. [IQR]	5 [3.0-7.3]	3 [2.0-5.0]	<0.001
Creatinine (mg/dL) med. [IQR]	0.90 [0.75-1.10]	1.00 [0.84-1.17]	<0.001
eGFR <60mL/min/1.73m^2	42.3	25.3	<0.001

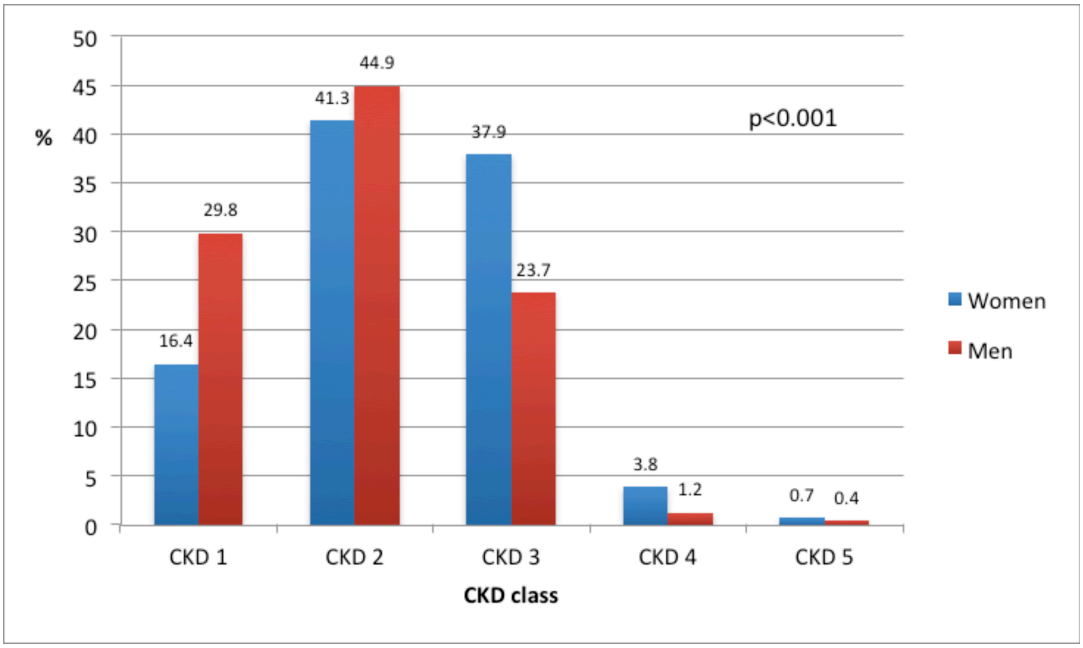
Y= years, kg= kilogram, CAD= coronary artery disease, PAD= peripheral artery disease, Ischaemic time= symptom to balloon time, CPR= cardiopulmonary resuscitation, HR= heart rate, bpm= beats per minute, BP= systolic blood pressure, AMI= acute myocardial infarction, eGFR= estimated glomerular filtration rate
Data are presented as percentage of patients unless otherwise specified

Gender and renal dysfunction

Median creatinine values were higher in men vs. women (median creatinine in men 1.0 [0.84-1.17] vs. 0.9 [0.75-1.10] in women, p<0.001). Renal dysfunction, defined as an eGFR below 60mL/min/1.73m^2 or a Chronic Kidney Disease (CKD) stage 3, 4 or 5 was more frequently observed in female patients (42.4% vs. 25.3%, p<0.001). **(Figure 2)** In a multivariable regression analysis, including age (/year), hypertension, diabetes, CAD or PAD and a body weight below 67 kg, female gender remained independently associated with renal dysfunction (OR=1.65 [95%CI 1.20-2.25], p=0.002). Age and PAD were two other powerful determinants of renal impairment (Age: OR =1.07 [95% CI 1.05-1.08], p<0.001, PAD: OR=1.89 [95% CI 1.26-2.84],

p=0.002). Coronary artery disease was borderline significant as a determinant of renal dysfunction (OR=1.35 [95% CI 1.00-1.82], p=0.05). **(Table 2)**

Figure 2 Chronic Kidney Disease (CKD) stage at admission according to gender



CKD 1: Chronic Kidney disease class 1: eGFR ≥ 90 mL/min/1.73m^2

CKD 2: Chronic Kidney disease class 2: eGFR ≥ 60 - < 90 mL/min/1.73m^2

CKD 3: Chronic Kidney disease class 3: eGFR ≥ 30 - < 60 mL/min/1.73m^2

CKD 4: Chronic Kidney disease class 4: eGFR ≥ 15 - < 30 mL/min/1.73m^2

CKD 5: Chronic Kidney disease class 5: eGFR < 15 mL/min/1.73m^2

Table 2 Determinants of admission renal dysfunction and Odds Ratios after multivariable adjustment

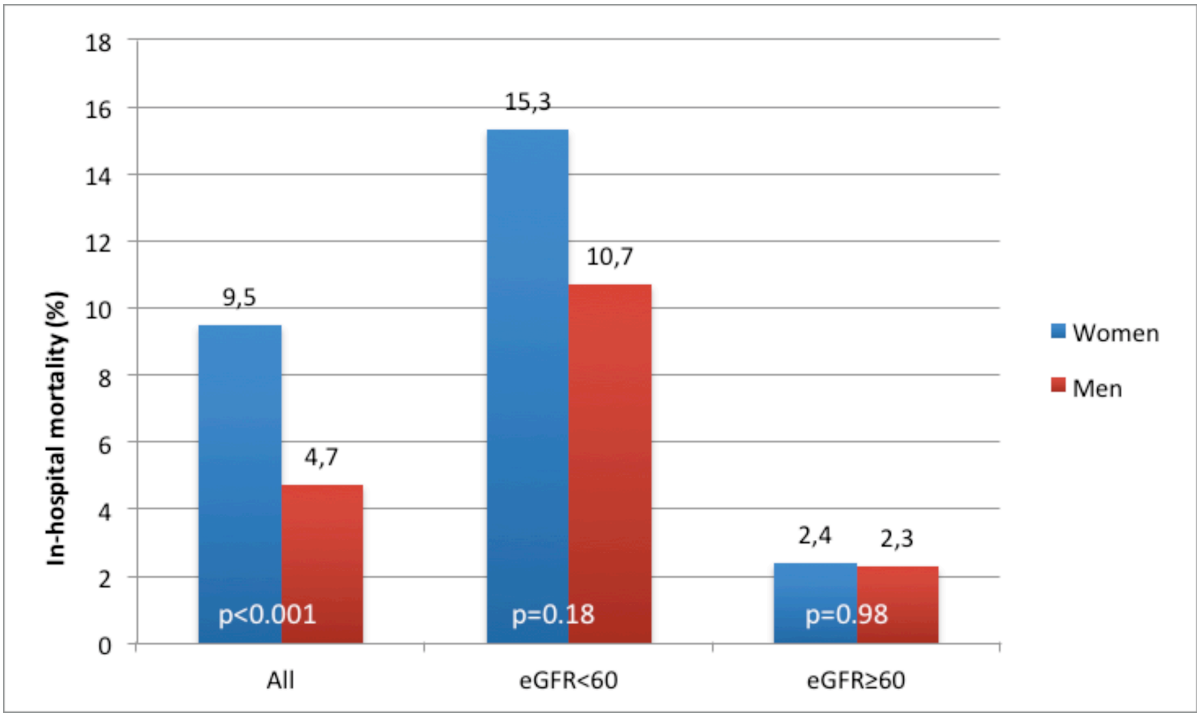
Variable	OR	95%CI	p-value
Female gender	1.65	1.20-2.25	0.002
Age (/y)	1.07	1.05-1.08	<0.001
Weight <67kg	0.87	0.61-1.23	0.87
CAD	1.35	1.00-1.82	0.05
PAD	1.89	1.26-2.84	0.002
AHT	1.10	0.84-1.43	0.49
DM	0.97	0.69-1.36	0.87

Y= year, kg= kilogram, CAD=coronary artery disease, PAD=peripheral artery disease, AHT=arterial hypertension, DM=diabetes

Gender, baseline renal dysfunction and in-hospital mortality

The in-hospital mortality rate for the entire cohort of pPCI treated patients was 5.7 %. Mortality in women was doubled as compared to men (9.5 vs. 4.7%, OR= 2.12 [95% CI 1.36-3.32], p<0.001). Mortality in patients with renal dysfunction at the time of hospital admission was much higher compared to those without (12.0% vs. 2.3%, p<0.001). In-hospital mortality was comparable in men and women without renal impairment: 2.3% vs. 2.4%, while there was a non-significant trend for higher mortality in women with renal dysfunction compared to men with renal dysfunction (15.3% vs. 10.7%, p=0.18). **(Figure 3)**

Figure 3 In-hospital mortality according to gender and renal function



TIMI risk score and additive prognostic performance of baseline renal dysfunction in men and women

In a multivariable regression analysis including gender, TIMI risk score and renal dysfunction, both TIMI risk score (OR=1.47 [95% CI 1.35-1.60]) and renal dysfunction (OR 2.71 [95% CI 1.56-4.69]) were strong predictors of in-hospital mortality; there was a trend towards higher mortality in women (OR 1.45 [95% CI 0.8-2.63]).

Adding renal dysfunction to the TIMI risk score in men and women separately in a multivariable logistic regression model demonstrated that renal dysfunction was an independent predictor of in-hospital mortality in both men (OR=2.39 [95% CI 1.27-4.51], p=0.007) and women (OR=4.03 [95% CI 1.26-12.92], p=0.02), the interaction test demonstrated that this impact was comparable for men and women (p=0.69).

DISCUSSION

In a sub-analysis of the Belgian STEMI registry, including 20.3 % of Belgian STEMI patients undergoing pPCI for STEMI, we found that renal dysfunction at the time of hospital admission (eGFR<60mL/min per 1.73m^2 or CKD class 3 or higher), assessed by the CKD-EPI formula, was a common finding and that more women (42.3%) than men (25.3%) suffered from this condition. As expected, a CKD class 3 or higher on admission was associated with in-hospital mortality, and this independently of the TIMI risk score. Although there was a trend towards higher mortality for women with renal dysfunction compared to men with this condition, we could not demonstrate a gender difference in the impact of renal dysfunction on in-hospital mortality.

Despite the fact that male STEMI patients had a higher serum creatinine concentration at admission, the prevalence of renal dysfunction defined by an eGFR <60mL/min per 1.73m^2 and assessed with the CKD-EPI formula was almost doubled in women as compared to men, even after correction for observed differences in age and risk profile between men and women. The higher serum creatinine concentrations in men can easily be explained by the larger muscle mass, resulting in greater creatinine generation, and a higher serum creatinine concentration for a given GFR. This illustrates that serum creatinine values should not be used to evaluate gender differences in the impact of renal function on outcome. It is not completely clear why the incidence of renal dysfunction is higher in women, we cannot exclude that there are unknown confounders that may explain this difference.

Many authors have demonstrated that women with STEMI have a higher risk of in-hospital mortality and some, but not all, could explain this higher mortality based on age and the presence of more comorbidities, especially hypertension and diabetes. [117, 118, 122, 144, 145] Lawesson et al. recently demonstrated in a small single centre study, including 274 STEMI patients undergoing pPCI, that female gender was a strong and independent predictor of renal dysfunction and that renal dysfunction had a possibly higher impact on 1-year mortality in women (p for interaction= 0.08). [123] We confirmed that renal dysfunction was more prevalent in pPCI treated women but we did not find a gender-impact on in-hospital mortality. Given the fact that the prevalence of renal dysfunction was independently related to female gender and that there was no difference in mortality between women and men with preserved renal

function we speculate that renal dysfunction could be an important reason why women with STEMI die more than men.

The presented data do not reveal why renal dysfunction was associated with worse outcome. There are numerous data that demonstrate that chronic kidney disease serves as an important modifier for outcome. Renal dysfunction may serve as a surrogate marker for general health and for unknown risk factors that may explain the worse outcome. Also renal dysfunction may be associated with complications, of which development of (contrast induced) acute kidney injury (AKI) and bleeding are the most likely to occur.[151] By implementing routine calculation of eGFR, based on the CKD-EPI formula, high risk patients can be identified, and strategies for prevention of contrast induced AKI (bicarbonate administration, optimization of hemodynamic status and discontinuation of nephrotoxic drugs) [152] and other complications (e.g. bleeding) can be initiated. More over, evidence based therapies such as β-blockers, ACE-inhibitors and statins should not be withheld in this subgroup. [153]

Today it is not clear whether the prognostic performance of the currently most used simple and bedside risk scores could improve by adding eGFR to the model. Kidney function, represented by various cut-offs for serum creatinine but not by eGFR, is already incorporated in the GRACE risk score. [154] Kidney function is not incorporated at all in the TIMI risk score for STEMI and this might be one of the reasons why the GRACE risk score performed better in STEMI patients in a recent meta-analysis of 15 derivation studies and 17 validation studies. [155] Given our finding that serum creatinine underestimates renal dysfunction, especially in women, future risk stratification should preferably use the eGFR based kidney function estimates such as the CKD-EPI equation.

Strenghts and limitations:

This study is unique as it represents the first dataset that links gender, renal dysfunction, assessed by the CKD-EPI equation, and outcomes in a subgroup of PCI-treated STEMI patients included in the Belgian STEMI registry. As 71.2% of this Belgian STEMI cohort presented with an eGFR>60mL/min/1.73 m^2, the use of the CKD-EPI equation was appropriate.

The study has some limitations. First, we only studied patients who underwent pPCI in a subgroup of 8 tertiary care centres that participated in the Belgian STEMI registry; since it has been demonstrated that patients with renal failure have less access to invasive therapy, a selection bias is not excluded. [156] Second, it is uncertain whether renal dysfunction at the time of hospital admission represents a steady state condition of chronic kidney disease or whether there was also a component of AKI. Third, we only collected data on in-hospital mortality rates; hence, it remains unclear whether our results can be extrapolated to long-term outcomes. Finally, it is not clear how missing values could have influenced our results, however we found no differences in proportions of women and baseline characteristics, except for a higher incidence of CPR in the group with missing values. This and the higher in-hospital mortality in this group suggest that these patients were more severely ill and probably also had renal dysfunction at the time of hospital admission, which would have reinforced our findings.

CONCLUSIONS:

Renal dysfunction, defined as an eGFR < 60mL/kg per 1.73m^2 was common in a subgroup of patients undergoing primary PCI for STEMI and female gender was independently associated with this condition. Renal dysfunction, independent of the TIMI risk score, was associated with higher in-hospital mortality rates in both men and women. There was no gender difference in the prognostic impact of renal dysfunction regarding in-hospital mortality. Glomerular filtration rates should routinely be assessed at baseline in these patients and these and not serum creatinine values should be accounted for when evaluating gender differences in outcome after STEMI. Whether eGFR, assessed by the CKD-EPI equation, could improve the prognostic performance of currently used bedside risk stratification models remains to be elucidated.

Competing interests

The authors declare that there are no disclosures related to the content of this article

Authors contributions:

SG designed the study. All authors but DDB collected data. SG and DDB performed data-analysis. The article was written by SG, MC and DDB and critically reviewed by all other authors.

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Chapter 3

Gender differences in the management and outcome of atrial fibrillation complicating acute heart failure

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ABSTRACT

Background: Little is known about sex differences in the prevalence, treatment, and outcome of atrial fibrillation complicating acute heart failure.

Methods and results: Among 957 patients (429 women, 528 men), included in the BIO-HF registry, 45.2% (N=194) of the women and 45.1% (N=238) of the men were admitted with atrial fibrillation. The primary endpoint was a composite of 1-year all-cause mortality and hospitalisation for heart failure. Adjusted 1-year mortality and hospitalisation rates were similar between sexes (women: 38.5%, men 36.0%; OR for female gender=1.1 [95% CI 0.65-1.86], *p*= 0.71). A significant interaction between female sex and age (*p*= 0.002) was observed; with worse prognosis for women <75years (OR=7.17 [95% CI 1.79-28.66], p=0.005) compared with men <75years. No sex differences in in-hospital treatment, restoration of sinus rhythm (16.5% in women vs. 14.2% in men, *p*= 0.58) or in-hospital mortality (5.7% in women vs. 6.7% in men, p=0.69) were observed.

Conclusions: Among patients hospitalised with acute heart failure, no sex differences in the prevalence and management of atrial fibrillation were observed. In-hospital mortality and the composite of 1-year mortality and re-hospitalisation were not different between sexes, but a significant sex-age interaction was observed, with worse outcome in women <75 years versus men <75 years-of-age.

Key words: acute heart failure, atrial fibrillation, gender.

INTRODUCTION

Acute heart failure (AHF) is one of the leading causes for urgent hospital admission in the adult population. In general, women comprise almost half of the patients hospitalised for AHF in the Western world. On average they are older and have other co-morbidities than men. Heart failure (HF) with preserved ejection fraction due to diastolic dysfunction predominates in women, whereas coronary artery disease (CAD) and ischaemic cardiomyopathy are more prevalent in men with HF. Despite sex differences in comorbidities and aetiology there seems to be no sex gap in both short- and long-term outcomes in large patient series. [32, 33, 35, 157]

Atrial fibrillation (AF) is more prevalent in patients with HF [125], furthermore AF and HF may interact: a rapid ventricular rate can trigger AHF, and HF increases atrial stretch which can make AF more resistant to therapy. Retrospective analysis of two randomised controlled trials suggested that patients with both HF and AF have an increased risk for HF exacerbation, hospitalisation for HF, and death. [101, 158] The risk for adverse outcome HF patients with AF has been demonstrated in those with reduced ejection fraction as well as those with preserved ejection fraction. [159] Overall prognosis seems to be worse in patients who develop HF first as opposed to patients who develop HF after AF. [160] Little is known about sex differences in AF on admission among patients hospitalised for AHF. In the Euro HF Survey II, the ALARM-HF survey and a registry by Opasich, AF on admission was more frequently seen in women (41.2%, 49 and 49.2%) than in men (37%, 42 and 40.6%) while in the larger ADHERE and OPTIMIZE-HF registries more men than women had a history of atrial arrhythmia (30 and 30.3 % in women vs. 31, 31.2 % in men). [31-33, 35, 37, 37] The Euro Heart Survey on AF demonstrated that women with AF had more comorbidities, more HF with preserved systolic function and received less rhythm control than men but that long-term outcomes were similar. [41] Women >65 years-of-age with AF have an increased risk of stroke compared with men, as incorporated in the CHA_2DS_2VASc score. [161, 162]

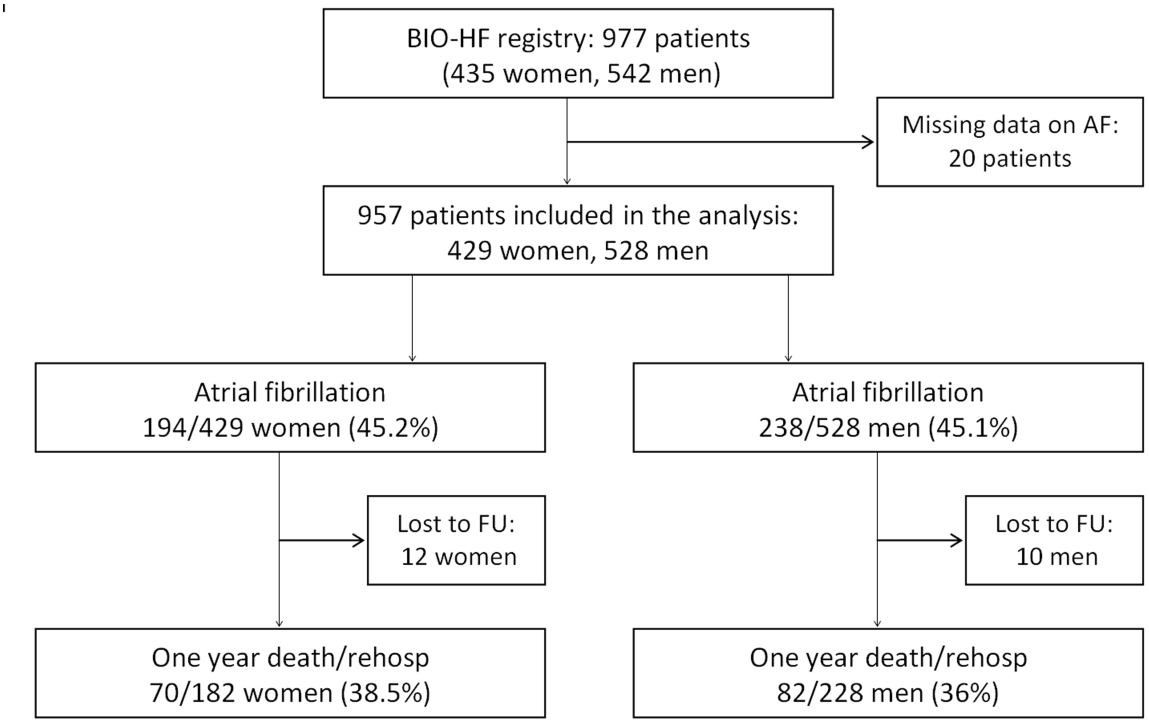
Here we compared the incidence and treatment of AF on admission between men and women admitted with AHF (BIO-HF registry, Belgium, November 2006-May 2012). Furthermore, we compared in-hospital mortality as well as the composite of all cause 1-year mortality or re-hospitalisation for HF among all women and men with AF complicating AHF as well as in the subgroup of patients <75 years-of-age.

METHODS

Study population:

The BIO-HF registry is a prospective registry evaluating all patients admitted with New York Heart Association (NYHA) class III-IV in 2 hospitals in Belgium from November 2006 to May 2012. A total of 977 (542 male [55.5%] and 435 female [44.5%]) patients, admitted in the AZ Maria-Middelares Ghent hospital or the UZ VUB Brussels hospitals were included in the registry. AF was diagnosed according to the admission electrocardiogram; these data were missing in 20 patients. Clinical and echocardiographic data as well as data on therapy for HF and AF, before, during and at discharge were recorded in all patients. HF with preserved left ventricular function (HF-PEF) was defined as a left ventricular ejection fraction (LVEF) ≥50%, HF with reduced ejection fraction (HF-REF) was defined as a LVEF <50%. Risk factors and comorbidities (smoking, history of hyperlipidaemia, history of hypertension, diabetes, anaemia [women: haematocrit <36%, men: haematocrit <39%], chronic obstructive pulmonary disease [COPD, as described in the patients medical record], renal dysfunction on admission [defined as: eGFR [CKD-EPI] <60mL/min/1.73m^2], CAD, peripheral artery disease [PAD], mitral valve regurgitation [MR] >grade 2, thyroid disease, earlier stroke, dementia, malignancy, history of AF and acute coronary syndrome [ACS]) were documented.

Figure 1 **Flowchart of patients included in the BIO-HF registry and selected for the present analysis.**



AF= atrial fibrillation, FU= follow up, rehosp= rehospitalisation

Outcome data:

The primary outcome measure was the composite of one-year all-cause mortality or readmission for HF. Secondary endpoints were in-hospital mortality and restoration of sinus rhythm at discharge.

Statistical Analysis:

Data are presented in percentage for categorical variables and as mean and standard deviation for continuous variables. Distributions of categorical variables were compared with the use of the chi-square test. The 2-tailed Student *t* test was used to compare continuous variables. Multivariable logistic regression analysis was used to determine the independent predictors of AF on admission including the following covariates in the model: sex, age (continuous variable), hypertension, diabetes, anaemia, renal dysfunction, HF-REF, left atrial diameter, CAD, PAD, MR>grade 2. To evaluate the composite of one year mortality and re-hospitalisation, the following covariates were included in the multivariable analysis: sex, variables that were associated with the primary endpoint in a univariate analysis in this database (age, admission HR, renal dysfunction, β-blocker at discharge, vitamin K antagonists [VKA] at discharge, angiotensin-converting enzyme inhibitor [ACE-I] or angiotensin receptor blocker [ARB] at discharge, aldosterone receptor antagonist at discharge) and variables that were different between sexes in univariate analysis (age, hypertension, renal dysfunction, CAD, HF-REF, active smoking, COPD and aldosterone receptor antagonist at discharge). To assess a possible interaction between sex and age regarding the primary endpoint, the product of sex and age (continuous variable) was added as an interaction term to the previous model. The following variables had missing data: renal dysfunction (all: 1.4%, <75y: 1.7%, ≥ 75y: 1.3%), LVEF<50% (all: 6.9%, <75y: 7.7%, ≥ 75y: 6.7%), admission heart rate (all: 0.7%, <75y: 0.9%, ≥ 75y: 0.6%) and COPD (all: 5.8%, <75 y: 5.1%, ≥ 75y: 6.0%).

Adjusted Odds Ratios (OR) with 95% confidence intervals (CI's) are reported. Statistical significance was defined as $p < 0.05$ or 95% confidence intervals (CI) for OR not including 1.0. All statistical analyses were performed using the SPSS v 19.0 statistical software.

Ethics:

The study complied with the Declaration of Helsinki. The BIO-HF database was approved by the Central Ethical Committee of the UZ Brussel and the Maria Middelares Hospital Gent.(2010/262). Informed consent was obtained from all patients or their legal representatives.

RESULTS

A total of 977 patients were included in the BIO-HF registry between November 2006 and May 2012.

Atrial fibrillation complicating acute heart failure

Data regarding AF on admission were missing in 20 patients (6 women, 14 men). AF occurred in 432 of the remaining 957 patients (45.1%); in 194 out of 429 women and in 238 out of 528 men (45.2% vs. 45.1%, p=0.97). **(Figure 1)** It was the first episode of AF in 31.5% of the women and 36.8% of the men (p=0.32) while AF was permanent in respectively 29.7% and 25.8% (p=0.42). In multivariable analysis, left atrial diameter was the single independent predictor for AF on admission; OR 1.07/mm (95% CI 1.03-1.10), p<0.001.

Baseline characteristics:

Baseline characteristics of all patients in the registry and those with AF (all and patients <75 years) are shown in **Table 1**.

Demographics, risk factors and comorbidities

Compared with men, women were older and more likely to have a history of hypertension while smoking, COPD and a history of CAD were less prevalent among women. An ACS was the precipitating factor for HF in 7.1% of the women with AF vs. 9.3% of the men with AF (p=0.48). Histories of hyperlipidaemia, diabetes, PAD, stroke, dementia, malignancy and thyroid disease were not different between sexes.

Clinical, biochemical and echocardiographic characteristics:

Mean heart rate was higher in women vs. men with HF (95.1 bpm vs. 91.5 bpm, p=0.04) but comparable among women and men with AF complicating AHF (104.4 bpm vs. 100.5 bpm, p=0.21). Mean systolic blood pressure was not significantly different between sexes.

There were no sex related differences in the presence of anaemia on admission but more women than men had RD on admission (all: 63.6 % vs. 54.4%, p=0.005, AF: 67% vs. 56.2%, p= 0.03).

Data on LVEF were available in 93% of the patients, the mean ejection fraction was higher in women vs. men and more women than men had HF-PEF. The presence of MR (> grade II) was not different between sexes. Medications from home recorded on admission were similar between female and male patients with AHF, except for aldosterone receptor antagonists in patients with AHF and AF (women: 22.7% vs. men: 14.3%, p=0.03).

Table 1	**All BIO-HF patients**		**All BIO-HF patients with AF**		**All BIO-HF patients with AF <75y**	
	Women (N=435)	Men (N=542)	Women (N=194)	Men (N=238)	Women (N=40)	Men (N=77)
Demographics, risk factors and comorbidities						
Age (mean, SD)	80.1 (8.9)	74.6 (11.9)***	80.6 (7.5)	77.3 (10.1)***	69.4 (4.3)	65.6 (8.1)**
Age <75y	21.6	41.7***	20.6	32.4**	_	_
History of AF	21.8	19	47.5	40	41.7	32
Smoker	5.1	17***	4.1	13**	10	22.1
Hypertension	67.1	57.6**	70.1	59.7*	75	54.5*
Diabetes	25.1	28.4	25.8	25.6	35	26
Hyperlipidaemia	43.8	48.6	41.8	45.9	30.6	44
CAD	25.1	43.9***	22.2	42.4***	15	31.2
PAD	14.9	19.2	15.5	17.2	10	17
Stroke	11.4	11.7	13.9	13.4	5	3.9
Dementia	4.8	3.5	6.2	2.9	2.5	1.3
COPD	15.9	21.2*	12.6	24.9**	8.3	10.7
Malignancy	12.1	12.3	14.4	14.0	6.9	8.0
Thyroid disease	19.6	15.0	20.8	14.7	12	15.7
ACS	14.9	18.7	7.1	9.3	8.3	8
Clinical, biochemical and echocardiographic characteristics on admission						
SBP (mean, SD)	142.3 (31.6)	139.0 (28.9)	142.1 (30.0)	138.6 (26.1)	144.1 (32.9)	137.8 (28.5)
HR (mean, SD)	95.1 (27.5)	91.5 (28.1)*	104.4 (30.8)	100.5 (33.2)	114 .6 (30.6)	115.6 (35.1)
RD	63.6	54.4**	67.0	56.2*	56.4	36.8
Anaemia	38.4	41.8	35.9	37.4	40.5	25.5
LVEF (mean,SD)	47.1 (16.3)	38.7(16.0)***	48.1 (16.0)	40.8 (16.2)***	42.1 (15.9)	35.9 (15.3)
HF-PEF	52.4	30.3***	53.9	35.7***	33.3	27.8
MR>grade II	20.7	16.7	19.6	16.2	11.1	17.7
Treatment on admission						
B-blocker	54.5	50.6	61.3	52.5	67.5	46.8
ACE-I/ARB	49.9	54.2	51	51.7	62.5	45.5
ARA	17	14.9	22.7	14.3*	25	13
Loop diuretic	46	46.9	46.7	54.1	41.7	40
Digoxin	10.7	12.5	10.7	12.5	11.1	20
Sotalol	4.6	3.5	6.8	5.4	2.8	5.3
Amiodarone	9.0	13.9*	9.6	13.1	8.3	16.0
VKA	22.3	26.2	40.7	42.4	45	36.4

AF= atrial fibrillation, y= years, CAD= coronary artery disease, PAD: peripheral artery disease, COPD= chronic obstructive pulmonary disease, ACS= acute coronary syndrome, SBP= systolic blood pressure, (mmHg), HR= heart rate (beats/minute), RD= renal dysfunction, LVEF= left ventricular ejection fraction, MR= mitral regurgitation, ACE-I= angiotensin converting enzyme inhibitor, ARB= angiotensin receptor blocker, ARA= aldosterone receptor antagonist, VKA= vitamin K antagonist. Data are presented as % unless otherwise indicated, *p<0.05; ** P<0.1; *** p<0.001

Treatment during and after hospitalisation

The general therapeutic approach of AHF and the specific treatment of AF was not different between men and women with AHF and AF; an equal amount of men and women were treated with intravenous diuretics (67.2% vs. 66.7%, p=0.92), intravenous nitrates (18.6% vs. 19.4%, p=0.89), inotropic therapy (2.8% vs. 6.3%, p=0.15), non invasive ventilation (2.3% vs. 3.2%, p=0.76) and electrical cardioversion (4.8% vs. 4.3%, p=0.81) A comparable proportion of women and men were prescribed amiodarone (28.2% vs. 31.1%, P=0.58), digoxin (29.4% vs. 29.7%, p=0.99) , β-blocker (73.7% vs. 76.1% , p=0.58) and sotalol at discharge (3.4% vs. 0.5%, p=0.05). More women than men were prescribed aldosterone receptor antagonists (36.1% vs. 26.5%, p=0.04) at discharge. Overall 60% of the women vs. 63.4% of the men (p=0.49) were prescribed oral anticoagulants at discharge. **(Table 2)**

Subgroup <75 years

In the subgroup of patients <75 years, 43% of the women had co-occurring AF vs. 35.2% of the men, p=0.20. The prevalence of AF in younger women was comparable to that in older women (p=0.64) while AF was less prevalent in the younger vs. the older men (35.2 vs. 52.1%, p<0.001). The women <75 years with AHF and AF were on average older and more frequently had a history of hypertension as compared to the men <75 years. Other sex differences, observed in the overall group of patients with HF and AF (smoking, CAD, COPD, renal dysfunction, HF-PEF and the use of an aldosterone receptor antagonist at discharge) did not reach statistical significance in this subgroup. Fewer women <75 years with HF and AF had HF-PEF as compared to women ≥75 years with AHF and AF (33.3% vs. 59.2%, p=0.008) whereas the proportion of male patients with HF-PEF was similar among men < and ≥75 years (27.8 vs. 39.5%, p=0.10). No sex differences in the treatment of HF and/or AF were observed in this subgroup. Patients younger than 75 years more often underwent electrical cardioversion (p=0.03) for their AF during hospital stay and were prescribed more often ACE-I or ARB at discharge as compared to patients ≥75 years (P=0.003). **(Table 2)**

Table 2 In-hospital treatment of patients with acute heart failure and atrial fibrillation

	All			AF<75years		
	Women (N=194)	Men (N=238)	p	Women (N=40)	Men (N=77)	p
IV nitrates	18.6	19.4	0.89	22.2	21.3	0.99
IV inotropics	2.8	6.3	0.15	5.6	9.3	0.71
IV diuretics	67.2	66.7	0.92	61.1	73.3	0.20
NIV	2.3	3.2	0.76	5.6	2.7	0.59
Electrical cardioversion	4.8	4.3	0.81	6.2	9.6	0.72
B-blocker at discharge	73.7	76.1	0.58	77.5	83.1	0.46
ACE-I/ARB at discharge	55.2	62.6	0.14	67.5	72.7	0.67
ARA at discharge	36.1	26.5	0.04	27.5	32.5	0.67
Amiodarone at discharge	28.2	31.1	0.58	30.6	37.3	0.53
Digoxin at discharge	29.4	29.7	0.99	25	37.3	0.28
Sotalol at discharge	3.4	0.5	0.05	2.8	1.3	0.54
VKA at discharge	59.8	63.4	0.49	67.5	64.9	0.84

IV= intravenous, NIV= non invasive ventilation, ACE-I= angiotensin converting enzyme inhibitor, ARB= angiotensin receptor blocker, ARA= aldosterone receptor antagonist, VKA= vitamin K antagonist, Data are presented as %

Outcome

Data on the primary outcome were available in >95% of the patients (10 men and 12 women were lost to follow-up, **Figure 1**). The composite of one-year all cause mortality or rehospitalisation occurred in 70 (out of 182, 38.5%) women and 82 (out of 228, 36%) men (p=0.93). When adjusting for sex, age, admission heart rate, hypertension, renal dysfunction, CAD, HF-REF, COPD, active smoking, β-blocker at discharge, VKA at discharge, ACE-I or ARB at discharge and aldosterone receptor antagonist at discharge, female sex was not independently associated with the primary endpoint (OR=1.1 [95% CI 0.65-1.86], p=0.71). Renal dysfunction (OR=2.88 [95% CI 1.68-4.92], p<0.001) and β-blocker at discharge (OR=0.46 [95%CI 0.26-0.79], p=0.005) were independently associated with the outcome measure. **(Table 3)** A significant interaction between sex and age was observed (p=0.002) with a doubling of the primary endpoint in women <75 years-of-age (42.5%) vs. men <75 years-of-age (20.3%); (OR=7.17 [95% CI 1.79-28.66], p=0.005). (**Table 4)**, **(Figure 2)**

Restoration of sinus rhythm at discharge occurred in 16.5% of the women and in 14.2% of the men (p=0.58). In-hospital mortality rates were comparable between sexes (5.7% in women vs. 6.7% in men; p=0.69).

Table 3 **Multivariable analysis of the composite endpoint:**

One-year mortality/rehospitalisation in female (N=194) and male (N=238) patients with atrial fibrillation complicating acute heart failure

	p-value	OR	95% CI
Gender	0.71	1.10	0.65-1.86
Age	0.05	1.03	1.00-1.07
Admission HR	0.69	0.99	0.99-1.01
Hypertension	0.19	1.41	0.85-2.36
Renal dysfunction	<0.001	2.88	1.68-4.92
COPD	0.40	1.31	0.70-2.42
Active smoking	0.14	1.92	0.81-4.53
CAD	0.88	1.05	0.61-1.79
LVEF < 50%	0.13	1.48	0.89-2.46
B-blocker discharge	0.005	0.46	0.26-0.79
VKA discharge	0.33	0.77	0.46-1.29
ACE-I/ARB discharge	0.20	0.72	0.44-1.19
ARA discharge	0.07	0.61	0.35-1.04

HR= heart rate, COPD= chronic obstructive pulmonary disease, CAD= coronary artery disease, LVEF= left ventricular ejection fraction, VKA= vitamin K antagonist, ACE-I= angiotensin converting enzyme inhibitor, ARB= angiotensin receptor blocker, ARA= aldosterone receptor antagonist

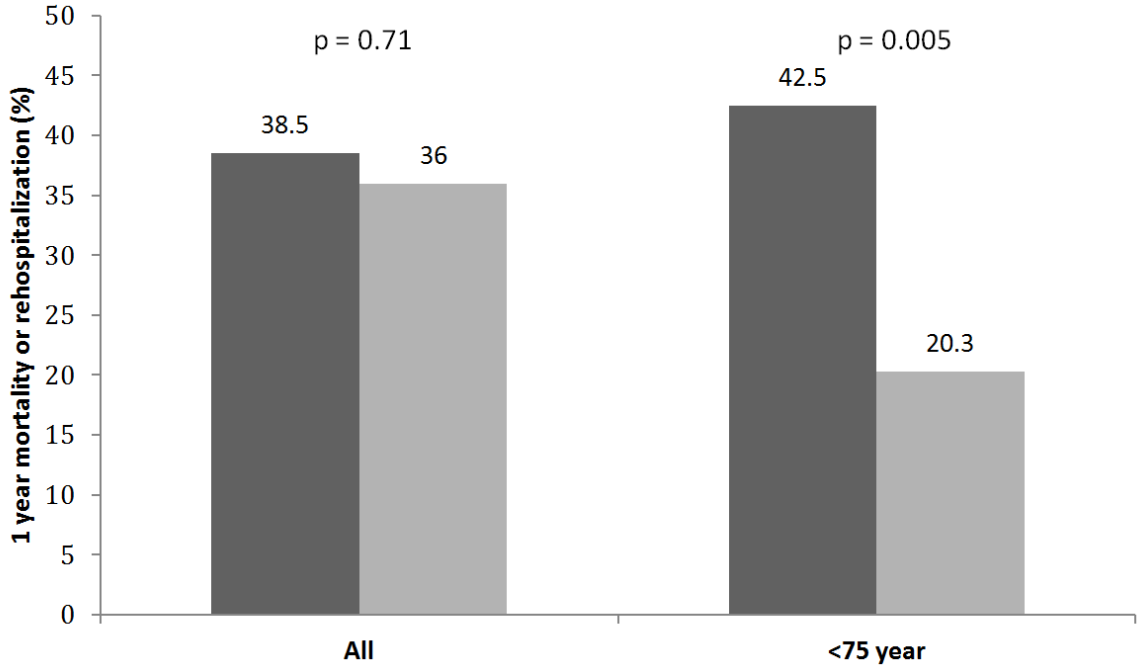
Table 4 **Multivariable analysis of the composite endpoint:**

1-year mortality/rehospitalisation in female (N=40) en male (N=77) patients <75 years-of-age with atrial fibrillation complicating acute heart failure

	p-value	OR	95% CI
Gender	0.005	7.17	1.79-28.66
Age	0.83	1.01	0.91-1.12
Admission HR	0.38	0.99	0.97-1.01
Hypertension	0.64	1.42	0.32-6.26
Renal dysfunction	0.12	3.01	0.75-12.01
COPD	0.04	10.18	1.05-98.51
Active smoking	0.08	4.51	0.86-23.76
CAD	0.69	0.76	0.20-2.91
LVEF <50%	0.12	2.95	0.75-11.67
B-blocker discharge	0.43	0.55	0.13-2.37
VKA discharge	0.04	0.24	0.06-0.94
ACE-I/ARB discharge	0.89	1.10	0.27-4.46
ARA discharge	0.15	0.37	0.09-1.42

HR= heart rate, COPD= chronic obstructive pulmonary disease, CAD= coronary artery disease, LVEF= left ventricular ejectionfraction, VKA= vitamin K antagonist, ACE-I= angiotensin converting enzyme inhibitor, ARB= angiotensin receptor blocker, ARA= aldosterone receptor antagonist

Figure 2 Adjusted 1-year mortality and rehospitalisation



Dark grey bars: Women

Light grey bars: men

DISCUSSION

This analysis, based on a large contemporary HF registry, conducted in 2 Belgian centres, demonstrated that AF was present in 45% of the patients admitted for AHF and that AF was equally prevalent among women and men. Despite gender differences in risk profile and comorbidities, the incidences of outcomes (composite of one year mortality and/or rehospitalisation, restoration of sinus rhythm and in-hospital mortality) were similar among these women and men presenting with AHF and AF. However a significant sex-age interaction was demonstrated and outcome in the group of women < 75 years-of-age was worse as compared with men <75 years. As far as we are aware this is the first report that demonstrates worse outcome in younger women hospitalised with AHF complicated by AF.

The high prevalence of AF in hospitalised HF patients in this contemporary registry is consistent with the findings of McManus et al. that the incidence of co-occurring AF is increasing in patients with AHF, in women as well as in men. [126] As in other AHF registries, the women in our registry differed from men in being older, more frequently having hypertension, more frequently having HF-PEF and less frequently having a history of CAD. [32, 33, 35, 107, 157] In contrast to previous reports [33] a higher incidence of renal dysfunction on admission was observed in women probably because renal function was assessed using eGFR (< or ≥ 60mL/min/1.73m^2), instead of a cut-off value for creatinine, the latter being a less accurate way to determine kidney function especially when evaluating sex differences.[163, 164] In the subgroup of patients <75 years no sex differences in comorbidities (except for hypertension) were observed, this could be attributed to the lower sample size. However, in contrast to the women ≥ 75years, less women <75years presented with HF-PEF.

We observed no sex disparities in the application of evidence-based HF therapies before and during admission and at discharge, with the exception for aldosterone receptor antagonists at discharge, which were prescribed more to women, despite the greater proportion of women with HF-PEF, who should not receive aldosterone receptor antagonists according to the current guidelines. The management of AF was similar between men and women with a predominant rate control strategy in both women and men, which may be a reflection from the lessons learned from the AF-CHF trial. [165]

In the BEST-trial including 2,708 patients (22% women) relatively young (mean age 58y [SD 13.3] and 61y [SD 12.0] in women and men respectively) chronic HF patients with reduced ejection fraction, AF was an independent predictor for mortality in women but not in men. [166] In a setting of AHF, we demonstrated worse outcome for women <75 years with AF compared with men <75 years, however, our data do not provide a clear insight into the reason for this worse outcome, because sex differences in baseline characteristics and treatment were less pronounced in this group compared with the older age group. Women have a higher risk of mortality and morbidity from stroke and thromboembolism (TE) associated with AF. [161] Based on this finding (reflected by the CHA_2DS_2 VASc score) all women with AF and at least one additional risk factor (HF, age >65 , DM, history of stroke/TIA/TE, vascular disease) are at higher risk (CHA_2DS_2 VASc ≥2). [162] Treatment with VKA or novel anticoagulants can reduce this risk by two thirds. This implies that all women, younger or older, admitted with HF and AF should be discharged with anticoagulant treatment. In the current database an equal amount of men and women were discharged on oral anticoagulants. Not prescribing VKA antagonists at discharge was associated with worse outcome in both sexes of the younger patient group, unfortunately reasons for not prescribing VKA were not recorded. Therefore the lack of VKA at discharge cannot explain the worse outcome in younger women but the results of the multivariable analysis stress the need for oral anticoagulation in all patients admitted with HF and AF. Women have longer QT-intervals than men and a treatment with sotalol makes them more susceptible for torsades de pointes [21, 167], however sotalol was prescribed only to a minority of these patients and adding sotalol to the multivariable model did not change the results in the age group <75 years (OR for female sex=10.99 [95%CI 2.29 -52.81], p=0.003). The use of digoxin at discharge was high (more than 25% of the patients), post hoc analyses of the Digitalis Investigation Group (DIG) trial demonstrated that digoxin at higher serum concentrations (≥ 1.2ng/mL) was associated with a HR for death of 1.33 in women. [22, 168] Unfortunately digoxin levels at discharge were not registered in the database. The addition of digoxin at discharge to the multivariable model did not affect the results in the age group<75 years either (OR for female sex=11.49 [95% CI 2.34-56.55], p=0.003).

Before speculating on other reasons behind the worse outcome in younger women with AHF and AF, this finding should be explored in larger patient series.

STRENGHTS AND WEAKNESSES

The BIO-HF registry is a contemporary HF registry that provides accurate assessment of baseline characteristics and follow-up data, allowing adjustment for differences in aetiologies and comorbidities. There are some weaknesses: First, the nonrandomised and observational design of the BIO-HF registry is subject to residual and unmeasured confounding. Second, AF can present in many ways, the current analysis was not pre-defined, when setting up the BIO-HF registry and it was not recorded in the database when AF started, whether AF was the trigger for AHF or merely a marker of the severity of the disease. Third, the sample size of the subgroup analysis based on age < or ≥ 75y is limited and limitations of subgroup analysis are known. The large confidence intervals for the main outcome of interest in women <75 years may reflect lack of precision due to the smaller sample size in this subgroup of younger patients, therefore we consider our results hypothesis generating.

CONCLUSION AND IMPLICATIONS

The BIO-HF registry conducted in 2 Belgian hospitals demonstrated no sex differences in prevalence and treatment of AF in patients hospitalised with AHF. The composite endpoint of one-year mortality and rehospitalisation among patients with AHF and AF was not different between sexes, except for women <75 years-of-age who were at higher risk for adverse outcome compared with men <75 years. The worse outcome for younger women is worrying and the reason behind this could be explored in larger patient series.

Disclosures

None

Chapter 4

Acute and critically ill peripartum cardiomyopathy and 'bridge to' therapeutic options: a single center experience with intra-aortic balloon pump, extra corporeal membrane oxygenation and continuous-flow left ventricular assist devices

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ABSTRACT

Introduction: Peripartum cardiomyopathy (PPCM) patients refractory to medical therapy and intra-aortic balloon pump (IABP) counterpulsation or in whom weaning from these therapies is impossible, are candidates for a left ventricular assist device (LVAD) as a bridge to recovery or transplant. Continuous-flow LVADs are smaller, have a better long-term durability and are associated with better outcomes. Extra corporeal membrane oxygenation (ECMO) can be used as a temporary support in patients with refractory cardiogenic shock. The aim of this study was to evaluate the efficacy and safety of mechanical support in acute and critically ill PPCM patients.

Methods: This was a retrospective search of the patient database of the Ghent University Hospital (2000-2010).

Results: Six PPCM-patients were treated with mechanical support. Three patients presented in the postpartum period and three patients at the end of pregnancy. All were treated with IABP, the duration of IABP support ranged from 1 to 13 days. An ECMO was inserted in one patient who presented with cardiogenic shock, multiple organ dysfunction syndrome and a stillborn baby. Two patients showed partial recovery and could be weaned off the IABP. Four patients were implanted with a continuous-flow LVAD (HeartMate II®, Thoratec Inc.), including the ECMO-patient. Three LVAD patients were successfully transplanted 78, 126 and 360 days after LVAD implant, one patient is still on the transplant waiting list. We observed one peripheral thrombotic complication due to IABP and five early bleeding complications in three LVAD patients. One patient died suddenly 2 years after transplantation.

Conclusions: In PPCM with refractory heart failure, IABP was safe and efficient as a bridge to recovery or as a bridge to LVAD. ECMO provided temporary support as a bridge to LVAD while the newer continuous-flow LVADs offered a safe bridge to transplant.

INTRODUCTION

Peripartum cardiomyopathy (PPCM) is a rare disease that affects women in the last month of their pregnancy or in the early puerpium (up to 5 months after delivery); it is characterised by left ventricular systolic dysfunction and symptoms of heart failure (HF) without any identifiable cause of HF. The incidence varies from 1:15,000 to 1:1,300 deliveries in some African countries and 1:299 in Haiti and is thought to be lower in Europe. [169, 170] The historically bad prognosis with mortality rates ranging from 4 to 80% has improved because of advances in HF treatment. [171]

Although already described in the 19th century the condition was only defined as Peripartum Cardiomyopathy in 1971 by Demakis *et al.* who also proposed diagnostic criteria that later were confirmed during the 'Peripartum Cardiomyopathy: National Heart Lung and Blood Institute and Office of Rare Disease Workshop' in 2000. [172] Several aetiologies have been proposed comprising myocarditis, auto-immune mechanisms and pregnancy associated hormonal changes. [173-175] Recent data support the hypothesis that PPCM may develop as a result of complex interactions of pregnancy-associated factors against a susceptible genetic background. [176, 177] The oxidative stress-cathepsin D-16 kDa prolactin hypothesis has been raised as a possible common pathway on which different aetiologies that induce PPCM may merge. While newer therapies such as bromocriptine appear promising and will be tested in larger trials one must also concentrate on an optimal treatment strategy for the acute and critically ill PPCM patients, allowing to increase survival in this young patient population. [178]

Heart transplantation is an accepted treatment option for patients with refractory HF due to PPCM although a higher incidence of rejection has been reported in parous women, particularly in the first six months after transplantation. [179, 180] Moreover, heart transplantation is limited by a lack of suitable donors. On the other hand there is a reasonable possibility of partial or complete recovery of left ventricular function, during the first year. The main predictors for recovery are an initial left ventricular end-diastolic dimension (LVEDD) <56mm and an ejection fraction >45% at two months. [171] As a consequence there is a need for appropriate temporary short- and long-term artificial support for the acute and critically ill patients. There are only a few reports on mechanical support devices as a bridge to recovery or transplantation in this setting. Data on the use of intra aortic balloon

pump (IABP) and extra corporeal membrane oxygenation (ECMO) in PPCM are scarce. [181-184] There are a few reports on the use of pulsatile assist devices in this setting, most of them as a bridge to transplant and in a minority of cases as bridge to recovery. [185-192]

Continuous-flow LVADs are a newer type of assist devices that have advantages over the older pulsatile devices: they are smaller, have a better long-term durability and their use is associated with improved survival and functional capacity. [193, 194] There are no published series on the use of a continuous-flow device in patients with PPCM.

MATERIALS AND METHODS

A retrospective 10-year study (2000-2010) was conducted of our patient database (department of Cardiology, Ghent University Hospital, Belgium) for patients with a need for mechanical support in the acute phase of PPCM. Mechanical support was defined as IABP, ECMO or LVAD. We received local Ethical Committee approval and informed consent from the patients or their relatives.

Diagnosis of PPCM was based upon development of symptoms of HF due to systolic dysfunction in the last month of pregnancy or within five months after delivery without any identifiable cause of HF or recognisable heart disease prior to the last month of pregnancy. Patients with hypertensive HF in the peripartum period were not included. Demographic, clinical, hemodynamic and echocardiographic data as well as data on serology were evaluated. Data on endo-myocardial biopsies and coronary angiography were reviewed. The outcomes of the different treatment strategies as well as their complications were evaluated.

RESULTS

Over a 10-year period 6 PPCM patients were treated with mechanical support for acute HF at our center. **(Table 1)** All six patients were treated with an IABP and one patient was treated with ECMO. Four patients were implanted with a continuous-flow LVAD (HeartMate II®, Thoratec Inc, Pleasanton, USA), three of them were transplanted and one patient is still on the transplant waiting list. The mean age at presentation was 34.7 years, the mean body surface area (BSA) was 1.76m^2 . Five patients were Caucasian, one was native African. All patients but one were multiparous with the number of pregnancies ranging from two to four. Serology was examined for Coxsackie virus B1-5, Mycoplasma pneumoniae, Toxoplasmosis, Hepatitis B and C, HIV, Ebstein-Barr and Adeno- and Entero virus in all patients. Active infection with Mycoplasma pneumoniae was found in 2 patients but active myocarditis was excluded by means of endo-myocardial biopsy. Endo-myocardial biopsies in 2 other patients, taken at the time of placement of the LVAD, were also negative for myocarditis.

Table 1 Patient characteristics

Patient	1	2	3	4	5	6
Year	2001	2008	2010	2007	2008	2009
Age (y)	34	35	36	37	38	28
BSA (m^2)	1.90	1.88	1.58	1.83	1.60	1.79
Race	C	A	C	C	C	C
Obstetrical Hx	G4A0P4	G2A0P2	G4A0P4	G1A0P0	G2A0P1	G3A1P1
Symptom onset	3wPP	5mPP	5mPP	38wPr	35wPr	38wPr
Diagnosis	3wPP	10mPP	18mPP	38wPr	36wPr	38wPr
Clinical picture	APE	ADHF	ADHF	ADHF	ADHF	CS
LVEDD (mm)	55	62	79	53	61	68
Serology	Negative	Mycoplasma IgM	Negative	Negative	Negative	Mycoplasma IgM
Coronary angio	Normal	-	Normal	-	Normal	-
Biopsy	-	Negative	Negative	-	Negative	Negative
IABP (d)	7	13	5	4	6	1
ECMO (d)	-	-	-	-	-	7
LVAD (d)	-	126	Since 26/04/2010	-	360	78
Complications	-	Perop. rupture aorta Tamponade 2x Pocket Infection	Rectus hematoma Occlusion AFC	-	-	Bleeding anast. aorta
Outcome	Recovery	Tx, SD 535 days postTx	Alive,on Tx list	Recovery	Tx	Tx

y= years, BSA= Body Surface Area, C= Caucasian, A= African, Hx= history, PP= Postpartum, Pr= Pregnancy, APE= Acute Pulmonary Edema, ADHF= Acute Decompensated Heart Failure, CS= Cardiogenic Shock, LVEDD= Left Ventricular End Diastolic Diameter at presentation, d= days, Perop.= peroperative, anast.= anastomosis, AFC= Arteria Femoralis Communis, Tx= cardiac transplantation, SD= Sudden Death

Presentation in the postpartum period

Patient 1 was a 34-year-old patient (G4A0P4) who presented with acute pulmonary oedema 16 days after delivery of a healthy son. She was initially treated with intravenous diuretics and vasodilators, but her condition only stabilised after insertion of an IABP. After initiation of conventional HF therapy with ACE-inhibitors, diuretics and low dose beta-blockers the patient was easily weaned off the IABP and discharged home 4 weeks after admission. She is still in follow-up and doing well under treatment with beta-blocking agents.

Patient 2 was a 35-year-old South African woman (G2A0P2) who developed progressive dyspnoea from the fifth month postpartum. She came to the Emergency Room a few months later with a clinical picture of severe decompensated HF with lactate acidosis and liver failure. After initiation of inotropic therapy and IABP insertion her condition stabilised with complete resolution of the lactate acidosis and liver function. Despite initiation of proper HF therapy weaning off the IABP was not possible and the implantation of a LVAD was decided. The implantation was complicated by a rupture and large hematoma of the descending aorta for which an endo-prosthesis was inserted. During the early postoperative phase 2 revisions were necessary because of pericardial tamponade. Long-term antibiotic therapy was initiated because of infection of the pocket. After a long postoperative period the patient could be mobilised and discharged home 67 days after placement of the LVAD. No recovery in left ventricular function was noted during follow-up. A total of 126 days after implantation of the LVAD she was successfully transplanted and did well. Unfortunately she died suddenly 2 years later, she developed EMD during hospitalisation for HF due to mild rejection, prolonged resuscitation was unsuccessful. An autopsy was not performed.

Patient 3, a 36-year-old mother of 4 children, presented very late in the postpartum period (18 months postpartum), she developed progressive symptoms of HF during the first months after her last delivery. She presented with cachexia and decompensated HF. The left ventricular end-diastolic diameter was 79 mm at presentation. After minor decongestion with diuretics, low dose dopamine was started and an IABP was inserted because of refractory hypotension and low output failure. Five days later an LVAD was implanted electively because of lack of left ventricular recovery and impossibility to wean the patient off the IABP and

dopamine. The postoperative course was complicated by a spontaneous rectus haematoma at the 11th postoperative day (supratherapeutic prothrombin time) and a thrombotic occlusion of the right common femoral artery. The arterial occlusion was a consequence of the IABP and a thrombectomy was performed at day 35 post LVAD with good clinical resolution afterwards. During ambulatory follow up, left ventricular end diastolic diameter decreased from 79 to 72 mm without recovery of left ventricular function.

Presentation late in pregnancy

Two patients presented with acute decompensated HF and were in New York Heart Association class III. An IABP was inserted in both patients prior to caesarean section.

Patient 4, a 37-year-old nulli-para could be weaned off the IABP four days later and is still under treatment with conventional HF therapy and is doing well.

Patient 5, a 38-year-old woman (G2A0P1) could be weaned off the IABP after six days but remained symptomatic the following weeks with severe hypotension necessitating a continuous dopamine infusion. She was treated with bromocriptine but remained inotrope-dependent. She was implanted with a LVAD 21 days after removal of the IABP. There were no complications. Follow-up echocardiography showed some recovery of left ventricular function but the right ventricular function remained moderate; a trial to remove the LVAD was not attempted. She was successfully transplanted almost one year after LVAD placement and is still doing well.

The sixth patient, a 28-year-old G3A1P1 developed rapidly progressive dyspnea at the end of pregnancy. HF was initially not recognized and delivery was induced with prostaglandins. Afterwards she rapidly progressed to cardiogenic shock. She was referred to our center. During transport a continuous infusion with adrenaline was initiated because of severe shock. Upon arrival the patient was immediately intubated, meanwhile an IABP was percutaneously inserted. A stillborn baby was delivered by caesarean section. The patient remained in shock with severe lactate acidosis and multiple organ dysfunction syndrome despite treatment with dobutamine, levosimendan and high doses of noradrenaline. Her condition worsened rapidly, she was not stable enough for implantation of a LVAD. An ECMO

was percutaneously inserted at the bedside without complications. The system comprised a Medos Hilite 7000 LT oxygenator (Medos Medizintechnik AG, Stolber, Germany) and a Sorin revolution centrifugal pump (Sorin Group, Arvado, Colorado, USA) (18 Fr arterial line: femoral approach, 18 Fr venous line: jugular approach). The following days we noted respiratory and metabolic improvement. Because of the absence of left ventricular recovery a LVAD was implanted after seven days of ECMO. There was a revision at day 1 because of bleeding at the anastomosis of the aortic cannula. During the postoperative course she was treated for ventilator associated pneumonia with complete recovery. Sildenafil treatment for moderate right ventricular function and pulmonary hypertension was initiated at the fourth day post-LVAD implantation until transplant. She was discharged home 37 days after initial admission and was successfully transplanted 78 days after LVAD implant and is doing well up till now

DISCUSSION

We describe six well-documented cases of severe PPCM that presented with AHF requiring mechanical support. The diagnosis was based upon development of symptoms of HF in the last month of pregnancy or during the first five months after delivery without arguments for pre-existing structural heart disease. In each patient an extensive work-up was performed to exclude other causes of HF. Two patients had arguments for active Mycoplasma Pneumoniae infection, but myocarditis was excluded by means of endo-myocardial biopsies.

We describe short- and/or long-term mechanical support when intensive medical therapy fails to stabilise a PPCM patient with severe HF. Mechanical short-term support can be provided percutaneous with IABP or ECMO. An IABP can easily be placed at the bedside and has little side effects in this young patient population. There are no randomised data on the use of IABP in non-ischaemic refractory HF and European guidelines recommend insertion of an IABP when inotropes fail to restore the blood pressure and signs of hypo-perfusion persist. [195] In our series the use of IABP up to 13 days was complicated by one thrombotic occlusion of the common right femoral artery which was corrected uneventfully after thrombectomy. All patients treated with IABP were anti-coagulated with unfractionated heparin (UFH) aiming at an activated partial thromboplastin time (aPTT) of 65-85 seconds. Weaning from the IABP is usually attempted over 1 to 3 days by gradually decreasing the 1:1 support to a 1:2 and a 1:3 support. If a 1:3 support is well tolerated for at least 4 hours, the IABP is removed. When weaning off the IABP is not possible, the IABP is removed at the time of implantation of the ECMO or the LVAD.

There is a current trend to use short-term support with ECMO in refractory cardiogenic shock but data from large randomised trials are lacking. ECMO is considered as an emergency rescue therapy for patients with refractory cardiogenic shock; their condition is so unstable that they are not eligible for immediate LVAD implantation. The ECMO can be inserted at the bedside; it is relatively cheap (as compared to the implantable LVAD) and it gives the treating physicians some time to wait for recovery or a more stable condition. However close monitoring of the coagulation parameters is needed and it is therefore, labour-intensive. Patients on ECMO are treated with UFH in order to obtain an activated clotting time (ACT) of

170-200 seconds. Anti-thrombin III (ATIII) levels are analysed daily, ATIII concentrate is given if the ATIII activity drops below 70%. A visco-elastic coagulation measurement is checked twice daily or whenever bleeding occurs. Patients on arterio-venous ECMO are ventilated with conventional settings, with a FiO2 to achieve an acceptable PaO2 (at least 60 mmHg). Inotropic support is reduced and stopped but milrinone is often continued for its dilator properties and positive effects on microcirculation. Fluid management is aimed at preserving renal function and ensuring a stable circulation. As ECMO flow depends on right atrial filling, this is monitored by means of echocardiography. During a weaning attempt each partial decrease in ECMO flow should be compensated by an increase in stroke volume without excessive increase in inotropic support. There are 3 case reports on ECMO in PPCM where ECMO served as a safe bridge to recovery. [182, 184] In our series ECMO was used in one patient because of refractory cardiogenic shock and multiple organ dysfunction syndrome one-day post caesarean section. ECMO allowed haemodynamic and metabolic stabilisation. In contrast to the above mentioned case reports we saw no recovery of left ventricular function and in our patient ECMO served as a bridge to LVAD.

LVADs offer a more long-term support. In a recent position statement Sliwa *et al.* promote the use of a mechanical assist device in PPCM in case of refractory HF despite optimal medical therapy. [96] The continuous-flow HeartMate II was introduced in 2004 and has shown improvement in survival, reduction in adverse events and improved functional capacity. [193] This axial flow pump draws the blood on a continuous basis from the left ventricle via an apical drainage cannula and propels it back into the aorta by a rotary pump in a non-phasic flow pattern. Its smaller size makes it suitable for patients with a low BSA, which is frequently the case in this young female population. After implantation of the LVAD NO-ventilation is routinely applied in our center to support the right ventricle, inotropic support is gradually decreased and replaced by oral HF therapy. Echocardiography is used to assess left ventricular filling, a neutral inter-ventricular septum position indicates adequate left ventricular filling. Bleeding complications in the immediate postoperative phase still pose a problem but recent data on the HeartMate IIe device support a less aggressive anticoagulation protocol. [186, 190] More recently late bleeding complications up to 44.3% have been observed in continuous-flow LVAD patients, possibly due to an acquired von Willebrand Syndrome. [196] In our center the antithrombotic regimen is started as soon as drain output reaches levels of 50 ml/h

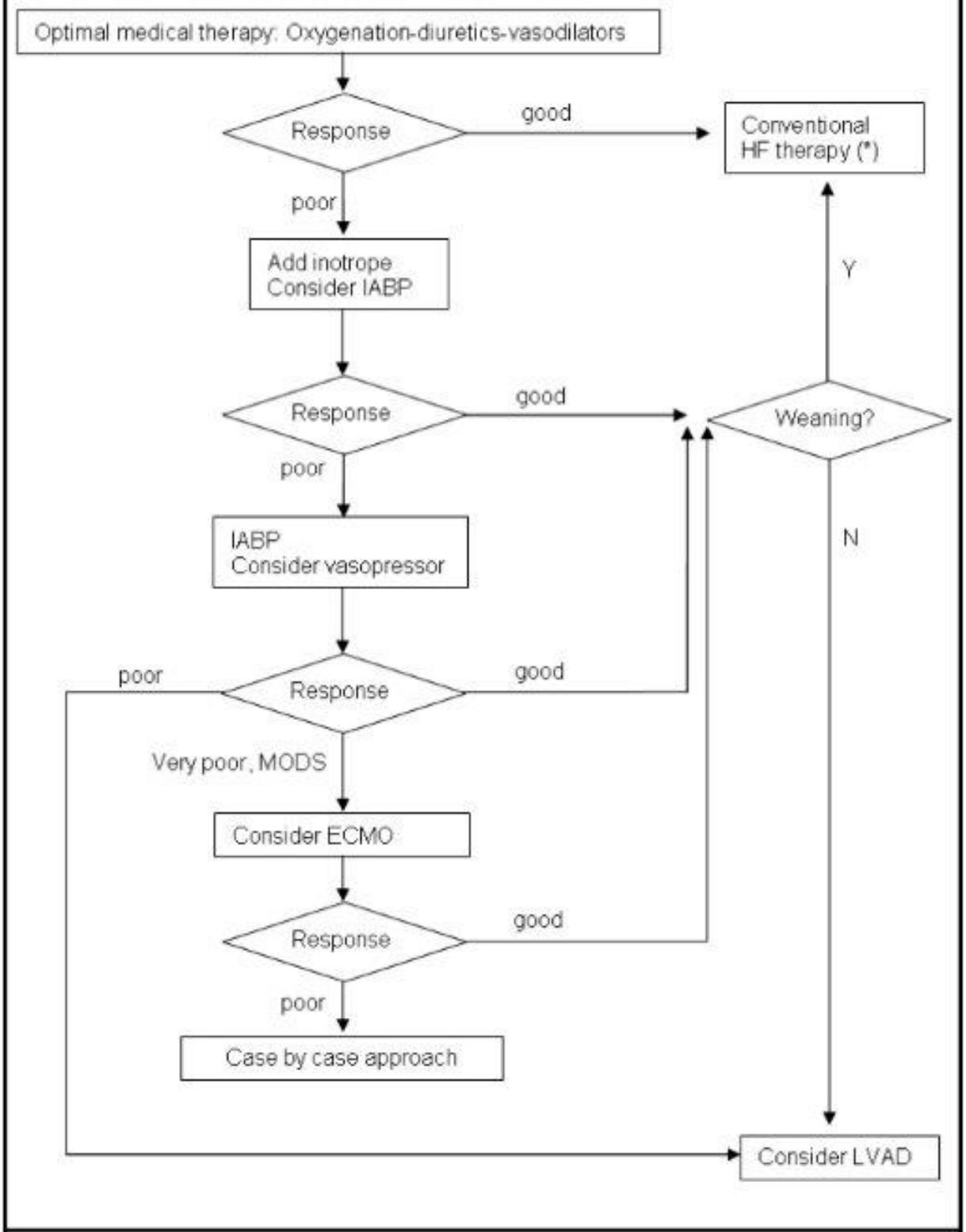
or less. It comprises Aspirin 100mg and Enoxaparin 40mg once daily (20mg in case of GFR<30ml/minute, 60mg in case of body weight>90kg). Acenocoumarol (target INR 1.5 to 2) is started as soon as a more stable hemodynamic condition is reached and in the absence of bleeding. Bleeding complications were observed in three patients during the early postoperative phase, with need for revision in two patients. We observed no late bleeding complications. Infection of the pocket with need for long-term antibiotic treatment occurred in one patient. There were no thrombotic complications related to the LVAD, despite the fact that PPCM is a pro-thrombotic condition. Right heart failure, defined as the postoperative need for temporary right ventricular mechanical or inotropic support for more than 14 days following implantation, was not noted although one patient was treated until transplantation with a low dose Sildenafil. Neurological complications did not occur in this small series. Sufficient recovery of left ventricular function to allow LVAD explantation is rare but has been described in PPCM patients treated with pulsatile devices, we found no data on explantation of continuous-flow devices in PPCM patients. In our series we saw a decrease in LVEDD and some improvement in left ventricular function, but the right ventricular function remained moderate. In our opinion the decrease in LVEDD and improvement in left ventricular function can be attributed to the unloading of the left ventricle.

These six patients presented over a wide time range between 2001 and 2010 with a trend towards an increasing incidence over the last three years at our center, this stresses the need for a national and international registry for this pathology. One could argue that the therapy has become more invasive over the years; the first two patients being managed with IABP alone. However the more invasive therapy (ECMO, LVAD) in the patients who presented later is attributable to the more severe condition of these patients with the inability to wean the patients off IABP and/or intravenous inotropes. Despite the fact that bromocriptine appears promising as a novel disease-specific treatment, we initiated it briefly in one patient (patient 5) and stopped it after implantation of the LVAD. Currently it is not clear whether the results of the proof of concept study by Sliwa *et al.* where bromocriptine was added to standard HF therapy (ACE-inhibitors, aldactone, betablockers and diuretics), can be extrapolated to this patient population dependent of IV inotropes and/or mechanical support. We hope that future trials will address this question. [178]

CONCLUSIONS

In acute and critically ill PPCM patients, mechanical support with IABP, even prior to delivery, is safe and feasible and serves as a bridge to partial recovery or as a bridge to LVAD. ECMO can serve as a bridge to LVAD, in case of refractory cardiogenic shock despite IABP and full inotropic support. The newer continuous-flow assist devices are a safe bridge to transplant for PPCM patients who cannot be weaned off intravenous inotropic support or mechanical support with IABP or ECMO. The role of bromocriptine treatment in these patients needs to be explored in future trials. Based on the literature and our experience we propose an algorithm for the treatment of acute and critically PPCM. **(Figure 1**)

Figure 1: Algorithm for the treatment of acute and critically ill PPCM



HF= heart failure, (*) Avoid ACE-inhibitors, Angiotensin-II receptorblockers and aldosterone antagonists during pregnancy, MODS= Multiple Organ Dysfunction Syndrome

Key messages

• Acute and critically ill PPCM patients refractory to medical therapy should be treated with mechanical support.

• IABP support is feasible and safe in the pre- and postpartum period as a bridge to recovery or as a bridge to assist device.

• In patients with refractory cardiogenic shock and Multiple Organ Dysfunction Syndrome despite IABP, ECMO should be considered as a temporary 'emergency rescue' support (bridge to recovery or bridge to LVAD).

• Continuous-flow LVADs are safe as a bridge to transplant in this young patient population.

• Bromocriptine, a novel disease-specific treatment, can be considered in these patients.

Abbreviations

PPCM: peripartum cardiomyopathy , IABP: intra aortic balloon pump, LVAD: left ventricular assist device, ECMO: extra corporeal membrane oxygenation, LVEDD= left ventricular end diastolic diameter, UFH: unfractionated heparin, aPTT: activated partial thromboplastin time; ACT: activated clotting time, ATIII: Anti-thrombin III.

Competing interests: The authors declare that they have no competing interests.

Author's contributions: The idea for the article came from SG and MDP. SG, MDP, EVDC, FT, FM and IH collected data and prepared the article. YVB, SB and FDS reviewed the paper critically. SG and MDP finalised the text. All authors read and approved the manuscript.

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V. Discussion

This thesis focuses on the clinical characteristics and outcomes of women with acute cardiac disease, more specifically STEMI and AHF, with specific attention for gender differences in outcome. In general one fourth of STEMI patients and half of AHF patients are comprised of women, which was also the case in the analysed STEMI- and HF- registries used in this work.

We compared in-hospital mortality and the predictive performance of the TIMI risk score in STEMI between male and female patients undergoing pPCI **(Chapter 1)** and we evaluated gender differences in the prevalence and prognostic impact (in-hospital mortality) of renal dysfunction in these patients **(Chapter 2)**. We studied gender differences in the prevalence, treatment and prognostic impact (in-hospital mortality and 1-year rehospitalisation and mortality) of AF in AHF **(Chapter 3)**. Furthermore the outcomes of STEMI-patients and AHF-patients with co-occurring AF were evaluated in two age groups, a younger and older age group (< and ≥ 65 years in STEMI, < and ≥ 75 years in AHF) **(Chapters 1 and 3)**. Finally we evaluated the safety and efficacy of mechanical support in critically ill PPCM patients in **Chapter 4**.

In **Chapter 1** we evaluated 8,073 patients included in the Belgian STEMI registry (23.8% female patients) who underwent pPCI and we demonstrated that, after adjusting for the TIMI risk score variables, the risk of in-hospital mortality was higher in women (OR=1.47 (95% CI 1.15-1.87, p=0.002). After further adjustment for age a sustained mortality gap was demonstrated in the younger population of <65 years-of-age (OR=1.73 [95% CI 1.07-2.82], p=0.03) but not in the population ≥ 65 years (OR=1.27 [95% CI 0.96-1.68], p=0.09). We further demonstrated that the TIMI risk score demonstrated a good prognostic discrimination in men and women but the mortality prediction for TIMI risk score was slightly better in men (p=0.02 for TIMI score x gender interaction).

Worse short-term outcome in younger women, suffering an ACS, was reported

earlier, however these older reports often included NSTEMI and STEMI patients and women were less likely than men to undergo a coronary intervention. [65] Other reports investigating short-term outcomes in men and women undergoing pPCI for STEMI were conflicting but the sample sizes were often small with exception of the paper by Benamer, including 16,760 STEMI patients of whom 82.6% of the male and 88.9% of the female patients were treated with pPCI, demonstrating a comparable in-hospital mortality difference between genders (10.1 % in women vs. 4.9% in men compared to our registry: 9.8% in women vs. 4.3% in men). [113] In contrast to our findings, this mortality difference remained only significant in patients >75 years-of-age after multivariable adjustment. This can be due to the fact that other and more clinical variables (history of hypertension, history of CAD, tachycardia, hypotension, ischaemic time>4h, low body weight, infarct localization) for adjustment were used in our analysis. A worse 30-day outcome for younger women <50 years as compared to men was also observed in a large real-world Italian population treated with PCI. [197] Just recently, the worse short-term (30-day) outcome in women <65 years treated with pPCI for STEMI was confirmed by a single centre study from the Netherlands, including the exact same amount of women <65 years (N=708). [198]

Why is female gender associated with mortality in this young patient population? In our analysis this could not be explained by the higher prevalence of hypertension or diabetes, nor by the lower bodyweight, the worse clinical profile (higher Killip class, more tachycardia and hypotension) nor the higher prevalence of ischaemic times >4 hours. Longer ischaemic times, defined as ischaemic times >4h were not related to mortality in our analysis but it remains unclear to what extent the worse clinical profile in women could be improved by reducing ischaemic times and what impact this would have on gender differences in outcome. Furthermore the use of ischaemic time as a dichotomous variable instead of a continuous variable and the cut-off of 4h can have influenced our results since mortality already increases at door to balloon times of > 90 minutes (irrespective of symptom onset time) and even shorter in high risk patients. [199] The longer ischaemic times may partly be related to the fact that more women than men present without chest pain, a sex difference that is even larger among younger women, however this lack of chest pain among younger women was not associated with increased mortality after adjustment. [25] A lack of awareness, both at the patient and at the physician level may also result in different access to care and longer time delays between symptoms and diagnosis followed by therapy. [200] Longer ischaemic times seem to be associated more with long-

term outcomes. [201] Reducing time delays is therefore one of the most important modifiable factors that might have an influence on outcome. We did not have data on severity of coronary artery disease but in the analysis by Otten et al. the younger women had less pronounced coronary artery disease (more single vessel disease and more TIMI 3 flow) at the moment of presentation as compared to the men while their outcome was worse. Data on smoking, the use of oral contraceptives or hormone replacement therapies were not available either in the registry but these are mere risk factors for the development of acute coronary syndromes and long-term outcome rather than risk factors for an adverse short-term outcome. [202] Women are also known to have a higher complication rate (especially vascular and bleeding complications, dissection, abrupt closure due to the smaller vessel size) [84, 85, 203] which was not recorded in our registry and not adjusted for. Despite the fact that women have been shown to have greater myocardial salvage with pPCI compared to men [92] they seem to be at higher risk for HF complicating MI [94, 204]. The higher risk for this HF complicating MI has been attributed to sex differences in remodelling (less ventricular dilatation) which may be protective in the long run but can lead to increased incidence of HF on the short-term. In our registry more women presented with cardiogenic shock, which was adjusted for, however we did not have information on the development of HF during hospitalisation for MI. We did not explore differences in use of evidence based therapies in women, some reports indicate that the prescription of evidence based therapies in the acute phase post-ACS is not different between women and men while others reported that these therapies were less often prescribed to women at discharge. [81, 198, 203] There is no information on gender differences in the short-term effects of these medications but their effectiveness on the long term was investigated demonstrating that the benefit of the combination of a of beta-blocker with a statin and the combination of a beta-blocker with an ACE-I or ARB was significantly greater in men than in women. [23]

Finally it is possible that other unknown confounders or an unidentified biological or non-biological factor might explain the gender-difference in in hospital-mortality among younger women suffering STEMI .

Despite the gender differences in outcome after adjustment for TIMI risk variables, the TIMI risk score for STEMI provided a good prognostic performance in both genders, indicating that the relative contribution of age, comorbidities and a worse clinical profile seems to be weighted well by this score confirming its value for

early risk stratification at the bedside in men as well as in women. The mortality risk prediction of the TIMI risk score was slightly better in men and interaction tests demonstrated a larger impact of admission tachycardia, admission hypotension and Killip class > I in men.

In **Chapter 2** we demonstrated in a subgroup (N=1,638) of patients included in the Belgian STEMI registry that, despite their lower levels of serum creatinine, more women than men suffered renal dysfunction (eGFR<60mL/min/1.73m^2) at the moment of hospital admission for STEMI. Renal dysfunction was associated with in-hospital mortality, independently of the TIMI risk score and gender. The interaction test demonstrated that this impact was comparable for men and women. Renal dysfunction, assessed by eGFR, could therefore be an important reason why women with STEMI die more than men and should be taken into account when evaluating gender differences. Our data do not reveal why female gender is associated with renal dysfunction nor why renal dysfunction is associated with worse outcome. Again we suppose that there are unknown confounders or an unidentified sex-specific factor that could explain the higher incidence of renal dysfunction among women with STEMI. Renal dysfunction is associated with complications of which acute kidney injury and bleeding are the most likely to occur, both associated with short-term mortality. [147, 205] Furthermore renal dysfunction may serve as a surrogate marker for general health and for unknown risk factors that influence outcome. Routine calculation of eGFR on admission allows to identify high-risk patients and to initiate preventive strategies for contrast-induced nephropathy and bleeding.

In **Chapter 3** we demonstrated that there were no gender differences in the prevalence and treatment of AF in patients hospitalised for AHF and that the composite end-point of 1-year mortality and re-hospitalisation was not different between sexes. However further subgroup analysis of patients < and ≥ 75 years revealed an adjusted worse outcome for women <75 years-of-age as compared to men <75 years-of-age with a significant sex-age interaction. AF on admission was present in 45% of the patients in the BIO-HF registry and this finding is in line with recent findings that the incidence of co-occurring AF in HF-patients is increasing. [126] Women differed from men in being older, more frequently having hypertension, more frequently having HF-PEF and less frequently having a history of CAD as in other registries. [33] Our data do not provide clear insight into the reason behind the worse outcome in the younger patient group, in fact these younger women were

more similar to the younger men in terms of baseline characteristics than the older women to the older men but this can be due to the lower sample size. Most importantly HF-PEF was less prevalent among the younger women than the older women. This suggests that when a woman becomes more equal to a man in terms of ejection fraction, her prognosis gets worse. Ghali *et al.* found in a group of relatively young HF patients that AF was an independent predictor for mortality in women but not in men but this was not yet demonstrated in the setting of AHF. [166] It is known that women with AF have a higher risk of mortality from stroke and thromboembolism especially when they have additional risk factors such as HF. [162] However 'not prescribing VKA' at discharge was adjusted for and did not change our results. We also adjusted for the use of Sotalol and Digoxin in these patients because their use is associated with worse outcome in women but this didn't change our findings either. [21, 22] Before speculating on other reasons for the worse outcome in younger women with HF and AF this finding should be explored in larger patients series.

In **Chapter 4** we evaluated the feasibility and safety of mechanical support in critically ill PPCM patients. First of all the need for mechanical support underscores the severity of the disease in this young population. Thanks to contemporary HF therapy the survival of these women has improved but in the acute phase mechanical support can be necessary as a temporary measure.

The last 2 decades more disease specific therapies have been proposed, of which bromocriptine seems the most promising. [178, 206] In 2007 it was demonstrated in mice that the development of PPCM was mediated by enhanced oxidative stress and the subsequent cleavage of prolactin into an anti-angiogenic and pro-apoptotic 16-k-Da form. A new concept was born for the treatment of PPCM: inhibition of prolactin release with bromocripitine. [175] In 2010 a proof of concept study was published demonstrating a larger degree of left ventricular recovery in the 10 patients treated with bromocriptine on top of standard HF therapy as compared to 10 conventionally treated patients. [178] While larger multicentre and randomised trials are needed to confirm the benefit of bromocriptine in PPCM patients, a prospective multi-centre registry in Germany supported the potential benefit of bromocriptine on top of standard HF treatment but pointed out that it may not be sufficiently effective in all patients, especially those with a very low ejection fraction (<25%).

As in the United States the use of mechanical support for PPCM also increased in our centre the last decade. [207] Improvement, or even better, recovery of left ventricular function is possible but less likely to occur when the left ventricle is severely dilated, as illustrated in this case series. [171] The two women with a LVEDD <56 mm showed recovery after respectively 4 and 7 days of uncomplicated support with IABP and initiation of proper HF therapy. The other 4 patients with a LVEDD ranging from 61 to 79 mm could not be weaned off the IABP (N=3) or ECMO (N=1) and were implanted with a continuous-flow assist device, which was safe as a bridge to transplant. Early bleeding complications were observed in three of these patients, there were no late bleeding complications. Despite the fact that PPCM is a pro-thrombotic condition we observed no thrombotic complications in the LVAD patients. Infection of the pocket occurred in one patient. A recently published larger patient's series demonstrated that PPCM patients who receive durable mechanical support have a better survival compared to women who receive it for non-PPCM. This is mostly related to the fact that these patients are younger and have less comorbidity at presentation. [98] This stresses the fact that this therapy should not be withheld in PPCM patients with refractory HF. Based on our findings we propose an algorithm for the treatment of acute and critically PPCM patients. In general, this is not so different from the algorithms for the treatment of acute HF. The initiation of conventional oral HF therapy during pregnancy remains challenging; ACE-I, ARB and aldosterone antagonists are contra-indicated; oral hydralazine with or without long-acting nitrates can serve as an alternative but this is not supported by evidence. [5, 96]

Limitations of this work*:*

The use of nonrandomised registries has several drawbacks. First, as in all registries one of the limitations are missing data. There were no missing data in **chapter 1** since a patient file could only be finalised when all required data were provided. For the sub-analysis on renal dysfunction in **chapter 2**, the eGFR could not be calculated in 11.9% of the cases, due to missing creatinine values while in the dataset used in **chapter 3** data on LVEF were missing in 6.9% of the cases. Second, the data were examined using risk adjustment models; however, we cannot exclude other confounding factors as mentioned above that were not registered in the databases. Third, the characterisation of some continuous characteristics into dichotomies (e.g. body weight, ischaemic times) was inherent to the registries and

may have introduced residual confounding and hence biased our results to some extent. Fourth, although the registries require enrolment of all consecutive patients at participating centres, selection biases cannot be excluded. Finally, the possibility of inaccuracies in data coding or entry cannot be totally ruled out; for the STEMI database yearly audits, conducted by an external commission, of 10% of all patient files was performed to verify the validity of the data; the evaluation of these files demonstrated a 96% concordance rate between source documents and case report forms.

Final post hoc hypothesis

The background of the worse adjusted (traditional risk factors, treatment delay, clinical presentation) outcome in young female STEMI-patients is probably multi-factorial with biological (e.g. renal dysfunction) and non-biological factors (e.g. psychosocial factors) interacting in a complex and currently unravelled way. Younger women may need a higher burden of traditional risk factors to overrule the presumed protective effect of oestrogen, which could lead to a higher incidence of reno-vascular disease and hence renal dysfunction predisposing to adverse outcome. Furthermore non-biological factors such as social class (often associated with unhealthy lifestyle) and psychological factors such as anxiety, depression [208] and mental stress [209] are more prevalent among younger women with STEMI and may also negatively affect outcome. At higher ages, when the potentially protective effects of pre-menopause have disappeared gender differences in outcome may be explained by co-morbidities, clinical characteristics and the higher age these women are presenting with. Claiming that the same factors are responsible for worse outcome in young women with HF and AF would be too speculative since this finding was based on a sub-group analysis in a small sample.

VI Future perspectives

Further efforts are necessary to reduce the 'gender gap' in STEMI at younger age. In order to reach this goal more research is needed into the reasons behind the sex-differences in pathophysiology, clinical presentation, management and outcome. Dedicated registries, including all consecutive patients, could reveal to what extent biological and non-biological factors are responsible for this difference in outcome.

In this era of the 'interventionalisation' of cardiology the main goal must remain to deliver optimal care to the individual patient, male or female, in a timely fashion. This starts with optimal tools for the selection of patients to undergo these interventions. Today it is not clear if sex-specific tools for history taking and interpretation of the ECG or different cut-offs for the interpretation of lab results, especially biomarkers, could be of any help. Meanwhile the suspicion for ACS should remain high in every patient with chest pain or common non-chest pain symptoms, also in the thirty- forty- and fifty-something woman coping with stress, especially those with cardiac risk factors such as diabetes, hypertension and smoking.

Specific attention must go to the prevention of complications of interventional cardiology such as bleeding and contrast-induced nephropathy, two entities occurring more in women and associated with significant morbidity and mortality. [210] Routine estimation of the GFR could be helpful for the selection of patients at risk and the initiation of preventive measures. Whether adding eGFR instead of serum creatinine could improve the prognostic performance of currently used bedside risk stratification models, especially in women, remains to be elucidated.

Women are underrepresented in clinical trials, especially in the field of HF indicating that more women should be included in these trials in order to provide evidence based information to the physicians caring for these patients. Furthermore clinical trials investigating new pharmacological and non-pharmacological agents or techniques should pre-specify and report sex-specific outcomes, which is already

increasingly seen in recent literature. [211, 212] However the inclusion of patients in clinical trials can be subject of selection bias and one must take into account the shortcomings of subgroup analysis.

Another on-going challenge is the timely diagnosis and the treatment of PPCM. Despite its low prevalence it is one of the main reasons for LVAD implantation in young women. Again the clinical suspicion for PPCM must be high in patients complaining of important dyspnoea in the peripartum period. Echocardiography and BNP are two tools that are easily accessible in the Western world that are very useful in this context because of their high negative predictive value. [96] Today it is not clear whether explanation of the LVAD is a safe option in patients demonstrating recovery of left ventricular function and what criteria should be used. Apart from the supportive treatment of HF, bromocriptine could be a disease specific treatment but data from a large randomised trial are lacking. [178] There might be another disease specific therapy emerging; unpublished data (oral communication, Mebazaa, 4th congress on Acute Cardiac Care, June 2014 Brussels) show lower levels of relaxin in women with PPCM. Serelaxin is a recombinant form of human relaxin-2, a naturally occurring peptide hormone that mediates the physiological cardiovascular and renal adaptations of pregnancy. [213] In the RELAX-AHF trial IV infusion of Serelaxin to patients with AHF was associated with reduction of cardiovascular and all cause mortality at 180 days. [214] A clinical trial investigating the effect of IV Serelaxin in women with PPCM would therefore be of great interest.

Last but not least the awareness of female specific and nonspecific CVD must improve among the public and the health care workers in order to reach better outcome in women.

VII Summary – Samenvatting

Summary:

This thesis focuses on the clinical characteristics and outcome of women with acute cardiac disease. These were evaluated in the setting of STEMI and AHF. We compared mortality rate in STEMI between men and women and we evaluated gender differences in the prevalence and impact on prognosis of selected clinical variables more specifically renal dysfunction in the setting of STEMI and AF in the setting of AHF. In patients with PPCM we evaluated the efficacy and safety of different forms of mechanical support.

We demonstrated that mortality in female patients undergoing pPCI for STEMI is doubled vs. that in men. This is largely explained by the different clinical profile these women present with: they are older, have more comorbidities, present later and in a worse condition than their male counterparts. The TIMI risk score incorporates this clinical profile in a weighted fashion and provided a good prognostic discrimination and calibration with regard to the in-hospital outcome, however the prognostic impact of the TIMI risk score was slightly better in men. Adjustment for TIMI risk score variables and age demonstrated a significant gender difference in outcome in the population <65 years-of-age but not in the population ≥65 years-of-age. The worse outcome in younger women was confirmed in other registries but the reason behind it remains unclear and could be investigated in future trials.

Renal dysfunction could be an important reason why women with STEMI undergoing pPCI die more than men: female gender was independently associated with renal dysfunction (defined as an eGFR <60mL/min/1.73m^2) at admission and renal dysfunction had an equal prognostic impact on in-hospital outcome in men and women on top of the TIMI risk score. Therefore we advise early assessment of the renal function by calculation of eGFR in order to identify high-risk patients and to initiate preventive measures. [215]

We observed no gender differences in the prevalence, the management and the prognostic impact on in-hospital and 1-year outcome of AF in patients with AHF. However a significant sex-age interaction was observed with worse outcome for women <75 years-of-age with AHF and AF compared to men <75 years-of-age with AHF and AF, a new finding that we consider hypothesis generating.

Finally we evaluated the efficacy and safety of mechanical support in critically ill PPCM patients. While the small sample size reflects the rare character of this disease, the need for mechanical support on top of supportive medical therapy reflects the severity of this disease, affecting young women during pregnancy or in the early puerpium. IABP was safe and efficient as a bridge to recovery and safe as a bridge to LVAD. In one patient with refractory cardiogenic shock ECMO provided a feasible and safe bridge to LVAD. Four patients were implanted with a continuous-flow LVAD (HeartMate II®, Thoratec Inc.) that offered a safe bridge to transplant. Based on our experience we propose a treatment algorithm for the treatment of acute and critically ill PPCM.

One of the striking findings of this thesis is the poor prognosis for younger women presenting with acute cardiac disease while worse outcome in older women is largely explained by their co-morbidities, the worse clinical profile they present with and their higher age. More research is needed to explore the reasons behind the worse outcome in pPCI treated STEMI patients <65 years-of-age and AHF patients with AF <75 years-of-age.

On-going efforts are needed to increase awareness for cardiac disease among women and their treating physicians in order to minimize delays to diagnosis and treatment in ACS as well as AHF.

Samenvatting:

In deze doctoraatsthesis ligt de nadruk op de klinische kenmerken en prognose van vrouwen met acute cardiale ziekte. Deze werden geëvalueerd in de setting van het ST- segment elevatie myocardinfarct (STEMI) en acuut hartfalen (AHF). We vergeleken de in-hospitaal mortaliteit tussen mannen en vrouwen bij STEMI. We onderzochten geslachtsverschillen in prevalentie en impact op prognose van geselecteerde klinische variabelen, meerbepaald nierfalen in de setting van STEMI en atriale fibrillatie (AF) in de setting van acuut hartfalen (AHF). Daarnaast evalueerden we de doeltreffendheid en veiligheid van verschillende vormen van mechanische cardiale ondersteuning bij patiëntes met peripartum cardiomyopathie.

We toonden aan dat vrouwen die een behandeling met pPCI ondergingen in het kader van een STEMI eens zoveel kans hadden op overlijden in het ziekenhuis als mannen. Dit kon grotendeels maar niet volledig verklaard worden door het slechter klinisch profiel waarmee deze dames zich aanboden: ze waren ouder, hadden meer comorbiditeit en kwamen later en in slechtere klinische toestand naar de spoedopname. De TIMI risico score houdt rekening met dit slechtere profiel op een gewogen wijze en bood in onze analyse een goede prognostische discriminatie en calibratie wat betreft in-hospitaal uitkomst van deze mannen en vrouwen; het prognostisch impact van deze score was echter iets beter bij mannen. Een multivariable regressie analyse die rekening hield met elk van de TIMI risk score variabelen en leeftijd toonde een significant slechtere uitkomst voor vrouwen <65 jaar maar niet voor vrouwen ≥65 jaar. Deze slechtere uitkomst voor jongere vrouwen werd aangetoond in andere recente en minder recente registers en de reden hierachter blijft tot op heden onduidelijk; dit zou een onderzoeksonderwerp kunnen zijn voor toekomstig onderzoek.

Nierinsufficiëntie bij opname zou een belangrijke reden kunnen zijn voor de hogere in-hospitaal mortaliteit na STEMI bij vrouwen: nierlijden (gedefineerd als een eGFR <60mL/min/1.73m^2) kwam meer voor bij vrouwen en ging gepaard met meer kans op in-hospitaal overlijden, onafhankelijk van de TIMI risico score. Daarom raden we aan om in de klinische praktijk de nierfunctie te bepalen op basis van de eGFR en aan te wenden om hoog risico patiënten te selecteren bij wie preventieve maatregelen kunnen worden genomen zoals bijvoorbeeld preventie van contrast geïnduceerde nefropathie.

We toonden aan dat er geen geslachtsverschillen zijn in de prevalentie, de behandeling en het prognostisch impact van AF bij patiënten met AHF. We toonden wel een interactie aan tussen geslacht en leeftijd met een slechtere uitkomst voor vrouwen <75 jaar met AHF en AF vergeleken met mannen <75 jaar met AHF en AF. Dit is een nieuwe bevinding in een kleine groep patiënten die we daarom als hypothese genererend beschouwen.

Tot slot evalueerden we de doeltreffendheid en de veiligheid van mechanische ondersteuning bij patiëntes die kritisch ziek waren ten gevolge van peripartum cardiomypathie. De kleine patiëntengroep illustreert het zeldzame karakter van deze aandoening terwijl de nood aan mechanische ondersteuning aantoont hoe ernstig deze aandoening is. Een intra-aortische ballonpomp was veilig en efficiënt als een brug naar herstel of brug naar linker ventrikel assist device (LVAD). In één patiënte met refractaire cardiogene shock was een extra-corporele membraan oxygenator veilig als brug naar LVAD. Vier patiëntes kregen een LVAD (HeartMate II® , Thoratec Inc.) met continue flow als veilige brug naar harttransplantatie. Op basis van onze bevindingen stelden we een algoritme op voor de behandeling van PPCM.

Eén van de belangrijke bevindingen van deze thesis is de slechtere prognose voor jongere vrouwen die zich presenteren met acute cardiale ziekte terwijl de minder goede uitkomst bij oudere vrouwen voornamelijk verklaard wordt door hun leeftijd, comorbiditeit en hun slechtere klinische profiel bij opname. Meer onderzoek is nodig naar de redenen voor de slechtere prognose bij vrouwen met STEMI <65 jaar en vrouwen met AHF en AF <75 jaar.

Blijvende inspanningen zijn nodig om de bewustwording van cardiale ziekte te verbeteren bij vrouwen en artsen die deze vrouwen behandelen. Dit zou kunnen leiden tot een snellere diagnostiek en behandeling zowel bij acute coronaire syndromen als bij acuut hartfalen.

Key findings of the thesis:

- *In-hospital mortality is higher in female patients undergoing pPCI for STEMI, this is largely explained by a worse clinical profile upon admission, as reflected by their higher TIMI risk score for STEMI, as well as their higher age.*
- *Female STEMI patients <65 years undergoing pPCI for STEMI remain at risk with a higher adjusted in-hospital mortality rate as compared to their male counterparts (OR=1.73).*
- *The TIMI risk score for STEMI is a reliable and simple bedside score suitable for early risk stratification in women as well as in men undergoing ppCI for STEMI.*
- *Renal dysfunction is more prevalent among women with STEMI and is associated with in-hospital mortality in both genders.*
- *There are no gender differences in the prevalence and treatment of AF in patients hospitalised with AHF and the composite of 1-year mortality or rehospitalisation is not different between men and women.*
- *Female patients hospitalised with AHF and AF <75 years-of-age are at higher risk for the composite of 1-year death or rehospitalisation compared to male patients <75 year-of-age.*
- *Mechanical support in critically ill PPCM is safe and efficient as a bridge to recovery (IABP), as a bridge to LVAD (IABP, ECMO) and as a bridge to heart transplant (LVAD).*

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Gent, 14 januari 2015

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Eur Heart J 2013;34 Suppl.1: 330-331

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Acta Cardiologica	Acta Clinica Belgica	International Journal of Cardiology
European Heart Journal	Nephrology Dialysis Transplantation	Journal of Atrial Fibrillation