GENDER DIFFERENCES IN DIAGNOSIS AND PROGNOSIS OF CORONARY ARTERY DISEASE

Manon van der Meer

GENDER DIFFERENCES IN DIAGNOSIS AND PROGNOSIS
OF CORONARY ARTERY DISEASE

ISBN: 978-94-6295-200-3
Design: wenz iD, Wendy Schoneveld
Printed by: Uitgeverij BOXPress, 's-Hertogenbosch

Financial support by the Netherlands Heart Foundation and the Heart Lung Foundation Utrecht for the publication of this thesis is gratefully acknowledged.

Further financial support for the publication of this thesis by Chipsoft and Servier Nederland Farma B.V. is also gratefully acknowledged.

GENDER DIFFERENCES IN DIAGNOSIS AND PROGNOSIS OF CORONARY ARTERY DISEASE

MAN VROUW VERSCHILLEN IN DIAGNOSE EN PROGNOSE VAN CORONAIRLIJDEN

(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht
op gezag van de rector magnificus, prof.dr. G.J. van der Zwaan,
ingevolge het besluit van het college voor promoties in het openbaar te verdedigen
op woensdag 17 juni 2015 des middags te 12.45 uur

door

Manon Geraldine van der Meer
geboren op 20 februari 1984 te 's Gravenhage

Promotoren:
Prof. dr. P.A.F.M. Doevendans
Prof. dr. Y. van der Graaf

Copromotoren:
Dr. Y. Appelman
Dr. H.M. Nathoe

"The gin and tonic has saved more Englishmen's lives, and minds, than all the doctors in the Empire."

Winston Churchill

CONTENTS

APPENDIX

CHAPTER 1

GENERAL INTRODUCTION

In the Netherlands cardiovascular disease (CVD) results in approximately 395.000 hospital admissions each year of which 224.000 (57%) in men and 171.000 (43%) in women.[1] Atherosclerosis is the underlying cause of CVD and builds up with increasing age, making CVD a disease of the elderly. Women with CVD are on average older than men with CVD. To illustrate: in Dutch men, the peak of hospital admissions is in the age range 65-74 years while in Dutch women this peak is between 75-84 years.[1] This difference can be explained by the favourable hormonal balance in pre-menopausal women, mainly caused by estrogens. Estrogens positively affect plasma lipids, have anti-atherogenic properties and positively influence all the steps involved in the formation of the atherosclerotic plaque (accumulation of cholesterol in the arterial wall, arterial smooth muscle cell proliferation, platelet aggregation, collagen and elastin production).[2] As a result menopause, with a decrease of the favourable estrogens, leads to a rapid increase of the prevalence of traditional risk factors of atherosclerosis and thus CVD in women. These traditional risk factors are smoking, diabetes, hypertension, dyslipidemia and obesity. Previous studies showed that the impact of most of the traditional risk factors is higher in women than in men.[3-8] For example, women that smoke have a higher risk of fatal and nonfatal CVD than man that smoke.[3,6] The same holds true for hypertension, dyslipidemia and most of all diabetes.[3-8] Besides the traditional risk factors women have so-called female-specific risk factors, related to the hormonal- or reproductive history of women (such as age at menopause or gestational hypertension). It remains unknown if these female-specific risk factors should be evaluated as separate risk factors or as precursors of the traditional cardiovascular risk factors.[8]

For a long time, CVD has been considered a men's disease. However, in the last decade there is increasing attention for differences between women and men in the diagnosis, treatment and prognosis of CVD and in particular of coronary artery disease (CAD). Previous studies described a delay in the diagnostic process of women, which can be caused by the patient, general practitioner or other referring specialists or cardiologists.[9-11] It has been described that women use lengthy decision-making processes before deciding to seek medical care, leading to postponement.[11,12] Moreover women with CAD tended to misclassify their symptoms relating them to non-cardiac causes.[9,12,13] On the other hand, previous studies also mentioned that management of chest pain by physicians is influenced by gender of the patient caused by an underestimation of the risk of CAD in women leading to delay in establishing the correct diagnosis.[14,15] Furthermore, former studies demonstrated that women undergo less additional tests as advised in the guidelines for CAD, subsequently leading to under diagnosis.[16,17] But it has also been suggested that diagnosing CAD based on symptoms would be more difficult in women than in men.[18-23] Women with CAD appeared to have an atypical clinical presentation compared to men, leading to misdiagnosis and suboptimal treatment.[18,19,21,23] Importantly, however, most studies only compared symptoms in women and men with an established diagnosis of CAD. The diagnostic value of clinical symptoms in women and men suspected of CAD, for example presenting with chest pain in general practice or at the emergency department

has hardly been evaluated. Therefore the *first* aim of this thesis was to evaluate the diagnostic value of clinical symptoms for the diagnosis of CAD in women and men presenting with chest pain in the general practice and the emergency department. The *second* aim of this thesis was to investigate the influence of gender on treatment success and (long-term) prognosis. The treatment of CVD in general has improved enormously over the last decades resulting in a better prognosis of women and men. In the Netherlands, the mortality rates of CVD have decreased between 1980 and 2011 with 64% in men and 59% in women.[1] The largest decline was the mortality of acute myocardial infarctions: 84% in men and 79% in women.[1] This improvement in treatment includes better prevention (primary and secondary) for CVD, new medical options, the rise and improvement in (primary) percutaneous coronary interventions (PCI) and a decline in peri- and postoperative mortality after coronary artery bypass grafting (CABG). It remains uncertain whether women receive the same treatment as men, if they respond as good to treatment as men and if there are differences in the prognosis of CVD between sexes. To illustrate: the treatment of a STEMI has improved mainly due to the shift from thrombolysis to primary PCI.[24] Therefore primary PCI is now the recommended treatment for STEMI in Europe and the United States.[25,26]

Many studies have looked for differences in outcome between women and men with a STEMI treated with primary PCI but the results remain conflicting. This is partly due to the fact that data are often difficult to compare as inclusion criteria frequently differ, and there is variation in outcome measures and duration of follow-up.[27-30] In this thesis we focused on the treatment and prognosis of women and men with a STEMI treated with primary PCI, gender differences in long-term outcome after CABG and in patients with known CVD.

Early recognition of high-risk individuals to prevent clinically manifest disease through lifestyle modifications or drug treatment is essential to prevent symptomatic cardiovascular disease.[31-34]

In an attempt to identify people at risk of CVD several prediction models have been developed throughout the years.[35-38] The Framingham Risk Score, SCORE, and the Pooled Cohort Equations are examples of such frequently used algorithms that aim to predict 10-year absolute risk of CVD for individuals without CVD.[35,37,38] Even though these prediction rules are sex-specific, they include the same combination of traditional risk factors for women and men.[35,37,38] Female-specific risk factors are known to affect CVD risk but it is however unknown whether female-specific risk factors have any added value on top of the traditional risk factors to predict future risk of CVD in women. The *third* aim of this thesis was to investigate the added value of female-specific risk factors on top of the traditional risk factors for the prediction of CVD in healthy women.

OUTLINE OF THIS THESIS

PART ONE Diagnosis

Chest pain is the second most common emergency department (ED) presenting complaint and can be an indicator of CAD. In patients presenting with chest pain at the ED a combination of diagnostic tests including patient' s symptoms, electrocardiography and troponin is routinely used to diagnose CAD. The diagnostic value of symptoms is particularly important in patients without suggestive ST-segment changes and/ or diagnostic troponin rise and fall. Previous studies suggested that diagnosing CAD based on symptoms would be more difficult in women than in men.[18-21] Women with CAD appeared to have an atypical clinical presentation compared to men, leading to misdiagnosis and suboptimal treatment.[18-21] To clarify this issue we examined in *chapter two* the predictive value of signs and symptoms and quantified its diagnostic value in women and men visiting the ED with chest pain in a large prospective multicenter study.

The prevalence of CAD in women is considerably lower than in men. As a consequence, diagnosis of CAD in women is much more difficult because other underlying causes that explain the complaints are much more likely such as gastric reflux. In *chapter three* we investigated in the same study population, patients admitted to the (cardiac) emergency department with chest pain, whether the interpretation of clinical symptoms by the physician is dependent of gender of the patient. In other words: if the physician interpreted symptoms of women differently than symptoms of men.

In the Netherlands out-of-hours general practitioner cooperatives play an important role in the acute primary care as they cover all every day from 5 pm till 8 am and the entire weekend, being in total 73% of all week hours. As the first presentation of chest pain is often at the general practitioner (GP), in *chapter four* we assessed what the influence is of gender of the patient on the triage, including the duration of the phone call, the questions asked by the triage nurse and the given urgency. On top of that we evaluated the performance of the triage: were the patients with potential life threatening diseases recognized and was this different in women and men?

PART TWO Prognosis

In *chapter five* we investigated whether differences in survival between women and men with segment-elevation myocardial infarction (STEMI) treated by primary percutaneous coronary intervention (pPCI) exist and whether they can be explained by traditional risk factors or by gender itself. Therefore, we systematically reviewed all available studies concerning gender differences in baseline characteristics, procedural features of pPCI, medical treatment and outcome of short- and long-term follow-up in patients with STEMI treated with pPCI. In *chapter six*, sex differences in long-term outcome after CABG, results

from the Ischemia Management with Accupril post-bypass Graft via inhibition of the coNverting Enzyme (IMAGINE) trial, were depicted.[39,40] This international randomized controlled study included 2553 consecutive patients with a left ventricular ejection fraction of > 40% who underwent isolated CABG. Median follow-up was 32 months (IQR 17 to 42 months). The composite endpoint comprised death, myocardial infarction, cerebrovascular event, angina, revascularization and congestive heart failure. In *chapter seven* we analyzed gender differences in long-term prognosis (all-cause mortality, cardiovascular mortality and combined cardiovascular outcome) in patients with symptomatic CVD, included in the Second Manifestations of ARTerial disease (SMART) study. In the SMART study patients with at least one type of atherosclerotic vascular disease (CAD, cerebrovascular disease, peripheral arterial disease or abdominal aortic aneurysm) were included.[41] In *chapter eight* we investigated the impact of polyvascular disease on long-term outcome in PCI patients included in the SMART study. This is the only study in this thesis that does not include a gender analysis. In women, gender-specific risk factors related to hormonal and reproductive status are known to affect CVD risk.[42-47]

It is, however, unknown whether female-specific risk factors have any added value on top of the traditional risk factors to predict future risk of CVD in women, which was analyzed in *chapter nine*. We used data from EPIC-NL, the Dutch contribution to the European Prospective Investigation into Cancer and Nutrition (EPIC). EPIC-NL consists of two population-based cohorts, the Monitoring Project on Risk Factors for Chronic Diseases (MORGEN) and the PROSPECT cohort and for this analysis we were able to use data from 24,795 healthy women aged 30-74 years. [48-50]

REFERENCES

1 Koopman C, van Dis I, Bots M, Visseren F, Vaartjes I. Hart- en vaatziekten in Nederland. In: Anonymous Hart- En Vaatziekten in Nederland 2011, Cijfers Over Leefstijl- En Risicofactoren, Ziekte En Sterfte. Den Haag, Hartstichting, 2013; pp. 7.
2 Rosano GM, Panina G. Oestrogens and the heart. Therapie 1999; 54: 381-385.
3 Grundtvig M, Hagen TP, German M, Reikvam A. Sex-based differences in premature first myocardial infarction caused by smoking: twice as many years lost by women as by men. Eur J Cardiovasc Prev Rehabil 2009; 16: 174-179.
4 Vasan RS, Larson MG, Leip EP, Evans JC, O'Donnell CJ, Kannel WB, et al. Impact of high-normal blood pressure on the risk of cardiovascular disease. N Engl J Med 2001; 345: 1291-1297.
5 Huxley R, Barzi F, Woodward M. Excess risk of fatal coronary heart disease associated with diabetes in men and women: meta-analysis of 37 prospective cohort studies. BMJ 2006; 332: 73-78.
6 Huxley RR, Woodward M. Cigarette smoking as a risk factor for coronary heart disease in women compared with men: a systematic review and meta-analysis of prospective cohort studies. Lancet 2011; 378: 1297-1305.
7 Abbey M, Owen A, Suzakawa M, Roach P, Nestel PJ. Effects of menopause and hormone replacement therapy on plasma lipids, lipoproteins and LDL-receptor activity. Maturitas 1999; 33: 259-269.
8 Appelman Y, van Rijn BB, Ten Haaf ME, Boersma E, Peters SA. Sex differences in cardiovascular risk factors and disease prevention. Atherosclerosis 2015.
9 O'Keefe-McCarthy S. Women's experiences of cardiac pain: a review of the literature. Can J Cardiovasc Nurs 2008; 18: 18-25.
10 Lefler LL, Bondy KN. Women's delay in seeking treatment with myocardial infarction: a meta-synthesis. J Cardiovasc Nurs 2004; 19: 251-268.
11 Sullivan AL, Beshansky JR, Ruthazer R, Murman DH, Mader TJ, Selker HP. Factors associated with longer time to treatment for patients with suspected acute coronary syndromes: a cohort study. Circ Cardiovasc Qual Outcomes 2014; 7: 86-94.
12 Lockyer L. Women's interpretation of their coronary heart disease symptoms. Eur J Cardiovasc Nurs 2005; 4: 29-35.
13 Gallagher R, Marshall AP, Fisher MJ. Symptoms and treatment-seeking responses in women experiencing acute coronary syndrome for the first time. Heart Lung 2010; 39: 477-484.
14 Mosca L, Linfante AH, Benjamin EJ, Berra K, Hayes SN, Walsh BW, et al. National study of physician awareness and adherence to cardiovascular disease prevention guidelines. Circulation 2005; 111: 499-510.
15 Poon S, Goodman SG, Yan RT, Bugiardini R, Bierman AS, Eagle KA, et al. Bridging the gender gap: Insights from a contemporary analysis of sex-related differences in the treatment and outcomes of patients with acute coronary syndromes. Am Heart J 2012; 163: 66-73.
16 Chang AM, Mumma B, Sease KL, Robey JL, Shofer FS, Hollander JE. Gender bias in cardiovascular testing persists after adjustment for presenting characteristics and cardiac risk. Acad Emerg Med 2007; 14: 599-605.
17 Roger VL, Farkouh ME, Weston SA, Reeder GS, Jacobsen SJ, Zinsmeister AR, et al. Sex differences in evaluation and outcome of unstable angina. JAMA 2000; 283: 646-652.
18 Dey S, Flather MD, Devlin G, Brieger D, Gurfinkel EP, Steg PG, et al. Sex-related differences in the presentation, treatment and outcomes among patients with acute coronary syndromes: the Global Registry of Acute Coronary Events. Heart 2009; 95: 20-26.
19 Culic V, Eterovic D, Miric D, Silic N. Symptom presentation of acute myocardial infarction: influence of sex, age, and risk factors. Am Heart J 2002; 144: 1012-1017.
20 Milner KA, Vaccarino V, Arnold AL, Funk M, Goldberg RJ. Gender and age differences in chief complaints of acute myocardial infarction (Worcester Heart Attack Study). Am J Cardiol 2004; 93: 606-608.

21 Patel H, Rosengren A, Ekman I. Symptoms in acute coronary syndromes: does sex make a difference? Am Heart J 2004; 148: 27-33.

22 Khan NA, Daskalopoulou SS, Karp I, Eisenberg MJ, Pelletier R, Tsadok MA, et al. Sex Differences in Acute Coronary Syndrome Symptom Presentation in Young Patients. JAMA Intern Med 2013.

23 Canto JG, Goldberg RJ, Hand MM, Bonow RO, Sopko G, Pepine CJ, et al. Symptom presentation of women with acute coronary syndromes: myth vs reality. Arch Intern Med 2007; 167: 2405-2413.

24 De Luca G, Cassetti E, Marino P. Percutaneous coronary intervention-related time delay, patient's risk profile, and survival benefits of primary angioplasty vs lytic therapy in ST-segment elevation myocardial infarction. Am J Emerg Med 2009; 27: 712-719.

25 American College of Emergency Physicians, Society for Cardiovascular Angiography and Interventions, O'Gara PT, Kushner FG, Ascheim DD, Casey DE,Jr, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013; 61: e78-140.

26 Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC), Steg PG, James SK, Atar D, Badano LP, Blomstrom-Lundqvist C, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J 2012; 33: 2569-2619.

27 Benamer H, Tafflet M, Bataille S, Escolano S, Livarek B, Fourchard V, et al. Female gender is an independent predictor of in-hospital mortality after STEMI in the era of primary PCI: Insights from the greater Paris area PCI Registry. EuroIntervention 2011; 6: 1073-1079.

28 Bufe A, Wolfertz J, Dinh W, Bansemir L, Koehler T, Haltern G, et al. Gender-based differences in long-term outcome after ST-elevation myocardial infarction in patients treated with percutaneous coronary intervention. J Womens Health (Larchmt) 2010; 19: 471-475.

29 Jakobsen L, Niemann T, Thorsgaard N, Nielsen TT, Thuesen L, Lassen JF, et al. Sex- and age-related differences in clinical outcome after primary percutaneous coronary intervention. EuroIntervention 2012; 8: 904-911.

30 Velders MA, Boden H, van Boven AJ, van der Hoeven BL, Heestermans AA, Cannegieter SC, et al. Influence of gender on ischemic times and outcomes after ST-elevation myocardial infarction. Am J Cardiol 2013; 111: 312-318.

31 Taylor F, Huffman MD, Macedo AF, Moore TH, Burke M, Davey Smith G, et al. Statins for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev 2013; 1: CD004816.

32 Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. BMJ 2009; 338: b1665.

33 Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-Year Follow-Up of Intensive Glucose Control in Type 2 Diabetes. N Engl J Med 2008; 359: 1577-1589.

34 Ockene JK, Kuller LH, Svendsen KH, Meilahn E. The relationship of smoking cessation to coronary heart disease and lung cancer in the Multiple Risk Factor Intervention Trial (MRFIT). Am J Public Health 1990; 80: 954-958.

35 Goff DC,Jr, Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB S, Gibbons R, et al. 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2013.

36 Ridker PM, Buring JE, Rifai N, Cook NR. Development and validation of improved algorithms for the assessment of global cardiovascular risk in women: the Reynolds Risk Score. JAMA 2007; 297: 611-619.

37 D'Agostino RB S, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation 2008; 117: 743-753.

38 Conroy RM, Pyorala K, Fitzgerald AP, Sans S, Menotti A, De Backer G, et al. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. Eur Heart J 2003; 24: 987-1003.

39 Rouleau JL, Warnica WJ, Baillot R, Block PJ, Chocron S, Johnstone D, et al. Effects of angiotensin-converting enzyme inhibition in low-risk patients early after coronary artery bypass surgery. Circulation 2008; 117: 24-31.
40 Warnica JW, Gilst WV, Baillot R, Johnstone D, Block P, Myers MG, et al. Ischemia Management with Accupril post bypass Graft via Inhibition of angiotensin coNverting enzyme (IMAGINE): a multicentre randomized trial - design and rationale. Can J Cardiol 2002; 18: 1191-1200.
41 Simons PC, Algra A, van de Laak MF, Grobbee DE, van der Graaf Y. Second manifestations of ARTerial disease (SMART) study: rationale and design. Eur J Epidemiol 1999; 15: 773-781.
42 de Groot PC, Dekkers OM, Romijn JA, Dieben SW, Helmerhorst FM. PCOS, coronary heart disease, stroke and the influence of obesity: a systematic review and meta-analysis. Hum Reprod Update 2011; 17: 495-500.
43 Fraser A, Nelson SM, Macdonald-Wallis C, Cherry L, Butler E, Sattar N, et al. Associations of pregnancy complications with calculated cardiovascular disease risk and cardiovascular risk factors in middle age: the Avon Longitudinal Study of Parents and Children. Circulation 2012; 125: 1367-1380.
44 Oliver-Williams CT, Heydon EE, Smith GC, Wood AM. Miscarriage and future maternal cardiovascular disease: a systematic review and meta-analysis. Heart 2013; 99: 1636-1644.
45 Smith GC, Pell JP, Walsh D. Pregnancy complications and maternal risk of ischaemic heart disease: a retrospective cohort study of 129,290 births. Lancet 2001; 357: 2002-2006.
46 Wellons M, Ouyang P, Schreiner PJ, Herrington DM, Vaidya D. Early menopause predicts future coronary heart disease and stroke: the Multi-Ethnic Study of Atherosclerosis. Menopause 2012; 19: 1081-1087.
47 Wenger NK. Recognizing pregnancy-associated cardiovascular risk factors. Am J Cardiol 2014; 113: 406-409.
48 Beulens JW, Monninkhof EM, Verschuren WM, van der Schouw YT, Smit J, Ocke MC, et al. Cohort profile: the EPIC-NL study. Int J Epidemiol 2010; 39: 1170-1178.
49 Boker LK, van Noord PA, van der Schouw YT, Koot NV, Bueno de Mesquita HB, Riboli E, et al. Prospect-EPIC Utrecht: study design and characteristics of the cohort population. European Prospective Investigation into Cancer and Nutrition. Eur J Epidemiol 2001; 17: 1047-1053.
50 Smit H, Verschuren W, Bueno-de-Mesquita H., Seidell J. Monitoring van Risicofactoren en Gezondheid in Nederland (MORGEN-project). Doelstellingen en werkwijze. Bilthoven: RIVM 1994; 263200001.

CHAPTER 2

THE DIAGNOSTIC VALUE OF CLINICAL SYMPTOMS IN WOMEN AND MEN PRESENTING WITH CHEST PAIN AT THE EMERGENCY DEPARTMENT, A PROSPECTIVE COHORT STUDY

PLoS One. 2015 Jan 15;10(1):e0116431

Manon G. van der Meer, Barbra E. Backus, Yolanda van der Graaf, Maarten J. Cramer, Yolande Appelman, Pieter A. Doevendans, A. Jacob Six, Hendrik M. Nathoe

Letter to the editor
Manon G. van der Meer, Hendrik M. Nathoe, Yolande Appelman
JAMA Intern Med. 2015 Apr 1;175(4):650

ABSTRACT

Background

Previous studies suggested that diagnosing coronary artery disease (CAD) is more difficult in women than in men. Studies investigating the predictive value of clinical signs and symptoms and compare its combined diagnostic value between women and men are lacking.

Methodology

Data from a large multicenter prospective study was used. Patients admitted to the emergency department (ED) with chest pain but without ST-elevation were eligible. The endpoint was proven CAD, defined as a significant stenosis at angiography or the diagnosis of a non-ST-elevation myocardial infarction or cardiovascular death within six weeks after presentation at the ED. Twelve clinical symptoms and seven cardiovascular risk factors were collected. Potential predictors of CAD with a p-value <0.15 in the univariable analysis were included in a multivariable model. The diagnostic value of clinical symptoms and cardiovascular risk factors was quantified in women and men separately and areas under the curve (AUC) were compared between sexes.

Results

A total of 2433 patients were included. We excluded 102 patients (4%) with either an incomplete follow up or ST-elevation. Of the remaining 2331 patients 43% (1003) were women. CAD was present in 111 (11%) women and 278 (21%) men. In women 11 out of 12 and in men 10 out of 12 clinical symptoms were univariably associated with CAD. The AUC of symptoms alone was 0.74 (95%CI: 0.69-0.79) in women and 0.71 (95%CI: 0.68-0.75) in men and increased to respectively 0.79 (95%CI: 0.74-0.83) in women versus 0.75 (95%CI: 0.72-0.78) in men after adding cardiovascular risk factors. The AUCs of women and men were not significantly different (p-value symptoms alone: 0.45, after adding cardiovascular risk factors: 0.11).

Conclusion

The diagnostic value of clinical symptoms and cardiovascular risk factors for the diagnosis of CAD in chest pain patients presenting on the ED was high in women and men. No significant differences were found between sexes.

INTRODUCTION

Chest pain is the second most common emergency department (ED) presenting complaint and can be an indicator of coronary artery disease (CAD).[1] In patients presenting with chest pain at the ED a combination of diagnostic tests including patient's symptoms, electrocardiography (ECG) and troponin is routinely used to diagnose CAD.[2,3] The diagnostic value of symptoms is particularly important in patients without suggestive ST-segment changes and/ or diagnostic troponin rise and fall.[4,5] Over 4% of patients with CAD are not recognized at the ED, leading to an increased mortality.[6]
Recently there is growing interest for differences in clinical presentation of women and men with CAD. Previous studies suggested that diagnosing CAD based on symptoms would be more difficult in women than in men.[7-11] Women with CAD appeared to have an atypical clinical presentation compared to men, leading to misdiagnosis and suboptimal treatment.[7-10,12] Importantly, however, most studies only compared symptoms in women and men with an established diagnosis of CAD. But the crucial unanswered clinical question is which clinical signs and symptoms are associated with CAD in women and men suspected of CAD and whether the combined diagnostic value differs between sexes. To clarify this issue we examined the predictive value of signs and symptoms and quantified its diagnostic value in women and men visiting the ED with chest pain in a large prospective multicenter study.

METHODS

Study population

Data from "The prospective validation of the HEART score" study were used.[13] This study was performed at ten hospitals in the Netherlands between 2008 and 2009. Any patient admitted to the (cardiac) ED with chest pain was eligible. The ethics committees of all participating hospitals approved the study and waived informed consent because all patients received standard medical care and the data was analysed anonymously. We excluded patients with a ST-elevation myocardial infarction (STEMI). Moreover, according to current guidelines, patients with a STEMI were directly referred to the catheterization laboratory.[14]
During admission of the patient at the ED, the residents filled in questions about the clinical symptoms, cardiovascular risk factors and past medical history in a structured Case Report Form. An extensive standard list of 12 clinical symptoms based on common practice and previous research was studied including 7 chest pain symptoms ("oppressive chest pain", "pain located in the sternal region", "radiation to jaw/ arm/ shoulder", "pain started during exercise", "pain diminished on nitrates", "same chest pain in last weeks", "same pain as previous angina pectoris") and 5 non-chest pain symptoms ("palpitations", "pulmonary complaints", "nausea/ vomiting", "diaphoresis", "dizziness/ syncope").[15,16] On top of that we collected the classical cardiovascular risk factors: age, diabetes, hypertension,

dyslipidaemia, current smoking, family history of cardiovascular disease, and medical history of cardiovascular disease. All patients received usual care and the decision for any additional diagnostic tests was left at the discretion of the treating physician.

Follow-up

Follow up data were retrieved from electronic patient records. In a few cases when data were not available from hospital records, the patient or general practitioner was contacted. Patients were excluded from the analysis in case of an incomplete follow-up not reaching the pre-defined time span of 6 weeks.

CAD

CAD was considered proven 1) in case of a significant stenosis at angiography requiring percutaneous coronary intervention (PCI)/coronary artery bypass grafting (CABG) or medical treatment within six weeks after presentation at the ED, 2) in patients without angiography, CAD was considered proven in case of a definite diagnosis of a Non-ST-elevation myocardial infarction (NSTEMI) or cardiovascular death within six weeks. NSTEMI was diagnosed using the universal consensus definition.[17] All endpoints were adjudicated by an independent event committee.

Statistical analyses

Patients were stratified by gender. The cardiovascular risk factors and clinical symptoms were expressed as mean ± standard deviation for continuous variables and as numbers (percentages) for categorical variables. The presence or absence of symptomatic atherosclerotic disease in the medical history, such as myocardial infarction and stroke, peripheral arterial disease and revascularisation procedures were combined into the variable past medical cardiovascular history. The use of different types of antithrombotic medication was combined in one variable. We combined four symptoms fitting a pulmonary origin of the chest pain in the variable "pulmonary complaints"(dyspnoea, coughing, fever and breathing-dependent pain).

We first tested the association between each clinical symptom or baseline characteristic and the presence or absence of CAD using univariable analysis, meaning chi-square in categorical variables and T-test in continuous variables. All candidate predictors with a p-value < 0.15, based on Akaike's Information Criterion, were included in a multivariable logistic regression model.[18] The first multivariable diagnostic model included only clinical symptoms (model 1). Subsequently cardiovascular risk factors were added to the first diagnostic model (model 2). The ability of the two diagnostic models to discriminate between patients with and without CAD was estimated by the area under the curve (AUC) with 95% confidence intervals (CI), separately in women and men. To compare the obtained AUC of women and men from both models we used bootstrapping by the roc.test from Rpackage "pROC". All authors had full access to all data.

Subgroup analyses

As clinical symptoms are most important in patients without typical ECG changes or an elevated first troponin we repeated the analyses in this subgroup of patients. Typical ECG changes were considered present in case of ≥ 1mm ST-segment depression in two continuous leads or elevations or negative T waves in absence of a bundle branch block, left ventricular hypertrophy, or the use of digoxin. Cut off points of Troponin T or I were according to local lab standards and reference values. The majority of the women included were older than 50 years suggesting that they were postmenopausal. Previous studies showed that premenopausal women experienced different clinical symptoms than postmenopausal women.[19,20] Therefore we repeated the analyses without women younger than 50 years of age.

RESULTS

A total of 2433 patients were included in "The prospective validation of the HEART score" study.[13] We excluded 102 patients (4%) since their follow up did not reach the time span of 6 weeks or they appeared to have a STEMI (Figure 1). We analyzed the remaining 2331 patients, of whom 43% (1003) were women.

Baseline characteristics

Women were at average 3 years older than men (62 years versus 59 years). More men than women had a medical history of cardiovascular disease (Table 1). The prevalence of diabetes was comparable between women and men. Compared to women, men were more often smokers and more men had dyslipidemia. The majority of patients experienced "oppressive chest pain", namely 68% of women and 71% of men. More women than men had accompanying symptoms such as "radiation to jaw/arm/schoulder", "nausea/vomiting", "palpitations" and "dizziness/syncope". Women experienced more "pain located in the sternal region" while more men had "recognizable pain to previous episode of angina pectoris".

CAD

In total 391 patients, of whom 111 women (11%) and 278 men (21%) were diagnosed with CAD within 6 weeks after the initial presentation at the ED. Among the patients with CAD 13 patients died a cardiovascular death, 139 developed MI, 237 underwent PCI, 66 received CABG and 43 patients had significant CAD by angiography treated conservatively (Figure 1).

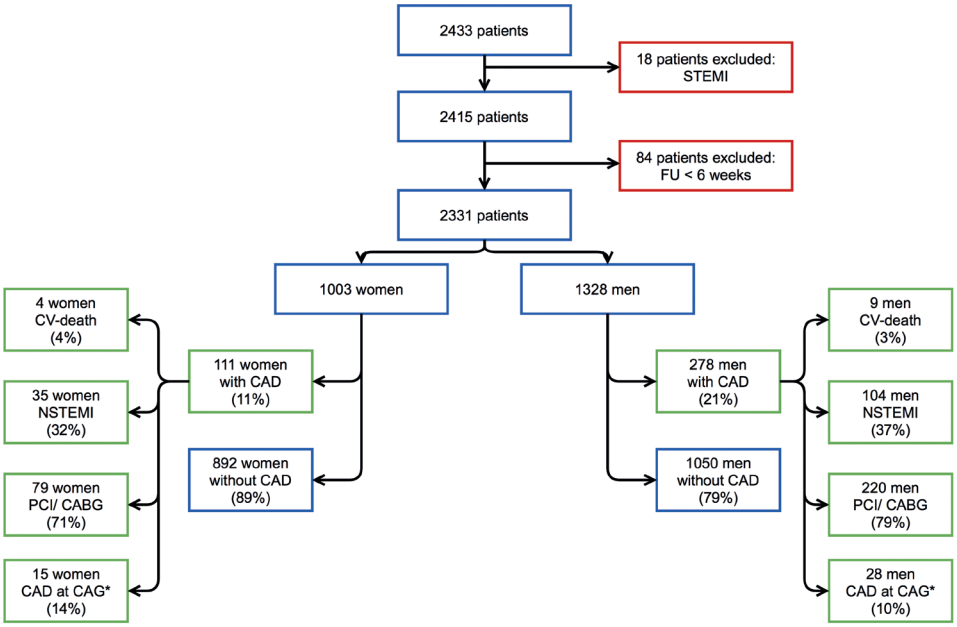
Univariable analysis

The univariable association between each clinical symptom and CAD in women and men is visualised in Figure 2. Overall, there were great similarities in the association of clinical symptoms between women and men. The presence of "dizziness/syncope" was associated

with the absence of CAD in women and men. There were a few differences in the magnitude of the association between clinical symptoms and CAD between sexes. For example, "nausea/ vomiting" and "diaphoresis" were positive predictors for CAD in women but not in men. All clinical symptoms except "pulmonary complaints" in women and "nausea/ vomiting" and "diaphoresis" in men had a p-value < 0.15 in the univariable analysis and were added to the multivariable model.
The univariable analysis of cardiovascular risk factors revealed that age, hypertension, dyslipidaemia and a history of cardiovascular disease had a p-value < 0.15 in both sexes. On top of that, in women a fifth cardiovascular risk factor, namely a positive family history of cardiovascular disease, also had a p-value < 0.15.

Multivariable analysis: clinical symptoms

In women and men, 8 clinical symptoms remained in this multivariable model (p-value < 0.15, Table 2). The presence of "pain located in the sternal region", "pain started during exercise", "pain diminished on nitrates" and "same chest pain in last weeks" were positive predictors for CAD in women and men. "Dizziness/syncope" had a negative predictive value in both sexes. There were some differences between women and men in the first model based on clinical symptoms. "Oppressive chest pain" still qualified as a positive



STEMI: ST-elevation myocardial infarction; FU: follow-up; CAD: coronary artery disease; CV-death: cardiovascular death; NSTEMI: non-ST-elevation myocardial infarction; PCI: percutaneous coronary intervention; CABG: coronary artery bypass grafting; CAG: coronary angiography; *: treated with medication

Figure 1. Flowchart

Table 1. Baseline characteristics of women and men (n=2331)

	Women	Men	p-value
	n (%)	n (%)	
	1003 (43)	1328 (57)	
Age in years (SD)	62 ± 16	59 ± 15	<0.01
Cardiovascular risk factors:			
Diabetes Mellitus	180 (18)	262 (20)	0.28
Hypertension	456 (46)	559 (42)	0.10
Dyslipidaemia	329 (33)	506 (38)	0.01
Smoking	302 (30)	455 (34)	0.03
Family history of CV disease	369 (37)	474 (36)	0.59
Past medical cardiovascular history*	281 (28)	609 (46)	<0.01
Myocardial infarction	102 (10)	271 (20)	<0.01
CABG	57 (6)	182 (14)	<0.01
PCI	145 (15)	359 (27)	<0.01
CVA	42 (4)	68 (5)	0.29
PAD	47 (5)	63 (5)	0.95
Clinical symptoms			
Oppressive chest pain	716 (71)	902 (68)	0.07
Pain located in the sternal region	682 (68)	801 (60)	<0.01
Radiation to jaw/ arm/ shoulder	521 (52)	569 (43)	<0.01
Pain started during exercise	248 (25)	377 (28)	0.05
Pain diminished on nitrates	173 (17)	264 (20)	0.11
Comparable chest pain in last weeks	459 (46)	601 (45)	0.81
Recognizable pain to previous episode of AP	379 (38)	557 (42)	0.04
Palpitations	172 (17)	119 (9)	<0.01
Pulmonary complaints	378 (38)	451 (34)	0.06
Nausea/ vomiting	307 (31)	259 (20)	<0.01
Diaphoresis	311 (31)	420 (32)	0.75
Dizziness/ syncope	170 (17)	184 (14)	0.04

n: number; SD: standard deviation; CV: cardiovascular; *: combination of CABG, PCI, CVA, PAD; CABG: coronary artery bypass grafting; PCI: percutaneous coronary intervention; CVA: cerebrovascular accident; PAD: peripheral arterial disease; ECG: electrocardiogram; AP: angina pectoris

predictor for CAD in women, but in men the p-value exceeded the 0.15 border because other clinical symptoms showed stronger associations. Other positive predictors in women were "nausea/ vomiting" and "diaphoresis". "Palpitations" and "pulmonary complaints" were negative predictors in men, but had no predictive value in women. The combined diagnostic value of clinical symptoms for the presence of CAD, expressed by the AUC,

was 0.74 (95%CI: 0.69-0.79) in women and 0.71 (95%CI: 0.68-0.75) in men (Figure 3A). This difference in AUC between women and men was not significantly different (p-value 0.45).

Multivariable analysis: cardiovascular risk factors additional to clinical symptoms

After adding cardiovascular risk factors to the multivariable model age and a history of cardiovascular disease remained positive predictors in women and men (Table 3). In women a positive family history of cardiovascular disease was also associated with CAD as was dyslipidemia in men. In both sexes one clinical symptom lost its predictive value, namely "pain located in the sternal region" in women and "dizziness/syncope" in men (p-value>0.15). After adding the cardiovascular risk factors to the clinical symptoms the AUC of the model increased to 0.79 (95%CI: 0.74-0.83) in women and 0.75 (95%CI: 0.72-0.78) in men (Figure 3B). The difference in AUC between women and men in model 2 was also not significantly different (p-value 0.11).

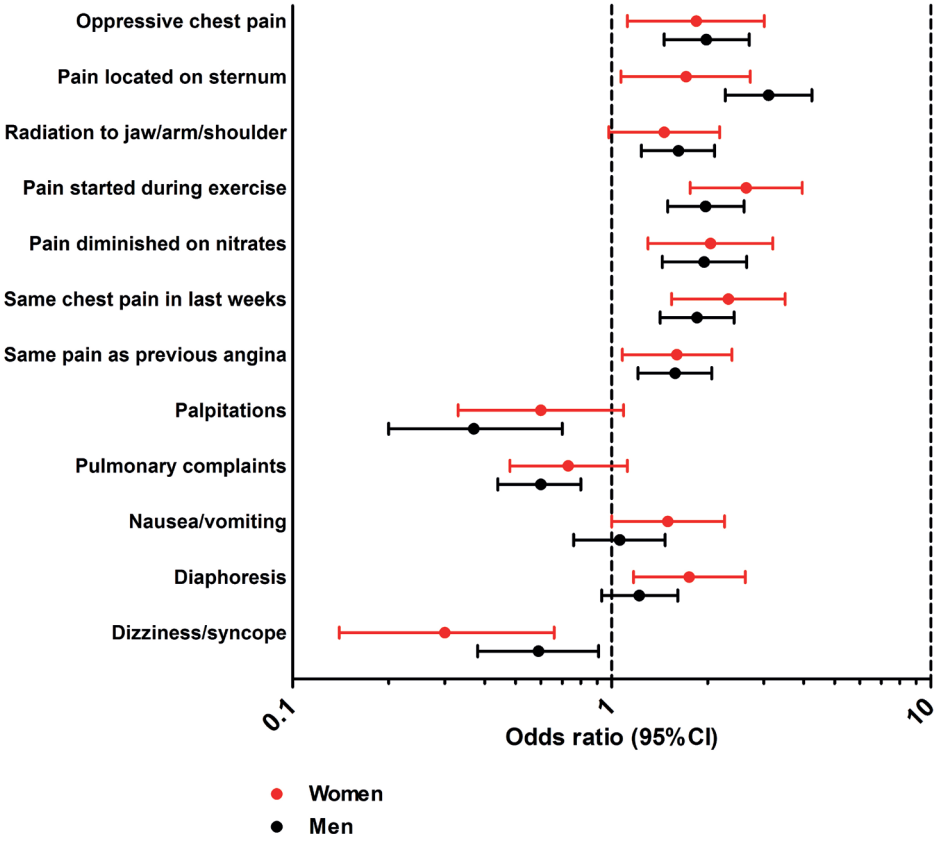


Figure 2. Univariable analysis (odds ratios) of all symptoms in women and men separately.

Table 2. Association (OR +95%CI) between symptoms and CAD in women and men as estimated by multivariable logistic regression analysis (model 1)

	Women	p-value	Men	p-value
	OR (95%CI)		OR (95%CI)	
Diagnostic model 1: symptoms				
Symptoms with positive predictive value				
Oppressive chest pain	1.66 (0.99-2.78)	0.05	--	
Pain located in the sternal region	1.50 (0.92-2.43)	0.11	2.78 (2.02-3.84)	<0.01
Radiation to jaw/arm/ shoulder	--		1.56 (1.18-2.07)	<0.01
Pain started during exercise	2.27 (1.45-3.55)	<0.01	1.60 (1.18-2.18)	<0.01
Pain diminished on nitrates	1.82 (1.13-2.93)	0.01	1.51 (1.09-2.09)	0.01
Same chest pain in last weeks	1.81 (1.16-2.83)	0.01	1.49 (1.11-2.00)	0.01
Nausea/ vomiting	1.53 (0.97-2.41)	0.07	--	
Diaphoresis	1.71 (1.10-2.66)	0.02	--	
Symptoms with negative predictive value				
Palpitations	--		0.36 (0.19-0.70)	<0.01
Pulmonary complaints	--		0.57 (0.42-0.79)	<0.01
Dizziness/ syncope	0.21 (0.09-0.46)	<0.01	0.70 (0.45-1.11)	0.13
AUC	0.74 (0.69-0.79)		0.71 (0.68-0.75)	

Only variables from the univariable analysis with a p-value < 0.15 (see table 1 and 2) were included in the multivariable analysis. AUC (area under the curve) was calculated using variables with a p-value <0.15 from the multivariable analysis. The presence of symptoms with a negative predictive value was associated with not having CAD.

Subgroup analyses

In the subgroup analysis of patients without typical ECG changes or an elevated first Troponin 1698 patients (928 men and 770 women) were included. The area under curve (AUC) of the first model (including clinical symptoms) was 0.72 (95%CI: 0.67-0.78) in men and 0.79 (95%CI: 0.72-0.86) in women. The second model (after adding baseline characteristics) presented comparable results: AUC in men 0.76 (95%CI: 0.71-0.81) and in women 0.84 (0.78-0.89). The AUC of both models differed in favour of women although this difference didn't reach statistical significance (p-value first model 0.11, second model 0.06). After excluding women younger than 50 years of age 754 women remained in the analyses. The AUC of model 1 (including clinical symptoms) was 0.72 (95%CI: 0.66-0.77) and of model 2 (after adding baseline characteristics) was 0.74 (95%CI: 0.69-0.79). When comparing these AUCs to the AUCs of all men no significant differences were found (p-value model 1: 0.82, model 2: 0.89).

Table 3. Association (OR +95%CI) between symptoms/cardiovascular risk factors and CAD in women and men as estimated by multivariable logistic regression analysis (model 2)

	Women	p-value	Men	p-value
	OR (95%CI)		OR (95%CI)	
Diagnostic model 2: clinical symptoms that remained in the model after adding cardiovascular risk factors				
Symptoms with positive predictive value				
Oppressive chest pain	1.80 (1.06-3.06)	0.03	--	
Pain located in the sternal region	--		2.63 (1.90-3.65)	<0.01
Radiation to jaw/arm/ shoulder	--		1.60 (1.21-2.13)	<0.01
Pain started during exercise	2.34 (1.46-3.75)	<0.01	1.57 (1.15-2.15)	<0.01
Pain diminished on nitrates	1.51 (0.92-2.47)	0.10	1.32 (0.94-1.84)	0.11
Same chest pain in last weeks	1.57 (0.99-2.50)	0.06	1.41 (1.05-1.91)	0.02
Nausea/ vomiting	1.77 (1.11-2.83)	0.02	--	
Diaphoresis	1.78 (1.12-2.82)	0.01	--	
Symptoms with negative predictive value				
Palpitations	--		0.39 (0.20-0.76)	0.01
Pulmonary complaints	--		0.52 (0.38-0.72)	<0.01
Dizziness/ syncope	0.21 (0.09-0.48)	<0.01	--	
Cardiovascular risk factors				
Dyslipidaemia	--		1.56 (1.16-2.09)	<0.01
Family history	2.45 (1.54-3.89)	<0.01	--	
Medical history of CVD	1.47 (0.94-2.31)	0.09	1.37 (1.00-1.89)	0.05
Age	1.05 (1.03-1.07)	<0.01	1.03 (1.02-1.05)	<0.01
AUC	**0.79 (0.74-0.83)**		**0.75 (0.72-0.78)**	

Only variables from the univariable analysis with a p-value < 0.15 (see table 1 and 2) were included in the multivariable analysis). AUC (area under the curve) was calculated using variables with a p-value <0.15 from the multivariable analysis. The presence of symptoms with a negative predictive value was associated with not having CAD.

DISCUSSION

The most important finding was that the diagnostic value of clinical symptoms and risk factors for the prediction of CAD in chest pain patients presenting on the ED was good and not different between women and men. To our knowledge, the quantification of the diagnostic value of clinical symptoms in chest pain patients and its direct comparison between sexes has not been reported before. Our findings in the univariable analysis were concordant with three analyses of chest pain characteristics in patients visiting the ED with chest pain.[21-23] One of these studies also performed a multivariable analysis but in both sexes a minority of the clinical symptoms remained in the multivariable model. Only the

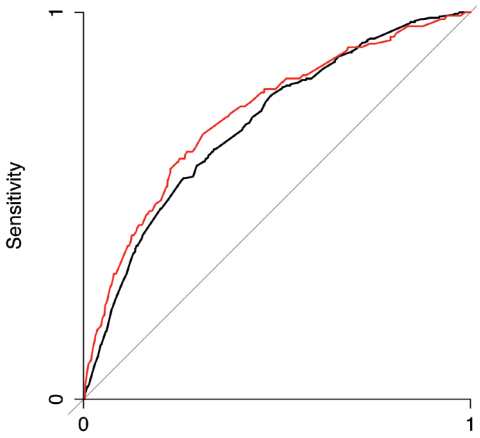


Figure 3a. ROC curves of model 1 consisting of symptoms. The black line describes the diagnostic value in men and the red line the diagnostic value in women. The AUC in women is not inferior to the AUC in men, p-value 0.45.

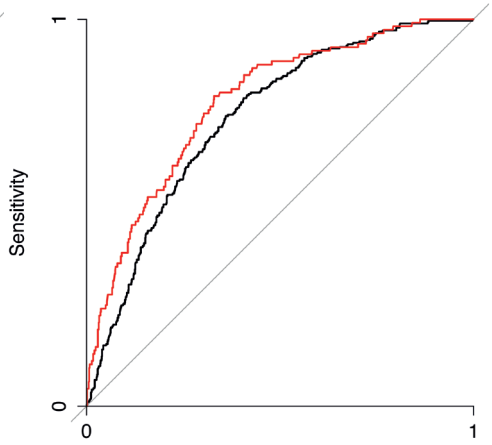


Figure 3b. ROC curves of model 2 consisting of symptoms added with baseline characteristics. The black line describes the diagnostic value in men and the red line in women. The AUC in women is not inferior to the AUC in men, p-value 0.11.

AUC of men was published which was poor (0.65). Possibly these results can be explained by the small study groups (246 women, 276 men). [22]

We have closed the existing gap from these previous analyses by adding a multivariable analysis in a large study group and, most importantly, by further quantifying and comparing the diagnostic value of clinical symptoms between sexes. The diagnostic value of symptoms alone was 0.74 in women and 0.71 in men, indicating that a correct diagnosis of CAD can be achieved in 74% in women and 71 % in men by taking the history using a standard set of questions. We added cardiovascular risk factors to the first model since these risk factors are part of risk stratification in patients with chest pain as shown by most risk scores, such as HEART, Framingham and TIMI.[24,25] After including the cardiovascular risk factors the diagnostic value improved to 0.79 in women and 0.75 in men.

Previous studies showed that more than 80% of patients with symptoms suspected of cardiac ischemia visiting the ED do not have diagnostic changes on the ECG.[13,26,27] In addition, in chest pain patients with a negative Troponin the adverse event rate is still 5-9%. [28,29] Thus a major diagnostic dilemma exists in patients with suspected ischemic symptoms, but normal ECG and Troponin at the ED. Therefore, our research question concerned the diagnostic value of clinical symptoms in patients presenting on the ED with chest pain without taking the ECG or Troponin levels into account. However as clinical symptoms are most important in patients without typical ECG changes or an elevated first troponin we repeated the analyses in this subgroup of patients and the results remained comparable.

Despite the higher age of women, the prevalence of CAD was significantly lower in women (11%) than in men (21%), which is in agreement with previous reports.[21,30,31] Since the majority of women was 50 years or older we repeated the analyses without the younger women as previous studies suggested that the clinical presentation could be different in younger women.[19,20]
"Oppressive chest pain", often described as the most typical symptom of angina pectoris, was as prevalent in women as in men. In the univariable analysis the predictive value of "oppressive chest pain" was also comparable between sexes but in the multivariable analysis it lost its predictive value in men while it remained the second strongest predictor of CAD in women. This can be explained by other clinical symptoms, closely associated with the presence of "oppressive chest pain", with a stronger association with CAD in men. Previous studies frequently compared clinical symptoms between women and men who were already diagnosed with CAD.[12,19,32,33] As the study population and research question are different from our study no comparison about the results can be made since in our study the presence of signs and symptoms was the starting point.

Strengths and limitations

Our study is a large multicenter prospective study making it possible to extrapolate our results to all patients presenting at the ED with chest pain. The thorough follow-up led to a low exclusion rate of 4%. Furthermore, the diagnosis of CAD was not only obtained at the ED but also at 6 weeks follow-up. On top of that, all endpoints were adjudicated by an independent event committee. A limitation of the study is that even though the results are interesting for patients consulting general practitioners (GP), our results cannot be extrapolated to these patients since our study population comprised only patients that presented at the ED. Two analyses from the primary care setting were however concordant with our findings: clinical symptoms of women and men presenting with acute chest pain at the GP's attention were largely similar.[34,35] Second, ideally all patients in a diagnostic study undergo the same reference test to diagnose the disease of interest.[36] As it is not ethical to perform a coronary angiography in all patients presenting at the ED with chest pain we pragmatically used a combination of clinical diagnoses and treatments as the reference standard. This could lead to differential verification bias as previous studies stated that more men than women undergo coronary angiography.[37] However since this would lead to a higher AUC in men, it seems not to be the case in this study. Third, no conclusion can be drawn about possible underlying microvascular disease as in this study only obstructive CAD was evaluated and no additional imaging was performed. Lastly, no information about chest pain duration was collected while this characteristic could have added value.

Conclusion

The diagnostic value of clinical symptoms and cardiovascular risk factors for the diagnosis of CAD in chest pain patients presenting on the ED was high in both women and men. No significant differences were found between sexes.

REFERENCES

1. Nawar EW, Niska RW, Xu J. (2007) National hospital ambulatory medical care survey: 2005 emergency department summary. Adv Data (386): 1-32.
2. Wright RS, Anderson JL, Adams CD, Bridges CR, Casey DE,Jr, et al. (2011) 2011 ACCF/AHA focused update incorporated into the ACC/AHA 2007 guidelines for the management of patients with unstable Angina/Non-ST-elevation myocardial infarction: A report of the american college of cardiology Foundation/American heart association task force on practice guidelines developed in collaboration with the american academy of family physicians, society for cardiovascular angiography and interventions, and the society of thoracic surgeons. J Am Coll Cardiol 57: e215-367.
3. Hamm CW, Bassand JP, Agewall S, Bax J, Boersma E, et al. (2011) ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The task force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the european society of cardiology (ESC). Eur Heart J 32: 2999-3054.
4. Panju AA, Hemmelgarn BR, Guyatt GH, Simel DL. (1998) The rational clinical examination. is this patient having a myocardial infarction? JAMA 280: 1256-1263.
5. Swap CJ, Nagurney JT. (2005) Value and limitations of chest pain history in the evaluation of patients with suspected acute coronary syndromes. JAMA 294: 2623-2629.
6. Pope JH, Aufderheide TP, Ruthazer R, Woolard RH, Feldman JA, et al. (2000) Missed diagnoses of acute cardiac ischemia in the emergency department. N Engl J Med 342: 1163-1170.
7. Dey S, Flather MD, Devlin G, Brieger D, Gurfinkel EP, et al. (2009) Sex-related differences in the presentation, treatment and outcomes among patients with acute coronary syndromes: The global registry of acute coronary events. Heart 95: 20-26.
8. Culic V, Eterovic D, Miric D, Silic N. (2002) Symptom presentation of acute myocardial infarction: Influence of sex, age, and risk factors. Am Heart J 144: 1012-1017.
9. Milner KA, Vaccarino V, Arnold AL, Funk M, Goldberg RJ. (2004) Gender and age differences in chief complaints of acute myocardial infarction (worcester heart attack study). Am J Cardiol 93: 606-608.
10. Patel H, Rosengren A, Ekman I. (2004) Symptoms in acute coronary syndromes: Does sex make a difference? Am Heart J 148: 27-33.
11. Khan NA, Daskalopoulou SS, Karp I, Eisenberg MJ, Pelletier R, et al. (2013) Sex differences in acute coronary syndrome symptom presentation in young patients. JAMA Intern Med 173: 1863-71.
12. Canto JG, Goldberg RJ, Hand MM, Bonow RO, Sopko G, et al. (2007) Symptom presentation of women with acute coronary syndromes: Myth vs reality. Arch Intern Med 167: 2405-2413.
13. Backus BE, Six AJ, Kelder JC, Bosschaert MA, Mast EG, et al. (2013) A prospective validation of the HEART score for chest pain patients at the emergency department. Int J Cardiol 168: 2153-8.
14. O'Gara PT, Kushner FG, Ascheim DD, Casey DE,Jr, Chung MK, et al. (2013) 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: A report of the american college of cardiology Foundation/American heart association task force on practice guidelines. Circulation 127: e362-425.
15. Rutherford J, Braunwald E. (1992) Chronic ischemic heart disease. In: Anonymous Heart Disease: A Textbook of Cardiovascular Medicines. Philadelphia: W.B. Saunders. pp. 1293-5.
16. Gibbons RJ, Chatterjee K, Daley J, Douglas JS, Fihn SD, et al. (1999) ACC/AHA/ACP-ASIM guidelines for the management of patients with chronic stable angina: A report of the american college of Cardiology/American heart association task force on practice guidelines (committee on management of patients with chronic stable angina). J Am Coll Cardiol 33: 2092-2197.
17. Thygesen K, Alpert JS, White HD, Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction. (2007) Universal definition of myocardial infarction. Eur Heart J 28: 2525-2538.
18. Steyerberg EW. (2008) Clinical prediction models. : Springer-Verlag New York Inc.

19. Canto JG, Rogers WJ, Goldberg RJ, Peterson ED, Wenger NK, et al. (2012) Association of age and sex with myocardial infarction symptom presentation and in-hospital mortality. JAMA 307: 813-822.
20. Milner KA, Funk M, Richards S, Vaccarino V, Krumholz HM. (2001) Symptom predictors of acute coronary syndromes in younger and older patients. Nurs Res 50: 233-241.
21. Rubini Gimenez M, Reiter M, Twerenbold R, Reichlin T, Wildi K, et al. (2013) Sex-specific chest pain characteristics in the early diagnosis of acute myocardial infarction. JAMA Intern Med 174: 241-9.
22. Milner KA, Funk M, Arnold A, Vaccarino V. (2002) Typical symptoms are predictive of acute coronary syndromes in women. Am Heart J 143: 283-288.
23. Devon HA, Rosenfeld A, Steffen AD, Daya M. (2014) Sensitivity, specificity, and sex differences in symptoms reported on the 13-item acute coronary syndrome checklist. J Am Heart Assoc 3: e000586.
24. D'Agostino RB S, Grundy S, Sullivan LM, Wilson P, CHD Risk Prediction Group. (2001) Validation of the framingham coronary heart disease prediction scores: Results of a multiple ethnic groups investigation. JAMA 286: 180-187.
25. Antman EM, Cohen M, Bernink PJ, McCabe CH, Horacek T, et al. (2000) The TIMI risk score for unstable angina/non-ST elevation MI: A method for prognostication and therapeutic decision making. JAMA 284: 835-842.
26. Forest RS, Shofer FS, Sease KL, Hollander JE. (2004) Assessment of the standardized reporting guidelines ECG classification system: The presenting ECG predicts 30-day outcomes. Ann Emerg Med 44: 206-212.
27. Halpern EJ, Deutsch JP, Hannaway MM, Estepa AT, Kenia AS, et al. (2013) Cardiac risk factors and risk scores vs cardiac computed tomography angiography: A prospective cohort study for triage of ED patients with acute chest pain. Am J Emerg Med 31: 1479-1485.
28. Searle J, Shih J, Muller R, Vollert JO, Muller C, et al. (2013) The role of myeloperoxidase (MPO) for prognostic evaluation in sensitive cardiac troponin I negative chest pain patients in the emergency department. Eur Heart J Acute Cardiovasc Care 2: 203-210.
29. Sanchis J, Bodi V, Llacer A, Nunez J, Consuegra L, et al. (2005) Risk stratification of patients with acute chest pain and normal troponin concentrations. Heart 91: 1013-1018.
30. Shaw LJ, Shaw RE, Merz CN, Brindis RG, Klein LW, et al. (2008) Impact of ethnicity and gender differences on angiographic coronary artery disease prevalence and in-hospital mortality in the american college of cardiology-national cardiovascular data registry. Circulation 117: 1787-1801.
31. Johnston N, Schenck-Gustafsson K, Lagerqvist B. (2011) Are we using cardiovascular medications and coronary angiography appropriately in men and women with chest pain? Eur Heart J 32: 1331-1336.
32. Milner KA, Funk M, Richards S, Wilmes RM, Vaccarino V, et al. (1999) Gender differences in symptom presentation associated with coronary heart disease. Am J Cardiol 84: 396-399.
33. Assiri AS. (2011) Gender differences in clinical presentation and management of patients with acute coronary syndrome in southwest of saudi arabia. J Saudi Heart Assoc 23: 135-141.
34. Bruins Slot MH, Rutten FH, van der Heijden GJ, Doevendans PA, Mast EG, et al. (2012) Gender differences in pre-hospital time delay and symptom presentation in patients suspected of acute coronary syndrome in primary care. Fam Pract 29: 332-337.
35. Bosner S, Haasenritter J, Hani MA, Keller H, Sonnichsen AC, et al. (2009) Gender differences in presentation and diagnosis of chest pain in primary care. BMC Fam Pract 10: 79.
36. Naaktgeboren CA, de Groot JA, van Smeden M, Moons KG, Reitsma JB. (2013) Evaluating diagnostic accuracy in the face of multiple reference standards. Ann Intern Med 159: 195-202.
37. Roger VL, Farkouh ME, Weston SA, Reeder GS, Jacobsen SJ, et al. (2000) Sex differences in evaluation and outcome of unstable angina. JAMA 283: 646-652.

SEX-SPECIFIC CHEST PAIN CHARACTERISTICS

To the Editor

Rubini Gimenez et al.(1) studied sex-specific chest pain 3 characteristics (CPCs) with the objective of improving the management of women with suspected acute myocardial infarction (AMI). They collected an impressive number of baseline and chest pain characteristics in a large sample of patients with chest pain.

Unfortunately, the prevalence of CPCs in women was only compared with the prevalence of CPCs in men. Whether the prevalence of CPCs in women with AMI differed from women without AMI (and men with and without AMI) was not evaluated, while such an analysis would demonstrate which symptoms are related to AMI in women and which in men. The knowledge that certain CPCs are more prevalent in women than in men is not that useful for a medical physician. In clinical practice either a man or a woman present themselves with certain symptoms, and therefore it is important to know which symptoms are predictive for an AMI in women and which in men. The choice to use likelihood ratio as statistical test is unfortunate because it only evaluates 1 symptom at a time, while the diagnosis of AMI is a multivariable process. Moreover, the likelihood ratio does not provide the diagnostic value of the combination of CPCs in women and men. The diagnostic value, expressed as the area under the curve or C statistic, shows in how many women and men an AMI can be diagnosed based on the CPCs present. This quantification combines the CPCs in 1 person as is done in clinical practice. In addition, it allows a direct comparison between sexes.

Possibly the authors could still carry out these analyses and report their findings, as this will definitely contribute to the current knowledge about this topic.

REFERENCES

1. Rubini Gimenez M, Reiter M, Twerenbold R, et al. Sex-7 specific chest pain characteristics in the early diagnosis 8 of acute myocardial infarction. JAMA Intern Med. 9 2014;174(2):241-249

CHAPTER 3

INTERPRETATION OF SYMPTOMS IN CHEST PAIN PATIENTS IS GENDER DEPENDENT

Submitted

Manon G. van der Meer, Yolanda van der Graaf, Hendrik M. Nathoe,
Pieter A. Doevendans, Barbra E. Backus, A. Jacob Six, Yolande Appelman

ABSTRACT

Objective
To investigate the influence of gender on the interpretation of symptoms by the physician in patients presenting with chest pain at the emergency department (ED). We hypothesized that the physician would interpret the symptoms in men more often as suspicious for coronary artery disease (CAD) than in women.

Design
Prospective, observational study.

Setting
Emergency department of 10 hospitals in the Netherlands.

Participants
Patients presenting with chest pain at the ED were eligible. In total 2433 patients (1030 women (42%)) were included.

Main outcome measures
The physician scored the combination of symptoms as "highly or not highly suspicious" for CAD. CAD was defined as a combination of (non-)ST-elevation myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, a new visually significant stenosis at angiography treated conservatively or CV death all occurring within six weeks after presentation at the ED. We investigated whether the predicate "highly suspicious" for CAD was influenced by gender of the patient. Furthermore, if this was different in patients whose symptoms were explained by CAD compared to patients whose symptoms were not explained by CAD using logistic regression analysis. We adjusted for age, symptoms and cardiovascular risk factors.

Results
In 731 (30%) patients the physician scored the symptoms as "highly suspicious" for CAD. The presence of CAD modified the relation between interpretation of the symptoms and gender. After stratifying for the presence of CAD male gender was significantly associated with the predicate "highly suspicious" in patients without CAD (OR 1.64 (95%CI: 1.24-2.17)) but not in patients with CAD (OR 0.96 (95%%CI: 0.55-1.68)).

Conclusion
Interpretation of symptoms by the physician was indeed gender dependent. In patients presenting with chest pain but without CAD men were more often interpreted as "highly suspicious" for CAD compared to women. This was independent of symptoms and cardiovascular risk factors and therefore could lead to unnecessary investigations, treatment and hospital admissions in men.

INTRODUCTION

Chest pain is the second most common complaint presented at the emergency department (ED) and can be an indicator of coronary artery disease (CAD).[1] As early treatment of CAD decreases morbidity and mortality, it is crucial to identify patients with symptomatic CAD as soon as possible in order to start with treatment. On the other hand, it is also important to recognize patients with a low suspicion of CAD in order to prevent unnecessary treatment or additional investigations leading to needless risks and costs.

Especially in patients with a normal electrocardiogram symptoms are important in recognizing CAD.[2,3] Furthermore, it takes some time before the results of laboratory tests (such as troponin) will demonstrate possible cardiac ischemia. Previous studies described a delayed recognition of women with CAD compared to men with CAD.[4-7] This difference between sexes could theoretically be explained by either a patient delay or a doctor's delay in identifying women with CAD. Former studies suggested that women use lengthy decision-making processes before deciding to seek medical care, which indeed leads to postponement.[6,8] Moreover women with CAD tended to misclassify their symptoms relating them to non-cardiac causes.[4,8,9] On the other hand, delayed recognition of CAD in women by healthcare providers has been related to an atypical presentation in women.[10-12] Previous studies also mentioned that management of chest pain by physicians is influenced by gender of the patient caused by an underestimation of the risk of CAD in women leading to delay in establishing the proper diagnosis.[13,14] Furthermore, former studies demonstrated that women undergo less additional tests as advised in the guidelines for CAD, subsequently leading to under diagnosis.[15,16]

It remains unknown whether women with CAD indeed have an atypical presentation or if the physician interprets their symptoms as atypical as they consider CAD as a "male-disease".

Therefore we investigated if interpretation of symptoms in patients with chest pain presenting at the ED is influenced by gender of the patient. We hypothesized that interpretation of symptoms was gender dependent and that physicians would interpret the symptoms of men more often as typical for CAD than the symptoms of women.

METHODS

Study population

Data from "The prospective validation of the HEART score" study were used.[17] This study was performed at ten hospitals in the Netherlands between 2008 and 2009. Any patient admitted to the (cardiac) ED with chest pain was eligible. The goal of the study was to validate the HEART score, a clinical risk score to facilitate decision-making in chest pain patients presenting on the ED.

One of the elements of the HEART score is "History" and the physician was asked to score the combination of symptoms of the patient as highly suspicious, moderately

suspicious or not suspicious for CAD by his or her own judgment. This judgment of the physician was solely based on the clinical symptoms of the patient and irrespective of additional tests like electrocardiogram or laboratory results and was used as the primary outcome of our study. An extensive standard list of 12 clinical symptoms was used in the HEART score based on common practice and previous research was studied including "oppressive chest pain", "pain located in the sternal region", "radiation to jaw/ arm/ shoulder", "pain started during exercise", "pain diminished on nitrates", "same chest pain

Table 1. Baseline characteristics (n=2433)

	Men n= 1,403	Women n= 1,030	p-value
Cardiovascular risk factors			
Age mean (sd)	58.7 (15.4)	61.3 (15.7)	< 0.01
Diabetes (%)	265 (18.9)	182 (17.7)	0.44
Smoking (%)	490 (34.9)	309 (30.0)	0.01
Dyslipidaemia (%)	528 (37.6)	334 (32.4)	0.01
Hypertension (%)	575 (41.0)	464 (45.0)	0.05
Family history of CV disease (%)	501 (35.7)	379 (36.8)	0.58
Past medical CV history (%)*	628 (44.8)	283 (27.5)	<0.01
Clinical symptoms			
Oppressive chest pain (%)	944 (67.3)	735 (71.4)	0.03
Pain located at sternal region (%)	841 (59.9)	702 (68.2)	<0.01
Radiation to jaws / shoulder/ arm (%)	604 (43.1)	537 (52.1)	<0.01
Pain started on exertion (%)	391 (27.9)	254 (24.7)	0.08
Pain diminished on nitrates (%)	268 (19.1)	178 (17.3)	0.25
Dyspnoea (%)	345 (24.6)	289 (28.1)	0.05
Nausea/ vomiting (%)	275 (19.6)	318 (30.9)	<0.01
Diaphoresis (%)	446 (31.8)	322 (31.3)	0.78
Palpitations (%)	122 (8.7)	180 (17.5)	<0.01
Dizziness/ collaps (%)	195 (13.9)	175 (17.0)	0.04
Same complaints in last weeks (%)	622 (44.3)	468 (45.5)	0.59
Same pain as previous angina (%)	581 (46.5)	387 (43.0)	0.11
Diagnosis			
Highly suspicious symptoms (%)	470 (33.5)	261 (25.3)	<0.01
Coronary artery disease (%)**	290 (20.7)	118 (11.5)	<0.01

sd: standard deviation; CV: cardiovascular; *Past medical cardiovascular history including myocardial infarction, coronary artery bypass grafting (CABG), percutaneous coronary intervention (PCI), peripheral arterial disease and stroke; **Coronary artery disease including (non-)ST-elevation myocardial infarction, PCI, CABG, a new visually significant stenosis at angiography treated conservatively or CV death all occurring within six weeks after presentation at the emergency department

in last weeks", "same pain as previous angina", "palpitations", "dyspnea", "nausea/ vomiting", "diaphoresis", "dizziness/ syncope".[18,19] On top of that the classical cardiovascular (CV) risk factors: age, diabetes, hypertension, dyslipidaemia, current smoking, family history of CV disease and past medical history of CV disease were collected. The ethics committees of all participating hospitals approved the study and waived informed consent because all patients received usual medical care. The decision for any additional diagnostic tests was left at the discretion of the treating physician.

Follow-up

Follow up data with the final diagnosis of the underlying cause of the chest pain was retrieved from electronic patient records. When data were not available from hospital records, the patient or general practitioner was contacted in order to retrieve the data. Patients were excluded from the analysis in case of an incomplete follow-up not reaching the pre-defined time span of 6 weeks.

Diagnosis CAD

The diagnosis, the presence or absence of CAD in this article, is a combination of (non-) ST-elevation myocardial infarction ((N)STEMI), percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG), a new visually significant stenosis at angiography treated conservatively or CV death all occurring within six weeks after presentation at the ED. (N)STEMI was diagnosed using the universal consensus definition.[20] Conservatively treated CAD was defined by the presence of significant coronary artery stenosis at angiography that was thought to be the cause of the chest pain for which revascularization was withheld because of high co-morbidity or expected high risk of complications. An independent event committee adjudicated all diagnoses.

Statistical analyses

The predicate the physician gave to the combination of symptoms (highly suspicious, moderately suspicious, not suspicious) was the outcome of our interest. We investigated if this outcome was influenced by gender of the patient. First we dichotomized the outcome in highly suspicious versus moderately/ not suspicious for CAD.

All variables were expressed as mean ± standard deviation for continuous variables and as numbers (percentages) for categorical variables. The different types of atherosclerotic disease from the past medical history, such as myocardial infarction and stroke, were combined into the variable past medical CV history.

We evaluated whether interpretation of the combination of symptoms by the physician (highly suspicious yes/ no) was influenced by gender of the patient using logistic regression analysis. Women were the reference category. To investigate the modifying effect of the final diagnosis, the presence of CAD, an interaction term was entered in the model. When interaction was present ($p < 0.05$) we repeated the logistic regression analysis stratified for the presence of CAD. In the first model we adjusted for age. In the second model, we adjusted for age and all clinical symptoms. In the third model we

adjusted for CV risk factors (hypertension, diabetes, smoking, dyslipidaemia, family history of CV disease and past medical CV history) on top of age and symptoms. Finally, we performed a sensitivity analysis dichotomizing the outcome as highly and moderately suspicious versus not suspicious and repeated all analyses. All statistical analyses were performed in IBM SPSS 20.

RESULTS

In total 2433 patients, 1403 men (58%) and 1030 women (42%) were included in "the prospective validation of the HEART score" study. The baseline characteristics are depicted in Table 1. Women were significantly older than men while men had a more disadvantageous risk profile with more smokers, a higher prevalence of dyslipidaemia and a past medical history of CV disease. There were several differences in the prevalence of clinical symptoms between sexes. In total 408 out of 2433 patients (17%) appeared to have CAD according to our predefined definition, as underlying cause of their complaints. The physician scored 731 anamneses (30%) as being highly suspicious of CAD. The symptoms of men were significantly more often considered as highly suspicious for CAD compared to women. Of these 731 patients 272 patients (37%), consisting of 80 women and 192 men, indeed had CAD as underlying cause while in the remaining 459 patients no cardiac cause was found. The presence of CAD modified the relationship between gender and the interpretation of

Table 2. Odds ratios of the relation between gender and interpretation of symptoms by the physician stratified for the presence of CAD

Highly suspicious versus not highly suspicious (moderate + not suspicious)	CAD**	Without CAD
Gender, reference female, adjusted for age	0.92 (0.58-1.46)	1.56 (1.25-1.94)
Gender, reference female, adjusted for age and symptoms	0.92 (0.53-1.58)	1.54 (1.18-2.00)
Gender, reference female, adjusted for age, symptoms and CV risk factors*	0.96 (0.55-1.68)	1.64 (1.24-2.17)
Highly + moderately suspicious versus not suspicious (sensitivity analysis)		
Gender, reference female, adjusted for age	0.38 (0.13-1.11)	1.31 (1.09-1.57)
Gender, reference female, adjusted for age and symptoms	0.36 (0.10-1.31)	1.43 (1.14-1.79)
Gender, reference female, adjusted for age, symptoms and CV risk factors*	0.36 (0.10-1.37)	1.54 (1.20-1.96)

CAD: coronary artery disease; *Cardiovascular risk factors including diabetes mellitus, smoking, dyslipidemia, hypertension, family history of cardiovascular disease and a medical history of cardiovascular disease; ** including (non-)ST-elevation myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, a new visually significant stenosis at angiography treated conservatively or cardiovascular death all occurring within six weeks after presentation at the emergency department.

symptoms (p-value for interaction <0.001) in all three models. Therefore we stratified the results by presence or absence of CAD. In patients without CAD male gender was in all three models significantly related to highly suspicious symptoms, as scored by the physician while this was not the case in patients with CAD (Table 2).

DISCUSSION

We demonstrated that interpretation of symptoms by the physician was indeed gender dependent in patients presenting with chest pain but without CAD as underlying cause. In men symptoms were more often interpreted as "highly suspicious" for CAD compared to women. This relation remained present after adjusting for age, symptoms and cardiovascular risk factors. In chest pain patients with CAD as underlying cause of the chest pain no gender difference in interpretation was found.

Our study was performed in ten different hospitals in the Netherlands; therefore the results are generalizable to the typical patients presenting with chest pain at the ED. Additionally, data on a large number of clinical symptoms were available in this cohort. Using these parameters we could adjust for all clinical symptoms, making it possible to evaluate the true influence of gender on the interpretation of the ED physician. On top of that, the diagnosis of CAD was not only obtained at the ED but also at 6 weeks follow-up, leading to less misdiagnosis.

It is important to stress in this regard that an independent event committee adjudicated all diagnoses. Two limitations of this study should be addressed. First, ideally all patients in a diagnostic study undergo the same reference test to diagnose the disease of interest. Because it is not ethical to perform coronary angiography in all patients presenting with chest pain at the ED we pragmatically used a combination of clinical diagnoses and treatments as the reference test. This could lead to differential verification bias as previous studies stated that more men than women undergo coronary angiography.[15,16] Second, no data about additional investigations or hospital admissions was available, only data concerning the diagnosis of CAD were registered. As a result we could not test the hypothesis that the misinterpretation of symptoms of men indeed lead to unnecessary investigations and admissions.

As far as we know this is the first study that evaluated the influence of gender of the patient to the interpretation of the symptoms in patients with chest pain presenting at the emergency department in a real-life setting. A previous study performed by Schulman et al found comparing results in a simulated setting as they described that management of chest pain by physicians is independently influenced by gender of the patient.[21] Using taped interviews of actors portraying symptoms, women were less often referred for coronary angiography than men.[21] Adjustment for estimate of probability of disease, level of coronary risk, and presenting symptoms didn't influence this difference between sexes.[21]

Green en al showed that in men overutilization of coronary angiography and hospital admissions was present instead of underutilization in women in patients evaluated for

potential acute cardiac ischemia in the emergency departments.[22] In a study by Bickell et al evaluating patients with catheterization-documented CAD, men with a low risk for cardiac death were even more often referred for coronary artery bypass grafting compared to women, while surgery offered little or no survival benefit over conventional medical treatment.[23]

Our results are important for clinical practice as this over interpretation of clinical symptoms in men whose symptoms were not explained by CAD could lead to unnecessary additional investigations, treatment and hospital admissions in men. It would be interesting to evaluate the exact consequences of this over interpretation of clinical symptoms. On top of that it would be useful to investigate if and how we could change this preconceived opinion in physicians.

Conclusion

In patients presenting with chest pain at the ED but without CAD, symptoms of men were more often interpreted as "highly suspicious" for CAD compared to women. This was independent of symptoms and cardiovascular risk profile and could therefore lead to unnecessary additional investigations, treatment and hospital admissions in men. In chest pain patients with CAD as underlying cause no gender difference in interpretation was found.

REFERENCES

1. Nawar EW, Niska RW, Xu J. National Hospital Ambulatory Medical Care Survey: 2005 emergency department summary. *Adv.Data* 2007;(386):1-32.
2. Swap CJ, Nagurney JT. Value and limitations of chest pain history in the evaluation of patients with suspected acute coronary syndromes. *JAMA* 2005;294:2623-2629.
3. Panju AA, Hemmelgarn BR, Guyatt GH, Simel DL. The rational clinical examination. Is this patient having a myocardial infarction? *JAMA* 1998;280:1256-1263.
4. O'Keefe-McCarthy S. Women's experiences of cardiac pain: a review of the literature. *Can.J.Cardiovasc.Nurs.* 2008;18:18-25.
5. Lefler LL, Bondy KN. Women's delay in seeking treatment with myocardial infarction: a meta-synthesis. *J.Cardiovasc.Nurs.* 2004;19:251-268.
6. Sullivan AL, Beshansky JR, Ruthazer R, Murman DH, Mader TJ, Selker HP. Factors associated with longer time to treatment for patients with suspected acute coronary syndromes: a cohort study. *Circ.Cardiovasc.Qual.Outcomes* 2014;7:86-94.
7. Jakobsen L, Niemann T, Thorsgaard N, Nielsen TT, Thuesen L, Lassen JF, Jensen LO, Thayssen P, Ravkilde J, Tilsted HH, Mehnert F, Johnsen SP. Sex- and age-related differences in clinical outcome after primary percutaneous coronary intervention. *EuroIntervention* 2012;8:904-911.
8. Lockyer L. Women's interpretation of their coronary heart disease symptoms. *Eur.J.Cardiovasc.Nurs.* 2005;4:29-35.
9. Gallagher R, Marshall AP, Fisher MJ. Symptoms and treatment-seeking responses in women experiencing acute coronary syndrome for the first time. *Heart Lung* 2010;39:477-484.
10. Brieger D, Eagle KA, Goodman SG, Steg PG, Budaj A, White K, Montalescot G, GRACE Investigators. Acute coronary syndromes without chest pain, an underdiagnosed and undertreated high-risk group: insights from the Global Registry of Acute Coronary Events. *Chest* 2004;126:461-469.
11. Canto JG, Shlipak MG, Rogers WJ, Malmgren JA, Frederick PD, Lambrew CT, Ornato JP, Barron HV, Kiefe CI. Prevalence, clinical characteristics, and mortality among patients with myocardial infarction presenting without chest pain. *JAMA* 2000;283:3223-3229.
12. Bosner S, Haasenritter J, Hani MA, Keller H, Sonnichsen AC, Karatolios K, Schaefer JR, Baum E, Donner-Banzhoff N. Gender bias revisited: new insights on the differential management of chest pain. *BMC Fam.Pract.* 2011;12:45-2296-12-45.
13. Mosca L, Linfante AH, Benjamin EJ, Berra K, Hayes SN, Walsh BW, Fabunmi RP, Kwan J, Mills T, Simpson SL. National study of physician awareness and adherence to cardiovascular disease prevention guidelines. *Circulation* 2005;111:499-510.
14. Poon S, Goodman SG, Yan RT, Bugiardini R, Bierman AS, Eagle KA, Johnston N, Huynh T, Grondin FR, Schenck-Gustafsson K, Yan AT. Bridging the gender gap: Insights from a contemporary analysis of sex-related differences in the treatment and outcomes of patients with acute coronary syndromes. *Am.Heart J.* 2012;163:66-73.
15. Roger VL, Farkouh ME, Weston SA, Reeder GS, Jacobsen SJ, Zinsmeister AR, Yawn BP, Kopecky SL, Gabriel SE. Sex differences in evaluation and outcome of unstable angina. *JAMA* 2000;283:646-652.
16. Chang AM, Mumma B, Sease KL, Robey JL, Shofer FS, Hollander JE. Gender bias in cardiovascular testing persists after adjustment for presenting characteristics and cardiac risk. *Acad.Emerg.Med.* 2007;14:599-605.
17. Backus BE, Six AJ, Kelder JC, Bosschaert MA, Mast EG, Mosterd A, Veldkamp RF, Wardeh AJ, Tio R, Braam R, Monnink SH, van Tooren R, Mast TP, van den Akker F, Cramer MJ, Poldervaart JM, Hoes AW, Doevendans PA. A prospective validation of the HEART score for chest pain patients at the emergency department. *Int.J.Cardiol.* 2013.
18. Rutherford J, Braunwald E. Chronic Ischemic Heart Disease. Heart Disease: A Textbook of Cardiovascular Medicines. 4th ed. Philadelphia: W.B. Saunders; 1992. p. 1293-5.

19. Gibbons RJ, Chatterjee K, Daley J, Douglas JS, Fihn SD, Gardin JM, Grunwald MA, Levy D, Lytle BW, O'Rourke RA, Schafer WP, Williams SV, Ritchie JL, Cheitlin MD, Eagle KA, Gardner TJ, Garson A,Jr, Russell RO, Ryan TJ, Smith SC,Jr. ACC/AHA/ACP-ASIM guidelines for the management of patients with chronic stable angina: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Patients With Chronic Stable Angina). *J.Am.Coll.Cardiol.* 1999;33:2092-2197.
20. Thygesen K, Alpert JS, White HD, Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction. Universal definition of myocardial infarction. *Eur.Heart J.* 2007;28:2525-2538.
21. Schulman KA, Berlin JA, Harless W, Kerner JF, Sistrunk S, Gersh BJ, Dube R, Taleghani CK, Burke JE, Williams S, Eisenberg JM, Escarce JJ. The effect of race and sex on physicians' recommendations for cardiac catheterization. *N.Engl.J.Med.* 1999;340:618-626.
22. Green LA, Ruffin MT,4th. A closer examination of sex bias in the treatment of ischemic cardiac disease. *J.Fam.Pract.* 1994;39:331-336.
23. Bickell NA, Pieper KS, Lee KL, Mark DB, Glower DD, Pryor DB, Califf RM. Referral patterns for coronary artery disease treatment: gender bias or good clinical judgment? *Ann.Intern.Med.* 1992;116:791-797.

CHAPTER 4

ARE THERE GENDER DIFFERENCES IN THE TRIAGE OF CHEST PAIN AT PRIMARY CARE OUT-OF-HOURS SERVICES?

Manon G. van der Meer, Yolande Appelman, Yolanda van der Graaf,
Hendrik M. Nathoe, Pieter A. Doevendans, Michelle Smit, Emmy Verheij,
Anne Botermans, Frans H. Rutten

ABSTRACT

Introduction

Previous studies described an atypical presentation of women with an acute coronary syndrome (ACS) leading to delayed recognition. Therefore we assessed the influence of gender of the patient on the triage, including duration of telephone calls, questions asked by the triage nurse and the given urgency, in patients presenting with chest pain to primary care out-of-hours services (OHS). On top of that we evaluated the performance of the triage: were women and men with an ACS equally recognized?

Methods

This study was carried out in the primary care OHS "de Gelderse Vallei" in Ede, the Netherlands. We used back-up tapes of all telephone contacts where the triage nurse used the "Netherlands Triage System" (NTS) module chest pain. We dichotomized the five possible urgencies in U1-2 (high) and U3-5 (low). The symptoms and the medical history of the patient were scored including if it was reported spontaneously by the patient, or after being asked by the triage nurse. We contacted the patient's GP to retrieve the medical diagnosis related to the OHS contact. Differences in triage characteristics, the urgency classification and final diagnoses between sexes were analyzed using Student's t- test and Chi-square test.

Results

In total, 832 patients were included: 395 men (48%) and 437 women (53%). No difference between sexes was found in the questions asked by the triage nurse, the duration of telephone calls and the given urgencies. In patients with a high urgency (U1-2) the telephone call was significantly shorter than in patients with a low urgency (U3-5). The final diagnosis could be retrieved in 518 patients (62%): 276 women and 242 men. Eight percent of women and 14% of men appeared to have had an ACS. The duration of the telephone calls was comparable in women with an ACS to men with an ACS. Women and men with an ACS received as often a high urgency (95.7% of women versus 88.2% of men, p-value=0.3).

Conclusion

There is no gender difference in the triage and urgency classification of patients with chest pain in primary care, also not in the subgroup of patients who eventually showed to have an ACS.

INTRODUCTION

Chest pain is a common reason for contacting primary care and around 1:7 has an underlying cardiac cause, mainly an acute coronary syndrome (ACS).[1] Timely diagnosis of an ACS is important because fast medical treatment and early coronary intervention may save myocardium ("time is muscle").
In the Netherlands primary care out-of-hours services (OHS) cover primary care in 73% of all week hours. The first contact to primary care OHS is by telephone, which is in initially handled by trained triage nurses who are supervised by a general practitioner (GP). Many Dutch OHS use the "Netherlands Triage System" (NTS) to triage patients that call the OHS.[2] This computer-based decision support system generates one of five urgencies (U1-U5, Appendix-Table 1) after filling in one of the 56 "complaint-modules".[2] The NTS-module "chest pain" is the same for women and men.[2] Severe pain (seven or more on a scale from zero to 10), radiation to arms or neck, additionally suffering from dypsnoea, and symptoms related to activation of the sympathetic system, i.e. sweating, nausea, and looking pale will result in the highest urgency level (U1).[2] The NTS has however never been formally validated by correlating the generated urgencies to clinical endpoints.[2]
The presentation of symptoms is key in the triage. Previous studies suggested that in a selection of patients who eventually appeared to have an ACS, women presented with different symptoms than men.[3-7] Women with an ACS would present more often with "atypical complaints" compared to men with an ACS leading to a delayed recognition.[8,9] These hospital-based studies however only studied patients who had an ACS. The clinically relevant questions if women with chest pain caused by an ACS present with different symptoms than women with chest pain who do not have an ACS and if this is different for men, remained unanswered. This information would allow GPs and triage nurses at primary care OHS to differentiate patients with an ACS from patients without an ACS.
By re-analysing back-up tapes of the initial telephone calls of patients contacting primary care OHS with chest pain we wanted to assess the influence of gender of the patient on the triage, including the duration of the telephone call, questions asked by the triage nurse and the given urgency. On top of that we evaluated the performance of the triage: were the patients with potential life threatening diseases recognized and was this different in women and men?

METHODS

Study population

This study was carried out in the primary care OHS "de Gelderse Vallei" in Ede, the Netherlands. Since 2001 in total 120 GPs provide emergency primary care services to a population of around 270,000 people. For the current analysis we used back-up tapes of all telephone contacts where the triage nurse used the NTS "complaint-module" chest pain. Calls in the months November and December 2012, and January, May, June, and

July 2013 were included in the analysis. We chose these two sets of three consecutive months to be able to analyze potential differences in triage due to passing of time.
We excluded persons < 30 years old, non-primary contacts, and contacts that could not be retrieved from the back-up system. The Ethical Committee of the University Medical Center Utrecht and the advisory board of General Practitioners Committee "De Gelderse Vallei" approved the study protocol. De-identified patient data were used for analysis.

Triage

A trained triage nurse handles every telephone request for medical care. They use the "Netherlands Triage System" (NTS) since November 2012 as a decision tool for the classification of the urgency.[2] The triage nurse chooses the NTS "complaint-module" that best fits the major complaint of the patient. Each NTS "complaint-module" consists of several questions (triage criteria) and answering these questions results in a recommended urgency level.[2] The triage nurse, but also the GP on duty can overrule the recommended urgency and change it whenever considered necessary. There are five urgency levels; urgency level 1 (U1) being the highest urgency and U5 being the lowest (Appendix-Table 1). In case of a (potential) life threatening situation an ambulance and/or the GP who is in charge for the home visits should arrive at the patient within 15 minutes (U1). U2 means that the patient should have been evaluated by the GP within 1 hour. When the patient should be assessed by a GP within a few hours the urgency is considered to be U3. If the complaint of the patient is not urgent, the GP may evaluate the patient later that same day (U4). In the remaining cases, only a telephone advice of the triage nurse or GP is considered necessary (U5).

Patient characteristics

Age, gender, date, time of the telephone contact, the diagnostic triage criteria completed by the triage nurse, and the eventually given urgency level could be extracted from the electronic "call management system". If there was a link between the digital record of the own GP and the OHS the medical history of the patient was also visible. Duration of the contact and the original telephone call were retrieved from the "Freedom Call Manager", a back-up system containing the digital registration of all telephone calls to the primary care OHS. A research student screened the telephone calls and scored them on a standardized case record form (Appendix-Table 2). The case record form consisted of items such as symptoms and medical history of the patient, either reported spontaneously by the patient, or after being asked by the triage nurse. As the real life telephone calls were our source of data we could only gather and analyze information (symptoms, medical history) that was mentioned by the patient spontaneously or after be questioned by the triage nurse.

Diagnosis

In an attempt to retrieve the medical diagnosis related to the OHS contact, we contacted the patient's own GP. They were asked to fill out a case record form about diagnoses related to the contact and made within 4 weeks of the contact with the OHS. If the final diagnosis

was an ACS, they classified it in ST-elevation myocardial infarction (STEMI), non-STEMI, or unstable angina pectoris (AP). We evaluated possible differences between patients with a final diagnosis and patients in whom no final diagnosis could be retrieved to exclude any selection bias.

Data analysis

Data were stratified by gender. Continuous variables were expressed as mean (standard deviation), and the duration of the telephone calls in mean (range). Categorical variables were expressed as number (percentage). Differences between sexes in the baseline characteristics, duration of the telephone calls, and the given urgencies were assessed with the Student's t- test or Mann-Whitney U test for continuous variables, and the Chi-square test or Fisher's exact test for categorical variables. The five urgency categories were dichotomized in high urgency (U1-2) and low urgency (U3-5). We used multivariable logistic regression analysis to compare the urgencies between sexes, and developed three models: a crude model, a model with adjustment for only age, and a model adjusting for age, presence of chest pain, the type of pain, and radiation to the one of the arms. Results were expressed as odds ratios (OR) with a 95% confidence interval (CI). The retrieved final diagnoses were categorized, and we combined rhythm disorders, heart failure, pericarditis, symptoms due to the blood pressure, and stable angina pectoris in "other cardiovascular diseases". We compared the prevalence of the final diagnoses between women and men using the Chi-square test. We repeated all analyses after combining all possible life-threatening diagnoses including an ACS, pulmonary embolism, pneumothorax, aortic dissection, cardiac asthma as all these diagnoses would deserve a high urgency.
All data analyses were performed with IBM SPSS version 20.0 for Windows (SPSS, Chicago, Illinois, USA).

RESULTS

Study population and baseline characteristics

The flowchart of the study population is visualized in Figure 1. In total, 832 patients were included: 395 men (48%) and 437 women (53%). The baseline characteristics of the participants are presented in Table 1. Women were on average 3.4 years older than men (63.2 versus 59.8 years). The mean duration of the telephone calls and a history of CVD or diabetes were comparable between sexes. Women more often spontaneously mentioned radiation of the pain than men.

Triage

We compared the urgencies in women and men (Table 2). In the crude analysis no significant difference in urgencies between sexes was found. But also after adjustment for age, and for age and several symptoms including presence of chest pain, type of pain, and radiation to the arms, the odds ratios remained comparable between sexes.

In women and men, the mean duration of the telephone calls was significantly shorter in patients who received a high urgency (U1-2) than in patients that received a low urgency (U3-5): in women 6.47 minutes versus 8.22 minutes (p-value < 0.001), and in men 6.50 minutes versus 7.52 minutes (p-value= 0.001).
There was no significant difference in the duration of the telephone calls between women and men, neither in the high urgency category (U1-2: 6.47 minutes versus 6.50 minutes, p-value=0.9) nor in the low urgency (U3-5, 8.22 minutes versus 7.52 minutes, p-value=0.2).

Diagnosis

The final diagnosis (Table 3) could be retrieved in 518 patients (62%); 276 women (63% of all women) and 242 men (62% of all men). Eight percent of women (n=23) and 14% of men (n=34) (p-value=0.04) appeared to have had an ACS related to the explored telephone contact (Table 3). When we compared sex, age, duration of the telephone calls, and the given urgencies in patients with a final diagnosis and patients without a final diagnosis no differences were found.

Duration of telephone calls related to the diagnosis

When we compared women with an ACS to men with an ACS the duration of the telephone calls was not significantly different: 5.22 minutes versus 6.27 minutes, p-value 0.2. In patients without ACS again no difference was found between the duration of the telephone call in women and men (3.11 minutes versus 2.51 minutes, p-value=0.8).
In women with an ACS the duration of the telephone call was significantly shorter than in women without an ACS (5.22 minutes versus 7.26 minutes, p-value=0.003), while there was no significant difference between men with and without an ACS (6.27 minutes versus 7.22 minutes, p-value=0.1).

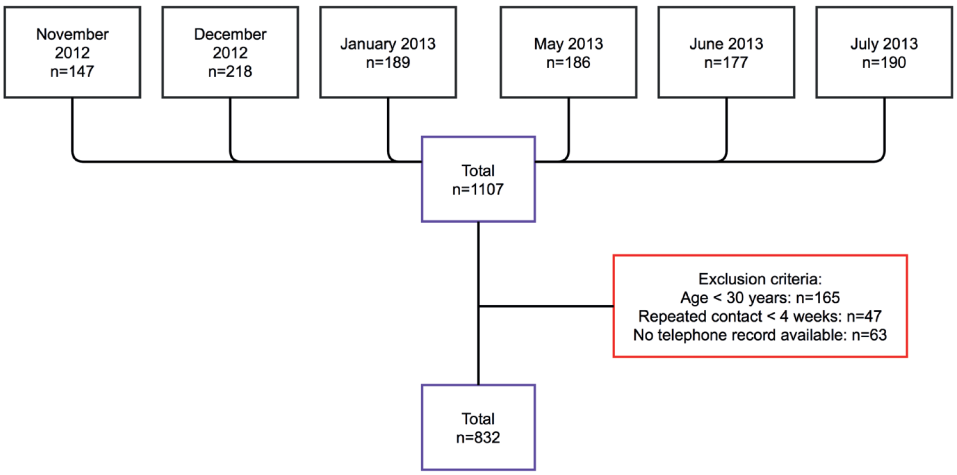


Figure 1. Flowchart

Table 1. Baseline characteristics of the study population (n=832)

	Reported spontaneously/ Being asked	Women n= 437 (53%)	Men n=395 (47%)	p-value
Mean age in years (SD)	n.a.	63.2 (18.0)	59.8 (16.3)	<0.01
Mean duration of telephone call in min:sec (range)	n.a.	7:21 (1:19-24:02)	7:11 (1:44-18:16)	0.5
History of cardiovascular disease (n=630)*	n.a.	169 (52.6)	167 (54.0)	0.7
History of diabetes mellitus (n=305)*	n.a.	39 (26.5)	34 (21.5)	0.3
Chest pain	R	336 (88.9)	314 (88.7)	0.9
(n=732)	A	42 (11.1)	40 (11.3)	
Type of chest pain (n=730)				
Pressing	R	118 (51.3)	95 (53.7)	0.6
(n=407)	A	112 (48.7)	82 (46.3)	
Stinging	R	36 (50.0)	40 (55.6)	0.5
(n=144)	A	36 (50.0)	32 (44.4)	
Pain location				
Left side of the chest	R	43 (56.6)	57 (61.3)	0.5
(n=169)	A	33 (43.4)	36 (38.7)	
Right side of the chest	R	15 (78.9)	20 (69.0)	0.5
(n=48)	A	4 (21.1)	9 (31.0)	
Midsternal	R	52 (40.3)	31 (33.7)	0.3
(n=221)	A	77 (59.7)	61 (66.3)	
Radiation of the pain				
Arm	R	84 (68.3)	64 (58.7)	0.1
(n=232)	A	39 (31.7)	45 (41.3)	
Back or shoulder	R	91 (78.4)	50 (61.0)	0.01
(n=198)	A	25 (21.6)	32 (39.0)	
Jaw	R	36 (76.6)	9 (40.9)	<0.01
(n=69)	A	11 (23.4)	13 (59.1)	
Any radiation	R	182 (70.3)	113 (56.5)	<0.01
(n=459)	A	77 (29.7)	87 (43.5)	
Additional symptoms				
Dyspnea	R	131 (69.3)	110 (65.5)	0.4
(n=357)	A	58 (30.7)	58 (34.5)	
Nausea or vomiting	R	70 (51.1)	47 (54.0)	0.7
(n=224)	A	67 (48.9)	40 (46.0)	
Perspiration	R	36 (29.8)	53 (40.5)	0.08
(n=252)	A	85 (70.2)	78 (59.5)	
Medical history				
Diabetes mellitus	R	17 (51.5)	18 (46.2)	0.7
(n=72)	A	16 (48.5)	21 (53.8)	
Cardiovascular disease	R	82 (66.7)	65 (58.6)	0.2
(n=234)	A	41 (33.3)	46 (41.4)	

n.a.: not applicable; R: reported spontaneously by the patient; A: being asked by the triage nurse; * obtained from the digital patient record

Table 2. The relation between gender and urgency, crude and adjusted for age and for age, presence of chest pain, type of pain, and radiation to the arms (n=832)

	Women n=437 (%)	Men n=395 (%)	Crude OR (95%CI)	Adjusted OR (95%CI)*	Adjusted OR (95%CI)**
U1-2	282 (51.8)	262 (48.2)	0.92 (0.69-1.23)	0.84 (0.62-1.13)	0.88 (0.60-1.29)
U3-5	155 (53.8)	133 (46.2)			

U: urgency; OR: odds ratio; CI: confidence interval; *: adjusted for age; ** adjusted for age, presence of chest pain, type of pain, and radiation to the arms

Table 3. Final diagnosis related to the OHS contact for chest discomfort that could be retrieved from the general practitioners (n=518)

	Women n= 276 (%)	Men n= 242 (%)	p-value
Acute coronary syndrome	23 (8.4)	34 (14.0)	0.04
UAP	8 (34.8)	12 (35.3)	
NSTEMI	10 (43.5)	7 (20.6)	
STEMI	3 (13.0)	6 (17.6)	
Non-classified myocardial infarction*	2 (8.7)	9 (26.5)	
Other cardiovascular diseases	35 (12.7)	30 (12.4)	0.9
Gastrointestinal tract disorders	38 (13.8)	23 (9.5)	0.1
Respiratory tract disorders	37 (13.4)	34 (14.0)	0.8
Psychogenic disorders	25 (9.1)	12 (5.0)	0.07
Non specific chest pain including musculoskeletal pain	99 (35.9)	98 (40.5)	0.3
Other diagnosis	19 (6.9)	11 (4.5)	0.3

UAP: unstable angina pectoris; NSTEMI: Non-ST-elevation myocardial infarction; STEMI: ST-elevation myocardial infarction; * No further information whether it was a STEMI or NSTEMI

Urgencies related to diagnosis

Women with an ACS received as often a high urgency level (U1-2) as men with an ACS (95.7% of the women with ACS versus 88.2% of the men with ACS, p-value=0.3).

When we evaluated the potential life-threatening diagnoses comparable results were found: no difference in the duration of the telephone calls between women and men with a potential life-threatening diagnosis, within women a significant shorter telephone call in women with a potential life-threatening disease than in women without, and comparable high percentages of women and men with a potential life-threatening diagnoses received a high urgency (U1-2).

DISCUSSION

In this study we demonstrated that there were no gender differences in the triage of chest pain patients at primary care OHS. The questions asked by the triage nurse, the duration of the telephone calls and the given urgencies were all comparable between sexes.
When we took the diagnosis into account, again no difference was found in the duration of the telephone calls between women and men with an ACS. However, when we looked at the duration of the telephone calls within women, we found that in women with an ACS the duration was significantly shorter than in women without an ACS while in men no significant difference was found. This would suggest that the triage nurses were earlier able to recognize an urgent diagnosis within women than within men. In both women and men the urgency classification in case of ACS was correctly chosen as 95.7% of women and 88.2% of men with an ACS got a high urgency (U1-2).
Our study has several strengths. First, our study is the best representation of a real-life setting as we listened to registrations of the original telephone calls. This gave us the opportunity to take the initial presentation of the patient into account. As this presentation has the tendency to change after multiple interrogations into typical textbook angina pectoris, this is the only moment to analyze the symptoms in its purest form without any recall bias. On top of that the triage nurses were not aware that these tapes would ever be used for study purposes so they treated the patient as usual.
Second we used data from primary care OHS "de Gelderse Vallei", providing primary care in 73% of the week-hours to 270.000 people, including rural and city area, making the included patients a good illustration of the general Dutch population with chest pain. Third, our study population of 832 patients was large enough to draw firm conclusions. Two limitations should be addressed. First, we were not able to retrieve the final diagnosis of 62% of the patients because some GPs unfortunately were not willing to provide the necessary follow up data. Various reasons were given but most GPs refused to provide patient data without permission of the patient, even though the Ethical Committee approved our study and we would save the data de-personalized. As the missing data was driven by the GPs we expected no selection bias. Second, by design of the study we could only present data of patients with chest pain who contacted the primary care in out of hours, and not from those who called immediately an ambulance or went on their own to an emergency department.
Somewhat more men (14.0%) than women (8.4%) were diagnosed with an ACS. This is in line with a previous study in primary care assessing patient with chest pain (17% in men and 14% in women).[10]
It is difficult to compare our study with previous studies regarding the triage of chest pain patients in a primary care OHS. One Norwegian study linked the urgency levels provided (three: red, yellow and green) to referral to the hospital, with as a result 50% referrals. Importanly, however, the final diagnoses was not retrieved.[11]
A previous study that analyzed gender differences in the symptom presentation of patients suspected of an ACS in primary care found no relevant differences between sexes but

only a small number of symptoms was collected.[12] They did find a significant longer doctor delay, which could in theory be interpreted as triage before sending a patient to the hospital, in women than in men: 45 minutes versus 33 minutes (p-value=0.01). Another study by Bosner et al. were able to evaluate which symptoms had predictive value for coronary heart disease (ACS and stable angina pectoris) in women and men presenting with chest pain in primary care.[10] For both sexes known clinical vascular disease, pain worse with exercise and age were associated positively with coronary heart disease.[10] In women pain duration above one hour was associated positively with coronary heart disease, while shorter pain durations showed an association with coronary heart disease in men.[10] In women negative associations were found for stinging pain and in men for pain depending on inspiration and localised muscle tension. Unfortunately we were not able to study this predictive value due to very selective reporting of symptoms and the large number of missing final diagnoses.[10]

Conclusion

There is no gender difference in the triage and urgency classification of patients with chest pain in primary care, also not in the subgroup of patients who eventually showed to have an ACS.

REFERENCES

1 Buntinx F, Knockaert D, Bruyninckx R, de Blaey N, Aerts M, Knottnerus JA, *et al.* Chest pain in general practice or in the hospital emergency department: is it the same? Fam Pract 2001; 18: 586-589.

2 van Ierland Y, van Veen M, Huibers L, Giesen P, Moll HA. Validity of telephone and physical triage in emergency care: the Netherlands Triage System. *Fam Pract* 2011; 28: 334-341.

3 Culic V, Eterovic D, Miric D, Silic N. Symptom presentation of acute myocardial infarction: influence of sex, age, and risk factors. *Am Heart J* 2002; 144: 1012-1017.

4 Dey S, Flather MD, Devlin G, Brieger D, Gurfinkel EP, Steg PG, *et al.* Sex-related differences in the presentation, treatment and outcomes among patients with acute coronary syndromes: the Global Registry of Acute Coronary Events. Heart 2009; 95: 20-26.

5 Patel H, Rosengren A, Ekman I. Symptoms in acute coronary syndromes: does sex make a difference? *Am Heart J* 2004; 148: 27-33.

6 Khan NA, Daskalopoulou SS, Karp I, Eisenberg MJ, Pelletier R, Tsadok MA, *et al.* Sex Differences in Acute Coronary Syndrome Symptom Presentation in Young Patients. *JAMA Intern Med* 2013.

7 Canto JG, Goldberg RJ, Hand MM, Bonow RO, Sopko G, Pepine CJ, *et al.* Symptom presentation of women with acute coronary syndromes: myth vs reality. *Arch Intern Med* 2007; 167: 2405-2413.

8 Sullivan AL, Beshansky JR, Ruthazer R, Murman DH, Mader TJ, Selker HP. Factors associated with longer time to treatment for patients with suspected acute coronary syndromes: a cohort study. *Circ Cardiovasc Qual Outcomes* 2014; 7: 86-94.

9 Brieger D, Eagle KA, Goodman SG, Steg PG, Budaj A, White K, *et al.* Acute coronary syndromes without chest pain, an underdiagnosed and undertreated high-risk group: insights from the Global Registry of Acute Coronary Events. *Chest* 2004; 126: 461-469.

10 Bosner S, Haasenritter J, Hani MA, Keller H, Sonnichsen AC, Karatolios K, *et al.* Gender differences in presentation and diagnosis of chest pain in primary care. BMC Fam Pract 2009; 10: 79.

11 Burman RA, Zakariassen E, Hunskaar S. Management of chest pain: a prospective study from Norwegian out-of-hours primary care. *BMC Fam Pract* 2014; 15: 51-2296-15-51.

12 Bruins Slot MH, Rutten FH, van der Heijden GJ, Doevendans PA, Mast EG, Bredero AC, *et al.* Gender differences in pre-hospital time delay and symptom presentation in patients suspected of acute coronary syndrome in primary care. *Fam Pract* 2012; 29: 332-337.

Appendix-Table 1. Urgency levels

Urgency level	Implication
U0	Reanimation
U1	Life-threatening, GP/ ambulance has to arrive within 15 minutes
U2	Emergency, GP has to arrive within 60 minutes
U3	Urgent, consultation by GP in a couple of hours
U4	Routine, consultation by GP the same day
U5	Advise by triage nurse

Appendix-Table 2. Case report form

Items to be registered on the case report form	
Duration of the telephone call	Dyspnoea or chest tightness *
Was the conversation with patient or relative?	Fever, cough or having a cold*
Presence of chest pain*	Smoking status*
Type of pain*	History of diabetes mellitus*
Location of the chest pain*	History of hypertension*
Intensity of the pain (score between 0 and 10)*	History of hypercholesterolemia*
Radiation of the pain*	History of cardiovascular disease
Symptoms during rest or during exercise*	Complaints similar to previous episodes of cardiac disease (when having a history of cardiac disease)
Duration of the symptoms*	Positive family history of cardiovascular disease*
Similar symptoms in the last 4 weeks*	Positive family history of sudden cardiac death below the age of 60 years*
Nausea or vomiting*	Suspicion of a life-threatening disease*
Perspiration*	Does the medical trainee suspect ACS after listening to the back-up of the telephone call

* We registered if the patient mentioned this symptom spontaneously or after being questioned about by the triage nurse

CHAPTER 5

WORSE OUTCOME IN WOMEN WITH STEMI
A SYSTEMATIC REVIEW OF PROGNOSTIC STUDIES

Eur J Clin Invest. 2015 Feb;45(2):226-35

Manon G. van der Meer, Hendrik M. Nathoe, Yolanda van der Graaf,
Pieter A. Doevendans, Yolande Appelman

ABSTRACT

Background

Treatment of ST elevation myocardial infarction (STEMI) has improved enormously since the introduction of primary percutaneous coronary intervention (pPCI). It remains unclear whether differences in survival between women and men treated with pPCI exist and if these potential differences can be explained by gender or by differences in baseline- or procedural characteristics. Therefore we systematically reviewed the available evidence.

Materials and methods

On 10-05-2013 Pubmed, Embase and Cochrane were searched for studies comprising original data on STEMI patients treated with pPCI. A separate gender analysis including > 100 women was a requirement. Data were extracted and pooled whenever possible.

Results

21 studies were included from 2001 to 2013 comprising 47.439 men and 16.927 women. Women were older, had more diabetes (women 24%, men 15%) and hypertension (women 58%, men 45%) and were less current smokers (women 30%, men 54%). The procedural characteristics were comparable except for a longer symptom-to-balloon-time (women 266 min, men 240 min) and less use of GP-IIb/IIIa-inhibitors in women (women 51%, men 57%). Crude short- and long-term mortality was higher in women. Although we could not pool adjusted mortality proportions due to heterogeneity, generally the difference in mortality disappeared after adjustment for baseline- and procedural characteristics.

In conclusion

Mortality is higher in women with STEMI and can be explained by their unfavourable risk profile and longer symptom-to-balloon time.

INTRODUCTION

Over the past 10 years, the treatment of an ST elevation myocardial infarction (STEMI) has improved enormously, mainly due to the shift from thrombolysis to primary percutaneous coronary intervention (pPCI).[1] Therefore pPCI is now the recommended treatment for STEMI in Europe and the United States.[2,3] Although many studies have looked for differences in outcome between women and men with a STEMI treated with pPCI, the results remain conflicting. This is partly due to the fact that data are often difficult to compare since inclusion criteria frequently differ and there is variation in outcome measures and duration of follow-up. Moreover, in studies that show poorer survival in women there is debate as to whether it is female gender or differences in baseline characteristics and treatment that explain the adverse outcome.[4] The aim of our study was to investigate if differences in survival between women and men with STEMI treated by pPCI exist and if they can be explained by traditional risk factors or by gender itself. Therefore, we systematically reviewed all available studies concerning gender differences in baseline characteristics, procedural features of pPCI, medical treatment and outcome of short- and long-term follow-up in patients with STEMI treated with pPCI.

METHODS

Eligibility criteria and selection of studies

On 10-05-2013 a systematic search was performed in Pubmed, Embase and the Cochrane library using the search string described in Supplementary Table 1. In Embase we used a filter to exclude conference abstracts. Publications were selected by two independent reviewers screening title and abstract. Studies were eligible if they included patients with STEMI treated with a pPCI without prior thrombolysis. The statistical analyses had to be carried out separately for women and men and the outcomes had to include mortality or a composite of major adverse cardiovascular events (MACE). We excluded all conference abstracts and studies if the full text was not in English or the number of women was below 100. After screening, the full text of all remaining studies was read and judged by two independent reviewers. Data on baseline characteristics, procedural features and outcome were extracted from the studies. For each baseline characteristic, procedural feature and the absolute mortality proportions at different points in time we pooled all available studies regarding that specific variable in women and men separately. We used a random effects model (R.package "Metafor") on the log-transformed scale leading to a pooled estimate with 95% confidence interval (95%CI). To compare the obtained estimates we calculated the risk difference between women and men with a random effects model (R.package "Metafor"). After pooling the data the number of patients was that large that the smallest differences in percentage between women and men would become statistically significant. Therefore we based our conclusions on the clinically relevant differences instead of on the statistically significant differences.

Since we wanted to compare the outcomes of women and men we recalculated the ratios when necessary setting men as the reference category. In addition if only crude percentages of women and men that develop an endpoint were given, we calculated the odds ratio and confidence interval if all the necessary information was available.
To compare the results on a visual scale, forest plots were made for crude and adjusted in-hospital mortality, mortality at 30 days, mortality at one-year and long-term mortality. We combined the hazard- and odds ratios in the plot at the time-fixed endpoints (30 days and one-year); for the other two time points (in-hospital and long-term mortality) we used the ratio that was described most often since they could not be combined as follow-up time was not comparable in all patients. When results in an article were unclear or contradictory we contacted the authors of the article in an attempt to retrieve the correct data.

Table 1. Study background information and baseline characteristics

Article	Country	Years of inclusion	Number of patients	Women (%)	Age (mean)
Benamer et al.[7]	France	2003-2007	13.673	23	X
Bufe et al.[8]	Germany	1999-2001	500	25	♀: 65 ♂: 58
De Luca et al.[9]	Netherlands	1997-2001	1.548	23	♀: 66 ♂: 59
De Luca et al.[10]	Several countries	1990-2007	1.662	23	♀: 67 ♂: 59
Ferrante et al.[11]	Italy	2004-2008	481	29	♀: 72 ♂: 63
Hailer et al.[12]	Duitsland	2004-2008	1.365	28	♀: 68 ♂: 61
Hurtado-Martinez et al.[13]	Spain	2000-2003	838	22	♀: 70 ♂: 62
Jackson et al.[14]	USA	2003-2008	8.771	29	♀: 65 ♂: 58
Jakobsen et al.[15]	Denmark	2002-2008	7.385	27	♀: 67 ♂: 62
Liu et al. [16]	China	2006-2007	259	45	♀: 69 ♂: 68
Motovska et al.[17]	Czech Republic	1997-2002	530	30	♀: 67 ♂: 62
Mrdovic et al.[18]	Serbia	2006-2009	2.096	27	♀: 63 ♂: 57
Pain et al.[19]	United Kingdom	2003-2010	2.467	22	♀: 68 ♂: 59
Pu et al.[20]	China	2005-2009	594	25	♀: 70 ♂: 61
Sadowski et al.Group DT*[21]	Poland	2005-2006	4.827	30	♀: 71 ♂: 63
Sadowski et al. Group TA*[21]	Poland	2005-2006	5.880	30	♀: 67 ♂: 60
Sjauw et al. [22]	Netherlands	1997-2006	3.277	28	♀: 66 ♂: 59
Valente et al.[23]	Italy	2004-2009	1.129	26	♀: 76 ♂: 65
Velders et al.[24]	Netherlands	2006-2009	3.483	25	♀: 68 ♂: 62
Waldecker et al.[25]	Germany	X	691	26	♀: 66 ♂: 60
Wijnbergen et al.[26]	Netherlands	2006-2008	870	23	♀: 65 ♂: 59
Zhang et al.[27]	China	2005-2008	2.042	23	♀: 72 ♂: 64
Pooled data	na	na	64.366	26.3 (26.1-26.7)	♀: 67.9 (66.6-69.2) ♂: 61.0 (59.9-62.1)

X: not described; *: DT = direct transport/ TA= transferred from another hospital; na: not applicable

Quality appraisal and heterogeneity

We assessed the quality of the studies included by scoring several items per study. These items are based on methodological guidelines for predictive studies and quality criteria previously used in reviews of prognostic studies.[5,6]

The heterogeneity between studies was assessed to determine whether a formal meta-analysis was possible. To evaluate possible publication bias we made funnel plots of the four major endpoints (in-hospital mortality, 30 days, one-year and long-term mortality).

Table 1. continued

Hypertension (%)	Smoking (%)	Dyslipidemia (%)	Diabetes mellitus (%)	Previous myocardial infarction (%)
X	X	X	X	X
♀: 55 ♂: 66	♀: 40 ♂: 67	♀: 50 ♂: 47	♀: 24 ♂: 11	♀: 8 ♂: 12
♀: 39 ♂: 24	♀: 43 ♂: 52	♀: 21 ♂: 21	♀: 16 ♂: 9	♀: 7 ♂: 12
♀: 53 ♂: 39	♀: 37 ♂: 56	♀: 37 ♂: 37	♀: 22 ♂: 15	♀: 8 ♂: 9
♀: 68 ♂: 55	♀: 30 ♂: 48	♀: 49 ♂: 48	♀: 28 ♂: 19	♀: 7 ♂: 16
♀: 77 ♂: 65	♀: 31 ♂: 47	♀: 57 ♂: 55	♀: 28 ♂: 20	X
♀: 59 ♂: 36	♀: 8 ♂: 53	♀: 33 ♂: 28	♀: 45 ♂: 27	X
♀: 74 ♂: 64	♀: 41 ♂: 47	X	♀: 27 ♂: 21	♀: 21 ♂: 24
♀: 39 ♂: 27	♀: 52 ♂: 55	♀: 26 ♂: 25	♀: 11 ♂: 9	♀: 14 ♂: 17
♀: 61 ♂: 48	♀: 33 ♂: 52	♀: 64 ♂: 62	♀: 44 ♂: 20	X
♀: 63 ♂: 43	♀: 17 ♂: 30	X	♀: 32 ♂: 19	♀: 13 ♂: 14
♀: 74 ♂: 61	♀: 43 ♂: 60	♀: 67 ♂: 65	♀: 23 ♂: 16	♀: 9 ♂: 12
♀: 48 ♂: 38	♀: 29 ♂: 40	♀: 34 ♂: 34	♀: 20 ♂: 16	♀: 12 ♂: 13
♀: 65 ♂: 50	♀: 16 ♂: 76	♀: 15 ♂: 20	♀: 32 ♂: 18	♀: 5 ♂: 7
♀: 66 ♂: 55	♀: 30 ♂: 51	♀: 43 ♂: 40	♀: 23 ♂: 14	♀: 10 ♂: 11
♀: 66 ♂: 57	♀: 30 ♂: 53	♀: 46 ♂: 44	♀: 26 ♂: 15	♀: 9 ♂: 13
♀: 36 ♂: 28	♀: 41 ♂: 47	♀: 21 ♂: 23	♀: 15 ♂: 10	♀: 15 ♂: 15
♀: 64 ♂: 50	♀: 36 ♂: 72	♀: 38 ♂: 36	♀: 31 ♂: 24	♀: 11 ♂: 15
♀: 46 ♂: 33	♀: 41 ♂: 48	♀: 22 ♂: 24	♀: 14 ♂: 10	♀: 7 ♂: 12
♀: 63 ♂: 53	X	♀: 57 ♂: 54	♀: 31 ♂: 14	♀: 10 ♂: 16
♀: 44 ♂: 25	includes ex-smoking ♀: 55 ♂: 66	♀: 25 ♂: 29	♀: 15 ♂: 9	X
♀: 69 ♂: 51	♀: 10 ♂: 66	♀: 45 ♂: 40	♀: 37 ♂: 22	♀: 14 ♂: 12
♀: 58 (53-64) ♂: 45 (39-52)	♀: 30 (24-37) ♂: 54 (48-59)	♀: 38 (31-46) ♂: 38 (31-44)	♀: 24 (21-29) ♂: 15 (13-18)	♀: 10 (9-12) ♂: 13 (12-15)

RESULTS

Study selection

After our initial search, (Supplementary Table 1), we ended up with 758 studies that were potentially relevant (Figure 1, flow chart). After reviewing titles and abstracts 62 studies were evaluated using full texts, and another 41 studies were excluded. Consequently, a total of 21 studies were added to this review.[7-27] All the included studies were prospective, observational studies.

Quality of the studies (Supplementary Table 2)

The majority of the quality assessment items were described in the studies. However, information on loss to follow-up and drop-outs was incomplete. Moreover, only six out of the 21 studies published results adjusted solely for age.[12,13,15,19,22,26] Of the 19 studies that contained a multivariable analysis, nine did not mention the exact confounders that had been included in the model.[7,8,10,14,17-20,27]

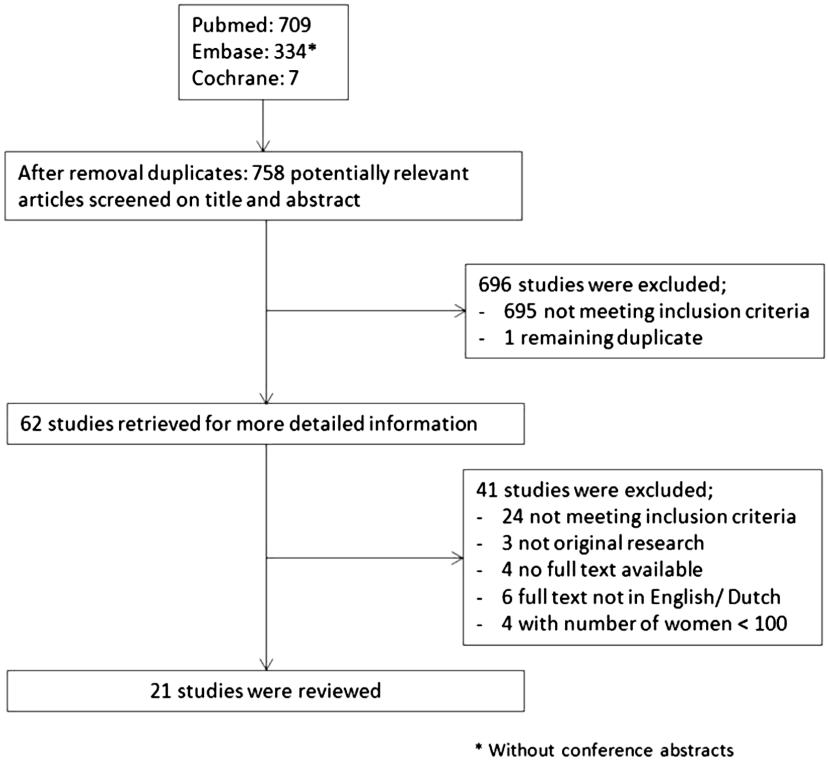


Figure 1. Flowchart

Studies were largely heterogeneous concerning the study outcomes and the possible confounders they adjusted for. Therefore the data extracted were not suitable to perform a meta-analysis beyond the systematic review. The funnel plots of the four major endpoints showed no very clear patterns or signs of publication bias but numbers per end point were small.

Background of the studies (Table 1)

Twenty studies mentioned the years of inclusion which varied between 1997 and 2010.[7-24,26,27] Sixteen studies were performed in Europe,[7-9,11-13,15,17-19,21-26] one in the USA,[14] three in China[16,20,27] and one study was a cooperation between several countries in Europe and the USA.[10] In 16 studies the time from the start of symptoms to primary PCI was <12 hours[8,10,13-18,20-27] in three studies it was <24 hours[7,9,11] and in the remaining two studies it was not mentioned.[12,19] The smallest study population comprised 259 patients[16] and the largest 13.673 patients.[7] In these 21 studies a total of 47.439 men and 16.927 women were included. The percentage of women in each study varied between 22% and 45% and the pooled percentage of women was 26.3% (95%CI: 24.8%-28.1%).

Cardiovascular risk factors and previous medical history (Table 1)

Most studies displayed an extensive overview of the prevalence of cardiovascular risk factors in their study population as depicted in Table 1. After pooling data of all studies describing age, women were on average 7 years older than men (67.9 years (95%CI: 66.6-69.2) versus 61.0 years (95%CI: 59.9-62.1), p-value <0.0001). Significantly more women than men had diabetes and hypertension while more men than women smoked. The percentage of dyslipidaemia and a positive family history was comparable between sexes. Only five studies presented the exact body mass index (BMI) and results were therefore not pooled.

After combining the results of the 16 studies that described a previous medical history 13% of the men and 10% of the women reported a previous myocardial infarction. A previous medical history of PCI was present in 6% of men and 4% of women and of coronary artery bypass grafting in 3% in men and 2% in women. Both previous PCI and coronary artery bypass grafting were described in 12 out of the 21 studies. Even though a previous medical history of myocardial infarction, PCI and coronary artery bypass grafting was more prevalent in men than in women, these differences in percentages were however very small and not clinically relevant.

Clinical and procedural characteristics

The symptom-to-balloon time was described by 16 studies and in all but two this time was significantly longer in women. Pooling the eight studies that provided mean with standard deviation resulted in a symptom-to-balloon time of 240 minutes (198 minutes-282 minutes) in men and 266 minutes (232 minutes-300 minutes) in women (p-value 0.003). Eleven studies published the door-to-balloon time[9,11,12,14,16,17,21,22,24,26,27] and in all

studies but two there was no significant difference between women and men.[11,14] Data could not be pooled as part of the studies did not mention the actual minutes. After combining the data of the eigth studies that described the Killip class on presentation we found that 20% (95%CI: 14%-28%) of the women and 16% (95%CI: 11%-22%) of the men had a Killip class > 1 (p-value=0.002).[9,10,15,17,18,20,23,27] Cardiogenic shock was present in 12% (95%CI: 8%-16%) of women versus 9% (95%CI: 7%-12%) of men (p-value=0.0003, nine studies).[8,12-14,16,19,22,24,25] There was no difference in the number of diseased vessels between women and men. Not all studies used the same cut off percentage to define a diseased vessel, but since this is not different for women and men it does not influence our results.
Equal percentages of women and men had a pre-procedural TIMI III flow after pooling the results of the 13 studies describing this characteristic (women 11% (95%CI: 8%-16%), men 10% (95%CI: 7%-14%), p-value= 0.02).[8,9,12,15-18,20-23,26,27] The proportion of patients receiving a stent was similar, namely 88% of men and 86% of women.[9-13,15-18,20,22-24] The percentage of drug eluting stents was also comparable between men (46%) and women (42%).[11,12,15,16,18,20,23,24,26] More men than women received glycoprotein IIb/IIIa inhibitors, namely 57% (95%CI: 42%-70%) of men versus 51% (95%CI: 39%-63%) of women (p-value <0.0001, 12 studies).[10,11,13-15,20-24,26,27] Pooling the results of 12 studies comparable post-procedural TIMI III flow was described in women and men.[8,9,12,15-18,21-23,26,27]
Since the left ventricular function (LVF) measurement technique and/ or the timing was different in most studies we did not pool these data. No clinical significant difference between sexes was reported.

In-hospital complications

Data about in-hospital complications, such as stroke, target lesion revascularisation, bleeding- and renal complications, was only published in a minority of the studies so no definite conclusions could be drawn.

Absolute, crude mortality proportions (Supplementary Tables 3-6)

The in-hospital mortality was described in nine studies and was in women almost twice as high as in men (8% (95%CI: 6%-10%) versus 4% (95%CI: 3%-6%), p-value <0.0001).[7,9,11-14,21,23,27] At 30 days after pPCI the mortality proportion was 8% (95%CI: 7%-8%) in women versus 6% (95%CI: 5%-6%) in men (p<0.0001, nine studies).[8,15,17,18,20-22,25,27] Pooling data from the seven studies describing one-year mortality these percentages increased to 12% (95%CI: 10%-14%) in women and 8% (95%CI: 7%-10%) in men (p-value <0.0001).[9,12,15,18,21,22,24] The absolute long term mortality proportions were also significantly higher in women (16%) than in men (9%), p-value <0.0001).[8,11,13,15,19,22,26] This long-term mortality was described in seven studies and the mean/ median follow-up differed between two and six years.

Adjusted mortality

Since most studies adjusted for different variables, we could not pool the adjusted mortality proportions. Six studies published age-adjusted results, but at different points in time making it impossible to pool the age-adjusted data from these six studies.[12,13,15,19,22,26]

In-hospital mortality (Supplementary Table 3, Figure 2)

Adjusted results were presented in six studies.[7,13,14,18,23,27] Four studies found no difference in mortality between women and men after adjustment for possible confounders[14,18,23,27] while in two studies the mortality remained higher in women.[7,13] The forest plot (Figure 2) visualizes all crude and adjusted odds ratios and confidence intervals of the studies describing in-hospital mortality. One study published mortality at seven days and crude- and adjusted mortality were higher in women.[24] As it is unknown whether patients were still in-hospital this study was not added to the table or forest plot.

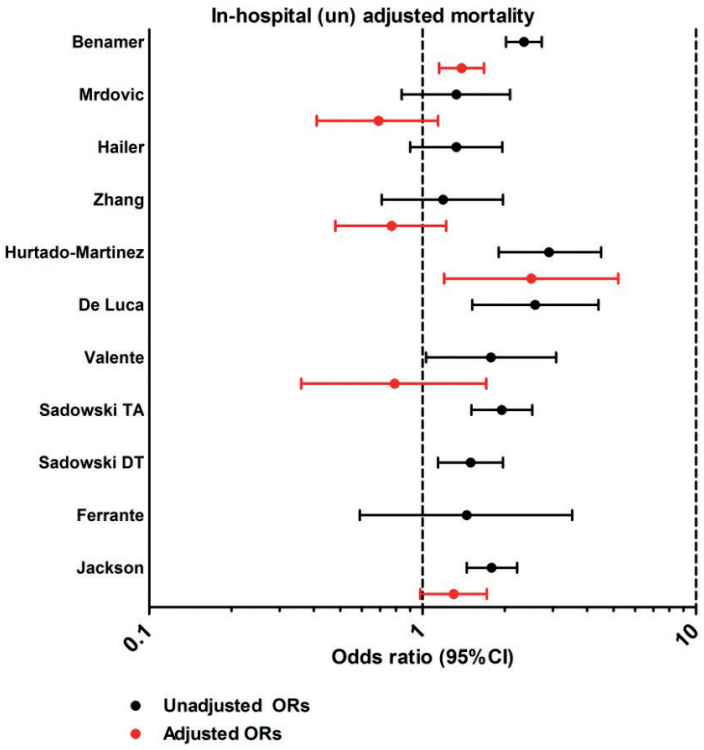


Figure 2. Crude and adjusted in-hospital mortality in women and men. All studies that published a crude or adjusted odds ratio were included.

30 days mortality (Supplementary Table 4, Figure 3)
Six studies published adjusted mortality proportions at 30 days.[15,17,18,22,25,27] In five of these six studies the crude mortality proportion was already comparable between women and men. [17,18,22,25,27] In the one study with a higher crude mortality in women this difference disappeared after stratifying for age.[15]

One-year mortality (Supplementary Table 5, Figure 4)
Seven studies presented adjusted mortality proportions at one-year.[9,12,15,18,21,22,24] In all studies there was no significant difference between women and men. In two the crude mortality proportions were already comparable between women and men[18,22] while in the remaining five studies the crude mortality was higher in women than in men. [9,12,15,21,24] In two of these five studies the difference between sexes disappeared after adjusting or stratifying for age.[12,15] In the remaining three studies adjustment was made for multiple confounders at the same time and female gender was no longer

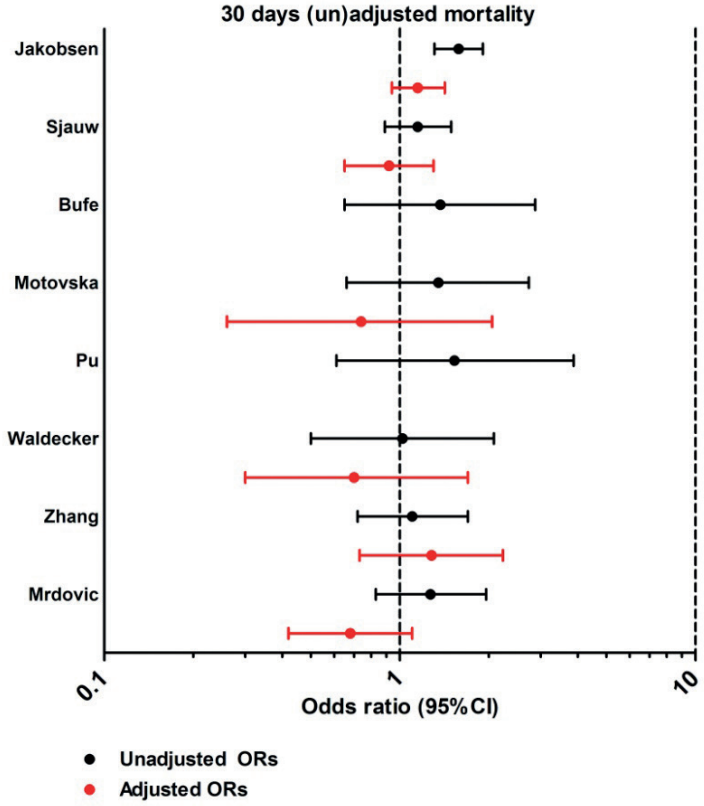


Figure 3. Crude and adjusted 30 days mortality in women and men. All studies that published a crude or adjusted odds or hazard ratio were included.

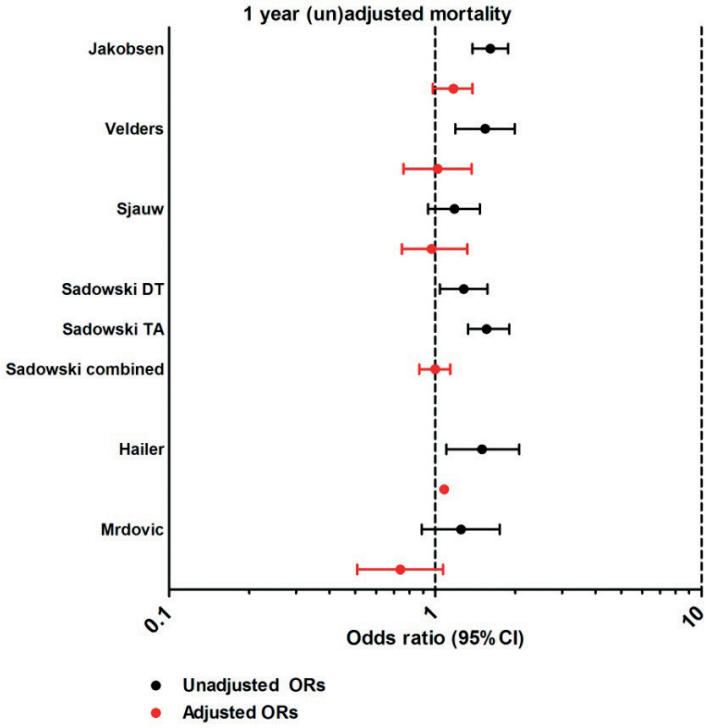


Figure 4. Crude and adjusted one-year mortality in women and men. All studies that published a crude or adjusted odds or hazard ratio were included.

associated with excess mortality.[9,21,24] Unfortunately we were not able to add the risk ratio of De Luca et al.[9] and the odds ratio without confidence interval of Hailer et al. to the forest plot.[12] Therefore the forest plot (Figure 4) visualises all crude and adjusted odds/ hazard ratios and confidence intervals of the remaining studies that presented one-year mortality.

Long-term mortality (Supplementary Table 6, Figure 5)

Seven studies described long-term mortality and no significant differences in mortality between sexes were found.[8,11,13,15,19,22,26] The long-term follow-up differed between two and seven years. In three studies there were no differences in absolute mortality proportions between women and men.[8,11,22] In the univariable analysis of the remaining four studies women had an increased mortality compared to men, [13,15,19,26]. In three out of these four studies this difference disappeared after adjustment or stratifying for age. [13,15,26] In the remaining study only a multivariable adjustment was performed and again the mortality proportions became comparable between the sexes.[19] The forest plot (Figure 5) visualises all the hazard ratios and confidence intervals of the studies that

published long-term mortality results. As the duration of follow-up in Bufe et al. and Hurtado-Martinez et al. is not comparable in all included patients and they only presented an odds- or risk ratio, we could not add these two studies to our plot.[8,13]

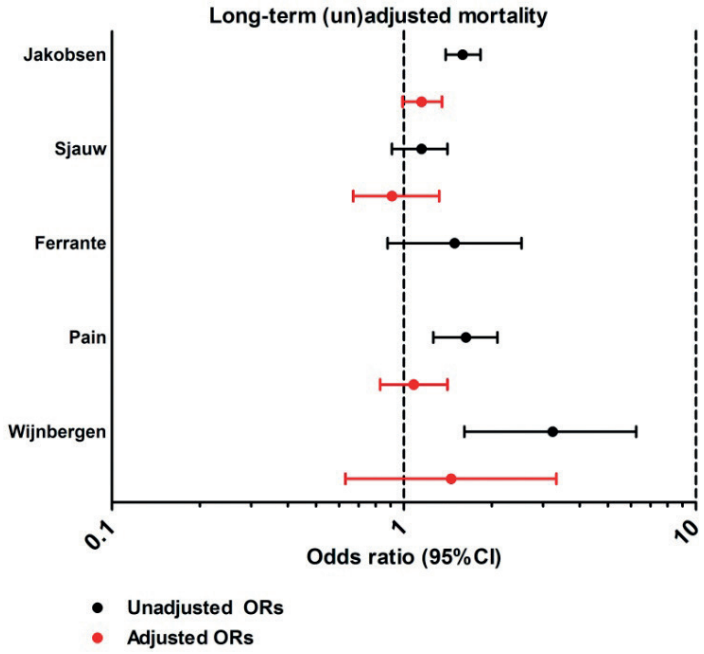


Figure 5. Crude and adjusted long-term mortality in women and men. All studies that published a crude or adjusted hazard ratio were included.

DISCUSSION

In this systematic review regarding gender differences in STEMI patients we not only evaluated the differences between women and men in baseline characteristics and short- and long-term outcomes, but also compared the procedural characteristics. When we evaluated the results of the 21 studies included in this review it became clear that overall women were older and had more often diabetes and hypertension. Remarkably, women had a longer symptom-to-balloon-time than men while the door-to-balloon-time was comparable, meaning that this difference between sexes is not caused by delayed treatment in women after arrival at the hospital. Apparently women tend to postpone seeking medical care longer than men do - confirming earlier reports.[28,29] Whether older age or female gender is the true cause for the delay remains debatable. Recently Velders et al. found in a multivariable analysis that not gender but older age and the presence of

diabetes were independent predictors for the prolonged ischaemic time in STEMI patients presented for pPCI.[24] Although our review showed increased ischaemic time in women, this did not lead to a difference in procedural success. Unfortunately the included studies did not assess if the prolonged symptom-to-balloon-time led to more myocardial damage. Women were however in a higher Killip class on presentation, an indicator of more advanced disease and a worse prognosis[30,31]. Some studies did not mention Killip class but cardiogenic shock and again, women were in a worse clinical condition when admitted to hospital. The exact cause of this finding remains uncertain as the extent of coronary artery disease was comparable. The procedural features were largely comparable between the sexes with one exception: significantly more men than women received GP IIb/IIIa inhibitors. The reason for the difference in GP IIb/ IIIa inhibitor use between sexes was not described. Previous studies also identified this discrepancy in usage between women and men.[32,33]

Since the age difference between women and men is rather large, it would have been most transparent and accurate if all studies presented age-adjusted results. Unfortunately only six studies presented these data. [12,13,15,19,22,26] In these six studies all significant differences in mortality proportions disappeared after stratifying or adjusting for age. [12,13,15,19,22,26] It appears that age might explain a big part of the increased mortality in women. In multivariable analysis several baseline characteristics and procedural features were added at once making it impossible to differentiate which variables can further explain the adverse outcome in women. If data had been presented in a more comparable way in all 21 studies it would have been possible to pool the data and perform a meta-analysis thus leading to a more definite conclusion about possible gender differences. Previous papers noted that cardiovascular medication recommended by guidelines following STEMI is often not prescribed to women either during admission or on discharge. Unfortunately, this review could not elucidate this issue since only two studies described the use of platelet inhibitors during admission[7,22] and two other studies mention discharge medication.[9,15] The same applies to several procedural characteristics such as the arterial access site used (radial/ femoral), medication given during the procedure and the use of a thrombosuction device during pPCI. As none or only a few papers published results on these topics, no conclusions could be drawn.

In this review we were unable to evaluate if female-specific cardiovascular risk factors, such as pre-eclampsia or gestational diabetes, are of any prognostic value, as they were not mentioned in any of the papers. This might play a role since we know from the recent literature that these risk factors are of prognostic value in women.[34-36]

This review demonstrates that risk factors like age, hypertension and diabetes are the cause of the worse prognosis in women. As mortality is indeed increased in women due to their unfavourable baseline risk profile it is very important that clinicians acknowledge this difference and optimise their treatment and prevention strategies. This strategy might have resulted in less extensive disease and a better outcome, as cardiovascular disease is still killer number one in women.

Limitations

Our systematic review was comprehensive and carefully conducted but papers might have been overlooked while screening title and abstract. However, our search results were reviewed by two independent reviewers. Also we might have missed relevant studies that published their full text in a language other than English. On top of that, it could be that there was selection in the inclusion of patients as study patients are often not completely comparable to the general population. For this systematic review we were limited to the available evidence. No formal tools to critically appraise the applied methods and biases are available for prognostic studies. Nevertheless, we assessed the quality of the included studies using quality criteria applied in previous reviews of prognostic studies.[5,6] Reporting was generally good in most studies, although often information about missing values and reasons for loss to follow-up were not given. This could lead to some selection bias in retrospective studies.

Conclusions

On comparison with men, women with a STEMI undergoing pPCI have a higher mortality at several points in time. This is not caused by their female gender but can be related to a disadvantageous risk profile and delayed presentation leading to a postponed treatment. Clinicians should be aware of this crucial difference and put all their effort into optimising care, prevention and treatment to improve the outcome in women.

REFERENCES

1 De Luca G, Cassetti E, Marino P. Percutaneous coronary intervention-related time delay, patient's risk profile, and survival benefits of primary angioplasty vs lytic therapy in ST-segment elevation myocardial infarction. *Am J Emerg Med* 2009; 27: 712.

2 American College of Emergency Physicians, Society for Cardiovascular Angiography and Interventions, O'Gara PT, Kushner FG, Ascheim DD, Casey DE,Jr*, et al.* 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2013; 61: e78.

3 Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC), Steg PG, James SK, Atar D, Badano LP, Blomstrom-Lundqvist C, *et al.* ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J 2012; 33: 2569.

4 Maas AH, Appelman YE. Gender differences in coronary heart disease. *Neth Heart J* 2010; 18: 598.

5 Altman DG. Systematic reviews of evaluations of prognostic variables. *BMJ* 2001; 323: 224.

6 Hayden JA, Cote P, Bombardier C. Evaluation of the quality of prognosis studies in systematic reviews. *Ann Intern Med* 2006; 144: 427.

7 Benamer H, Tafflet M, Bataille S, Escolano S, Livarek B, Fourchard V*, et al.* Female gender is an independent predictor of in-hospital mortality after STEMI in the era of primary PCI: insights from the greater Paris area PCI Registry. *EuroIntervention* 2011; 6: 1073.

8 Bufe A, Wolfertz J, Dinh W, Bansemir L, Koehler T, Haltern G*, et al.* Gender-based differences in long-term outcome after ST-elevation myocardial infarction in patients treated with percutaneous coronary intervention. *J Womens Health (Larchmt)* 2010; 19: 471.

9 De Luca G, Suryapranata H, Dambrink JH, Ottervanger JP, van't Hof AW, Zijlstra F*, et al.* Sex-related differences in outcome after ST-segment elevation myocardial infarction treated by primary angioplasty: data from the Zwolle Myocardial Infarction study. *Am Heart J* 2004; 148: 852.

10 De Luca G, Gibson CM, Gyongyosi M, Zeymer U, Dudek D, Arntz H-*, et al.* Gender-related differences in outcome after ST-segment elevation myocardial infarction treated by primary angioplasty and glycoprotein IIb-IIIa inhibitors: Insights from the EGYPT cooperation. *J Thromb Trombolysis* 2010; 30: 342.

11 Ferrante G, Corrada E, Belli G, Zavalloni D, Scatturin M, Mennuni M*, et al.* Impact of female sex on long-term outcomes in patients with ST-elevation myocardial infarction treated by primary percutaneous coronary intervention. *Can J Cardiol* 2011; 27: 749.

12 Hailer B, Naber C, Koslowski B, van Leeuwen P, Schafer H, Budde T*, et al.* Gender-related differences in patients with ST-elevation myocardial infarction: results from the registry study of the ST elevation myocardial infarction network Essen. *Clin Cardiol* 2011; 34: 294.

13 Hurtado-Martinez JA, Pinar-Bermudez E, Teruel-Carrillo F, Gimeno-Blanes JR, Lacunza-Ruiz J, Valdesuso R*, et al.* In-hospital and long-term mortality in women with acute myocardial infarction treated by primary angioplasty. *Rev Esp Cardiol* 2006; 59: 1113.

14 Jackson EA, Moscucci M, Smith DE, Share D, Dixon S, Greenbaum A*, et al.* The association of sex with outcomes among patients undergoing primary percutaneous coronary intervention for ST elevation myocardial infarction in the contemporary era: Insights from the Blue Cross Blue Shield of Michigan Cardiovascular Consortium (BMC2). *Am Heart J* 2011; 161: 106.

15 Jakobsen L, Niemann T, Thorsgaard N, Nielsen TT, Thuesen L, Lassen JF*, et al.* Sex- and age-related differences in clinical outcome after primary percutaneous coronary intervention. *EuroIntervention* 2012; 8: 904.

16 Liu Y, Wang L-, Yang X-, Ge Y-, Wang H-, Xu L*, et al.* Gender differences in efficacy of primary percutaneous coronary intervention in patients with ST-elevation myocardial infarction. *Chin Med J* 2008; 121: 2374.

17 Motovska Z, Widimsky P, Aschermann M. The impact of gender on outcomes of patients with ST elevation myocardial infarction transported for percutaneous coronary intervention: analysis of the PRAGUE-1 and 2 studies. *Heart* 2008; 94: e5.

18 Mrdovic I, Savic L, Asanin M, Cvetinovic N, Brdar N, Djuricic N*, et al.* Sex-Related Analysis of Short- and Long-term Clinical Outcomes and Bleeding Among Patients Treated With Primary Percutaneous Coronary Intervention: An Evaluation of the RISK-PCI Data. *Can J Cardiol* 2013.

19 Pain TE, Jones DA, Rathod KS, Gallagher SM, Knight CJ, Mathur A*, et al.* Influence of female sex on long-term mortality after acute coronary syndromes treated by percutaneous coronary intervention: a cohort study of 7304 patients. *Coron Artery Dis* 2013.

20 Pu J, Shan P, Ding S, Qiao Z, Jiang L, Song W*, et al.* Gender differences in epicardial and tissue-level reperfusion in patients undergoing primary angioplasty for acute myocardial infarction. *Atherosclerosis* 2011; 215: 203.

21 Sadowski M, Janion-Sadowska A, Gasior M, Gierlotka M, Janion M, Polonski L. Gender-related benefit of transport to primary angioplasty: is it equal? *Cardiol J* 2011; 18: 254.

22 Sjauw KD, Stegenga NK, Engstrom AE, van der Schaaf RJ, Vis MM, Macleod A*, et al.* The influence of gender on short- and long-term outcome after primary PCI and delivered medical care for ST-segment elevation myocardial infarction. *EuroIntervention* 2010; 5: 780.

23 Valente S, Lazzeri C, Chiostri M, Giglioli C, Zucchini M, Grossi F*, et al.* Gender-related difference in ST-elevation myocardial infarction treated with primary angioplasty: a single-centre 6-year registry. *Eur J Prev Cardiol* 2012; 19: 233.

24 Velders MA, Boden H, van Boven AJ, van der Hoeven BL, Heestermans AA, Cannegieter SC, *et al.* Influence of gender on ischemic times and outcomes after ST-elevation myocardial infarction. *Am J Cardiol* 2013; 111: 312.

25 Waldecker B, Grempels E, Waas W, Haberbosch W, Voss R, Tillmanns H. Direct angioplasty eliminates sex differences in mortality early after acute myocardial infarction. *Am J Cardiol* 2001; 88: 1194.

26 Wijnbergen I, Tijssen J, van 't Veer M, Michels R, Pijls NH. Gender differences in long-term outcome after primary percutaneous intervention for st-segment elevation myocardial infarction. *Catheter Cardiovasc Interv* 2013.

27 Zhang Q, Qiu JP, Zhang RY, Li YG, He B, Jin HG*, et al.* Absence of gender disparity in short-term clinical outcomes in patients with acute ST-segment elevation myocardial infarction undergoing sirolimus-eluting stent based primary coronary intervention: a report from Shanghai Acute Coronary Event (SACE) Registry. *Chin Med J (Engl)* 2010; 123: 782.

28 Kaul P, Armstrong PW, Sookram S, Leung BK, Brass N, Welsh RC. Temporal trends in patient and treatment delay among men and women presenting with ST-elevation myocardial infarction. *Am Heart J* 2011; 161: 91.

29 Ladwig KH, Meisinger C, Hymer H, Wolf K, Heier M, von Scheidt W*, et al.* Sex and age specific time patterns and long term time trends of pre-hospital delay of patients presenting with acute ST-segment elevation myocardial infarction. *Int J Cardiol* 2011; 152: 350.

30 DeGeare VS, Boura JA, Grines LL, O'Neill WW, Grines CL. Predictive value of the Killip classification in patients undergoing primary percutaneous coronary intervention for acute myocardial infarction. *Am J Cardiol* 2001; 87: 1035.

31 El-Menyar A, Zubaid M, AlMahmeed W, Sulaiman K, AlNabti A, Singh R*, et al.* Killip classification in patients with acute coronary syndrome: insight from a multicenter registry. *Am J Emerg Med* 2012; 30: 97.

32 Hess CN, McCoy LA, Duggirala HJ, Tavris DR, O'Callaghan K, Douglas PS*, et al.* Sex-based differences in outcomes after percutaneous coronary intervention for acute myocardial infarction: a report from TRANSLATE-ACS. *J Am Heart Assoc* 2014; 3: e000523.

33 Birkemeyer R, Schneider H, Rillig A, Ebeling J, Akin I, Kische S*, et al.* Do gender differences in primary PCI mortality represent a different adherence to guideline recommended therapy? a multicenter observation. *BMC Cardiovasc Disord* 2014; 14: 71.

34 Magnussen EB, Vatten LJ, Smith GD, Romundstad PR. Hypertensive disorders in pregnancy and subsequently measured cardiovascular risk factors. *Obstet Gynecol* 2009; 114: 961.

35 Shaw LJ, Bairey Merz CN, Azziz R, Stanczyk FZ, Sopko G, Braunstein GD*, et al.* Postmenopausal women with a history of irregular menses and elevated androgen measurements at high risk for worsening cardiovascular event-free survival: results from the National Institutes of Health--National Heart, Lung, and Blood Institute sponsored Women's Ischemia Syndrome Evaluation. *J Clin Endocrinol Metab* 2008; 93: 1276.

36 Retnakaran R, Qi Y, Connelly PW, Sermer M, Zinman B, Hanley AJ. Glucose intolerance in pregnancy and postpartum risk of metabolic syndrome in young women. *J Clin Endocrinol Metab* 2010; 95: 670.

SUPPLEMENTAL

Supplementary Table 1. Search string

Date search: 10-05-2013 Layout search as performed in Pubmed	((("acs"[Title/Abstract] OR "mi"[Title/Abstract] OR "ami"[Title/Abstract] OR "myocardial infarction"[Title/Abstract] OR "acute myocardial infarction"[Title/Abstract] OR "acute coronary syndrome"[Title/Abstract] OR "infarction"[Title/Abstract] OR "myocardial infarct"[Title/Abstract] OR "coronary syndrome"[Title/Abstract] OR "heart attack"[Title/Abstract] OR "myocardial ischemia"[Title/Abstract]) AND ("st elevation"[Title/Abstract] OR "st segment elevation"[Title/Abstract] OR "st segment"[Title/Abstract] OR "st elevated"[Title/Abstract])) OR "steacs"[Title/Abstract] OR "steami"[Title/Abstract] OR "stemi"[Title/Abstract]) AND ((("pci"[Title/Abstract] OR "ptca"[Title/Abstract] OR "percutaneous coronary"[Title/Abstract] OR "percutaneous intervention"[Title/Abstract] OR "percutaneous transluminal coronary"[Title/Abstract] OR "percutaneous interventional procedure"[Title/Abstract] OR "percutaneous interventional procedures"[Title/Abstract] OR "angioplasty"[Title/Abstract] OR "intervention"[Title/Abstract]) AND ("direct"[Title/Abstract] OR "rescue"[Title/Abstract] OR "emergency"[Title/Abstract] OR "primary"[Title/Abstract] OR "acute"[Title/Abstract])) OR ppci[Title/Abstract] OR pptca[Title/Abstract]) AND ("gender"[Title/Abstract] OR "women"[Title/Abstract] OR "woman"[Title/Abstract] OR "females"[Title/Abstract] OR "female"[Title/Abstract] OR "sex"[Title/Abstract])

Supplementary Table 2. Quality assessment

	Study participants				Study attrition			
Articles	Population of interest	Sampling and recruitment	In- and exclusion criteria	Baseline characteristics	Response rate	Data collection drop-outs	Reasons loss to follow-up	Description patients loss to follow-up
Benamer et al.[7]	+-	+	+	+	+	Na	Na	Na
Bufe et al.[8]	+	+	+	+	+	-	-	-
De Luca et al.[9]	+	+	+	+	+	Na	Na	Na
De Luca et al.[10]	+	+	+	+	+	Na	Na	Na
Ferrante et al.[11]	+	+	+	+	+	-	-	-
Hailer et al.[12]	+	+	+	+	+	-	-	-
Hurtado-Martinez et al.[13]	+	+	+	+	+	-	-	-
Jackson et al.[14]	+	+	+	+	+	Na	Na	Na
Jakobsen et al.[15]	+	+	+	+	+	Na	Na	Na
Liu et al.[16]	+	+	+	+	+	Na	Na	Na
Motovska et al.[17]	+	+	+	+	+	Na	Na	Na
Mrdovic et al.[18]	+	+	+	+	+	-	-	-
Pain et al.[19]	+	+	+	+	+	-	-	-
Pu et al.[20]	+	+	+	+	+	Na	Na	Na
Sadowski et al.[21]	+	+	+	+	+	Na	Na	Na
Sjauw et al.[22]	+	+	+	+	+	-	-	-
Valente et al.[23]	+	+	+	+	+	Na	Na	Na
Velders et al.[24]	+	+	+	+	+	-	-	-
Waldecker et al.[25]	+	+	+	+	+	-	-	-
Wijnbergen et al.[26]	+	+	+	+	+	-	-	-
Zhang et al.[27]	+	+	+	+	+	Na	Na	Na

+: described and suitable for this review; +-: described but not suitable for this review; -: not described; Na: not applicable

Supplementary Table 2. continued

Outcome measurement			Confounding measurement & account			Analysis			
Definition outcome of interest	Measurement of outcome described	Duration of follow-up	Confounders measured	Accounted for confounders	Correct imputation	Providing univariate analysis	Providing age-adjusted results	Providing multivariate analysis	Presenting the exact confounders adjusted for in the model
+	+	+	+	+	Na	+	-	+	-
+	+	+	+	+	Na	+	-	+	-
+	+	+	+	+	Na	+	-	+	+
+	+	+	+	+	Na	+	-	+	-
+	+	+	+	+	Na	+	-	+	+
+	+	+	+	+	Na	+	+	-	Na
+	+	+	+	+	Na	+	+	+	+
+	+	+	+	+	Na	+	-	+	-
+	+	+	+	+	+	+	+	+	+
+	+	+	+	+	Na	+	-	-	Na
+	-	+	+	+	Na	+	-	+	-
+	+	+	+	+	Na	+	-	+	-
+	+	+	+	+	Na	+	+	+	-
+	+	+	+	+	Na	+	-	+	-
+	+	+	+	+	Na	+	-	+	+
+	+	+	+	+	Na	+	+	+	+
+	+	-	+	+	Na	+	-	+	+
+	+	+	+	+	Na	+	-	+	+
+	-	+	+	+	Na	+	-	+	+
+	-	+	+	+	Na	+	+	+	+
+	+	+	+	+	Na	+	-	+	-

Supplementary table 3. In-hospital mortality

Articles	In-hospital mortality unadjusted. OR/HR/RR: women versus men (95%CI)	In-hospital mortality adjusted. OR/HR/RR: women versus men (95%CI)	For which variables were adjusted on top of gender
Benamer et al.[7]	Women 9.8%, Men 4.3%; OR 2.35 (2.02-2.73)	OR 1.39 (1.15-1.68)	Age, diabetes, cardiogenic shock, lesion and PCI procedural characteristics (not further specified)
De Luca et al.[9]	Women 6.0%, Men 2.3%; RR 2.58 (1.52-4.40)	X	X
Ferrante et al.[11]	Women: 5.8%, Men: 4.1%; *OR: 1.45 (0.59-3.53)*	X	Propensity matching[1]
Hailer et al.[12]	Women 11%, Men 8.5%; *OR 1.33 (0.90-1.96)*	X	X
Hurtado-Martinez et al.[13]	Women 21.5%, Men 8.6%. OR: 2.9 (1.9-4.5)	OR: 2.5 (1.2-5.2)	Age, treatment delay. Treatment success, diabetes mellitus, smoking, anterior myocardial infarction, number of vessels, cardiogenic shock
Jackson et al.[14]	Women 6.0%, Men 3.5%; OR: 1.79 (1.45-2.22)	OR: 1.30 (0.98-1.72)	Propensity matching (not further specified)
Mrdovic et al.[18]	OR 1.33 (0.84-2.09)	OR 0.69 (0.41-1.14)	Propensity matching[1]
Sadowski et al.[21]	DT[2]: Women 6.0%, Men 4.1%; *OR 1.50 (1.14-1.97)* TA[3]: Women 6.4%, Men 3.4%; *OR 1.95 (1.51-2.52)*	X	X
Valente et al.[23]	Women 7.5%, Men 4.3%; *OR 1.78 (1.03-3.08)*	OR: 0.79 (0.36-1.71)	Age, PCI failure, LVEF, admission glycaemia, admission eGFR, Peak TnI.
Zhang et al.[27]	Women 4.5%, Men 3.8%; *OR 1.19 (0.71-1.97)*	OR 0.77 (0.48-1.22)	Patients demographics, angiographic and procedural features.
Pooled data	**Women 8% (6%-10%), Men 4% (3%-6%), p-value <0.0001**	**na**	**na**

OR: Odds Ratdio; RR: Risk Ratio; HR: Hazard Ratio; MACE: major adverse cardiac event; X: not described; na: not applicable. [1]: Very extensive list of variables in the propensity score and therefore not displayed in this table. [2]: DT = direct transport. [3]: TA= transferred from another hospital. *Italic: calculated odds ratios and confidence intervals.*

Supplementary table 4. 30 days mortality

Articles	30 days mortality unadjusted. OR/HR/RR: women versus men (95%CI)	30 days mortality adjusted. OR/HR/RR: women versus men (95%CI)	For which variables were adjusted on top of gender
Bufe et al.[8]	Women 8.9%, Men 6.6%; *OR 1.37 (0.65-2.87)*	X	X
Jakobsen et al.[14]	Women 8.5%, Men 5.5%; HR 1.58 (1.31-1.91)	HR 1.15 (0.94-1.42)	Age, comorbidity (not further specified), duration of symptoms, eGFR, grade of anaemia
Motovska et al.[17]	Women 8.2%, Men 6.2%; OR 1.35 (0.66-2.73)	1. OR 1.35 (0.67-2.75). 2: OR 1.08 (0.51-2.38). 3: OR 0.74 (0.26-2.05)	1: time delay; 2: time delay and age; 3: all covariates
Mrdovic et al.[18]	OR 1.27 (0.83-1.96)	OR 0.68 (0.42-1.10)	Propensity matching[1]
Pu et al.[20]	Women 4.7%, Men 3.1%; *OR 1.53 (0.61-3.87)*	X	X
Sadowski et al.[21]	DT[2]: Women 6.9%, Men 4.6%; *OR 1.49 (1.16-1.93)* TA[3]: Women 7.4%, Men 4.7%; *OR 1.56 (1.24-1.96)*	X	X
Sjauw et al.[22]	Women 9.2%, Men 8.1%; HR 1.15(0.89-1.49)	1: HR 0.86 (0.66-1.12). 2: HR 0.92 (0.65-1.30).	1: Age. 2: age, diabetes, hypertension, hypercholesterolemia, bmi, previous CABG, VF before PCI, cardiogenic shock, multivessel disease, LAD/RCA related myocardial infarction
Waldecker et al.[25]	Women 6.2%, Men 6%; *OR 1.02 (0.50-2.08)*	OR 0.7 (0.3-1.7)	Age, number of vessel disease, diabetes mellitus, anterior myocardial infarction, previous myocardial infarction, collateralization, time from onset
Zhang et al.[27]	Women 6.1%, Men 5.7%; *OR 1.10 (0.72-1.70)*	OR 1.28 (95%CI: 0.73-2.23)	Patients demographics, angiographic and procedural features (not further specified)
Pooled data	**Women 8% (7%-8%), Men 6% (5%-6%), p-value <0.0001**	**na**	**na**

OR: Odds Ratdio; RR: Risk Ratio; HR: Hazard Ratio; MACE: major adverse cardiac event; X: not described; na= not applicable. [1]: Very extensive list of variables in the propensity score and therefore not displayed in this table, [2]: DT = direct transport, [3]: TA= transferred from another hospital. *Italic: calculated odds ratios and confidence intervals*

Supplementary table 5. One-year mortality

Articles	One-year unadjusted mortality. OR/HR/RR: women verus men (95%CI)	One-year adjusted mortality. OR/HR/RR: women verus men (95%CI)	For which variables were adjusted on top of gender
De Luca et al.[9]	Women 9.3%, Men 4.9%; RR 1.79 (1.14-2.8)	RR 1.54 (0.97-2.34)	Kilip class >1, MBG 0-1, age>65 y, hypertension, anterior infarction, no angiographic success, previous infarction, multivessel disease, time delay > 4 h, diabetes, TIMI pre 0-1, vessel size
Hailer et al.[12]	Women 18.6%, Men 13.2%; *OR 1.50 (1.10-2.07)*	OR 1.08 (no CI given); p-value 0.68	Age
Jakobsen et al.[15]	Women 12.9%, Men 8.2%. HR 1.61 (1.38-1.88)	HR 1.17 (0.98-1.38)	Age, comorbidity (not further specified), duration of symptoms, eGFR, grade of anaemia
Mrdovic et al.[18]	OR 1.25 (0.89-1.75)	OR 0.74 (0.51-1.07)	Propensity matching[3]
Sadowski et al.[21]	DT[1]: Women 10.3%, Men 8.3%; *OR 1.28 (1.04-1.57)* TA[2]: Women 12.3%, Men 8.1%; *OR 1.56 (1.33-1.90)*	Combining DT[1] & TA[2] HR 1.00 (0.87-1.14)	Age, hypertension, diabetes, hypercholesterolemia, smoking, obesity, prior MI, prior PCI/ CABG, CA before admission, anterior MI, killip class 3-4, transfer from another hospital
Sjauw et al.[22]	Women 12.2%, Men 10.5%. HR 1.18 (0.94-1.47)	1: HR 0.87 (0.69-1.10). 2: HR 0.97 (0.75-1.32)	1: Age. 2: age, diabetes, hypertension, hypercholesterolemia, bmi, previous CABG, VF before PCI, cardiogenic shock, multivessel disease, LAD/RCA related myocardial infarction
Velders et al.[24]	Women 9.9%, Men 6.6%. HR 1.54 (1.19-1.99)	HR 1.02 (0.76-1.37)	Age, IDDM, NIDDM, anemia on admission, peripheral vascular disease, left main culprit artery, OHCA, cardiogenic shock, abciximab treatment, TIMI<III after treatment, CPK>5000
Pooled data	**Women 11% (9%-14%), Men 8% (6%-10%), p-value <0.0001**	**na**	**na**

OR: Odds Ratdio; RR: Risk Ratio; HR: Hazard Ratio; MACE: major adverse cardiac event; X: not described; na: not applicable
[1]: DT = direct transport. [2]: TA= transferred from another hospital. [3]: Very extensive list of variables in the propensity score and therefore not displayed in this table. *Italic: calculated odds ratios and confidence intervals*

Supplementary table 6. Long-term mortality

Articles	Duration of long-term FU	Long-term mortality unadjusted. OR/HR/RR: women verus men (95%CI)	Long-term mortality adjusted. OR/HR/RR: women verus men (95%CI)	For which variables were adjusted on top of gender
Bufe et al.[8]	Mean 5.6 years	Women 9.7%, Men 6.9%, p-value=0.417	OR 1.30 (0.68-2.5)	X
Ferrante et al.[11]	Median 2.9 years	Women 16.7%, Men 11.4%. HR 1.49 (0.88-2.53)	X	X
Hurtado-Martinez et al.[13]	Median 3 years	Women 18%, Men 9.3%. RR 1.9 (1.2-3.0)	RR 1.15 (0.7-1.9)	Age
Jakobsen et al.[15]	2 years	Women 16.1%, Men 10.4%. HR 1.59 (1.39-1.83)	HR 1.15 (0.99-1.35)	Age, comorbidity (not further specified), duration of symptoms, eGFR, grade of anaemia
Pain et al.[19]	Median 3.2 years	Women 15.8%, Men 10.0%, p-value<0.001. HR 1.63 (1.26-2.09)	HR 1.08 (0.83-1.41)	Multiple covariates (not further specified)
Sjauw et al.[22]	3 years	Women 15.6%, Men 13.8%. HR 1.15 (0.91-1.41)	1. HR 0.82 (0.67-1.01) 2. HR 0.91 (0.67-1.32)	1: Age. 2: age, diabetes, hypertension, hypercholesterolemia, bmi, previous CABG, VF before PCI, cardiogenic shock, multivessel disease, LAD/RCA related myocardial infarction
Wijnbergen et al.[26]	2 years	Women 8.0%, Men 2.6%, HR 3.23 (1.61-6.25)	1. HR 1.72 (0.85-3.57) 2. HR 1.45 (0.63-3.33)	1: Age. 2: age, diabetes, hypertension, smoking, stent diameter, symptom-to-balloon-time
Pooled data	**na**	**Women 16% (14%-17%), Men 9% (6%-13%), p-value <0.0001**	**na**	**na**

OR: Odds Ratdio; RR: Risk Ratio; HR: Hazard Ratio; MACE: major adverse cardiac event; X: not described; na: not applicable

CHAPTER 6

LONG-TERM OUTCOME IN MEN AND WOMEN AFTER CABG; RESULTS FROM THE IMAGINE TRIAL

Accepted in Atherosclerosis

Hester M. den Ruijter*, Saskia Haitjema*, Manon G. van der Meer, Pim van der Harst, Jean L. Rouleau, Folkert W. Asselbergs, Wiek H. van Gilst; IMAGINE Investigators.

**Shared first author*

ABSTRACT

Background

The aim of this study is to determine sex differences in long-term outcome after coronary artery bypass grafting (CABG).

Methods

The international randomized controlled IMAGINE study included 2553 consecutive patients with a left ventricular ejection fraction of > 40% who underwent isolated CABG. Median follow-up was 32 months (IQR 17 to 42 months). The composite endpoint comprised of death, myocardial infarction (MI), cerebrovascular event, angina, revascularization and congestive heart failure. Cox regression analysis was used to examine sex differences in outcome post-CABG.

Results

Of the 2553 patients, 2229 were men and 324 (13%) were women. Women were older and more often reported diabetes and hypertension. Smoking and impaired renal function were more prevalent in men. Women experienced a higher event rate during follow-up (composite endpoint 18% vs. 12%; P=0.007). Cox regression showed an increased risk of the composite endpoint in women after adjustment for age (HR 1.48 (95%CI: 1.11-1.97)), which was non-significant after additional adjustment for other confounders (HR 1.26 (95%CI: 0.92-1.72)).

Conclusion

Women have a worse long-term outcome after CABG than men in univariate analysis. However, after adjusting for potential confounders female sex became a non-significant predictor for prognosis, possibly due to the small sample size of women. Definite answers regarding sex-differences in long-term outcome after CABG should come from future pooling of studies comprising a larger number of women.

INTRODUCTION

Coronary artery disease (CAD) is the main cause of death in women older than 65 years.[1] In 2008 the prevalence of cardiovascular disease in the United States was 35.0% in women compared to 37.4% in men. However age-adjusted mortality rates were higher in women, namely 51.7% versus 48.3%.[1] Previous studies suggest sex differences in treatment and prognosis of CAD, but many discrepancies exist between different studies.[2-16] It remains uncertain whether these differences in outcome are due to a different risk burden between men and women or whether female sex is an independent risk factor of worse outcome and prognosis. Age is a major confounder, as younger, but not older, women have a higher mortality rate than men after myocardial infarction with or without intervention.[17-19] Furthermore, women undergo coronary angiography or percutaneous coronary intervention less often as compared to men.[19-21] The influence of female sex on the outcome after coronary artery bypass grafting (CABG) remains unclear, as previous studies are contradictory.[2, 3, 8, 13] In order to determine possible sex differences in long-term outcome after CABG, data from the Ischemia Management with Accupril post-bypass Graft via inhibition of the coNverting Enzyme (IMAGINE) were analysed. IMAGINE is a multicentre, international randomized controlled trial with extensive data concerning baseline characteristics and operational techniques.

METHODS

Patient characteristics

The design and the main results of the Ischemia Management with Accupril post-bypass Graft via Inhibition of the coNverting Enzyme (IMAGINE) trial have been previously described in detail.[22, 23] In brief, the IMAGINE trial is an international, randomized, double-blind, placebo-controlled, multicentre study that investigated whether early administration of an angiotensin-converting enzyme (ACE) inhibitor after CABG reduced cardiovascular events compared to placebo in stable patients. Patients older than 18 years with a left ventricular ejection fraction (LVEF) of ≥ 40% who were stable after CABG were included. Exclusion criteria consisted of intolerance or contraindication to ACE inhibitors, insulin-dependent diabetes, concomitant cardiac surgery, serious concomitant disease including severe renal impairment, significant perioperative myocardial infarction, pregnancy and investigational drug use < 30 days. The 2553 patients included in this study between 1999 and 2004 were randomly assigned to quinapril 10-20 mg (n=1280) or to placebo (n=1273). On average patients were randomized 4 ±2 days after CABG, with a maximum of 7 days (10 days in France). The primary endpoint was a composite of time to first occurrence of cardiovascular death or resuscitated cardiac arrest, nonfatal myocardial infarction, coronary revascularization, unstable angina, stroke and congestive heart failure that required hospitalization. Five patients were lost to follow-up (0.2%).

For the current analyses all available follow up time was used. The ethics committees of all participating institutions approved the research protocol and all patients gave written informed consent.

Statistical analysis

Patients were stratified by sex. Baseline categorical variables are presented as percentages (numbers). Differences between sexes were calculated by Chi-Square test. Continuous variables are described as the mean value ± standard deviation (SD) if normally distributed or the median value if the distribution was skewed. Possible differences were tested by t-test. All statistical tests were two-sided using $p < 0.05$ as level of significance. The primary endpoint was evaluated using a Cox proportional hazard model where men served as the reference category. Results are expressed as hazard ratios (HR) with 95% confidence intervals (95%CI). To identify possible confounders all baseline characteristics and surgical characteristics were related to the composite endpoint separately, adjusted for age. Correlation with the determinant sex was evaluated by a Pearson's correlation chi-square in variables that were significantly associated with the composite endpoint. Those with a p-value <0.1 at Pearson's correlation chi-square, as well as age and sex, were added in the multivariate model. Since previous studies demonstrated that body surface area (BSA) is associated with a worse outcome post-CABG in female sex we used BSA instead of body mass index.[13, 14] Because of the well-documented surgical characteristics, a subanalysis was made regarding the type of grafts used during CABG. All statistical analyses were performed using SPSS Version 21.0.

RESULTS

Patient characteristics

Out of the 2553 included patients 324 (13%) were women. Median follow-up was 32 months in both men and women (IQR 17-42 in men, IQR 15-42 in women). Baseline characteristics are shown in Table 1. Women were on average 5 years older than men and more often reported hypertension and a family history of CAD. Men more often smoked and revealed decreased renal function (all $P<0.01$).

Characteristics of CABG

On average men received more grafts (3.3 versus 3.0 in women; $P<0.01$). The percentage of off-pump CABG compared to CABG on cardiopulmonary bypass did not differ between men and women (18% versus 21%, $P=0.19$). Furthermore, there was no difference in complete revascularization, defined as all vessels > 1 mm with a stenosis > 70% having been bypassed, between women and men ($P=0.21$).

Table 1. Baseline characteristics (n=2553)

	Men (n=2229)	Women (n=324)	P-value
Age, years (SD)	60 ± 10	65 ± 10	<0.01
Median follow-up in months (IQR)	32 (17-42)	32 (15-42)	0.21
Medical history			
Myocardial infarction	40 (887)	35 (114)	0.11
CABG	3 (58)	2 (6)	0.42
Percutaneous coronary intervention	17 (388)	21 (67)	0.15
Peripheral vascular disease	7 (151)	9 (30)	0.10
Stroke/ TIA	1 (33)	1 (4)	0.73
Cardiovascular risk factors			
LDL cholesterol (mmol/L) (SD)	2.9 ± 1	2.9 ± 1	0.95
Diabetes	10 (212)	13 (41)	0.08
HbA1c (mmol/mol) (SD)	39 ± 8	41 ± 32	<0.01
Systolic blood pressure (mmHg) (SD)	121 ± 14	124 ± 15	0.11
Current or former smoker	74 (1658)	52 (167)	<0.01
Family history of coronary artery disease	67 (1480)	73 (235)	0.03
Body surface area (m^2) (SD)	2.0 ± 0.2	1.8 ± 0.2	<0.01
Heart rate (bpm) (SD)	82 ± 13	81 ± 12	0.23
Left ventricular ejection fraction (%) (SD)	60 ± 7	61 ± 10	0.43
MDRD (estimated GFR based on creatinine) (SD)	63 ± 15	108 ± 32	<0.01
Medication			
Acetylsalicyclic acid (ASA)	74 (1567)	72 (205)	0.44
Betablockers	78 (1657)	79 (224)	0.92
Calcium-channel blockers	767 (36)	107 (38)	0.67
Diuretics	9 (184)	9 (25)	0.97
ACE inhibitors	21 (433)	19 (54)	0.55
Statins	65 (1384)	60 (172)	0.09

Continuous variables are presented as mean ± SD; categorical variables are presented as percentages (n)
SD, standard deviation; IQR, inter quartile range; LDL, low-density lipoprotein; MDRD, modification of diet in renal disease; GFR, glomerular filtration rate.

Endpoint

Women were more likely to experience the composite endpoint, 18% versus 12% in men (P<0.01), as shown in Table 3. This difference is mainly driven by the distribution of unstable angina (5% in women vs 1.9% in men), coronary revascularization (1.2% in women vs 0.4% in men) and congestive heart failure (2.5% in women vs 0.9% in men).

Cox regression analysis demonstrated an increased risk of the composite endpoint in women compared to men after adjustment for age with a HR of 1.48 (95%CI 1.11-1.97).

Seven other variables were after adjustment for age associated with the composite endpoint, family history of CAD (HR 1.36 (95%CI: 1.06-1.74)), a medical history of PCI (HR 1.65 (95%CI: 1.28-2.11)), CABG (HR 2.28 (95%CI: 1.39-3.72)) or peripheral vascular disease (HR 1.80 (95%CI: 1.30-2.51)), BSA (HR 0.61 (95%CI: 0.38-0.98)), complete revascularization (HR 0.63 (95%CI: 0.48-0.85)) and number of grafts used (HR 0.78 (95%CI 0.71-0.87)). Of these seven variables only a family history of CAD (P= 0.03), number of grafts (P<0.01) and BSA (P<0.01) correlated with sex and were added to the multivariate model (Figure 1). Female sex was not associated with the composite endpoint in the multivariate analysis (HR 1.26 (95%CI: 0.92-1.72), Figure I) nor was BSA (HR 0.74 (95%CI: 0.45-1.23).

Table 2. Surgical characteristics (n=2553)

Patient characteristics % (n)	Men (n=2229)	Women (n=324)	P-value
Off-pump CABG	18 (407)	21 (69)	0.19
Number of grafts	3.3 ± 1.1	3.0 ± 1.1	<0.01
Use of LIMA	95 (2120)	92 (297)	0.01
Use of RIMA	19 (415)	9 (28)	<0.01
Use of free IMA	3 (61)	6 (18)	<0.01
Use of other arterial grafts	20 (445)	10 (31)	<0.01
Use of saphenous vein	79 (1757)	79 (257)	0.84
Endarterectomy	6 (111)	8 (22)	0.21
Complete revascularization	88 (1962)	90 (293)	0.21

Continuous variables are presented as mean ± SD; categorical variables are presented as percentages (n) CABG, coronary artery bypass grafting; Free artery bypass, composite of radial artery, all other arteries than LIMA or RIMA; IMA, internal mammary artery; LIMA, left internal mammary artery; mixed grafts, arterial or venous grafts; RIMA, right internal mammary artery.

Table 3. Composite endpoint (n=2553)

Patient characteristics	Men (n=2229)	Women (n=324)	P-value
Composite endpoint	12 (273)	18 (57)	<0.01
Cardiovascular death	0.8 (17)	1.2 (4)	
Myocardial infarction (non-fatal)	1 (22)	1.2 (4)	
Documented angina (not req. hosp.)	6.1 (137)	6.2 (20)	
Unstable angina (req. hosp.)	1.9 (43)	5 (15)	
Coronary revascularization	0.4 (9)	1.2 (4)	
Stroke	1.0 (23)	0.3 (1)	
Resuscitation or cardiac arrest	0.1 (2)	0.3 (1)	
Congestive heart failure (req. hosp.)	0.9 (20)	2.5 (8)	

Categorical variables are presented as percentages (n). MDRD, estimated GFR based on creatinine; Req. hosp., requiring hospitalization; TIA, transient ischemic attack

A family history of CAD remained associated with the composite endpoint (HR 1.35 (95%CI: 1.05-1.73)) as well as number of grafts used (HR 0.79 (95%CI: 0.72-0.88)).
In the original IMAGINE trial, there were no differences in the incidence of the primary endpoint between the quinapril and placebo group after subdividing by sex.

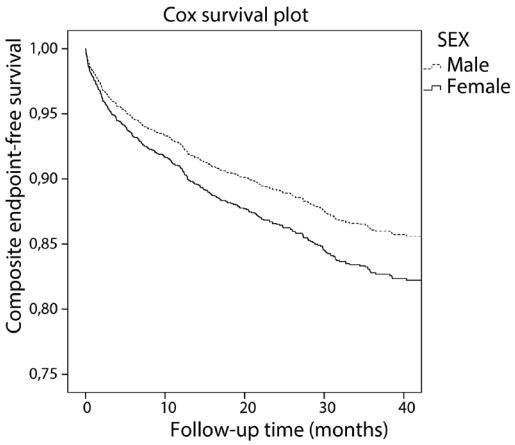


Figure 1. Cox survival plot. Cox survival plot for composite endpoints in women and men

DISCUSSION

The current study demonstrates that women have an increased risk of an adverse outcome after CABG compared to men during 2.5 years of follow-up. However, in the multivariate analysis female sex is not an independent predictor for developing the composite endpoint in this cohort potentially due to lack of power. At baseline women were older and more often had hypertension, a family history of CAD and a smaller BSA. On the other hand men smoked more often and had more frequently renal dysfunction. In regard to other studies both men and women included in the IMAGINE trial reported a relatively low burden of cardiovascular risk factors. Interestingly, our results showed no differences in percentage of off-pump CABG between men and women and no benefit of off-pump CABG for the composite endpoint in both men and women. Previous studies showed an increased risk of adverse outcome in women for CABG on cardiopulmonary bypass, compared to off-pump CABG.[4-8, 10, 14] The majority of prior studies included emergency CABGs whereas we excluded these unstable patients, which makes it difficult to directly compare results.[4-8, 10-15] Furthermore, we used a composite endpoint where others used death as primary outcome. Some studies showed an increased risk in women for early mortality,[2, 8, 10] but the majority found no sex differences.[3, 4, 12-15] Others only found an increased risk for mortality in women after CABG on cardiopulmonary bypass and not after

off-pump CABG.[5-7, 11, 16] The higher risk in women we found in the univariate analysis is caused primarily by a higher rate of unstable angina and coronary revascularization as the number of deaths was equal in both sexes. This is consistent with the finding in this study that the number of grafts used is significant between women and men in the multivariate analysis. The difference in univariate analysis between women and men could therefore point towards a difference in coronary artery diameter: as women are smaller, they have smaller coronary arteries that are technically more demanding in CABG. Indeed, BSA was a confounding factor in this study.

Limitations

Main limitation of this study is the small sample size of women. Women comprised only 13% of our study population compared to 24% on average in other studies.[2-8, 10-16] Unfortunately no screenings log, with numbers screened patients and the reason of exclusion, is available so the low inclusion rate in women remains elusive. One of the possible explanations is the exclusion of patients with severe comorbidities, as women are known to be more severely impaired. The sample size of women introduces an unexpected power problem in the multivariate model, where sex does not seem to associate with the composite endpoint whereas the cox survival plot shows a difference between women and men.

Our results are only applicable to stable patients undergoing CABG since unstable patients were excluded from the study, just as patients with a clinical need for ACE-inhibitors (e.g. severe renal insufficiency and insulin dependent diabetes). We are to our knowledge the first study to include only stable patients and since a large part of the CABG population is stable before surgery, it is relevant to investigate sex differences in outcome in this subpopulation. It could be that sex differences are still present in the unstable group.

Echocardiography testing for diastolic dysfunction which may eventually evolve in to heart failure with preserved ejection fraction (HFpEF) was not performed. As diastolic dysfunction is common in the general population [24] more prevalent among women undergoing cardiac surgery [25] and associated with worse outcome in CAD patients [26], this could be a confounding factor. Also, no data were available on relief of angina symptoms, one of the indications for CABG surgery. However, we do not think this affected the results, since persisting angina was well-documented.

The difference between women and men found in this study was mainly due to differences in 'soft' endpoints such as unstable angina and cardiac revascularization, rather than more robust endpoints such as death. As these 'soft' endpoints are more prone to misclassification, this could potentially have induced non-differential (more in women) misclassification of the outcome. Unfortunately, this type of bias is difficult to overcome and may have overestimated the sex difference.

The duration of follow-up was limited to 2.5 years. Although the majority of the present studies had a limited follow-up of 30 days after CABG, [2, 4, 6, 7, 10-15] some have shown a decrease in the sex gap after long-term follow-up, [3,27] as described earlier by M Claassen et al[28]. Future studies should examine a larger number of women during long-

term follow-up. For example, an individual participant data analysis of current studies could improve the power to detect sex-specific differences and their determinants in outcome between women and men after CABG.

Conclusion

Women have a worse long-term outcome after CABG than men in univariate analysis. However, after adjusting for potential confounders female sex became a non-significant predictor for prognosis, possibly due to the small sample size of women. Definite answers regarding sex-differences in long-term outcome after CABG should come from future pooling of studies comprising a larger number of women.

REFERENCES

1. Group Members, Roger VL, Go AS, Lloyd-Jones DM, Benjamin EJ, Berry JD, Borden WB, Bravata DM, Dai S, Ford ES, Fox CS, Fullerton HJ, Gillespie C, Hailpern SM, Heit JA, Howard VJ, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Makuc DM, Marcus GM, Marelli A, Matchar DB, Moy CS, Mozaffarian D, Mussolino ME, Nichol G, Paynter NP, Soliman EZ, Sorlie PD, Sotoodehnia N, Turan TN, Virani SS, Wong ND, Woo D, Turner MB, on behalf of the American Heart Association Statistics Committee and Stroke Statistics Subcommittee, On behalf of the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart Disease and Stroke Statistics--2012 Update: A Report From the American Heart Association, *Circulation* 2012;125:e2-e220.
2. Alam M, Lee VV, Elayda MA, Shahzad SA, Yang EY, Nambi V, Jneid H, Pan W, Coulter S, Wilson JM, Ramanathan KB, Ballantyne CM, Virani SS. Association of gender with morbidity and mortality after isolated coronary artery bypass grafting. A propensity score matched analysis. *Int J Cardiol* 2012: doi:10.1016/j.ijcard.2011.12.047.
3. Cartier R, Bouchot O, El-Hamamsy I. Influence of sex and age on long-term survival in systematic off-pump coronary artery bypass surgery. *Eur J Cardiothorac Surg* 2008;34:826-832.
4. Ennker IC, Albert A, Pietrowski D, Bauer K, Ennker J, Florath I. Impact of gender on outcome after coronary artery bypass surgery. *Asian Cardiovasc Thorac Ann* 2009;17:253-258.
5. Fu SP, Zheng Z, Yuan X, Zhang SJ, Gao HW, Li Y, Hu SS. Impact of off-pump techniques on sex differences in early and late outcomes after isolated coronary artery bypass grafts. *Ann Thorac Surg* 2009;87:1090-1096.
6. Puskas JD, Edwards FH, Pappas PA, O'Brien S, Peterson ED, Kilgo P, Ferguson TB,Jr. Off-pump techniques benefit men and women and narrow the disparity in mortality after coronary bypass grafting. *Ann Thorac Surg* 2007;84:1447-54.
7. Puskas JD, Kilgo PD, Kutner M, Pusca SV, Lattouf O, Guyton RA. Off-pump techniques disproportionately benefit women and narrow the gender disparity in outcomes after coronary artery bypass surgery. *Circulation* 2007;116:I192-9.
8. Puskas JD, Kilgo PD, Lattouf OM, Thourani VH, Cooper WA, Vassiliades TA, Chen EP, Vega JD, Guyton RA. Off-pump coronary bypass provides reduced mortality and morbidity and equivalent 10-year survival. *Ann Thorac Surg* 2008;86:1139-46.
9. Basaran M, Selimoglu O, Ozcan H, Ogus H, Kafali E, Ozcelebi C, Ogus TN. Being an elderly woman: is it a risk factor for morbidity after coronary artery bypass surgery? *Eur J Cardiothorac Surg* 2007;32:58-64.
10. Bukkapatnam RN, Yeo KK, Li Z, Amsterdam EA. Operative mortality in women and men undergoing coronary artery bypass grafting (from the California Coronary Artery Bypass Grafting Outcomes Reporting Program). *Am J Cardiol* 2010;105:339-342.
11. Czech B, Kucewicz-Czech E, Pacholewicz J, Wojarski J, Puzio J, Przybylski R, Farmas A, Ryfinski B, Zembala M. Early results of coronary artery bypass graft surgery in women. *Kardiol Pol* 2007;65:627-33.
12. Fukui T, Takanashi S. Gender differences in clinical and angiographic outcomes after coronary artery bypass surgery. *Circ J* 2010;74:2103-2108.
13. Humphries KH, Gao M, Pu A, Lichtenstein S, Thompson CR. Significant improvement in short-term mortality in women undergoing coronary artery bypass surgery (1991 to 2004). *J Am Coll Cardiol* 2007;49:1552-1558.
14. Ried M, Lunz D, Kobuch R, Rupprecht L, Keyser A, Hilker M, Schmid C, Diez C. Gender's impact on outcome in coronary surgery with minimized extracorporeal circulation. *Clin Res Cardiol* 2012;101:437-444.
15. Uva MS, Freitas S, Pedro A, Matias F, Mesquita A, Bau J, Pinho J, Fernandes J, Magalhaes MP. Off-pump coronary artery bypass surgery in women. *Rev Port Cardiol* 2009;28:813-824.
16. Eifert S, Kilian E, Beiras-Fernandez A, Juchem G, Reichart B, Lamm P. Early and mid term mortality after coronary artery bypass grafting in women depends on the surgical protocol: retrospective analysis of 3441 on- and off-pump coronary artery bypass grafting procedures. *J Cardiothorac Surg* 2010;5:90.

17. Vaccarino V, Abramson JL, Veledar E, Weintraub WS. Sex differences in hospital mortality after coronary artery bypass surgery: evidence for a higher mortality in younger women. *Circulation* 2002;105:1176-1181.
18. Vaccarino V, Krumholz HM, Yarzebski J, Gore JM, Goldberg RJ. Sex differences in 2-year mortality after hospital discharge for myocardial infarction. *Ann Intern Med* 2001;134:173-181.
19. Radovanovic D, Erne P, Urban P, Bertel O, Rickli H, Gaspoz JM, AMIS Plus Investigators. Gender differences in management and outcomes in patients with acute coronary syndromes: results on 20,290 patients from the AMIS Plus Registry. *Heart* 2007;93:1369-1375.
20. Matsui K, Fukui T, Hira K, Sobashima A, Okamatsu S, Hayashida N, Tanaka S, Nobuyoshi M. Impact of sex and its interaction with age on the management of and outcome for patients with acute myocardial infarction in 4 Japanese hospitals. *Am Heart J* 2002;144:101-107.
21. Reynolds HR, Farkouh ME, Lincoff AM, Hsu A, Swahn E, Sadowski ZP, White JA, Topol EJ, Hochman JS, GUSTO V Investigators. Impact of female sex on death and bleeding after fibrinolytic treatment of myocardial infarction in GUSTO V. *Arch Intern Med* 2007;167:2054-2060.
22. Rouleau JL, Warnica WJ, Baillot R, Block PJ, Chocron S, Johnstone D, Myers MG, Calciu CD, Dalle-Ave S, Martineau P, Mormont C, van Gilst WH, IMAGINE (Ischemia Management with Accupril post-bypass Graft via Inhibition of the coNverting Enzyme) Investigators. Effects of angiotensin-converting enzyme inhibition in low-risk patients early after coronary artery bypass surgery. *Circulation* 2008;117:24-31.
23. Warnica JW, Gilst WV, Baillot R, Johnstone D, Block P, Myers MG, Chocron S, Ave SD, Martineau P, Rouleau JL. Ischemia Management with Accupril post bypass Graft via Inhibition of angiotensin coNverting enzyme (IMAGINE): a multicentre randomized trial - design and rationale. *Can J Cardiol* 2002;18:1191-1200.
24. Kuznetsova T, Herbots L, López B, Jin Y, Richart T, Thijs L, González A, Herregods MC, Fagard RH, Díez J, Staessen JA. Prevalence of left ventricular diastolic dysfunction in a general population. *Circ Heart Fail* 2009;2:105-12.
25. Ferreira RG, Worthington A, Huang CC, Aranki SF, Muehlschlegel JD. Sex differences in the prevalence of diastolic dysfunction in cardiac surgical patients. *J Card Surg* 2015 (epub ahead of print)
26. Ren X, Ristow B, Na B, Ali S, Schiller NB, Whooley MA, Prevalence and prognosis of asymptomatic left ventricular diastolic dysfunction in ambulatory patients with coronary heart disease. Am J Cardiol 2007;15:1643-7.
27. Koch CG, Weng YS, Zhou SX, Savino JS, Mathew JP, Hsu PH, Saidman LJ, Mangano DT, Ischemia Research and Education Foundation, Multicenter Study of Perioperative Ischemia Research Group. Prevalence of risk factors, and not gender per se, determines short- and long-term survival after coronary artery bypass surgery. *J Cardiothorac Vasc Anesth* 2003;17:585-593.
28. Claassen M, Sybrandy KC, Appelman YE, Asselbergs FW, Gender gap in acute coronary heart disease: myth or reality?. *World J Cardiol* 2012;4:36-47

CHAPTER 7

GENDER DIFFERENCE IN LONG-TERM PROGNOSIS AMONG PATIENTS WITH CARDIOVASCULAR DISEASE

Eur J Prev Cardiol. 2014 Jan;21(1):81-9

Manon G. van der Meer, Maarten J. Cramer, Yolanda van der Graaf,
Pieter A. Doevendans, Hendrik M. Nathoe

ABSTRACT

Background

Differences in prognosis between women and men with atherosclerosis are currently under attention. Previous studies describe contradictory results and are restricted to one cardiovascular bed while atherosclerosis is a systemic disease. We therefore studied the prognosis of women versus men in the SMART study, a large cohort of patients with clinically manifest atherosclerosis with extensive baseline and follow-up information.

Methods

5349 patients (1347 women, 4002 men) with at least one type of atherosclerotic vascular disease (coronary artery disease, cerebrovascular disease, peripheral arterial disease or abdominal aortic aneurysm) were included in the SMART study, an ongoing long-term follow-up study. They all received a standardized cardiovascular work-up with a personalized therapy advice. All future cardiovascular events were collected prospectively. All-cause mortality, cardiovascular mortality and cardiovascular outcome (composite of myocardial infarction, stroke and cardiovascular death) were evaluated using Cox regression and expressed as hazard ratios (HR) with 95% confidence intervals (95%CI). Men served as the reference category. Different models were used to adjust for differences in baseline characteristics.

Results

Women and men had a mean age of 60 years and their median follow-up (range) was 5 years (13.5).

The hazard ratios of all-cause mortality, cardiovascular death and cardiovascular outcome were 0.62 (95%CI: 0.51-0.75), 0.59 (95%CI: 0.46-0.75) and 0.73 (95%CI: 0.60-0.87). Neither differences in risk-factor profile nor the different vascular beds involved could explain this advantage.

Conclusion

Women with cardiovascular disease who received a similar standardized cardiovascular work-up and personalized therapy advice as men had a favorable long-term outcome.

INTRODUCTION

The difference in prognosis between women and men with clinically manifest atherosclerosis is currently under attention. Atherosclerosis is a systemic disease, which implies that to a certain extent arteries in the whole body are involved.[1] Several studies however describe gender differences restricted to only one vascular bed such as coronary heart disease, ischemic cerebral disease or peripheral arterial disease (PAD).[2-4] A recent study shows this is an incorrect approach as more than 37% of patients with stable coronary heart disease also suffer clinical or subclinical PAD.[5]
The clinical course confirms this since for example patients with PAD have a relative risk of 6.6 for deaths from coronary heart disease compared to the general population.[6] Moreover patients with angina have a 5.2 fold increased risk at intermittent claudication compared to the reference group free of cardiovascular disease.[7] On top of this limitation the results of these studies are contradictory as some state that women or men have a better prognosis and others claim that there is no difference between both sexes.[2,4,8-10] One previous study did investigate a large cohort of patients with atherosclerosis in different vascular beds, namely coronary artery disease, peripheral arterial disease or ischemic stroke.[11] They demonstrated a higher 5-year mortality in men in comparison to women. Unfortunately they did not have any insights in risk factors, past medical history and medication use of their patients. Consequently they could not adjust for possible confounders.
We therefore studied the prognosis of women and men in the SMART study, a large cohort of patients with clinically manifest atherosclerosis in at least one vascular bed with extensive background information at baseline and during follow up.

METHODS

Study design and patient population

Patient population

The Second Manifestations of ARTerial disease (SMART) study is an ongoing prospective follow-up study at the University Medical Center Utrecht in the Netherlands. Since 1996 newly referred patients, aged 18 to 80, with at least one type of atherosclerotic vascular disease (coronary artery disease, cerebrovascular disease, peripheral arterial disease or abdominal aortic aneurysm (AAA)) were included. The referral diagnosis was the atherosclerotic disease for which the patient was referred to our hospital at that time. However, since atherosclerosis is a generalized process often more cardiovascular beds were involved. Patients were referred to the SMART study by their treating physician or were identified on hospital registration lists. Thus patients who visited our hospital for elective care as well as for emergency care were eligible for the SMART study. However, emergency patients were included in the study in a more stable phase namely at least six weeks after an acute event or intervention. Patients with terminal malignant disease,

those not independent in daily activities (Rankin scale >3) or not sufficiently fluent in Dutch were excluded.

Study design

A detailed description of the study was previously published.[12] In short, patients who gave their written informed consent underwent a standardized cardiovascular work-up, including a health questionnaire, electrocardiogram (ECG), physical examination, laboratory assessment (blood sample and morning urine sample), ultrasonography (abdominal aorta and duplex of the carotids) and ankle/brachial index. The results of this work-up were discussed by a multidisciplinary team of in-hospital cardiovascular specialists at weekly meetings. For each patient an individualized treatment advice regarding cardiovascular risk factors and cardiovascular disorders was made. The results of the cardiovascular work-up together with the treatment recommendations (such as repeat measurement, start/ adjust medication, adjust lifestyle or refer to specialist) were reported in writing to the treating physician and general practitioner. Treatment recommendations were given according to the Joint Task Force of European Societies recommendations.[13]

The Ethics Committee of the hospital approved the study. For the present sub-study data was used from all patients enrolled in the SMART study between September 1996 and March 2010.

Coronary artery disease was defined as either a diagnosis of angina pectoris, myocardial infarction or coronary revascularization (coronary bypass surgery of percutaneous coronary intervention). Cerebrovascular disease was described as patients with a transient ischemic attack, cerebral infarction, amaurosis fugax or retinal infarction. Peripheral arterial disease included patients with symptomatic or documented obstruction of distal arteries of the leg or vascular surgery of the leg. Patients with AAA were referred for an aneurysm of the aorta or recent abdominal aortic aneurysm surgery.

Definitions, follow-up procedure and outcome evaluation

Definitions

Past medical history, smoking status, medication use and pre- and postmenopausal status in women was assessed by the health questionnaire. Body mass index was calculated as weight to height squared (kg/m^2). The weight was measured without heavy clothing by traditional scales and the height without shoes by a fixed stadiometer. Hypertension was defined as a systolic blood pressure ≥ 140 mmHg and/ or a diastolic blood pressure ≥ 90 mmHg and/ or the use of blood pressure- lowering drug therapy. In patients with diabetes a blood pressure above 130/85 mmHg was considered as hypertension. Dyslipidemia at screening was defined as a total cholesterol ≥ 5.0 mmol/l or LDL cholesterol ≥ 3.0 mmol/l or triglycerides > 2.0 mmol/l or HDL cholesterol ≤1.0 mmol/l in men and HDL cholesterol ≤ 1.3 mmol/l in women. Among subjects without a history of diabetes, those with a fasting plasma glucose level > 11.1 mmol/l at baseline or with fasting plasma glucose ≥7.0 mmol/l at baseline and receiving treatment with glucose-lowering agents within 1 year after baseline were considered as having diabetes at baseline. An ankle/brachial index < 0.9 was

considered abnormal. Follow-up duration was defined as the period between study inclusion and death from any cause or the preselected date of the first of March 2010.

Follow-up procedure

First, the hospital electronic patient dossier or the city registration database was checked if the patient was alive. In case the patient passed away, all relevant documents concerning the cause of death were collected. All living patients were followed every 6 months with use of a standard questionnaire send by mail or by telephone to find out whether a cardiovascular event or arterial intervention had occurred. When a possible event was reported, hospital discharge letters and results of relevant laboratory and radiology examinations were collected to verify the occurrence of an event. Three members of the SMART Outcome Committee independently adjudicated all events. This Committee, formed to evaluate all outcomes, consisted of physicians from different medical specialties. In case of disagreement, consensus was reached by consulting other members of the Outcome Committee.

Outcome evaluation

Outcomes of interest for this study were all cause mortality, cardiovascular mortality and cardiovascular outcome (composite of cardiovascular mortality, stroke and myocardial infarction). Cardiovascular mortality was defined as sudden death (unexpected cardiac death occurring within 1 hour after onset of symptoms or within 24 hours given convincing circumstantial evidence) or death from stroke, myocardial infarction, congestive heart failure or ruptured aneurysm of the abdominal aorta. Myocardial infarction was determined by a combination of at least two of the following: 1.) chest pain for at least 20 minutes, 2.) ST elevation > 1 mm in at least two consecutive leads or a new left bundle branch block on the ECG, 3.) CK elevation of at least two times the normal value of CK and a MB-fraction > 5% or a troponine rise exceeding the upper limit threshold. Stroke was defined as relevant clinical features which caused an increase in handicap or at least one grade on the modified Rankin scale accompanied by a fresh infarct or a hemorrhage on a repeat CT scan.

Baseline, laboratory analyses and statistical methods

Patients were stratified by gender. The baseline characteristics are expressed as mean ± standard deviation for continuous variables and as numbers (percentages) for categorical variables. High-sensitivity (hs)-CRP was compared between women and men. Hs-CRP differences between sexes were analyzed using the Mann-Whitney U test since values are skewed. All cause mortality, cardiovascular mortality and cardiovascular outcome was evaluated using a Cox proportional hazard model. Men served as the reference category. Results are expressed as hazard ratios (HR) with 95% confidence intervals (95%CI). All analyses were conducted with four different models: one crude model (model I), one model adjusted for age (model II), the third model adjusting for potential confounding factors like cardiovascular risk factors (hypertension, dyslipidemia, diabetes mellitus, smoking and body mass index) and kidney function (estimated glomerular filtration rate, eGFR (ml/

min/1.73m²) = 32788 x (serum creatinine)-1.154 x (age)-0.203 x (0.742 if female)[14]) and the final model (model IV) adjusted for all confounding factors present in model III extended with an adjustment for differences in number and location of the vascular beds involved, including the vascular beds involved in the past medical history of the patient. If patients were lost to follow-up the data of these patients is used in the analysis until they are lost. In the Cox regression analysis these patients are censored.
We analyzed whether the relation between gender and outcome was modified by age and year of inclusion in the study. To exclude possible hormonal influences, the analyses were repeated after excluding premenopausal women. All statistical analyses were performed with SPSS 17.0 for Windows (SPSS, Chicago, Illinois, USA).

RESULTS

Baseline characteristics

In total 5349 patients were included, of whom 1347 women (25%) and 4002 (75%) men (table 1). In total 120 men (3%) and 53 women (4%) were lost to follow-up. The mean age of women was 59.9 (± 11.1) years and of men 60.4 (± 9.8) years. In men, the age at inclusion varied from 23 to 80 years. After dividing age in quartiles, quartile (Q) 1 is between 23 and 53 years old, Q2 from 53 until 61 years old, Q3 is between 61 and 68 years old and the last quartile from 68 until 80 years old. In women, the age at inclusion varied from 19 to 80 years. In women Q1 is from 19 to 51 years old, the second quintile is between 51 and 61 years old, Q3 is between 61 and 68 years old and Q4 is from 68 until 80 years old. Eighty percent of women were in the menopause. Myocardial infarction and AAA was more prevalent in the past medical history of men while more women had a stroke. Comparable percentages of women and men were known with peripheral arterial disease. Women had an unfavorable risk profile with 7% more dyslipidemia, 8% more hypertension and 6% more BMI above 30. In contrast only 59% of women used lipid lowering medication in comparison to 64% of men. The same pattern was observed in the use of other medication like beta-blockers (47% of women, 54% of men) and platelet aggregation inhibitors (71% versus 77%). The percentage of current smokers was higher in women than in men (37% versus 31%). Men had more packyears and a higher amount of smoking years than women.

Cardiovascular work-up

The cardiovascular work-up revealed a diminished ankle/brachial index in 28% of women and 20% of men. Equal percentages of women and men had a carotid artery stenosis above 70% (12% and 13%). More men were diagnosed with an AAA above 5 cm, namely 3 percent in men versus 0.5 percent in women. Median hs-CRP was 2.4 mg/l in women and 2.0 mg/l in men. The Mann-Whitney U test showed a significant difference in hs-CRP between both sexes ($p<0.001$). Proteinuria (protein loss > 300 mg/ 24 hours) was present in 19% of men and 15% of women.

Table 1. Baseline characteristics of the cohort (n=5349)

	Men n = 4002 (75)	Women n = 1347 (25)	P-value
Age (years)	60.4±9.8	59.9±11.1	0.15
Median follow-up in years (range)	5.0 (13.5)	4.8 (13.5)	0.56
Menopause	not applicable	1085 (81)	-
If yes, age at menopause (years)	not applicable	47.4±6.3	-
Referral diagnosis (%)			
Coronary artery disease	2206 (55)	500 (37)	<0.01
Peripheral artery disease	611 (15)	331 (25)	<0.01
Aneurysm abdominal aorta	287 (7)	19 (1)	<0.01
Cerebrovascular disease	898 (22)	497 (37)	<0.01
Past medical history (%)			
Myocardial infarction	1344 (34)	236 (18)	<0.01
Stroke	511 (13)	282 (21)	<0.01
Aneurysm abdominal aorta	350 (9)	43 (3)	<0.01
Peripheral arterial disease	252 (6)	89 (7)	0.69
Dyslipidemia	1730 (43)	676 (50)	<0.01
Hypertension	1997 (50)	785 (58)	<0.01
Diabetes mellitus	632 (16)	204 (15)	0.57
Body mass index			<0.01
Body mass index < 20 kg/m²	52 (1)	68 (5)	
Body mass index 20-25 kg/m²	1235 (31)	483 (36)	
Body mass index 25-30 kg/m²	2070 (52)	503 (37)	
Body mass index > 30 kg/m²	645 (16)	293 (22)	
Smoking (%)			<0.01
Never	634 (16)	392 (29)	
Past	2027 (51)	458 (34)	
Current	1324 (33)	493 (37)	
Pack years	23±21	17±18	<0.01
Estimated glomerular filtration rate (ml/min/1.73 m²)	77.5±17.4	72.4±16.9	<0.01
Proteinuria (%)			
Micro	650 (16)	177 (13)	
Macro	99 (2)	30 (2)	
High sensitive CRP (range)	2.0 (247.3)	2.4 (120.9)	<0.01
Medication at inclusion (%)			
RAAS inhibitors	1357 (34)	451 (33)	0.78
Beta blockers	2173 (54)	629 (47)	<0.01
Lipid lowering medication	2573 (64)	791 (59)	<0.01
Platelet aggregation inhibitors	3083 (77)	951 (71)	<0.01
Oral anticoagulation	414 (10)	136 (10)	0.80
Oral glucose-lowering medication	387 (10)	127 (9)	0.80
Insulin	150 (4)	49 (4)	0.85

Continuous variables are expressed as mean ± standard deviation and categorical variables as numbers (percentages of subgroup), with the exception of follow-up and high sensitive CRP which are expressed as median (range). RAAS, renin-angiotensin-aldosteron-system.

Table 2. Hazard ratios for gender in relation to all cause mortality, cardiovascular mortality and combined cardiovascular outcome

	Men n= 4002	Women n=1347
All cause mortality (# events)	589	130
Model I *	1.00 (reference)	0.66 (95%CI: 0.54-0.79)
Model II †	1.00 (reference)	0.62 (95%CI: 0.51-0.75)
Model III ‡	1.00 (reference)	0.64 (95%CI: 0.52-0.78)
Model IV **	1.00 (reference)	0.67 (95%CI: 0.55-0.82)
Cardiovascular mortality (# events)	354	75
Model I *	1.00 (reference)	0.63 (95%CI: 0.49-0.80)
Model II †	1.00 (reference)	0.59 (95%CI: 0.46-0.75)
Model III ‡	1.00 (reference)	0.56 (95%CI: 0.43-0.73)
Model IV **	1.00 (reference)	0.62 (95%CI: 0.47-0.81)
Combined cardiovascular outcome¶ (# events)	575	142
Model I *	1.00 (reference)	0.73 (95%CI: 0.61-0.88)
Model II †	1.00 (reference)	0.73 (95%CI: 0.60-0.87)
Model III ‡	1.00 (reference)	0.68 (95%CI: 0.56-0.82)
Model IV **	1.00 (reference)	0.73 (95%CI: 0.60-0.89)

Events in numbers. * model I: crude model; † model II: Hazard ratios (HRs) adjusted for age; ‡ model III: HRs adjusted for age, diabetes mellitus, hypertension, dyslipidemia, body mass index, packyears and estimated glomerular filtration rate (ml/min/1.73 m^2); ** model IV: HRs adjusted for model III and the presence of coronary artery disease, cerebrovascular disease, peripheral arterial disease and an AAA at inclusion or in the past medical history. ¶ myocardial infarction, stroke, cardiovascular mortality.

Follow-up, incidence of cardiovascular events and interaction

The median follow-up duration was comparable in women and men, namely 4.8 years in women (range 13.5 years) versus 5.0 years in men (range 13.5 years). Women had a significant better long-term prognosis than men (table 2). They were less likely to die (HR after adjusting for age 0.62 (95%CI: 0.51-0.75)), had a lower amount of cardiovascular mortality (HR after adjusting for age 0.59 (95%CI: 0.46-0.75)) and developed less combined cardiovascular outcome (HR after adjusting for age 0.73 (95%CI: 0.60-0.87)) (figure 1A-1C). Additional adjustment for possible confounders did not change the results substantially (model III). Even after adjusting for differences in number and location of the vascular beds involved, including the vascular beds involved in the past medical history of the patient, the hazard ratios remained comparable (model IV). The year at inclusion did not modify the relation between gender and outcome (p-value of 0.39 for all-cause mortality, 0.49 for cardiovascular mortality and 0.43 for the combined cardiovascular outcome). In the younger age group the effect of gender and the combined cardiovascular outcome was more pronounced (p-value < 0.01) but there was no modifying effect on all-cause mortality (p-value 0.32) or cardiovascular mortality (p-value 0.81). After excluding the pre-menopausal

women (n=262; 19%) the analyses were repeated and these results were comparable to the results of the complete population. Since more men than women had an AAA of 5 cm or more at the cardiovascular work-up and this could explain the better prognosis in women given the substantial risk of rupture we repeated the analyses after excluding these patients.[15] The results did not change meaningfully.

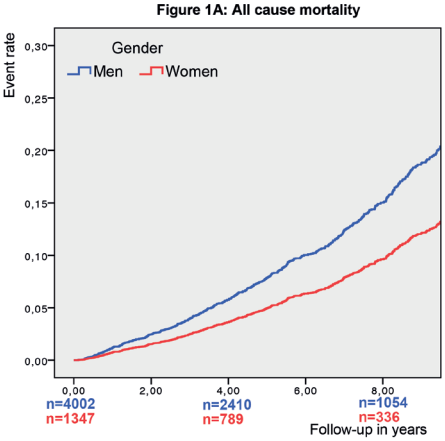


Figure 1A. All cause mortality
Occurrence of all cause mortality stratified by gender in an age-adjusted Cox proportional hazard model (model II).

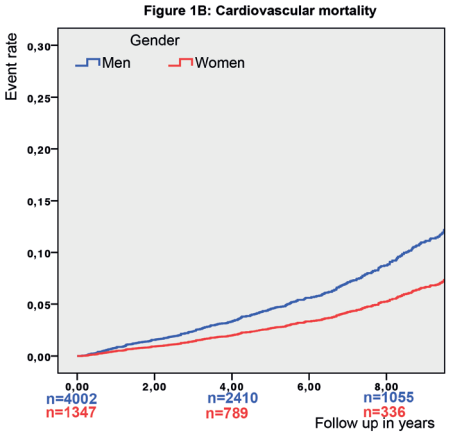


Figure 1B. Cardiovascular mortality
Occurrence of cardiovascular mortality stratified by gender in an age-adjusted Cox proportional hazard model (model II).

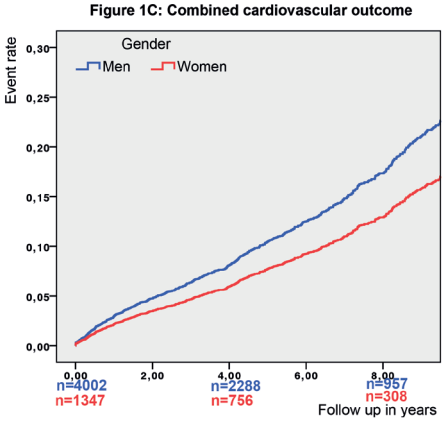


Figure 1C. Combined cardiovascular outcome
Occurrence of the combined cardiovascular outcome stratified by gender in an age-adjusted Cox proportional hazard model (model II).

DISCUSSION

This study demonstrates that women have a better long-term prognosis than men in a large cohort of patients with clinically manifest atherosclerosis. The relationship between gender and outcome did not change remarkably after adjusting for age and other potential confounders such as cardiovascular risk factors and a past medical cardiovascular history. Our cohort has some notable baseline characteristics. Women are relatively young in comparison to men. This age difference could in theory explain the better long-term prognosis in women but after adjusting for age in the multivariate analysis the difference in risk between women and men remains.

We also found remarkable differences in smoking behaviour between women and men in our study. Although more women had never smoked, fewer women quit smoking resulting in more current smokers among women at the time of inclusion in the study. Previous reports showed that smoking is more detrimental to women than to men. Female smokers namely develop their first myocardial infarction 14 years earlier than women who never smoked in comparison to a difference of 6 years in men.[16,17] Moreover other studies demonstrated that female smokers experience more cardiovascular complications than male smokers.[18]. However, in our study women had still a better prognosis than men regardless of their smoking behaviour. The number of packyears in our study is lower in women just like previously published data from around the world.[19,20] Adjusting for packyears in our model did not change the differences in long-term prognosis between women and men. The risk profile of women in our cohort is unfavourable in comparison to men with more often hypertension; more frequent dyslipidemia and more women with a BMI above 30 kg/m^2, which is in agreement with previous data.[2,9,21,22] Men had more myocardial infarction and AAA in their past medical history while women had more strokes, corresponding to prior studies[23,24]. However adjusting for these differences in past medical cardiovascular history did not change the favourable outcome in prognosis in women.

Since hs-CRP as a marker of inflammation, is associated with a higher risk of cardiovascular disease and death in women we also evaluated the effect of baseline hs-CRP levels in the present analysis.[25,26] There was a statistically significant difference in hs-CRP between both sexes, even though the median value of women was only 0.4 mg/l higher than in men. It is obvious that the higher CRP levels in women cannot explain their better prognosis in our study. Thus we could not find a clear explanation for the better long-term prognosis in women even though we analysed all plausible explanations with the data that we have available in our study.

Differences in atherosclerotic plaque characteristics between women and men could be of importance, but we have no data to validate this theory in our cohort. Previous studies describe that men have more vulnerable plaques than women in subgroups of patients with (a)symptomatic carotid artery disease or with coronary artery disease. [27,28] These vulnerable plaques lead to more strokes and acute coronary syndromes and could thus explain the difference in outcome between women and men with atherosclerosis.[27,28]

One important difference in our cohort in comparison to other studies is that all patients, men and women alike, underwent a standardized cardiovascular work-up. Differences in the frequency of using diagnostic tools in women and men, the so-called diagnostic bias, are thus not present in our cohort. This cardiovascular work-up revealed more peripheral arterial disease in women, equal percentages of carotid artery stenosis in both sexes and more proteinuria and AAA > 5 cm in men. The high number of PAD in women may be explained by their smoking behaviour.[29] Since an AAA with a diameter of 5 cm or more is associated with a substantial risk of rupture[15], we repeated all analyses after exclusion of the patients with an AAA of 5 cm or more to see if this could explain the better prognosis in women. The results remained comparable.
The findings of the work-up at inclusion are discussed by cardiovascular specialists in our hospital and the treating physician receives a tailored therapy advice based on the most recent guidelines for secondary prevention[13]. Unfortunately we don't know to which extent this advice was followed by the treating physician nor were therapy goals further assessed in the present study. Thus although it could be possible that we demonstrate the actual interaction between gender and outcome by excluding the effect of suboptimal treatment in women, we can not be certain.[30,31] Better compliance in women could explain the better prognosis in our study. Earlier studies describe contradictory results concerning differences in compliance between women and men.[32,33]

Limitations

Our study results can be extrapolated to patients who survive their index cardiovascular event since inclusion in the SMART study occurred after diagnosis and in some cases treatment of the atherosclerotic disease. Patients who died during this event could thus not be included. Previous studies describe a worse in-hospital outcome of women in comparison to men which equalizes after a longer follow-up, meaning a higher mortality rate in men after discharge.[34,35] This could be a possible explanation of the better survival in women in our study. The strengths of this study include the prospective cohort design, the large number of patients included and the different clinically relevant types of cardiovascular disease. Furthermore, there was a long follow-up duration and the clinical outcomes were thoroughly assessed and adjudicated by an independent event committee. In addition, all patients received an extensive cardiovascular work-up and a personalized treatment therapy advice for secondary prevention.

Conclusion

Women with documented cardiovascular disease who received a similar standardized cardiovascular work-up and tailored secondary prevention therapy advice as men had a favorable long-term outcome.

REFERENCES

1. Kannel WB. Overview of atherosclerosis. Clin Ther 1998;20 Suppl B:B2-17.
2. Alfredsson J, Lindback J, Wallentin L, Swahn E. Similar outcome with an invasive strategy in men and women with non-ST-elevation acute coronary syndromes: From the Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies (SWEDEHEART). *Eur Heart J* 2011;32:3128-36.
3. Isaksson RM, Jansson JH, Lundblad D, Naslund U, Zingmark K, Eliasson M. Better long-term survival in young and middle-aged women than in men after a first myocardial infarction between 1985 and 2006. an analysis of 8630 patients in the Northern Sweden MONICA Study. *BMC Cardiovasc Disord* 2011;11:1.
4. Vaartjes I, de Borst GJ, Reitsma JB, de Bruin A, Moll FL, Grobbee DE, et al. Long-term survival after initial hospital admission for peripheral arterial disease in the lower extremities. *BMC Cardiovasc Disord* 2009;9:43.
5. Bouisset F, Bongard V, Ruidavets JB, Hascoet S, Taraszkiewicz D, Roncalli J, et al. Prognostic Usefulness of Clinical and Subclinical Peripheral Arterial Disease in Men With Stable Coronary Heart Disease. *Am J Cardiol* 2012;Epub ahead of print 16 April 2012:DOI: 10.1016/j.amjcard.2012.03.013.
6. Criqui MH, Langer RD, Fronek A, Feigelson HS, Klauber MR, McCann TJ, et al. Mortality over a period of 10 years in patients with peripheral arterial disease. *N Engl J Med* 1992;326:381-386.
7. Kannel WB, Evans JC, Piper S, Murabito JM. Angina pectoris is a stronger indicator of diffuse vascular atherosclerosis than intermittent claudication: Framingham study. *J Clin Epidemiol* 2008;61:951-957.
8. Andersen KK, Olsen TS. One-month to 10-year survival in the Copenhagen stroke study: interactions between stroke severity and other prognostic indicators. *J Stroke Cerebrovasc Dis* 2011;20:117-123.
9. D'Ascenzo F, Gonella A, Quadri G, Longo G, Biondi-Zoccai G, Moretti C, et al. Comparison of mortality rates in women versus men presenting with ST-segment elevation myocardial infarction. *Am J Cardiol* 2011;107:651-654.
10. Ronning OM, Stavem K. Predictors of Mortality Following Acute Stroke: A Cohort Study with 12 Years of Follow-Up. *J Stroke Cerebrovasc Dis* 2010;Epub:DOI:10.1016/j.jstrokecerebrovasdis.2010.09.012.
11. Vaartjes I, van Dis I, Grobbee DE, Bots ML. The dynamics of mortality in follow-up time after an acute myocardial infarction, lower extremity arterial disease and ischemic stroke. *BMC Cardiovasc Disord* 2010;10:57.
12. Simons PC, Algra A, van de Laak MF, Grobbee DE, van der Graaf Y. Second manifestations of ARTerial disease (SMART) study: rationale and design. *Eur J Epidemiol* 1999;15:773-781.
13. Graham I, Atar D, Borch-Johnsen K, Boysen G, Burell G, Cifkova R, et al. European guidelines on cardiovascular disease prevention in clinical practice: full text. Fourth Joint Task Force of the European Society of Cardiology and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of nine societies and by invited experts). *Eur J Cardiovasc Prev Rehabil* 2007;14 Suppl 2:S1-113.
14. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med* 1999;130:461-470.
15. Nevitt MP, Ballard DJ, Hallett JW,Jr. Prognosis of abdominal aortic aneurysms. A population-based study. *N Engl J Med* 1989;321:1009-1014.
16. Grundtvig M, Hagen TP, German M, Reikvam A. Sex-based differences in premature first myocardial infarction caused by smoking: twice as many years lost by women as by men. *Eur J Cardiovasc Prev Rehabil* 2009;16:174-179.
17. Howe M, Leidal A, Montgomery D, Jackson E. Role of Cigarette Smoking and Gender in Acute Coronary Syndrome Events. *Am J Cardiol* 2011;108:1382-6.

18. Huxley RR, Woodward M. Cigarette smoking as a risk factor for coronary heart disease in women compared with men: a systematic review and meta-analysis of prospective cohort studies. *Lancet* 2011;378:1297-1305.
19. Centers for Disease Control and Prevention (CDC). Cigarette smoking among adults--United States, 2004. *MMWR Morb Mortal Wkly Rep* 2005;54:1121-1124.
20. Woodward M, Lam TH, Barzi F, Patel A, Gu D, Rodgers A, et al. Smoking, quitting, and the risk of cardiovascular disease among women and men in the Asia-Pacific region. *Int J Epidemiol* 2005;34:1036-1045.
21. Hvelplund A, Galatius S, Madsen M, Rasmussen JN, Rasmussen S, Madsen JK, et al. Women with acute coronary syndrome are less invasively examined and subsequently less treated than men. *Eur Heart J* 2010;31:684-690.
22. Nicholls SJ, Wolski K, Sipahi I, Schoenhagen P, Crowe T, Kapadia SR, et al. Rate of progression of coronary atherosclerotic plaque in women. *J Am Coll Cardiol* 2007;49:1546-1551.
23. Morrell J, Zeymer U, Baumgartner I, Limbourg T, Rother J, Bhatt DL, et al. Differences in management and outcomes between male and female patients with atherothrombotic disease: results from the REACH Registry in Europe. *Eur J Cardiovasc Prev Rehabil* 2011;18:270-277.
24. Aboyans V, Kownator S, Lafitte M, Brochet E, Emmerich J, Tribouilloy C, et al. Screening abdominal aorta aneurysm during echocardiography: literature review and proposal for a French nationwide study. *Arch Cardiovasc Dis* 2010;103:552-558.
25. Kip KE, Marroquin OC, Shaw LJ, Arant CB, Wessel TR, Olson MB, et al. Global inflammation predicts cardiovascular risk in women: a report from the Women's Ischemia Syndrome Evaluation (WISE) study. *Am Heart J* 2005;150:900-906.
26. Cook NR, Buring JE, Ridker PM. The effect of including C-reactive protein in cardiovascular risk prediction models for women. *Ann Intern Med* 2006;145:21-29.
27. Hellings WE, Pasterkamp G, Verhoeven BA, De Kleijn DP, De Vries JP, Seldenrijk KA, et al. Gender-associated differences in plaque phenotype of patients undergoing carotid endarterectomy. *J Vasc Surg* 2007;45:289-96; discussion 296-7.
28. Rittersma SZ, van der Wal AC, Koch KT, Piek JJ, Henriques JP, Mulder KJ, et al. Plaque instability frequently occurs days or weeks before occlusive coronary thrombosis: a pathological thrombectomy study in primary percutaneous coronary intervention. *Circulation* 2005;111:1160-1165.
29. Willigendael EM, Teijink JA, Bartelink ML, Kuiken BW, Boiten J, Moll FL, et al. Influence of smoking on incidence and prevalence of peripheral arterial disease. *J Vasc Surg* 2004;40:1158-1165.
30. Blomkalns AL, Chen AY, Hochman JS, Peterson ED, Trynosky K, Diercks DB, et al. Gender disparities in the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes: large-scale observations from the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the American College of Cardiology/American Heart Association Guidelines) National Quality Improvement Initiative. *J Am Coll Cardiol* 2005;45:832-837.
31. Yusuf S, Islam S, Chow CK, Rangarajan S, Dagenais G, Diaz R, et al. Use of secondary prevention drugs for cardiovascular disease in the community in high-income, middle-income, and low-income countries (the PURE Study): a prospective epidemiological survey. *Lancet* 2011;378:1231-1243.
32. Rasmussen JN, Chong A, Alter DA. Relationship between adherence to evidence-based pharmacotherapy and long-term mortality after acute myocardial infarction. *JAMA* 2007;297:177-186.
33. Wei L, Flynn R, Murray GD, MacDonald TM. Use and adherence to beta-blockers for secondary prevention of myocardial infarction: who is not getting the treatment? *Pharmacoepidemiol Drug Saf* 2004;13:761-766.
34. Grundtvig M, Hagen TP, Amrud ES, Reikvam A. Mortality after myocardial infarction: impact of gender and smoking status. *Eur J Epidemiol* 2011;26:385-393.
35. Al-Fiadh AH, Andrianopoulos N, Farouque O, Yan BP, Duffy SJ, Charter K, et al. Contemporary outcomes in women undergoing percutaneous coronary intervention for acute coronary syndromes. *Int J Cardiol* 2011;151:195-199.

CHAPTER 8

THE IMPACT OF POLYVASCULAR DISEASE ON LONG-TERM OUTCOME IN PCI PATIENTS

Eur J Clin Invest. 2014 Mar;44(3):231-9

Manon G. van der Meer, Maarten J. Cramer, Yolanda van der Graaf,
Yolande Appelman, Pieter A. Doevendans, Hendrik M.Nathoe

ABSTRACT

Background

Previous studies demonstrated the prognostic importance of concomitant polyvascular disease in patients with coronary artery disease (CAD). However, the significance of the number of diseased vascular territories and subclinical disease is unknown.

Materials and methods

The number of diseased vascular territories was evaluated in 2299 percutaneous coronary intervention (PCI) patients. Vascular disease was defined by documented atherosclerotic disease, either diagnosed in the medical history (clinical) or at the standardized cardiovascular screening (subclinical). The following territories were evaluated: cerebrovascular disease, peripheral arterial disease, abdominal aortic aneurysm and vascular renal disease. The outcome measures were all-cause mortality, cardiovascular mortality and a composite cardiovascular endpoint (myocardial infarction, stroke, cardiovascular mortality). Patients with monovascular disease (CAD) served as the reference category. Hazard ratios (HRs) were adjusted for baseline characteristics.

Results

Mean follow-up was 7.3 years. The HRs (95% confidence interval) for patients with two diseased territories compared to monovascular disease were for all-cause mortality 1.60 (1.14-2.25), cardiovascular mortality 2.13 (1.29-3.50) and the combined cardiovascular endpoint 1.66 (1.20-2.31). Moreover, the HRs (95% confidence intervals) for patients with more than two diseased territories compared to monovascular disease were for all-cause mortality 3.81 (2.45-5.92), cardiovascular mortality 4.40 (2.32-8.35) and the combined cardiovascular endpoint 2.75 (1.69-4.47). The HRs of patients with subclinical disease were comparable to the HRs of patients with clinical disease.

Conclusions

In patients undergoing PCI the presence of subclinical and clinical polyvascular disease is associated with an increased long-term mortality and morbidity. Moreover, the outcome is highly influenced by the number of diseased territories.

INTRODUCTION

Patients with atherosclerotic disease have an increased risk of concomitant arterial disease in other vascular territories, since atherosclerosis is a progressive and generalized process.[1] It has been shown that the prognosis of patients with symptomatic polyvascular disease is impaired in comparison to patients with only one atherosclerotic vascular bed. The OPUS-TIMI 16 study demonstrated that in patients with coronary artery disease (CAD) who presented with an acute coronary syndrome (ACS) the presence of prior clinical atherosclerotic cardiovascular disease (cerebrovascular disease (CVD) and peripheral arterial disease (PAD)) was associated with a worse 10 months outcome.[2] In the Dynamic Registry clinical atherosclerotic disease on top of CAD was an independent predictor of both in-hospital cardiovascular events, and death or myocardial infarction at 1 year after PCI.[3] Also long-term survival is impaired in patients undergoing coronary revascularization with concomitant PAD as compared to patients without PAD.[4,5] Although the previously mentioned studies have shown the prognostic importance of polyvascular disease in a population with known CAD, the prognostic significance of the number of diseased atherosclerotic vascular territories was not studied. Moreover the importance of subclinical concomitant atherosclerotic disease in all vascular territories in patients undergoing PCI was not considered. Therefore we analyzed the impact of the number of diseased vascular territories on top of CAD on long-term outcome in a large cohort of patients undergoing PCI. In addition we addressed whether subclinical polyvascular disease leads to a comparable outcome as clinical polyvascular disease.

METHODS

Study design and patient population

The Second Manifestations of ARTerial disease (SMART) study is an ongoing prospective follow-up study at the University Medical Centre Utrecht in the Netherlands. Since 1996, newly referred patients, aged 18 to 80 years, with traditional cardiovascular risk factors or with clinical arterial disease were included. Patients with end-stage malignancy, those dependent in daily activities or not sufficiently fluent in the Dutch language were excluded. A detailed description of the study was previously published.[6] The Smart study protocol was approved by The Ethics Committee of our hospital. In short, patients who gave their written informed consent were asked to fill in a standardized health questionnaire and to undergo a standardized vascular screening that includes physical examination, laboratory tests, electrocardiogram (ECG), ankle-brachial index and ultrasonographic examination of the abdominal aorta and carotid arteries. All patients received a personalized cardiovascular secondary prevention therapy advice based on the findings of the screening. In the present analysis, only patients who participated in the SMART study after undergoing a PCI were included (n=2299). These patients were included between April 1996 and March 2012 and were followed until March 2012 or death.

Definitions, follow-up procedure and endpoint evaluation

Definitions

The number of diseased vascular territories on top of their known CAD was determined in all patients. The vascular territories that were taken into account were cerebrovascular disease (CVD), peripheral arterial disease (PAD), aneurysm of the abdominal aorta (AAA) and vascular renal disease. The definition of atherosclerosis in a vascular territory consisted of either clinical arterial disease (medical history) or subclinical atherosclerosis that was determined by the SMART vascular screening. A medical history of CVD consisted of either a stroke or carotid endarterectomy. Patients were considered to have PAD when they underwent an amputation, bypass surgery or percutaneous transluminal angioplasty (PTA) of the peripheral arteries in the past. A medical history of AAA comprised the diagnosis of an aneurysm of the abdominal aorta treated conservatively or with open/ endovascular surgery. Macrovascular renal disease was considered present when patients had documented renal artery disease at angiography. The standardized SMART cardiovascular screening for the evaluation of subclinical disease comprised a duplex ultrasonography of the carotid artery (cut off > 50% stenosis), an ankle-brachial index to determine PAD (cut off <0.9) and ultrasonography of the abdominal aorta (cut off ≥ 3.5 cm). Microvascular renal disease was considered present when there was either macroproteinuria (> 30 mg albumin/ mmol creatinine in24 hours urine sample) or microproteinuria (> 3 < 30 mg albumin/ mmol creatinine in24 hours urine sample) in combination with an estimated glomerular filtration rate (eGFR) in a blood sample below 60 ml/min/1,73m^2 or an eGFR below 30 ml/ min/1,73m^2. Patients were divided in subgroups based on the number of diseased atherosclerotic arterial territories. Patients with solely CAD were considered to have monovascular disease. Patients with one concomitant diseased vascular territory on top of CAD were considered to have two diseased vascular territories. Patients with two or more diseased vascular territories in addition to their CAD were categorized as more than two diseased vascular territories.

Hypertension was defined by a systolic blood pressure ≥ 140 mmHg and/ or the use of anti-hypertensive drugs. In patients with diabetes a blood pressure above 130/85 mmHg was classified as hypertension.[7,8] Hyperlipidemia at screening was defined by a LDL cholesterol ≥ 2.5 mmol/l or triglycerides > 2.0 mmol/l or HDL cholesterol ≤1.0 mmol/l in men and HDL cholesterol ≤ 1.3 mmol/l in women. Among subjects without a history of diabetes, those with a fasting plasma glucose level > 11.1 mmol/l at baseline or with fasting plasma glucose ≥7.0 mmol/l at baseline and receiving treatment with glucose-lowering agents within 1 year after baseline were considered as having diabetes at baseline. High-sensitive CRP (hs-CRP) was measured in all patients to evaluate the inflammatory state.

Follow-up procedure

All patients were followed every 6 months with use of a standardized questionnaire or by telephone to find out whether a cardiovascular event or arterial intervention had occurred. When a possible event was reported, hospital discharge letters were retrieved to verify

the diagnosis. Three members of the SMART Endpoint Committee independently adjudicated all events. This Committee consists of physicians from different cardiovascular specialties. In case of disagreement, the event was evaluated in detail by members of the SMART study group.

Data-analysis

Patients with polyvascular disease (2 diseased vascular territories or more than 2 diseased vascular territories) were compared to patients with monovascular disease (CAD only). The measures of outcome were all-cause mortality, cardiovascular mortality and a combined cardiovascular endpoint (composite of cardiovascular mortality, stroke and myocardial infarction). Cardiovascular mortality was defined by sudden death (unexpected cardiac death occurring within 1 hour after onset of symptoms or within 24 hours given convincing circumstantial evidence) or death from stroke, myocardial infarction, congestive heart failure or ruptured aneurysm of the abdominal aorta. Myocardial infarction was defined by a combination of at least two of the following: 1.) chest pain for at least 20 minutes, 2.) ST elevation > 1 mm in at least two consecutive leads or a new left bundle branch block on the ECG, 3.) CK elevation of at least two times the normal value of CK and a MB-fraction > 5% or a Troponin rise exceeding the upper limit of normal.

Descriptives are expressed as mean (standard deviation) for continuous variables that have a normal distribution and as mean (range) for continuous variables that are not normally distributed. Categorical variables are presented as numbers (percentages). Difference in all-cause mortality, cardiovascular death and cardiovascular outcome between patients with 1 (CAD), 2 (CAD + 1) and at least 3 (CAD + 2 or more) diseased vascular territories was calculated with Cox proportional hazard model analysis. Patients with monovascular disease (CAD only) served as the reference category in the analyses. Any first occurrence of an event during the follow up period was used in the model. Results are expressed as hazard ratios (HR) with 95% confidence intervals (95%CI). All analyses were conducted with three different models. One model adjusting for age and gender (model I) and a second model adjusting for potential confounding factors besides age and gender: diabetes mellitus, packyears (20 cigarettes a day/ year, in quartiles), hypertension, hyperlipidemia, body mass index (BMI) and previous myocardial infarction. The latter was added in an attempt to approximate the left ventricular function. Model III was performed in the subgroup of patients with known extent of CAD. On top of all the potential confounding factors of model II we adjusted in model III also for the extent of CAD. A subgroup analysis was performed to compare the impact of subclinical and clinical polyvascular disease on the prognosis of PCI patients. All statistical analyses were performed with IBM SPSS 20.0 for Windows.

RESULTS

Baseline characteristics

A total of 2299 patients who underwent a PCI between 1996 and 2012 at the University Medical Center Utrecht, the Netherlands, were included in the SMART study. A total of 462 (21%) patients had polyvascular disease and were categorized by the number of diseased vascular territories. The baseline characteristics are summarized in Table 1.

Table 1. Baseline characteristics according to the number of diseased vascular territories (n=2299)

	1 territory n (%) 1837 (80)	2 territories n (%) n=375 (16)	more than 2 territories n (%) n=87 (4)
Age in years, mean (sd)	58.6 (9.4)	63.0 (9.1)	64.7 (7.0)
Male	1518 (83)	289 (77)	70 (81)
Packyears, median (IQR)	21.6 (9.8-33.6)	21.6 (9.9-35.1)	27.3 (10.8-44.1)
Previous myocardial infarction	850 (46)	172 (46)	42 (48)
Extent of coronary artery disease			
One vessel	785 (43)	141 (38)	27 (31)
Two vessel	538 (29)	120 (32)	25 (29)
Three vessel	234 (13)	59 (16)	26 (30)
Unknown	280 (15)	55 (15)	9 (10)
Hypertension	805 (44)	231 (62)	55 (63)
Hyperlipidemia	613 (33)	119 (32)	37 (43)
Diabetes	251 (14)	77 (21)	26 (30)
Body Mass Index (kg/m²), median (IQR)	27.1 (24.9-29.4)	26.9 (25.0-29.7)	27.2 (25.5-30.7)
High-sensitive CRP, median (IQR)	1.5 (0.8-3.0)	2.1 (1.1-4.1)	3.3 (1.8-5.8)
Medication use			
Beta-blockers	1481 (81)	289 (77)	68 (78)
ACE-inhibitors	520 (28)	123 (33)	36 (41)
Diuretics	267 (15)	105 (28)	33 (38)
Statins	1162 (63)	262 (70)	58 (67)
Platelet aggregation inhibitors	1664 (91)	336 (90)	72 (83)
Oral anticoagulants	111 (6)	47 (13)	21 (24)
Platelet aggregation inhibitors or oral anticoagulants	1704 (93)	349 (93)	78 (90)
Oral glucose lowering medication	154 (8)	54 (14)	14 (16)
Insulin	64 (4)	28 (8)	6 (7)

N: number; sd: standard deviation; IQR: interquartile range

Table 2. Type of diseased vascular territory according to clinical (medical history) or subclinical (finding at screening) polyvascular disease

	2 territories n=375 (%)	more than 2 territories n= 87 (%)
Cerebrovascular disease		
Clinical	50 (13)	22 (25)
Stroke	46 (12)	15 (17)
Carotid endarterectomy	6 (2)	9 (10)
Subclinical**		
Carotid stenosis > 50%	66 (18)	42 (48)
Peripheral arterial disease		
Clinical	48 (13)	24 (28)
Amputation	8 (2)	2 (2)
Bypass surgery/ PTA	43 (11)	23 (26)
Subclinical**		
Ankle-brachial index < 0.9	99 (26)	51 (59)
Aneurysm of the abdominal aorta		
Clinical	26 (7)	21 (24)
Open/ endovascular repair	4 (1)	7 (8)
Conservative management	22	14
Subclinical**		
Aorta diameter of ≥ 3.5 cm	5 (1)	7 (8)
Renal disease		
Clinical	49 (13)	13 (15)
PTA	1 (0)	0 (0)
Subclinical**		
Microvascular renal disease***	57 (15)	26 (30)

*: including CAD; **: subclinical: atherosclerotic disease diagnosed with SMART standardized cardiovascular screening; PTA: percutaneous transluminal angioplasty; ***estimated glomerular filtration rate (eGFR) ≤ 30 or eGFR ≤60 and micro albuminuria or macro albuminuria

Patients with polyvascular disease were older, and had an unfavourable risk profile as illustrated by more extensive CAD, heavy smoking and a higher prevalence of hypertension and diabetes mellitus. The median hs-CRP levels increased gradually with the number of diseased vascular territories. Patients with polyvascular disease use more ACE inhibitors, diuretics, glucose-lowering medication and oral anticoagulants, but less anti-platelet drugs. The use of statins and beta-blockers were not different.

Type of diseased vascular territories

The type of diseased vascular territories in the patients with polyvascular disease are shown in Table 2. Remarkably, 48% of patient with more than 2 diseased territories had a carotid

stenosis of more than 50%. Moreover 59% of these patients had a diminished ankle-brachial index (<0.9) and 30% had microvascular renal disease.

Incidence of cardiovascular events

During a mean follow-up time of 7.3 (±4.0) years 62 patients (2.7%) were lost to follow up. A total of 211 patients (9%) died of whom 92 (44%) from a cardiovascular death (Table 3). A total of 243 patients (11%) developed the combined cardiovascular endpoint.

Survival analysis

Compared to patients with monovascular disease (CAD only), patients with polyvascular disease were associated with a higher risk for all-cause mortality, cardiovascular mortality and the combined cardiovascular endpoint (Table 3). This increased risk was different among the patients with polyvascular disease as patients with more than two diseased vascular territories had an even higher risk than patients with two atherosclerotic vascular territories. The HRs (with 95% confidence intervals) for patients with two diseased vascular territories compared to patients with monovascular disease were for all-cause mortality 1.60 (1.14-2.25), cardiovascular mortality 2.13 (1.29-3.50) and the combined cardiovascular endpoint 1.66 (1.20-2.31). Moreover, the HRs (95% confidence intervals) for patients with more than two diseased vascular territories compared to patients with monovascular disease were for all-cause mortality 3.81 (2.45-5.92), cardiovascular mortality 4.40 (2.32-8.35) and the combined cardiovascular endpoint 2.75 (1.69-4.47). No large differences were found between the two different statistical models. Event-free survival curves, derived from the second Cox proportional hazard model, are shown for all-cause mortality and the combined cardiovascular outcome (Figures 1 and 2).

After adjusting for the extent of CAD in the subgroup of patients in whom the extent of CAD was known (model III), the relation between the number of territories and the outcomes was slightly attenuated but evidently still present.

Subclinical polyvascular disease

We repeated the survival analysis after subdividing the polyvascular patients based on whether the concomitant atherosclerotic disease was previously diagnosed (clinical) or detected at the SMART screening (subclinical) (Table 4). A total of 226 patients (49%) out of the 462 patients with polyvascular disease had clinical atherosclerotic disease. The remaining 236 patients (51%) were identified with subclinical atherosclerotic disease. Patients with clinical or subclinical polyvascular disease had an impaired long-term prognosis as compared with monovascular disease. The hazard ratios for different outcomes in patients with clinical and subclinical polyvascular disease compared to patients with monovascular disease were as follows: all-cause mortality: 2.05 (1.40-3.01) and 1.94 (1.34-2.81); cardiovascular mortality 2.28 (1.29-4.06) and 2.85 (1.68-4.83) and for the combined cardiovascular endpoint: 1.51 (1.00-2.28) and 2.22 (1.55-3.17).

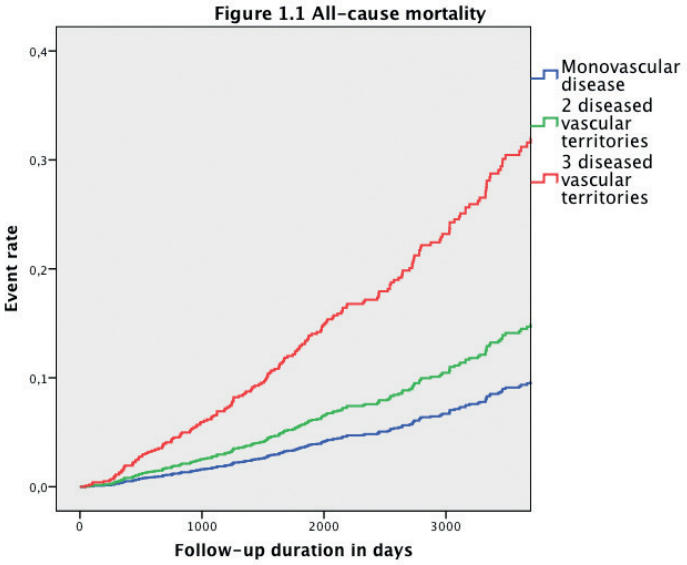


Figure 1. All-cause mortality in PCI patients, subdivided in subgroups of number of diseased atherosclerotic territories (derived from an age-, gender-, diabetes mellitus-, hypertension-, packyears (in quartiles), previous myocardial infarction-, body mass index-, hyperlipidemia- adjusted Cox proportional hazards model. The X-axis shows follow up duration in days. The Y-axis shows the event rate.

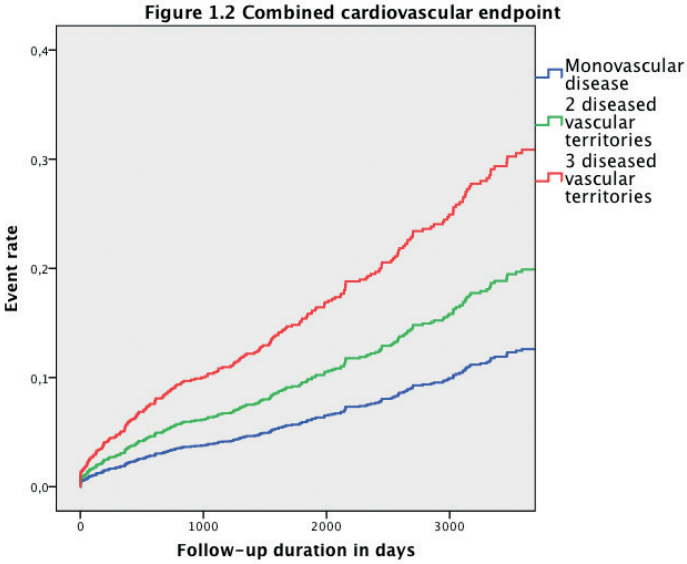


Figure 2. The combined cardiovascular endpoint (myocardial infarction, stroke, cardiovascular mortality) in PCI patients, subdivided in subgroups by the number of diseased atherosclerotic territories (derived from an age-, gender-, diabetes mellitus-, hypertension-, packyears (in quartiles), previous myocardial infarction-, body mass index-, hyperlipidemia- adjusted Cox proportional hazards model. The X-axis shows follow up duration in days. The Y-axis shows the event rate.

Table 3. The risk of the number of diseased vascular territories on long-term mortality, cardiovascular mortality and a combined cardiovascular endpoint

	1 territory n=1837 Reference category	2 territories n=375 HR (95%CI)	more than 2 territories n=87 HR (95%CI)
All-cause mortality (# events (%))	137 (7)	48 (13)	26 (30)
Model I	1.00	1.55 (1.11-2.17)	3.92 (2.57-5.99)
Model II	1.00	1.60 (1.14-2.25)	3.81 (2.45-5.92)
Model III*	1.00	1.53 (1.05-2.22)	3.41 (2.11-5.50)
Cardiovascular mortality (# events (%))	57 (3)	22 (6)	13 (15)
Model I	1.00	1.78 (1.08-2.94)	4.85 (2.63-8.92)
Model II	1.00	2.13 (1.29-3.50)	4.40 (2.32-8.35)
Model III*	1.00	1.80 (1.02-3.18)	3.38 (1.65-6.92)
Combined cardiovascular endpoint (# events (%))	173 (9)	50 (13)	20 (23)
Model I	1.00	1.58 (1.15-2.18)	2.92 (1.82-4.67)
Model II	1.00	1.66 (1.20-2.31)	2.75 (1.69-4.47)
Model III*	1.00	1.55 (1.08-2.23)	2.25 (1.33-3.82)
(myocardial infarction, stroke, cardiovascular death)			

HR: hazard ratio; CI: confidence interval. Model I: Hazard ratios (HRs) adjusted for age and gender; Model II: HRs adjusted for age, gender, diabetes mellitus, hypertension, hyperlipidemia, body mass index, packyears(in quartiles)and previous myocardial infarction; Model III*: Subgroup analysis in patients with known extent of coronary artery disease (CAD) and adjusted for extent of CAD on top of age, gender, diabetes mellitus, hypertension, hyperlipidemia, body mass index, packyears(in quartiles) and previous myocardial infarction. Number of patients in subgroup analysis: 1 territory: 1555 patients, 2 territories: 319 patients, more than 2 territories: 78 patients.

DISCUSSION

In this study we demonstrate that the presence of polyvascular disease in patients undergoing PCI is associated with an unfavorable long-term outcome. Impaired prognosis is present for both clinical and subclinical atherosclerosis. Moreover, the outcome is highly influenced by the number of diseased vascular territories. Several explanations are possible for the impaired prognosis of patients with polyvascular disease. First, it is certain that the high atherosclerotic burden plays an important role. It is established that a high atherosclerotic burden in just one vascular bed (CAD) is associated with a worse 1-year mortality.[9-11] The same holds for patients with polyvascular disease as found by previous studies.[12-14] Secondly, there is evidence that several plasma biomarkers such as fibrinogen and CRP are higher in CAD patients with concomitant PAD compared to patients with exclusive CAD.[15] It has been hypothesized that these procoagulant and

Table 4. The risk of subclinical and clinical polyvascular disease on long-term mortality, cardiovascular mortality and a combined cardiovascular endpoint

	1 territory n=1837 Reference category	Clinical disease More than 1 territory n=226 HR (95%CI)	Subclinical disease More than 1 territory n=236 HR (95%CI)
All-cause mortality (# events (%))	137 (7)	35 (15)	39 (17)
Model I	1.00	2.04 (1.40-2.97)	1.91 (1.33-2.75)
Model II	1.00	2.05 (1.40-3.01)	1.94 (1.34-2.81)
Cardiovascular mortality (# events (%))	57 (3)	15 (7)	20 (8)
Model I	1.00	2.19 (1.23-3.90)	2.44 (1.45-4.11)
Model II	1.00	2.28 (1.29-4.06)	2.85 (1.68-4.83)
Combined cardiovascular endpoint (# events (%))	173 (9)	28 (12)	42 (18)
Model I	1.00	1.52 (1.01-2.27)	2.09 (1.48-2.95)
Model II	1.00	1.51 (1.00-2.28)	2.22 (1.55-3.17)
(myocardial infarction, stroke, cardiovascular death)			

HR: hazard ratio; CI: confidence interval. Model I: Hazard ratios (HRs) adjusted for age and gender; Model II: HRs adjusted for age, gender, diabetes mellitus, hypertension, hyperlipidemia, body mass index, packyears (ln quartiles) and previous myocardial infarction. Given the relatively small numbers of clinical and subclinical polyvascular disease, there was no room for subanalysis of two or more diseased vascular territories.

proinflammatory states are related to a worse outcome in terms of cardiac death and nonfatal cardiac events.[16,17] We also found a statistically significant higher CRP in our cohort of patients with polyvascular disease as compared to those with monovascular disease. Moreover among the polyvascular patients CRP was significantly higher in patients with more than 2 diseased vascular territories compared to patients with 2 diseased territories. The question remains whether there is a causal relation between CRP levels and outcome or that CRP levels rose secondary to the severity of the atherosclerotic process involved.[18] Nevertheless, intensive treatment of inflammation and cholesterol lowering may be beneficial to stabilize the atherosclerotic process.[19,20] Finally, several studies showed that patients with polyvascular disease are treated suboptimal.[2,15,21,22] For example, beta-blockers and statins were prescribed less often in patients with polyvascular disease than in patients with monovascular disease.[15,23] Potentially the outcome of polyvascular patients might be improved if treated according to current guidelines. Although not proven in polyvascular patients, a more aggressive statin therapy might be more beneficial because of its atherosclerotic disease stabilisation/regression properties.[19,24] In contrast, in the GRACE registry and in our study population there were no differences in the use of evidence-based medication between patients

with or without polyvascular disease.[13] In our study patients with more than 2 diseased vascular territories did use less platelet aggregation inhibitors compared to the other 2 groups. However after combining platelet aggregation inhibitors and oral coagulants no difference was found between the three groups.

We are the first to assess the number of diseased vascular territories, clinical and subclinical, in a comprehensive way. We demonstrate that not only the presence of clinical but also subclinical polyvascular disease is associated with a worse prognosis. Our findings are in line with three small studies in which the presence of subclinical concomitant disease is associated with a worse prognosis compared to patients with monovascular disease (CAD).[5,25,26] However, two studies only describe subclinical PAD and the other one PAD and carotid atherosclerotic lesions. We confirm these findings in a large cohort of patients in which subclinical disease was determined systematically in all vascular territories. The presence of subclinical disease was determined by a standardized cardiovascular screening comprising non-invasive ultrasound imaging and routine laboratory tests. Half of the patients with polyvascular disease were identified with this screening protocol. Of note, our standardized vascular screening protocol carries no safety issues compared to novel screening techniques such as radiation-based calcium scoring of vascular disease. The prognosis of patients with polyvascular disease is associated with the number of diseased vascular territories. According to our protocol, a thorough enquiry of the medical history in combination with a simple standardized screening is helpful to reclassify the risk of patients undergoing PCI.[27-33] Reclassification may be important for optimisation of personalized secondary prevention strategies.

According to the SMART study protocol, all participating patients received patient-tailored secondary prevention and therapy recommendations from the multidisciplinary team in order to improve patients' prognosis. These recommendations include guideline-based lifestyle management, improvement of medical treatment (e.g. antihypertensive drugs) and - if indicated - invasive treatment. However, since all patients, with and without polyvascular disease, receive the same personalized advice based on general risk factors, we did not expect any influence on the results.

The strengths of this study include the prospective cohort design, large sample size, long follow-up duration and the thorough assessment of the clinical endpoints. In addition, all patients received extensive screening of subclinical atherosclerotic disease leading to a more accurate identification of patients with polyvascular disease.

A limitation of our study is that compliance of patients to the multidisciplinary therapy advice and medication use is unknown. Furthermore data on left ventricle function was not available in most patients and therefore could not be included in the current analysis. Moreover, we acknowledge that there have been innovations in coronary stents during the relatively long time frame of inclusion of patients. The emerging use of drug eluting stents for example may have influenced the outcome of the PCI procedures in general. However, since patients with and without polyvascular disease were equally presented during all timeframes we expect no influence on the findings.

CONCLUSIONS

In patients undergoing PCI the presence of subclinical and clinical polyvascular disease is associated with an increased long-term mortality and morbidity. Moreover, the outcome is highly influenced by the number of diseased vascular territories.

REFERENCES

1 Kannel WB. Overview of atherosclerosis. Clin Ther 1998; 20 Suppl B: B2.
2 Cotter G, Cannon CP, McCabe CH, Michowitz Y, Kaluski E, Charlesworth A, et al. Prior peripheral arterial disease and cerebrovascular disease are independent predictors of adverse outcome in patients with acute coronary syndromes: are we doing enough? Results from the Orbofiban in Patients with Unstable Coronary Syndromes-Thrombolysis In Myocardial Infarction (OPUS-TIMI) 16 study. Am Heart J 2003; 145: 622.
3 Naidu SS, Vlachos H, Faxon D, Jacobs AK, Selzer F, Detre K, et al. Usefulness of noncoronary vascular disease in predicting adverse events in the year following percutaneous coronary intervention. Am J Cardiol 2005; 95: 575.
4 Singh M, Lennon RJ, Darbar D, Gersh BJ, Holmes DR,Jr, Rihal CS. Effect of peripheral arterial disease in patients undergoing percutaneous coronary intervention with intracoronary stents. Mayo Clin Proc 2004; 79: 1113.
5 Burek KA, Sutton-Tyrrell K, Brooks MM, Naydeck B, Keller N, Sellers MA, et al. Prognostic importance of lower extremity arterial disease in patients undergoing coronary revascularization in the Bypass Angioplasty Revascularization Investigation (BARI). J Am Coll Cardiol 1999; 34: 716.
6 Simons PC, Algra A, van de Laak MF, Grobbee DE, van der Graaf Y. Second manifestations of ARTerial disease (SMART) study: rationale and design. Eur J Epidemiol 1999; 15: 773.
7 European Society of Hypertension-European Society of Cardiology Guidelines Committee. 2003 European Society of Hypertension-European Society of Cardiology guidelines for the management of arterial hypertension. J Hypertens 2003; 21: 1011.
8 Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, et al. 2007 Guidelines for the management of arterial hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J 2007; 28: 1462.
9 Ndrepepa G, Tada T, Fusaro M, Cassese S, King L, Hadamitzky M, et al. Association of coronary atherosclerotic burden with clinical presentation and prognosis in patients with stable and unstable coronary artery disease. Clin Res Cardiol 2012; 101: 1003.
10 Huang G, Zhao JL, Du H, Lan XB, Yin YH. Coronary score adds prognostic information for patients with acute coronary syndrome. Circ J 2010; 74: 490.
11 Uchida Y, Ichimiya S, Ishii H, Kanashiro M, Watanabe J, Yoshikawa D, et al. Impact of plaque burden in the left main coronary artery determined by intravascular ultrasound on cardiovascular events in a Japanese population undergoing percutaneous coronary intervention. Am J Cardiol 2012; 109: 352.
12 Bhatt DL, Peterson ED, Harrington RA, Ou FS, Cannon CP, Gibson CM, et al. Prior polyvascular disease: risk factor for adverse ischaemic outcomes in acute coronary syndromes. Eur Heart J 2009; 30: 1195.
13 Mukherjee D, Eagle KA, Kline-Rogers E, Feldman LJ, Juliard JM, Agnelli G, et al. Impact of prior peripheral arterial disease and stroke on outcomes of acute coronary syndromes and effect of evidence-based therapies (from the Global Registry of Acute Coronary Events). Am J Cardiol 2007; 100: 1.
14 Suarez C, Zeymer U, Limbourg T, Baumgartner I, Cacoub P, Poldermans D, et al. Influence of polyvascular disease on cardiovascular event rates. Insights from the REACH Registry. Vasc Med 2010; 15: 259.
15 Narins CR, Zareba W, Moss AJ, Marder VJ, Ridker PM, Krone RJ, et al. Relationship between intermittent claudication, inflammation, thrombosis, and recurrent cardiac events among survivors of myocardial infarction. Arch Intern Med 2004; 164: 440.
16 Niccoli G, Biasucci LM, Biscione C, Fusco B, Porto I, Leone AM, et al. Independent prognostic value of C-reactive protein and coronary artery disease extent in patients affected by unstable angina. Atherosclerosis 2008; 196: 779.

17 Zebrack JS, Muhlestein JB, Horne BD, Anderson JL, Intermountain Heart Collaboration Study Group. C-reactive protein and angiographic coronary artery disease: independent and additive predictors of risk in subjects with angina. J Am Coll Cardiol 2002; 39: 632.
18 Yousuf O, Mohanty BD, Martin SS, Joshi PH, Blaha MJ, Nasir K, et al. High-sensitivity C-reactive Protein and Cardiovascular Disease: A Resolute Belief or an Elusive Link? J Am Coll Cardiol 2013.
19 Nissen SE, Tuzcu EM, Schoenhagen P, Crowe T, Sasiela WJ, Tsai J, et al. Statin therapy, LDL cholesterol, C-reactive protein, and coronary artery disease. N Engl J Med 2005; 352: 29.
20 Ridker PM, Cannon CP, Morrow D, Rifai N, Rose LM, McCabe CH, et al. C-reactive protein levels and outcomes after statin therapy. N Engl J Med 2005; 352: 20.
21 Lee TC, Goodman SG, Yan RT, Grondin FR, Welsh RC, Rose B, et al. Disparities in management patterns and outcomes of patients with non-ST-elevation acute coronary syndrome with and without a history of cerebrovascular disease. Am J Cardiol 2010; 105: 1083.
22 Wong JA, Goodman SG, Yan RT, Wald R, Bagnall AJ, Welsh RC, et al. Temporal management patterns and outcomes of non-ST elevation acute coronary syndromes in patients with kidney dysfunction. Eur Heart J 2009; 30: 549.
23 Makowsky MJ, McAlister FA, Galbraith PD, Southern DA, Ghali WA, Knudtson ML, et al. Lower extremity peripheral arterial disease in individuals with coronary artery disease: prognostic importance, care gaps, and impact of therapy. Am Heart J 2008; 155: 348.
24 Puri R, Nissen SE, Ballantyne CM, Barter PJ, Chapman MJ, Erbel R, et al. Factors underlying regression of coronary atheroma with potent statin therapy. Eur Heart J 2013; 34: 1818.
25 Nakata S, Yokoi Y, Matsumoto R, Shirai N, Otsuka R, Sugioka K, et al. Long-term cardiovascular outcomes following ischemic heart disease in patients with and without peripheral vascular disease. Osaka City Med J 2008; 54: 21.
26 Romano G, Corrado E, Muratori I, Novo G, Andolina G, Cospite V, et al. Carotid and peripheral atherosclerosis in patients who underwent primary percutaneous coronary intervention and outcome associated with multifocal atherosclerosis. Int Angiol 2006; 25: 389.
27 Bendermacher BL, Teijink JA, Willigendael EM, Bartelink ML, Peters RJ, Langenberg M, et al. Applicability of the ankle-brachial-index measurement as screening device for high cardiovascular risk: an observational study. BMC Cardiovasc Disord 2012; 12: 59.
28 Leng GC, Fowkes FG, Lee AJ, Dunbar J, Housley E, Ruckley CV. Use of ankle brachial pressure index to predict cardiovascular events and death: a cohort study. BMJ 1996; 313: 1440.
29 Salonen JT, Salonen R. Ultrasound B-mode imaging in observational studies of atherosclerotic progression. Circulation 1993; 87: II56.
30 Kim LG, P Scott RA, Ashton HA, Thompson SG, Multicentre Aneurysm Screening Study Group. A sustained mortality benefit from screening for abdominal aortic aneurysm. Ann Intern Med 2007; 146: 699.
31 Quill DS, Colgan MP, Sumner DS. Ultrasonic screening for the detection of abdominal aortic aneurysms. Surg Clin North Am 1989; 69: 713.
32 Hallan SI, Stevens P. Screening for chronic kidney disease: which strategy? J Nephrol 2010; 23: 147.
33 Romano G, Corrado E, Muratori I, Novo G, Andolina G, Cospite V, et al. Carotid and peripheral atherosclerosis in patients who underwent primary percutaneous coronary intervention and outcome associated with multifocal atherosclerosis. Int Angiol 2006; 25: 389.

CHAPTER 9

NO ADDED VALUE OF FEMALE-SPECIFIC RISK FACTORS ON TOP OF TRADITIONAL RISK FACTORS FOR THE PREDICTION OF CARDIOVASCULAR DISEASE IN WOMEN

Submitted

Manon G. van der Meer, Yolanda van der Graaf, Ewoud Schuit, Linda M. Peelen, W.M. Monique Verschuren, Jolanda M.A. Boer, Karel G.M. Moons, Hendrik M. Nathoe, Yolande Appelman, Yvonne T. van der Schouw

ABSTRACT

Background

It remains unknown whether female-specific risk factors have added value on top of traditional risk factors for predicting cardiovascular disease (CVD).

Methods

We used data from 24,795 healthy women aged 30-74 years from two Dutch population-based cohort studies (PROSPECT, MORGEN). Outcome was 10-year risk of (non)-fatal CVD. Female-specific risk factors (age at menarche, menopausal status/age, hormone use, gestational hypertension and diabetes, number of children, miscarriages/stillbirths) were added on top of traditional risk predictors (age, diabetes, blood pressure, cholesterol, smoking) using a Cox proportional hazards model. Reproductive status variables were investigated in ever-pregnant women only. Improvement in discrimination, calibration and reclassification were determined.

Findings

Mean age±SD was 57·6±6·0 in PROSPECT and 46·0±8·7 in MORGEN. During a median follow-up of 11·7 years 1,605 (PROSPECT 10%) and 551 (MORGEN 6%) CVD events occurred. In both cohorts late menarche, having ≥5 children and menopausal status were associated with increased risk of CVD, and oral contraceptive/hormone therapy use with decreased risk in univariable analysis. The c-statistic of the model with traditional risk factors was 0·70 (95%CI: (0·67-0·73)) in PROSPECT and 0·72 (95%CI: 0·67-0·77)) in MORGEN. 66·0% and 84·5% were at low (<10%) and 8·2% and 2·5% at high (≥20%) 10-year CVD risk in PROSPECT and MORGEN, respectively. Adding female-specific risk factors neither improved discrimination nor calibration and there was no net reclassification improvement.

Interpretation

Although female-specific risk factors are associated with CVD risk they have no added value on top of traditional risk factors for the prediction of 10-year risk of CVD in women.

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death and disability-adjusted life years worldwide.[1,2] The well-known "traditional" risk factors for CVD include age, hypertension, dyslipidemia, diabetes mellitus, family history of CVD and smoking. In women, gender-specific risk factors related to hormonal and reproductive status are known to affect CVD risk.[3-8]

Nowadays, pregnancy is viewed as a stress test for long-term risk of CVD.[9,10] Women who develop complications during pregnancy, such as pre-eclampsia or gestational diabetes, are hypothesized to have a higher underlying cardiovascular risk, and are at increased risk of hypertension, diabetes, heart disease or stroke in later life.[11] Early menarche and early menopause have also previously been associated with increased risk of CVD.[7,12-15]

Previous studies showed that the absolute risk of CVD is directly related to the number of traditional risk factors present.[16,17] Moreover, management of these risk factors leads to a decrease of the risk of CVD, thus early recognition of high-risk individuals to prevent clinically manifest disease through lifestyle modifications or drug treatment is essential.[18-22] In an attempt to identify people at risk of CVD several prediction models have been developed throughout the years.[23-26] Most prediction models contain a combination of the same risk factors (age, smoking, diabetes, hypertension/ systolic blood pressure, and lipid levels), but the weight assigned to the risk factors differs.[23-26] The Framingham Risk Score (FRS), SCORE, and the Pooled Cohort Equations are examples of such frequently used algorithms that aim to predict 10-year absolute risk of CVD for individuals without CVD.[23,24,26]

Even though these prediction rules are sex-specific, they include the same combination of traditional risk factors for women and men.[24] Despite aforementioned associations between female-specific risk factors and CVD it is unknown whether female-specific risk factors have any added value on top of the traditional risk factors to predict future risk of CVD in women. Nevertheless, the American Heart Association advises to evaluate and treat traditional CVD risk factors in women who use oral contraceptives or with a history of pre-eclampsia in the 2013 guidelines for stroke prevention in women.[27]

Therefore, our aim is to evaluate the added value of female-specific risk factors on top of traditional risk factors for the prediction of 10-year risk of CVD in women included in PROSPECT and MORGEN, two large population-based prospective cohorts from the Netherlands.

METHODS

Study Population

MORGEN and PROSPECT are the two Dutch contributions to the European Prospective Investigation into Cancer and Nutrition (EPIC) and consists of the Monitoring Project on Risk Factors for Chronic Diseases (MORGEN) and the PROSPECT cohort, together known

as EPIC-NL.[28-30] The MORGEN cohort consists of 22,654 men and women aged 20–65 years who were recruited through random population sampling in three Dutch towns (Amsterdam, Maastricht and Doetinchem). The PROSPECT cohort included 17,357 women aged 50–70 years, who participated in a breast cancer-screening program in the province of Utrecht. All participants signed an informed consent form prior to study inclusion. MORGEN and PROSPECT comply with the Declaration of Helsinki and were approved by the institutional board of the University Medical Center Utrecht (PROSPECT) and the Medical Ethical Committee of TNO Nutrition and Food Research (MORGEN). The full details of both cohorts have been described elsewhere.[28-30] Baseline data of the participants were collected between 1993 and 1997. For the present study all women with a known pregnancy status (never/ ever) were eligible (PROSPECT n=17,234, MORGEN n=12,364). We excluded women who did not give permission for linkage or with missing information on vital status or cardiovascular events (PROSPECT n=620, MORGEN n=1,264). Moreover, we excluded women with prevalent CVD (defined as a medical history of coronary heart disease, cerebrovascular disease, pulmonary embolism, peripheral arterial disease, aneurysm of the abdominal aorta and heart failure, PROSPECT n=1,395, MORGEN n=893), and those younger than 30 years (PROSPECT n=0, MORGEN n=2,232). In total 15,922 women from PROSPECT, of whom 14,069 women were ever pregnant, and 8,873 women from MORGEN, of whom 7,216 women were ever pregnant, were included in the analyses (Figure 1).

Traditional risk factors

The variables in the female-specific 2008 FRS predicting 10-year risk of CVD in a primary care population were used as traditional risk factors in our study. The model included age, systolic blood pressure, antihypertensive medication use, cigarette smoking status,

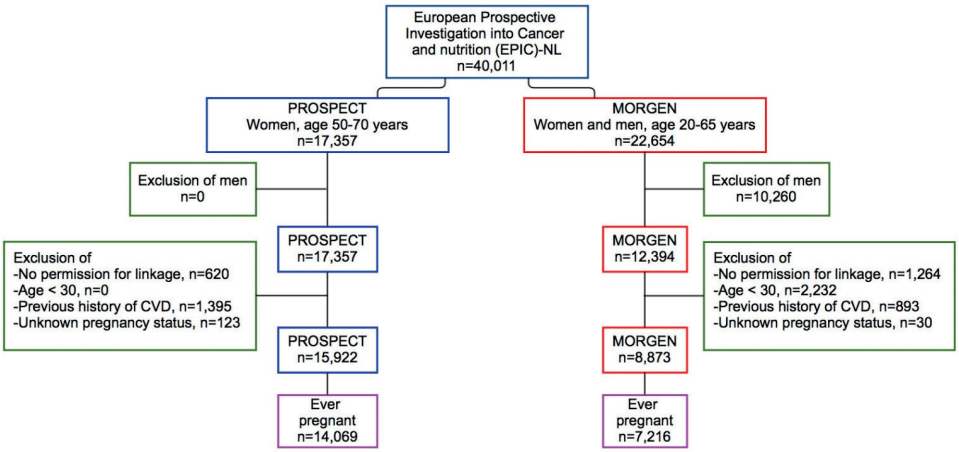


Figure 1. Flowchart of study population

diabetes mellitus, serum high-density-lipoprotein (HDL) cholesterol and total cholesterol.[24] These risk factors were all assessed in MORGEN and PROSPECT at baseline. Systolic and diastolic blood pressure were averaged over two measurements in supine position on the right arm using a Boso Oscillomat (Bosch & Son, Jungingen, Germany)(PROSPECT) or on the left arm using a random zero sphygmomanometer (MORGEN). Non-fasting total cholesterol was measured using an enzymatic method and high-density lipoprotein (HDL)-cholesterol was measured using a homogeneous assay with enzymatic endpoint, both on an autoanalyser (LX20, Beckman Coulter, Mijdrecht, the Netherlands). Information on smoking status, treatment for hypertension, and presence of diabetes mellitus was obtained from the general baseline questionnaire, and information on diabetes was clinically validated.[28,31]

Female-specific risk factors

The presence of female-specific risk factors was assessed by a self-administered questionnaire,[28] containing questions on pregnancies (number of pregnancies, gestational diabetes, gestational hypertension), miscarriages and stillbirths (in PROSPECT only, defined as a pregnancy that spontaneously ended before 7 months gestation or a pregnancy that spontaneously ended after 7 months gestation, respectively), cycle characteristics (age at menarche, age at menopause), use of hormone preparations (oral contraceptives or postmenopausal hormone therapy (age at start using, duration of use)), and on (one- or two sided) ovariectomy or hysterectomy.

For the continuous female-specific predictors we univariably assessed the linearity of the association between the predictors and the outcome using restricted cubic splines. If results indicated non-linearity, an appropriate transformation into categories was made. For categorical predictors we defined categories conform those in previous literature. This resulted in the following seven categorical female-specific risk factors: 1) age at menarche (early (≤ 12 years), average 13-14 years, late (≥ 15 years)); 2) menopausal status (pre-/peri-menopausal, early menopause (< 45 year), average menopause (≥ 45 year); 3) oral contraceptive (OC)/ postmenopausal hormone therapy (HT) use (never, past, current); 4) number of children (< 5, ≥ 5); 5) self-reported gestational hypertension (yes/ no), 6) self-reported gestational diabetes (yes/no), 7) miscarriages/ stillbirths (never, once, multiple).

Fatal and Nonfatal CVD Events

Participants were censored at death, the first nonfatal cardiovascular event, emigration, or at 31-12-2007. The vital status of all EPIC-NL participants was obtained through linkage with the municipal population registries. Subsequently, primary (underlying) and secondary causes of death were obtained through linkage with data from 'Statistics Netherlands'. Data on morbidity were obtained from the National Medical Registry (NMR), which holds a standardized computerized register of hospital discharge diagnoses, coded according to the *International Classification of Diseases, Ninth Revision (ICD9), Clinical Modification*.[32] The National Medical Registry collects and checks these data in the Hospital Discharge Diagnosis Database. This database is linked to the cohort based on information on the date

of birth, sex, postal code, and general practitioner with a validated probabilistic method.[33] In a validation study of coronary heart disease diagnoses conducted in a subsample of this population a positive predictive value of 91% was found for hospital discharge diagnoses compared with a detailed clinical registry.[34] We defined CVD as morbidity or mortality from coronary heart disease (ICD-9 410-414), heart failure (ICD-9 428), cerebrovascular disease (including ischemic and hemorrhagic stroke, transient ischemic attack and intracranial hemorrhage (ICD-9 430-438), pulmonary embolism (ICD-9 415.1), peripheral arterial disease (ICD-9 440–444), or sudden death (427.5, 798.1,798.2,798.9), whichever came first.[32] For instance, when a person experienced a myocardial infarction followed by a stroke, the myocardial infarction was the endpoint for analysis and further events were censored.

Data analyses

We calculated person-years of follow-up for each participant from the date of return of the baseline questionnaire to the date of the first cardiovascular event, loss to follow-up, or January 1, 2008, whichever came first. Participants' characteristics were calculated as mean (standard deviation) for continuous variables and percentages for categorical variables. The percentage of missing values per predictor ranged from 0% to 19·6%. Since exclusion of participants with missing data can result in biased results and loss of precision, [35,36] missing values in the candidate predictors were imputed in R (version 2·15·0) by multiple imputation (m=10) using the MICE library.[37,38]

We analysed the association between possible predictors and CVD risk using Cox Proportional hazards analysis in a stepwise approach. We first calculated the univariable hazard ratios (HR) for all traditional predictors and female-specific risk factors with their 95% confidence intervals. In a second step, a regression model was built for each female-specific risk factor including that specific risk factor and the traditional risk predictors. Third, we fitted a model containing all traditional risk factors, added all female specific risk factors to this model, and applied stepwise backward selection of the female-specific risk factors[39] (forcing the traditional risk predictors to be retained in the model) based on Akaike's Information Criterion.[40]

This final model was then compared to a model containing only all traditional risk predictors in terms of discrimination, calibration, and net reclassification. The discriminative value of these models was expressed with Harrell's c-statistic for censored data.[41] Calibration was evaluated by visualizing the observed/ predicted ratio in a calibration plot. Net reclassification improvement (NRI) was calculated using the percentage of correct movement across categories of risk for those with and without events.[42] Women were classified into a risk category based on their predicted risk. We used cut-off values according to the European 2007 treatment guideline: <10% (low risk), ≥10% to < 20% (intermediate risk), ≥20% (high risk).[43] Correct movement is an upward classification after adding the female-specific risk factors in those with an event and downward classification in those without an event.

The added value of the female-specific risk factors related to childbearing was analysed in the women that were ever pregnant only (MORGEN n=7,216, PROSPECT n=14,069). Since information about miscarriages was not collected in the MORGEN cohort we assessed the added value of the presence of miscarriages or stillbirths in the PROSPECT cohort only.

RESULTS

The baseline characteristics of all participants in PROSPECT and MORGEN are enlisted in Table 1. Mean age of women in PROSPECT was 57·6 years (±6·0) and in MORGEN 46·0 years (±8·7). The prevalence of cardiovascular risk factors was higher in women in PROSPECT than in women in MORGEN. In PROSPECT more women were postmenopausal. Mean follow-up of the participants was 11·6 years in PROSPECT and 12·1 years in MORGEN.

A total of 1,605 CVD events occurred in PROSPECT (10%) and 551 in MORGEN (6%).

The results of the univariable analysis are shown in Table 2. In the univariable analysis all traditional risk predictors were significantly related to CVD risk in both cohorts and the associations were of the expected magnitude and in the expected direction.

Menopausal status and OC/HT use were the female-specific risk factors that were significantly associated with CVD risk in both PROSPECT and MORGEN. In the ever-pregnant women, having ≥ 5 live-born children was also significantly related to CVD risk in both cohorts. Additionally, in PROSPECT, gestational hypertension and multiple miscarriages/ stillbirths were significantly related to CVD risk. When we adjusted each female-specific risk factor for the traditional risk predictors only early menopause remained significantly associated with CVD risk in PROSPECT.

After fitting the traditional risk predictors to our data, sixty-six percent and 84·5% were at low (<10%), 25·7% and 13·0% at intermediate (≥10–<20%), and 8·2% and 2·5% at high (≥20%) 10-year CVD risk in PROSPECT and MORGEN, respectively. The c-statistics of the models containing traditional risk predictors were 0·70 (95%CI 0·67-0·73) for PROSPECT and 0·72 (95%CI 0·67-0·77) for MORGEN, respectively (Table 3). In the ever-pregnant women C-statistics were virtually similar. The calibration plots of the traditional risk models in PROSPECT and MORGEN are shown in Figure 2a and 2b, and the calibration plots of the models in the ever-pregnant women in Figure 2c and 2d.

After adding all female-specific risk factors to the traditional risk model in PROSPECT and applying the stepwise selection only menopausal status was retained in the prediction model. In MORGEN menopausal status and OC/HT use were retained. In the ever-pregnant women in PROSPECT menopausal status, number of children and miscarriages/ stillbirths were retained while in the ever-pregnant women in MORGEN no female-specific risk factors were retained in the model. There were no essential differences in c-statistic between the traditional model and the model additionally containing the retained female-specific risk factors (c-statistics ranging between 0·70 and 0·73, Table 3). The NRI of the 2 models with and without female-specific risk factors are shown in Table 3.

Table 1. Baseline characteristics of women in PROSPECT and MORGEN

	PROSPECT n=15,922	MORGEN n= 8,873
Follow-up (years)	11·6 (2·5)	12·1 (2·4)
Traditional risk predictors		
Age (years)	57·6 (±6·0)	46·0 (±8·7)
Diabetes mellitus (%)	320 (2·0)	70 (0·8)
Antihypertensive Medication (%)	2,522 (15·8)	497 (5·6)
Mean systolic blood pressure (mmHg)	133·1 (20·0)	119·2 (16·8)
Total cholesterol (mmol/l)	6·1 (1·1)	5·4 (1·1)
HDL cholesterol (mmol/l)	1·5 (0·4)	1·5 (0·4)
Smoking (%)	3,579 (22·4)	3,139 (35·3)
Female-specific risk factors- hormonal status		
Age at menarche (%)		
≤ 12 years	4,827 (30·3)	2,978 (33·6)
13-14 years	7,145 (44·9)	4,287 (48·3)
≥ 15 years	3,611 (22·7)	1,575 (17·8)
Menopausal status (%)		
Pre- or perimenopausal	4,532 (28·5)	6,685 (75·3)
Postmenopausal < age 45 years	2,160 (13·6)	404 (4·6)
Postmenopausal ≥45 years	8,469 (53·2)	1,349 (15·2)
HT/ OC use (%)		
Never	4,450 (27·9)	1,210 (13·6)
Past	10,013 (62·9)	4,790 (54·0)
Current	1,015 (6·4)	1,284 (14·5)
Female-specific risk factors- reproductive history		
Number of children (%)		
< 5 live-born children	12,889 (91·6)	7,007 (97·1)
≥ 5 live-born children	1,180 (8·4)	171 (2·4)
Gestational hypertension (%)	4,345 (30·9)	1,318 (18·3)
Gestational diabetes (%)	511 (3·6)	191 (2·6)
Miscarriage/ stillbirth (%)		
Never	10,120 (71·9)	Unknown
Once	2,804 (19·9)	Unknown
Multiple	1,034 (7·3)	Unknown

HT: hormone therapy; OC: oral contraceptive

The categorical NRI varied between -0·01 and -0·00. The calibration plots of the models after adding the female-specific risk factors are shown in Figures 3a and 3b, and the calibration plot of the model in the ever-pregnant women in PROSPECT is shown in Figure 3c. In both cohorts the 10-year risk of CVD was overestimated, which was more pronounced in the women with a higher risk of CVD.

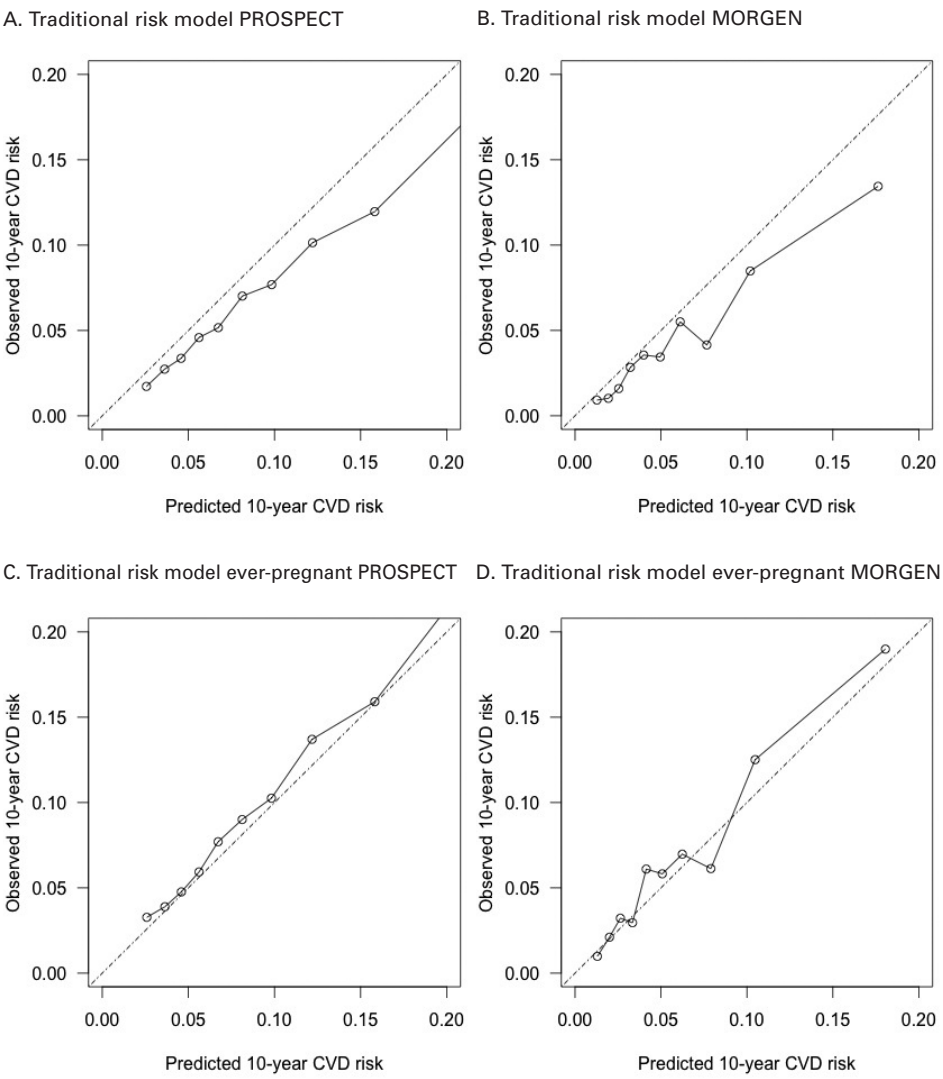
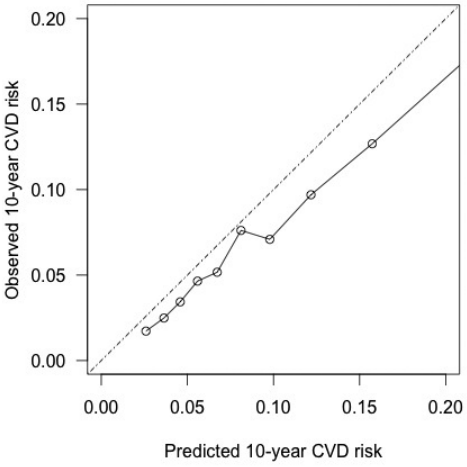
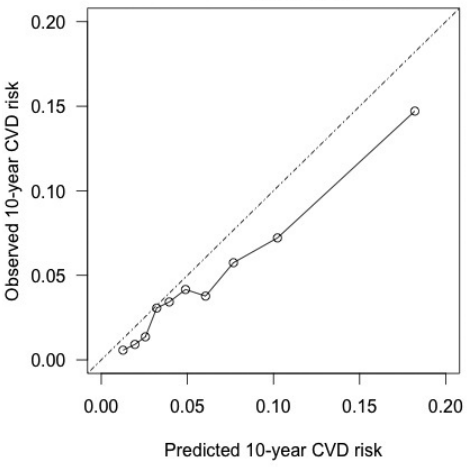


Figure 2 A-D. Calibration plots of the traditional risk factor model in PROSPECT and MORGEN

A. Traditional model + female-specific risk factors PROSPECT



B. Traditional model + female-specific risk factors MORGEN



C. Traditional model + female-specific risk factors ever-pregnant PREGNANT

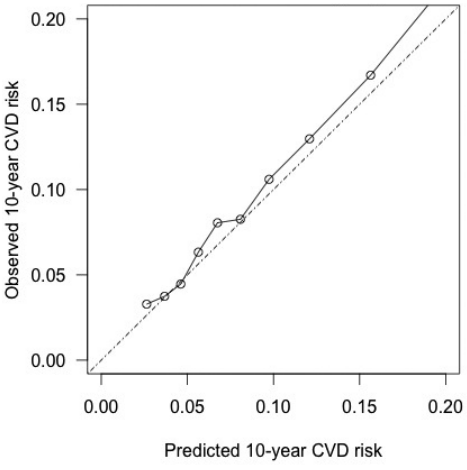


Figure 3 A-C. Calibration plots of the models after adding the female-specific risk factors in PROSPECT and MORGEN

Table 2. Hazard ratio's (HR) for CVD of traditional predictors and female-specific risk factors predictors

	PROSPECT (n=15,922)		MORGEN (n=8,873)	
	Univariable	Adjusted for traditional risk factors	Univariable	Adjusted for traditional risk factors
	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)
Age (year)	1·08 (1·07-1·09)		1·07 (1·06-1·08)	
Diabetes mellitus present	6·98 (5·97-8·15)		4·47 (2·68-7·46)	
Systolic blood pressure (mmHg)	1·02 (1·02-1·02)		1·03 (1·02-1·03)	
Total cholesterol (mmol/l)	1·17 (1·12-1·22)		1·38 (1·27-1·50)	
HDL cholesterol (mmol/l)	0·41 (0·36-0·47)		0·38 (0·29-0·50)	
Smoking, current	1·64 (1·47-1·82)		1·64 (1·37-1·97)	
Age at menarche				
≤ 12 years	1·09 (0·97-1·22)	1·06 (0·94-1·19)	1·25 (1·02-1·54)	1·22 (0·99-1·50)
13-14 years	ref	ref	ref	ref
≥ 15 years	1·27 (1·12-1·43)	1·10 (0·76-1·24)	1·26 (0·99-1·61)	1·14 (0·89-1·45)
Menopausal status				
Pre- or perimenopausal	ref	ref	ref	ref
Postmenopausal < age 45 years	2·48 (2·10-2·95)	1·18 (1·00-1·39)	2·48 (1·89-3·25)	1·13 (0·86-1·48)
Postmenopausal ≥ age 45 years	1·93 (1·69-2·21)	0·91 (0·80-1·05)	2·43 (1·96-2·97)	1·01 (0·82-1·24)
OC/HT use				
Never	ref	ref	ref	ref
Past	0·66 (0·60-0·74)	0·94 (0·85-1·05)	0·75 (0·59-0·95)	1·05 (0·83-1·33)
Current	0·63 (0·50-0·78)	1·05 (0·84-1·31)	0·61 (0·44-0·81)	1·35 (0·98-1·86)
Number of children				
< 5 children	ref	ref	ref	ref
5 or more children	1·22 (1·03-1·45)	0·81 (0·68-0·97)	1·82 (1·17-2·84)	1·15 (0·74-1·80)
Gestational hypertension	1·20 (1·08-1·34)	1·07 (0·96-1·19)	0·83 (0·64-1·06)	1·02 (0·79-1·31)
Gestational diabetes	0·95 (0·71-1·27)	0·99 (0·74-1·32)	0·78 (0·38-1·59)	0·77 (0·38-1·57)
Miscarriages/ stillbirths	ref	ref	Unknown	Unknown
None	1·03 (0·90-1·17)	0·97 (0·85-1·11)		
One	1·34 (1·12-1·61)	1·18 (0·99-1·41)		
Multiple				

HR: hazard ratio; ref: reference category; OC: oral contraceptive; HT: hormone therapy

Table 3. C-statistics and net reclassification improvement of the traditional risk factors and the traditional risk factors + female-specific risk factors in PROSPECT and MORGEN

Cohort	c-statistic traditional risk factors (95%CI)	c-statistic traditional risk factors + female-specific risk factors (95%CI)	Categorical NRI (95%CI)
PROSPECT	0·70 (0·67-0·73)	0·70 (0·68-0·73)	-0·01 (-0·02 ; 0·00)
MORGEN	0·72 (0·67-0·77)	0·73 (0·68-0·78)	-0·01 (-0·04 ; 0·01)
PROSPECT ever pregnant	0·70 (0·67-0·73)	0·70 (0·67-0·73)	-0·00 (-0·02 ; 0·01)
MORGEN ever pregnant	0·71 (0·67-0·76)	n.a.	n.a.

CI: confidence interval; NRI: net reclassification improvement; n.a.: not applicable

DISCUSSION

This study showed that although female-specific risk factors are in univariable analysis associated with CVD risk they have no added value on top of traditional risk factors for the prediction of 10-year risk of CVD in women. Existing risk charts and guidelines for primary prevention of CVD in women do not need to be changed. Previous studies mainly focused on the independent relation between one female-specific risk factor and future CVD risk in terms of relative risk.[4-7,12,14,15] Also in our study, several female-specific risk factors were associated with CVD risk in univariable analysis. However, associations for almost all female-specific risk factors lost statistical significance after adding traditional risk predictors to the regression model. Even so, the presence of an independent association does not necessary imply added prognostic value.[44]

Our study has several strengths. The study was performed in two large population-based cohorts comprising the 24,795 women with a large number of endpoints. Additionally, data on a large number of female-specific risk factors were available in this cohort, including information on pregnancy complications. Furthermore coefficients for the traditional risk factors were fitted to our data instead of using published coefficients. This was preferred over using original published coefficients or recalibration of the existing scores to our populations (i.e. adjustment of baseline hazard or overall predictor-outcome associations), to ensure optimal fit of the traditional risk factors and to avoid the suggestion of added value of the female-specific risk factors due to a poor fit of the traditional risk factors in these specific cohorts.[45]

Several limitations of this study should be addressed. First our definition of CVD differs from the definitions as used in existing scores, eg SCORE was developed for predicting fatal CVD events.[23] However, since we evaluated the added value of female-specific risk factors on top of the traditional risk factors and we used the same definition of CVD in both models, using different endpoints does not invalidate our findings regarding added value. Second, the presence of female-specific risk factors was assessed using self-administered questionnaires. This could have led to misclassification. For example, miscarriages were

not subdivided by the duration of gestation while the underlying causes of the miscarriage differ across the trimesters of pregnancy.[46,47] It could be hypothesized that the miscarriages caused by inadequate vascularization may have added value for the prediction of CVD. We were also not able to differentiate between gestational hypertension and pre-eclampsia. In PROSPECT almost 31% and in MORGEN 18% of women reported gestational hypertension while the incidence of pre-eclampsia in the Western World is around 3-6%.[48] Therefore it is likely that most women who reported gestational hypertension in our cohort had pregnancy induced hypertension and not pre-eclampsia. We expect that the misclassification for other female-specific risk factors will be small, as previous studies have shown that reproducibility and validity of for instance remembered age at menarche and menopause is reasonably good.[49-54] Furthermore, endpoint information was collected prospectively and independent of determinant information, therefore misclassification is most likely not related to the occurrence of CVD. However, we cannot exclude underestimation of true risks as a result of non-differential misclassification.

Third, in the MORGEN cohort, the age range at baseline varied between 20 and 59. Therefore, a substantial proportion will not have had a finished reproductive history at baseline, which is visible in the lower percentages of women with ≥ 5 children, gestational complications and postmenopausal status compared to PROSPECT. For prediction purposes on individual person level, this is however not problematic, as we aim to estimate absolute 10-year risk from the woman's actual age onwards, and it is impossible to take into account what will happen in the future. Moreover, the findings in PROSPECT show that in women with a finished reproductive history female-specific risk factors also do not add to prediction of 10-year CVD risk.

Fourth, information about the presence of polycystic ovary syndrome (PCOS) was not collected. PCOS is a metabolic disorder, characterized by decreased insulin sensitivity which leads to an excess lifetime risk of type 2 diabetes and CVD.[55,56] However, women with PCOS are often obese, hypertensive, dyslipidemic and insulin resistant; all components of an adverse cardiovascular risk profile that are partly included in the traditional risk predictors already.[55,56] Previous studies stated therefore that the value of polycystic ovary syndrome for the prediction of CVD might be limited as the increased prevalence of CVD can be explained by their disadvantageous cardiovascular risk profile.[55,56]

It is possible that female-specific risk factors increased the risk of CVD through increasing the levels of the traditional cardiovascular risk factors. This would explain both the results from the previous studies appraising the relation between the separate female-specific risk factors and CVD, and our findings. As both pre-eclampsia and gestational hypertension increase the risk of hypertension later in life it is conceivable that gestational hypertension does not have added predicted value to a model already containing hypertension.[57-61] The same reasoning holds for gestational diabetes, which is a risk factor for diabetes later in life.[62] For all other female-specific risk factors there are also suggestions in literature that they adversely affect levels of traditional risk factors, potentially leaving little room for independent added predictive value.[63-68]

In both PROSPECT and MORGEN the traditional risk factors overpredicted the risk of CVD. This phenomenon has been reported before, for instance for the pooled cohort equations,[26,69,70] and an explanation is not readily given. Decreasing risk of CVD through initiation of medication or event-preventing procedures during follow-up in high-risk women has been suggested as explanations. Indeed, in the part of MORGEN that is invited for follow-up visits every five years, the percentage of women on medication increased from 20%-32% for blood pressure and 3%-19% for cholesterol lowering medication, respectively, over the course of our follow-up.[71] In the Women's Health Study increased initiation of treatment could not explain the overestimation.[72] Underestimation of the observed risk could also explain this phenomenon. For certain diseases, like heart failure, transient ischemic attack, or peripheral arterial disease, hospitalization is not or not always indicated, and therefore use of a hospital discharge diagnosis registry may yield an underestimation of the true number of events.

In this study we included women between 30-74 years since most risk scores are developed for women in this age range. It is conceivable that in younger women (age < 30 years) the presence of female-specific risk factors is of added value to the traditional risk factors as at that age the traditional risk factor levels will still be low and not cross thresholds for abnormality. However, cardiovascular events tend to occur in women after the age of 60, so current risk models predicting 10-year probability of CVD will not be adequate to answer this question. We would need lifetime models to evaluate to which extent female-specific risk factors will have added value on top of the traditional risk factors in these younger women.

In conclusion, although female-specific risk factors are univariably associated with CVD risk they have no added value on top of the traditional risk factors for the prediction of 10-year risk of CVD in women.

REFERENCES

1. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012;380:2095-128.
2. Murray CJ, Vos T, Lozano R, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012;380:2197-223.
3. de Groot PC, Dekkers OM, Romijn JA, Dieben SW, Helmerhorst FM. PCOS, coronary heart disease, stroke and the influence of obesity: a systematic review and meta-analysis. Hum Reprod Update 2011;17:495-500.
4. Fraser A, Nelson SM, Macdonald-Wallis C, et al. Associations of pregnancy complications with calculated cardiovascular disease risk and cardiovascular risk factors in middle age: the Avon Longitudinal Study of Parents and Children. Circulation 2012;125:1367-80.
5. Oliver-Williams CT, Heydon EE, Smith GC, Wood AM. Miscarriage and future maternal cardiovascular disease: a systematic review and meta-analysis. Heart 2013;99:1636-44.
6. Smith GC, Pell JP, Walsh D. Pregnancy complications and maternal risk of ischaemic heart disease: a retrospective cohort study of 129,290 births. Lancet 2001;357:2002-6.
7. Wellons M, Ouyang P, Schreiner PJ, Herrington DM, Vaidya D. Early menopause predicts future coronary heart disease and stroke: the Multi-Ethnic Study of Atherosclerosis. Menopause 2012;19:1081-7.
8. Wenger NK. Recognizing pregnancy-associated cardiovascular risk factors. Am J Cardiol 2014;113:406-9.
9. Williams D. Pregnancy: a stress test for life. Curr Opin Obstet Gynecol 2003;15:465-71.
10. Bilhartz TD, Bilhartz PA, Bilhartz TN, Bilhartz RD. Making use of a natural stress test: pregnancy and cardiovascular risk. J Womens Health (Larchmt) 2011;20:695-701.
11. Sattar N, Greer IA. Pregnancy complications and maternal cardiovascular risk: opportunities for intervention and screening? BMJ 2002;325:157-60.
12. Atsma F, Bartelink ML, Grobbee DE, van der Schouw YT. Postmenopausal status and early menopause as independent risk factors for cardiovascular disease: a meta-analysis. Menopause 2006;13:265-79.
13. van der Schouw YT, van der Graaf Y, Steyerberg EW, Eijkemans JC, Banga JD. Age at menopause as a risk factor for cardiovascular mortality. Lancet 1996;347:714-8.
14. Lakshman R, Forouhi NG, Sharp SJ, et al. Early age at menarche associated with cardiovascular disease and mortality. J Clin Endocrinol Metab 2009;94:4953-60.
15. Qiu C, Chen H, Wen J, et al. Associations between age at menarche and menopause with cardiovascular disease, diabetes, and osteoporosis in Chinese women. J Clin Endocrinol Metab 2013;98:1612-21.
16. Yusuf HR, Giles WH, Croft JB, Anda RF, Casper ML. Impact of multiple risk factor profiles on determining cardiovascular disease risk. Prev Med 1998;27:1-9.
17. Lowe LP, Greenland P, Ruth KJ, Dyer AR, Stamler R, Stamler J. Impact of major cardiovascular disease risk factors, particularly in combination, on 22-year mortality in women and men. Arch Intern Med 1998;158:2007-14.
18. Steering Committee of the Physicians' Health Study Research Group. Final report on the aspirin component of the ongoing Physicians' Health Study. N Engl J Med 1989;321:129-35.
19. Taylor F, Huffman MD, Macedo AF, et al. Statins for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev 2013;1:CD004816.
20. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. BMJ 2009;338:b1665-84.
21. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-Year Follow-Up of Intensive Glucose Control in Type 2 Diabetes. N Engl J Med 2008;359:1577-89.

22. Ockene JK, Kuller LH, Svendsen KH, Meilahn E. The relationship of smoking cessation to coronary heart disease and lung cancer in the Multiple Risk Factor Intervention Trial (MRFIT). Am J Public Health 1990;80:954-8.
23. Conroy RM, Pyorala K, Fitzgerald AP, et al. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. Eur Heart J 2003;24:987-1003.
24. D'Agostino RB S, Vasan RS, Pencina MJ, et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation 2008;117:743-53.
25. Ridker PM, Buring JE, Rifai N, Cook NR. Development and validation of improved algorithms for the assessment of global cardiovascular risk in women: the Reynolds Risk Score. JAMA 2007;297:611-9.
26. Goff DC,Jr, Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014;129:S49-73.
27. Bushnell C, McCullough LD, Awad IA, et al. Guidelines for the Prevention of Stroke in Women: A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke 2014; 45:1545-88.
28. Beulens JW, Monninkhof EM, Verschuren WM, et al. Cohort profile: the EPIC-NL study. Int J Epidemiol 2010;39:1170-8.
29. Boker LK, van Noord PA, van der Schouw YT, et al. Prospect-EPIC Utrecht: study design and characteristics of the cohort population. European Prospective Investigation into Cancer and Nutrition. Eur J Epidemiol 2001;17:1047-53.
30. Smit H, Verschuren W, Bueno-de-Mesquita H., Seidell J. Monitoring van Risicofactoren en Gezondheid in Nederland (MORGEN-project). Doelstellingen en werkwijze. 263200001, 1994.
31. Sluijs I, van der ADL, Beulens JW, et al. Ascertainment and verification of diabetes in the EPIC-NL study. Neth J Med 2010;68:333-9.
32. World Health Organization. International classification of diseases, 9th revision (ICD-9). Geneva. 1977.
33. Herings RM, Bakker A, Stricker BH, Nap G. Pharmaco-morbidity linkage: a feasibility study comparing morbidity in two pharmacy based exposure cohorts. J Epidemiol Community Health 1992;46:136-40.
34. Merry AH, Boer JM, Schouten LJ, et al. Validity of coronary heart diseases and heart failure based on hospital discharge and mortality data in the Netherlands using the cardiovascular registry Maastricht cohort study. Eur J Epidemiol 2009;24:237-47.
35. Greenland S, Finkle WD. A critical look at methods for handling missing covariates in epidemiologic regression analyses. Am J Epidemiol 1995;142:1255-64.
36. White IR, Carlin JB. Bias and efficiency of multiple imputation compared with complete-case analysis for missing covariate values. Stat Med 2010;29:2920-31.
37. White IR, Royston P. Imputing missing covariate values for the Cox model. Stat Med 2009;28:1982-98.
38. Rubin D. Multiple imputation for non response in surveys. New York: Wiley, 1987.
39. Steyerberg EW. Clinical prediction models. Springer-Verlag New York Inc., 2008.
40. Sauerbrei W, Royston P, Binder H. Selection of important variables and determination of functional form for continuous predictors in multivariable model building. Stat Med 2007;26:5512-28.
41. Harrell FE,Jr, Lee KL, Califf RM, Pryor DB, Rosati RA. Regression modelling strategies for improved prognostic prediction. Stat Med 1984;3:143-52.
42. Pencina MJ, D'Agostino RB S, Steyerberg EW. Extensions of net reclassification improvement calculations to measure usefulness of new biomarkers. Stat Med 2011;30:11-21.
43. Graham I, Atar D, Borch-Johnsen K, et al. European guidelines on cardiovascular disease prevention in clinical practice: full text. Fourth Joint Task Force of the European Society of Cardiology and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of nine societies and by invited experts). Eur J Cardiovasc Prev Rehabil 2007;14 Suppl 2:S1-113.
44. Wang TJ, Gona P, Larson MG, et al. Multiple biomarkers for the prediction of first major cardiovascular events and death. N Engl J Med 2006;355:2631-9.

45. Xanthakis V, Sullivan LM, Vasan RS, et al. Assessing the incremental predictive performance of novel biomarkers over standard predictors. Stat Med 2014;33:2577-84.
46. Brown S. Miscarriage and its associations. Semin Reprod Med 2008;26:391-400.
47. Regan L, Rai R. Epidemiology and the medical causes of miscarriage. Baillieres Best Pract Res Clin Obstet Gynaecol 2000;14:839-54.
48. Hernandez-Diaz S, Toh S, Cnattingius S. Risk of pre-eclampsia in first and subsequent pregnancies: prospective cohort study. BMJ 2009;338:b2255-59.
49. den Tonkelaar I. Validity and reproducibility of self-reported age at menopause in women participating in the DOM-project. Maturitas 1997;27:117-23.
50. Colditz GA, Stampfer MJ, Willett WC, et al. Reproducibility and validity of self-reported menopausal status in a prospective cohort study. Am J Epidemiol 1987;126:319-25.
51. Must A, Phillips SM, Naumova EN, et al. Recall of early menstrual history and menarcheal body size: after 30 years, how well do women remember? Am J Epidemiol 2002;155:672-9.
52. Casey VA, Dwyer JT, Coleman KA, Krall EA, Gardner J, Valadian I. Accuracy of recall by middle-aged participants in a longitudinal study of their body size and indices of maturation earlier in life. Ann Hum Biol 1991;18:155-66.
53. Cairns BJ, Liu B, Clennell S, et al. Lifetime body size and reproductive factors: comparisons of data recorded prospectively with self reports in middle age. BMC Med Res Methodol 2011;11:7,2288-11-7.
54. Stuart JJ, Bairey Merz CN, Berga SL, et al. Maternal recall of hypertensive disorders in pregnancy: a systematic review. J Womens Health (Larchmt) 2013;22:37-47.
55. Bajuk Studen K, Jensterle Sever M, Pfeifer M. Cardiovascular risk and subclinical cardiovascular disease in polycystic ovary syndrome. Front Horm Res 2013;40:64-82.
56. Cussons AJ, Stuckey BG, Watts GF. Cardiovascular disease in the polycystic ovary syndrome: new insights and perspectives. Atherosclerosis 2006;185:227-39.
57. Bellamy L, Casas JP, Hingorani AD, Williams DJ. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. BMJ 2007;335:974-85.
58. Lykke JA, Langhoff-Roos J, Sibai BM, Funai EF, Triche EW, Paidas MJ. Hypertensive pregnancy disorders and subsequent cardiovascular morbidity and type 2 diabetes mellitus in the mother. Hypertension 2009;53:944-51.
59. Drost JT, van der Schouw YT, Maas AH, Verschuren WM. Longitudinal analysis of cardiovascular risk parameters in women with a history of hypertensive pregnancy disorders: the Doetinchem Cohort Study. BJOG 2013;120:1333-9.
60. Wilson BJ, Watson MS, Prescott GJ, et al. Hypertensive diseases of pregnancy and risk of hypertension and stroke in later life: results from cohort study. BMJ 2003;326:845-49.
61. Ray JG, Vermeulen MJ, Schull MJ, Redelmeier DA. Cardiovascular health after maternal placental syndromes (CHAMPS): population-based retrospective cohort study. Lancet 2005;366:1797-803.
62. Kjos SL, Buchanan TA. Gestational diabetes mellitus. N Engl J Med 1999;341:1749-56.
63. Kuh D, Langenberg C, Hardy R, et al. Cardiovascular risk at age 53 years in relation to the menopause transition and use of hormone replacement therapy: a prospective British birth cohort study. BJOG 2005;112:476-85.
64. Charalampopoulos D, McLoughlin A, Elks CE, Ong KK. Age at menarche and risks of all-cause and cardiovascular death: a systematic review and meta-analysis. Am J Epidemiol 2014;180:29-40.
65. The Writing Group for the PEPI Trial. Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women. The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. JAMA 1995;273:199-208.
66. Kaminski P, Szpotanska-Sikorska M, Wielgos M. Cardiovascular risk and the use of oral contraceptives. Neuro Endocrinol Lett 2013;34:587-9.
67. Rich-Edwards JW, Fraser A, Lawlor DA, Catov JM. Pregnancy characteristics and women's future cardiovascular health: an underused opportunity to improve women's health? Epidemiol Rev 2014;36:57-70.
68. Kharazmi E, Dossus L, Rohrmann S, Kaaks R. Pregnancy loss and risk of cardiovascular disease: a prospective population-based cohort study (EPIC-Heidelberg). Heart 2011;97:49-54.

69. Kavousi M, Leening MJ, Nanchen D, et al. Comparison of application of the ACC/AHA guidelines, Adult Treatment Panel III guidelines, and European Society of Cardiology guidelines for cardiovascular disease prevention in a European cohort. JAMA 2014;311:1416-23.
70. Muntner P, Colantonio LD, Cushman M, et al. Validation of the atherosclerotic cardiovascular disease Pooled Cohort risk equations. JAMA 2014;311:1406-15.
71. Hulsegge G, Picavet HS, Blokstra A, et al. Today's adult generations are less healthy than their predecessors: generation shifts in metabolic risk factors: the Doetinchem Cohort Study. Eur J Prev Cardiol 2014;21:1134-44.
72. Cook NR, Ridker PM. Further Insight Into the Cardiovascular Risk Calculator: The Roles of Statins, Revascularizations, and Underascertainment in the Women's Health Study. JAMA Intern Med 2014;174:1964-71.

CHAPTER 10

GENERAL DISCUSSION

DIAGNOSIS

The results of our studies do not support the general belief that women with an acute coronary syndrome (ACS) present with atypical symptoms leading to misdiagnosis. The majority of previous studies compared symptoms in women and men already diagnosed with an ACS and they reported no information about the diagnostic value of symptoms in women and men presenting with chest pain and being suspected of ACS.[1-6] Differences in the predictive value of symptoms between women and men in the diagnosis of ACS can only be answered by investigating the diagnostic value of symptoms in patients suspected of ACS and reporting ROC (receiver operating characteristics' analyses). Therefore we evaluated this diagnostic value in patients presenting with chest pain at the emergency department using data from the HEART score study (*chapter two*).[7,8] We found a good and comparable diagnostic value of symptoms for the prediction of an ACS in women as well as in men. Nevertheless, it could be that a selected group of patients were admitted to the emergency department and that as a consequence patients with an atypical presentation were not included in this study, as they might not be referred to the emergency department by their general practitioner or emergency medical services (EMS). So in an attempt to include patients with symptoms in an earlier phase at first medical contact and with a less typical or urgent presentation we started studies at these two institutions.

For our study in the general practice we were given the opportunity to use backup tapes of the original telephone calls at primary care out-of-hours service "de Gelderse Vallei" in Ede, the Netherlands (*chapter four*). This unique study method had the advantage that we could listen to the primary symptom presentation of the patients. As this presentation has the tendency to change after multiple interrogations into typical textbook angina pectoris, this is a perfect way to analyse the symptoms in its purest form. The symptoms were comparable between women and men. On top of that we were able to evaluate if the triage was different in women and men, which was not the case. Unfortunately we were not able to include patients with a truly atypical presentation as we had to define a selection criterion to select our study population (or telephone calls) from all patients that contacted the out-of-hours service. We chose all patients where at least one question in the triage-module chest pain was filled in.

Our study in collaboration with EMS the "Regional Ambulance Service Utrecht" (RAVU) did unfortunately not succeed. We designed a study in which we included all patients that were visited by the ambulance and who presented with symptoms that could possibly be explained by an ACS but without an evident underlying other cause (for example chest pain, dyspnoea, epigastric pain, syncope etcetera). The ambulance personnel were asked to fill in a questionnaire about the symptoms of the patient and asked the patient permission to obtain the discharge letter including the diagnosis when they were sent to a hospital. If they were not sent to a hospital permission was asked to contact their general practitioner in order to get the final diagnosis related to the symptoms. Unfortunately, we had to discontinue the study with less than 250 patients included because the EMS enclosed an

extreme selection of patients as in these seven months more than 6 times as many patients could in theory have been included. Consequently our results would not be generalizable. As a result of the discontinuation no conclusions could be drawn while the EMS play a crucial role in the recognition of patients with an ASC. Timely and appropriate identification would lead to less delay and early adequate treatment. One previous study did examine the relationship between patient symptom characteristics and the development of an ACS in patients transported with EMS because of symptoms that might indicate an ACS including chest pain, syncope, a feeling of arrhythmia, dyspnoea, excessive fatigue, muscle pain, epigastric pain and "general malaise".[9] In this study only a small number of symptoms were collected so no conclusions about the diagnostic value of clinical symptoms in women and men could be drawn.[9]

After our attempts to evaluate the signs of symptom of the patients we also analysed if the physician interprets symptoms of women and men equally serious as previous studies showed that management of chest pain by physicians is influenced by gender of the patient and that the risk of CAD is underestimated in women.[10-13] Therefore we investigated this using data from the HEART score study (*chapter three*). We found that in patients presenting with chest pain but without an ACS as underlying cause the symptoms of men were more often interpreted as "highly suspicious" for an ACS compared to women. This was independent of symptoms and cardiovascular risk factors and therefore could lead to unnecessary investigations, treatment and hospital admissions in men.

A previous study found comparing results in a simulated setting asking physicians to interpret taped interviews of actors portraying chest pain like symptoms.[14] Women were less often referred for coronary angiography than men and adjustment for estimate of probability of disease, level of coronary risk, and presenting symptoms didn't influence this difference between sexes.[14] On top of that, Green en al showed that in men overutilization of coronary angiography and hospital admissions was present instead of underutilization in women in patients evaluated for potential acute cardiac ischemia in the emergency departments.[15]

PROGNOSIS

Because previous studies showed contradictory results concerning differences in prognosis between women and men with cardiovascular disease (CVD) we analyzed the prognosis of women and men with an ST-elevation myocardial infarction (STEMI), after coronary artery bypass grafting (CABG) and with different types of CVD (*chapter 5-7*). We found that after correction for age and cardiovascular risk factors or comorbidities there were no differences in (long-term) prognosis between sexes. However, as women with CVD are older and indeed have more risk factors and comorbidities their prognosis is thus worse.[16,17] It is therefore very important to evaluate the presence of risk factors in women timely and treat them as early and optimal as possible. This applies not only to postmenopausal women as it has been proven that women with so-called female-specific risk factors, related to

their hormonal and reproductive history, are at increased risk of CVD.[18-24] We believe that female-specific risk factors increased the risk of CVD through increasing the levels of the traditional cardiovascular risk factors. For example, gestational hypertension or diabetes increase the risk of hypertension and diabetes later in life.[24-29] Timely monitoring and treatment is therefore of importance. The CREW consortium (funded by the Dutch Heart Foundation) is currently investigating what the best monitoring and treatment would be. The results of previous studies concerning the prognosis of patients with CVD could be influenced by the inclusion period as older studies seemed to find more often differences in outcome between women and men.[30-34] One of the explanations might be that CVD was indeed considered a "male-disease" during that time leading to suboptimal treatment and prognosis in women.[11,30,32] Another explanation could be that the in some fields of CVD the treatment has changed dramatically, for example the primary percutaneous coronary intervention instead of thrombolysis, which led to more bleeding in women than men.[32,35-37] In more recent studies these differences disappeared, probably at least partly as a result of the increasing attention for CVD in women during the last decades. During the evaluation of previous studies regarding the prognosis of patients with CVD we concluded that often the studies were hampered by methodological shortcomings.[38-43] For example, unfortunately often no crude or age-adjusted results were presented but only a model adjusted for several factors at once. While these crude and age-adjusted results would make it possible to compare different studies in a meta-analysis to find more stable results.

In conclusion: we found that symptoms related to an ACS did not differ between men and women presenting at the emergency department as well as in the general practice. Furthermore, in men presenting at the emergency department with chest pain but without an ACS as underlying cause symptoms were more frequently interpreted as "highly suspicious" for an ACS compared to women.

With respect to prognosis in STEMI and post-CABG patients we found that after correction for age and risk factors there was no difference between men and women; however attention should be on the worse risk profile in women including lifestyle changes and adequate treatment of risk factors.

Lastly we found no added value of female-specific risk factors on top of the traditional risk factors for the prediction of CVD in women.

FUTURE PERSPECTIVES

In our opinion each study should evaluate if their results hold for important subgroups of the study population, such as women and/ or older people. This current focus should definitely be continued in the future and implemented in the medical education. We doubt if it will ever be possible to give a definite conclusion about differences in symptoms between women and men with an ACS. It is simply not possible to design a study including patients with all possible (atypical) symptoms in all possible settings (general

practice, emergency department). On top of that, the low prevalence of an acute coronary syndrome particularly in women would ask for enormous numbers of patients. In our view there is enough evidence to state that women and men with CVD have a comparable prognosis when we adjust for age and comorbidities. In other words, women with CVD have a worse prognosis but this can be explained by their older age and comorbidities and not by their sex. Thus optimal and timely screening and treatment of risk factors is most important to improve the prognosis of women. Our results only account for obstructive coronary artery disease and do not include non-obstructive coronary artery disease or microvascular disease.

REFERENCES

1 Khan NA, Daskalopoulou SS, Karp I, Eisenberg MJ, Pelletier R, Tsadok MA, *et al.* Sex Differences in Acute Coronary Syndrome Symptom Presentation in Young Patients. JAMA Intern Med 2013.

2 Dey S, Flather MD, Devlin G, Brieger D, Gurfinkel EP, Steg PG, *et al.* Sex-related differences in the presentation, treatment and outcomes among patients with acute coronary syndromes: the Global Registry of Acute Coronary Events. *Heart* 2009; 95: 20-26.

3 Milner KA, Vaccarino V, Arnold AL, Funk M, Goldberg RJ. Gender and age differences in chief complaints of acute myocardial infarction (Worcester Heart Attack Study). *Am J Cardiol* 2004; 93: 606-608.

4 Culic V, Eterovic D, Miric D, Silic N. Symptom presentation of acute myocardial infarction: influence of sex, age, and risk factors. *Am Heart J* 2002; 144: 1012-1017.

5 Patel H, Rosengren A, Ekman I. Symptoms in acute coronary syndromes: does sex make a difference? *Am Heart J* 2004; 148: 27-33.

6 Canto JG, Goldberg RJ, Hand MM, Bonow RO, Sopko G, Pepine CJ, *et al.* Symptom presentation of women with acute coronary syndromes: myth vs reality. *Arch Intern Med* 2007; 167: 2405-2413.

7 Six AJ, Cullen L, Backus BE, Greenslade J, Parsonage W, Aldous S, *et al.* The HEART score for the assessment of patients with chest pain in the emergency department: a multinational validation study. *Crit Pathw Cardiol* 2013; 12: 121-126.

8 Backus BE, Six AJ, Kelder JC, Bosschaert MA, Mast EG, Mosterd A, *et al.* A prospective validation of the HEART score for chest pain patients at the emergency department. *Int J Cardiol* 2013.

9 Svensson L, Nordlander R, Axelsson C, Herlitz J. Are predictors for myocardial infarction the same for women and men when evaluated prior to hospital admission? *Int J Cardiol* 2006; 109: 241-247.

10 Mosca L, Linfante AH, Benjamin EJ, Berra K, Hayes SN, Walsh BW, *et al.* National study of physician awareness and adherence to cardiovascular disease prevention guidelines. *Circulation* 2005; 111: 499-510.

11 Poon S, Goodman SG, Yan RT, Bugiardini R, Bierman AS, Eagle KA, *et al.* Bridging the gender gap: Insights from a contemporary analysis of sex-related differences in the treatment and outcomes of patients with acute coronary syndromes. *Am Heart J* 2012; 163: 66-73.

12 Chang AM, Mumma B, Sease KL, Robey JL, Shofer FS, Hollander JE. Gender bias in cardiovascular testing persists after adjustment for presenting characteristics and cardiac risk. *Acad Emerg Med* 2007; 14: 599-605.

13 Roger VL, Farkouh ME, Weston SA, Reeder GS, Jacobsen SJ, Zinsmeister AR, *et al.* Sex differences in evaluation and outcome of unstable angina. *JAMA* 2000; 283: 646-652.

14 Schulman KA, Berlin JA, Harless W, Kerner JF, Sistrunk S, Gersh BJ, *et al.* The effect of race and sex on physicians' recommendations for cardiac catheterization. *N Engl J Med* 1999; 340: 618-626.

15 Green LA, Ruffin MT,4th. A closer examination of sex bias in the treatment of ischemic cardiac disease. *J Fam Pract* 1994; 39: 331-336.

16 Yusuf HR, Giles WH, Croft JB, Anda RF, Casper ML. Impact of multiple risk factor profiles on determining cardiovascular disease risk. *Prev Med* 1998; 27: 1-9.

17 Lowe LP, Greenland P, Ruth KJ, Dyer AR, Stamler R, Stamler J. Impact of major cardiovascular disease risk factors, particularly in combination, on 22-year mortality in women and men. *Arch Intern Med* 1998; 158: 2007-2014.

18 Wellons M, Ouyang P, Schreiner PJ, Herrington DM, Vaidya D. Early menopause predicts future coronary heart disease and stroke: the Multi-Ethnic Study of Atherosclerosis. *Menopause* 2012; 19: 1081-1087.

19 Sattar N, Greer IA. Pregnancy complications and maternal cardiovascular risk: opportunities for intervention and screening? *BMJ* 2002; 325: 157-160.

20 Atsma F, Bartelink ML, Grobbee DE, van der Schouw YT. Postmenopausal status and early menopause as independent risk factors for cardiovascular disease: a meta-analysis. *Menopause* 2006; 13: 265-279.

21 van der Schouw YT, van der Graaf Y, Steyerberg EW, Eijkemans JC, Banga JD. Age at menopause as a risk factor for cardiovascular mortality. *Lancet* 1996; 347: 714-718.

22 Lakshman R, Forouhi NG, Sharp SJ, Luben R, Bingham SA, Khaw KT*, et al.* Early age at menarche associated with cardiovascular disease and mortality. J Clin Endocrinol Metab 2009; 94: 4953-4960.

23 Qiu C, Chen H, Wen J, Zhu P, Lin F, Huang B*, et al.* Associations between age at menarche and menopause with cardiovascular disease, diabetes, and osteoporosis in Chinese women. J Clin Endocrinol Metab 2013; 98: 1612-1621.

24 Appelman Y, van Rijn BB, Ten Haaf ME, Boersma E, Peters SA. Sex differences in cardiovascular risk factors and disease prevention. *Atherosclerosis* 2015.

25 Bellamy L, Casas JP, Hingorani AD, Williams D. Type 2 diabetes mellitus after gestational diabetes: a systematic review and meta-analysis. *Lancet* 2009; 373: 1773-1779.

26 Bellamy L, Casas JP, Hingorani AD, Williams DJ. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. *BMJ* 2007; 335: 974.

27 Lykke JA, Langhoff-Roos J, Sibai BM, Funai EF, Triche EW, Paidas MJ. Hypertensive pregnancy disorders and subsequent cardiovascular morbidity and type 2 diabetes mellitus in the mother. *Hypertension* 2009; 53: 944-951.

28 Wilson BJ, Watson MS, Prescott GJ, Sunderland S, Campbell DM, Hannaford P*, et al.* Hypertensive diseases of pregnancy and risk of hypertension and stroke in later life: results from cohort study. BMJ 2003; 326: 845.

29 Barbour LA. New concepts in insulin resistance of pregnancy and gestational diabetes: long-term implications for mother and offspring. *J Obstet Gynaecol* 2003; 23: 545-549.

30 Greenland P, Reicher-Reiss H, Goldbourt U, Behar S. In-hospital and 1-year mortality in 1,524 women after myocardial infarction. Comparison with 4,315 men. *Circulation* 1991; 83: 484-491.

31 Benderly M, Behar S, Reicher-Reiss H, Boyko V, Goldbourt U. Long-term prognosis of women after myocardial infarction. SPRINT Study Group. Secondary Prevention Reinfarction Israeli Nifedipine Trial. *Am J Epidemiol* 1997; 146: 153-160.

32 Bucholz EM, Butala NM, Rathore SS, Dreyer RP, Lansky AJ, Krumholz HM. Sex differences in long-term mortality after myocardial infarction: a systematic review. *Circulation* 2014; 130: 757-767.

33 Jakobsen L, Niemann T, Thorsgaard N, Nielsen TT, Thuesen L, Lassen JF*, et al.* Sex- and age-related differences in clinical outcome after primary percutaneous coronary intervention. EuroIntervention 2012; 8: 904-911.

34 Alfredsson J, Lindback J, Wallentin L, Swahn E. Similar outcome with an invasive strategy in men and women with non-ST-elevation acute coronary syndromes: From the Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies (SWEDEHEART). *Eur Heart J* 2011; 32: 3128-36.

35 De Luca G, Cassetti E, Marino P. Percutaneous coronary intervention-related time delay, patient's risk profile, and survival benefits of primary angioplasty vs lytic therapy in ST-segment elevation myocardial infarction. *Am J Emerg Med* 2009; 27: 712-719.

36 Nauta ST, Deckers JW, van Domburg RT, Akkerhuis KM. Sex-related trends in mortality in hospitalized men and women after myocardial infarction between 1985 and 2008: equal benefit for women and men. *Circulation* 2012; 126: 2184-2189.

37 Gottlieb S, Goldbourt U, Boyko V, Harpaz D, Mandelzweig L, Khoury Z*, et al.* Mortality trends in men and women with acute myocardial infarction in coronary care units in Israel. A comparison between 1981-1983 and 1992-1994. For the SPRINT and the Israeli Thrombolytic Survey Groups. Eur Heart J 2000; 21: 284-295.

38 Benamer H, Tafflet M, Bataille S, Escolano S, Livarek B, Fourchard V*, et al.* Female gender is an independent predictor of in-hospital mortality after STEMI in the era of primary PCI: Insights from the greater Paris area PCI Registry. EuroIntervention 2011; 6: 1073-1079.

39 Bufe A, Wolfertz J, Dinh W, Bansemir L, Koehler T, Haltern G*, et al.* Gender-based differences in long-term outcome after ST-elevation myocardial infarction in patients treated with percutaneous coronary intervention. J Womens Health (Larchmt) 2010; 19: 471-475.
40 De Luca G, Suryapranata H, Dambrink JH, Ottervanger JP, van't Hof AW, Zijlstra F*, et al.* Sex-related differences in outcome after ST-segment elevation myocardial infarction treated by primary angioplasty: data from the Zwolle Myocardial Infarction study. Am Heart J 2004; 148: 852-856.
41 De Luca G, Gibson CM, Gyongyosi M, Zeymer U, Dudek D, Arntz H-*, et al.* Gender-related differences in outcome after ST-segment elevation myocardial infarction treated by primary angioplasty and glycoprotein IIb-IIIa inhibitors: Insights from the EGYPT cooperation. J Thromb Trombolysis 2010; 30: 342-346.
42 Ferrante G, Corrada E, Belli G, Zavalloni D, Scatturin M, Mennuni M*, et al.* Impact of female sex on long-term outcomes in patients with ST-elevation myocardial infarction treated by primary percutaneous coronary intervention. *Can J Cardiol* 2011; 27: 749-755.
43 Jackson EA, Moscucci M, Smith DE, Share D, Dixon S, Greenbaum A*, et al.* The association of sex with outcomes among patients undergoing primary percutaneous coronary intervention for ST elevation myocardial infarction in the contemporary era: Insights from the Blue Cross Blue Shield of Michigan Cardiovascular Consortium (BMC2). *Am Heart J* 2011; 161: 106-112.e1.

APPENDIX

SUMMARY

In the Netherlands cardiovascular disease (CVD) results in approximately 395.000 hospital admissions each year of which 224.000 (57%) in men and 171.000 (43%) in women.(1) Atherosclerosis is the underlying cause of CVD and builds up with increasing age, making CVD a disease of the elderly. For a long time, CVD has been considered a men's disease. However, in the last decade there is increasing attention for CVD in women. Previous studies showed contradictory results about gender differences in the diagnosis and prognosis of CVD and in particular of coronary artery disease (CAD). Therefore the first aim of this thesis was to evaluate the diagnostic value of clinical symptoms for the diagnosis of CAD in women and men presenting with chest pain in the general practice and the emergency department. The second aim of this thesis was to investigate the influence of gender on treatment success and (long-term) prognosis. The third aim of this thesis was to investigate the added value of female-specific risk factors on top of the traditional risk factors for the prediction of CVD in healthy women.

PART ONE Diagnosis

In *chapter 2* we showed that in patients presenting with chest pain at the emergency department clinical symptoms are important for the prediction of an acute coronary syndrome (ACS). The diagnostic value was comparable between sexes with an area under the curve (AUC) 0f 0.74 (95%CI: 0.69-0.79) in women and 0.71 (95%CI: 0.68-0.75) in men. After adding the traditional cardiovascular risk factors the AUC increased to 0.79 (95%CI: 0.74-0.83) in women and 0.75 (95%CI: 0.72-0.78) in men. In *chapter 3* we demonstrated in the same patient population that physicians allow themselves to be influenced by the gender of the patient in their interpretation of the symptoms. In patients presenting with chest pain but without an ACS men were more often interpreted as "highly suspicious" for ACS compared to women. This was independent of symptoms and cardiovascular risk factors and therefore could lead to unnecessary investigations, treatment and hospital admissions in men. In *chapter 4* we depicted triage of women and men presenting with chest pain to out-of-hours primary care service "De Gelderse Vallei" in Ede, the Netherlands. We used a unique study method: we replayed all original phone calls. There were no differences between sexes with regard to the interpretation of the severity of the complaints, in other words no differences in the questions asked by the triage nurse, the duration of the phone call and the chosen urgencies. Results were comparable in the subgroup of patients who later proved that an ACS caused their complaints.

PART TWO Prognosis

Chapter 5 is a systematic review of all available evidence about differences in short- and long-term outcome between women and men treated with a primary percutaneous coronary intervention (PCI) because of an ST elevation myocardial infarction. Due to the large methodological differences we could only pool baseline data. Mortality was higher in women than men but this could be explained by the disadvantageous risk profile and the longer symptom-to-balloon time. In *chapter 6* we described long-term outcome of women and men after coronary artery bypass grafting surgery. Women had a worse prognosis but after adjustment for possible confounders this difference disappeared. *Chapter 7* depicts differences in long-term prognosis between women and men with a form of CVD (coronary artery disease, cerebrovascular disease, abdominal aortic aneurysm, peripheral arterial disease). This study used data from The Second Manifestations of ARTerial disease (SMART) study and in this study all patients receive a standardized cardiovascular screening with personalized therapy advice. Women had a better long-term prognosis than men, the hazard ratios for mortality, cardiovascular mortality and a combined cardiovascular endpoint were: 0.62 (95%CI: 0.51-0.75), 0.59 (95%CI: 0.46-0.75) and 0.73 (95%CI: 0.60-0.87). Neither differences in risk factor profile nor the different vascular beds involved could explain this advantage. In *chapter 8* we described the impact of the number of diseased vascular territories on long-term prognosis in PCI patients, included in the SMART study. The presence of subclinical and clinical polyvascular disease was associated with an increased long-term mortality and morbidity. Moreover, the outcome is highly influenced by the number of diseased territories. Finally, in *chapter 9*, we analyzed the added value of so-called female-specific risk factors, related to the reproductive history, on top of the traditional cardiovascular risk factors for the prediction of CVD. We used data from EPIC-NL, consisting of two cohorts: PROSPECT and MORGEN. In total we could use data from 24.795 healthy women aged between 30 and 74 years old. We evaluated seven female-specific risk factors: age at menarche, age at menopause, hormone use, number of children, gestational hypertension, gestational diabetes and number of miscarriages/ stillbirths. The endpoint was 10-year risk of CVD. Adding the female-specific risk factors did not improve discrimination (differentiation of future sick and non-sick) or calibration (accurate prediction of the risk by the model). This led to the conclusion that female-specific risk factors have no added value on top of traditional risk factors for the prediction of 10-year risk of CVD in women.

REFERENCES

1. Koopman C, van Dis I, Bots M, Visseren F, Vaartjes I. Hart- en vaatziekten in Nederland. In: Hart-En Vaatziekten in Nederland 2011, Cijfers Over Leefstijl- En Risicofactoren, Ziekte En Sterfte. Den Haag, Hartstichting, 2013.

NEDERLANDSE SAMENVATTING

Hart- en vaatziekten (HVZ) leiden in Nederland tot 395.000 ziekenhuisopnamen per jaar.(1) Hiervan betreft het in 224.000 (57%) opnamen van mannen en in 171.000 (43%) opnamen van vrouwen.[1] Atherosclerose (slagaderverkalking) is het onderliggende proces wat leidt tot HVZ en aangezien dit toeneemt bij het stijgen van de leeftijd komen HVZ met name bij de oudere populatie voor.
Voorheen werden HVZ met name gezien als mannenziekte, maar in de laatste jaren is er meer aandacht voor HVZ bij vrouwen. Eerdere studies lieten tegenstrijdige resultaten zien over verschillen tussen mannen en vrouwen ten aanzien van de diagnose en prognose van HVZ en met name coronairlijden. Daarom was het eerste doel van dit proefschrift om de diagnostische waarde van de anamnese voor de diagnose van coronairlijden te analyseren in mannen en vrouwen die met pijn op de borst bij de huisarts of de spoedeisende hulp komen. Het tweede doel was om eventuele verschillen in behandeleffecten en prognose van mannen en vrouwen met HVZ vast te stellen. Het derde doel was om te evalueren of kennis van de zogenoemde vrouwspecifieke risicofactoren naast de traditionele risicofactoren helpt bij het voorspellen van HVZ op de langere termijn.

DEEL 1 Diagnose

In *hoofdstuk 2* laten we zien dat bij patiënten die met pijn op de borst op de spoedeisende hulp komen, met alleen de anamnese al heel goed de aanwezigheid van acuut coronair syndroom (ACS) kan worden voorspeld. De diagnostische waarde van anamnestische symptomen was vergelijkbaar in mannen en vrouwen met een area under the curve (AUC) van 0.74 (95%CI: 0.69-0.79) in vrouwen en 0.71 (95%CI: 0.68-0.75) in mannen. Indien ook de traditionele cardiovasculaire risicofactoren werden betrokken, steeg de AUC in vrouwen naar 0.79 (95%CI: 0.74-0.83) en 0.75 (95%CI: 0.72-0.78) in mannen.
In *hoofdstuk 3* hebben we in dezelfde patiëntenpopulatie aangetoond dat artsen zich laten beïnvloeden door het geslacht van de patiënt als ze de anamnese interpreteren. Het bleek dat ze de anamnese van mannen met pijn op de borst maar zonder onderliggend ACS vaker interpreteerden als "typisch" voor coronairlijden dan de anamnese van vrouwen. Dit verschil bleef aanwezig als we corrigeerden voor de aanwezige symptomen en traditionele cardiovasculaire risicofactoren en zou kunnen leiden tot onnodige aanvullende onderzoeken en ziekenhuisopnamen in mannen. In *hoofdstuk 4* beschrijven we de triage van mannen en vrouwen die buiten kantoortijden naar de Huisartsenpost "De Gelderse Vallei" te Ede bellen in verband met pijn op de borst. We hebben in deze studie een unieke studiemethode gebruikt: de originele telefoontjes werden opnieuw beluisterd door studenten. Er waren geen verschillen tussen mannen en vrouwen wat betreft het beoordelen van de ernst van de klachten, oftewel geen verschillen in de vragen die werden gesteld door de triagist, in de duur van het telefoongesprek en in de

gekozen urgentie. Ook in de subgroep van patiënten waarvan later bleek dat hun klachten inderdaad werden veroorzaakt door een ACS werden geen verschillen tussen mannen en vrouwen gevonden.

DEEL 2 Prognose

Hoofdstuk 5 bestaat uit een systematische review van het beschikbare bewijs over verschillen in korte- en lange termijn uitkomst tussen mannen en vrouwen behandeld met een primaire percutane coronaire interventie (PCI) in verband met een myocardinfarct met ST-elevatie. Door de grote methodologische verschillen in de studies konden we alleen de informatie over de prevalentie van risicofactoren poolen. Het bleek dat vrouwen vergeleken met mannen een hogere sterfte hadden maar dat dit verklaard kon worden door het ongunstige risicoprofiel en langere ischemietijd. In *hoofdstuk 6* wordt de langere termijn uitkomst van mannen en vrouwen na een coronaire bypass operatie beschreven. Vrouwen hadden, gecorrigeerd voor leeftijd, een slechtere prognose dan mannen maar na het corrigeren voor zeven andere potentiële confounders (onder andere een PCI, CABG of perifeer vaatlijden in de voorgeschiedenis en lichaamsoppervlak) verdween dit verschil. *Hoofdstuk 7* beschrijft verschillen in de langere termijn prognose tussen mannen en vrouwen met allerlei vormen van cardiovasculair lijden (coronairlijden, cerebrovasculair lijden, aneurysma van de abdominale aorta, perifeer vaatlijden). Deze studie is uitgevoerd met data van de The Second Manifestations of ARTerial disease (SMART) studie en in deze studie krijgen alle patiënten een standaard cardiovasculaire work-up met persoonlijk therapieadvies. Vrouwen hadden een betere langere termijn prognose dan mannen. De hazard ratios voor mortaliteit, cardiovasculaire mortaliteit en een gecombineerde cardiovasculaire uitkomst waren: 0.62 (95%CI: 0.51-0.75), 0.59 (95%CI: 0.46-0.75) en 0.73 (95%CI: 0.60-0.87). Deze verschillen konden niet worden verklaard door het risicoprofiel of het aangedane vaatbed. In *hoofdstuk 8* beschrijven we de impact van de aanwezigheid van meerdere aangedane vaatbedden op de lange termijn uitkomst van PCI patiënten, die werden geïncludeerd in de SMART studie. Het blijkt dat de aanwezigheid van zowel subklinisch als klinisch manifest polyvasculair lijden leidt tot een slechtere lange termijn prognose. Deze prognose is direct gerelateerd aan het aantal aangedane vaatbedden. Tot slot hebben we in *hoofdstuk 9* geanalyseerd of er toegevoegde waarde is van de zogenoemde vrouwspecifieke risicofactoren bovenop de traditionele cardiovasculair risicofactoren voor het voorspellen van HVZ. We hebben voor deze studie data van EPIC-NL gebruikt, bestaande uit 2 cohorten: PROSPECT en MORGEN. In totaal konden we data van 24.795 gezonde vrouwen met een leeftijd tussen de 30 en 74 jaar gebruiken. We hebben naar de volgende vrouwspecifieke risicofactoren gekeken: menarche-leeftijd, menopauze-leeftijd, hormoongebruik, aantal kinderen, zwangerschapshypertensie, zwangerschapsdiabetes, aantal miskramen/ doodgeborenen. Het eindpunt was het 10-jaar risico op HVZ. Het toevoegen van de vrouwspecifieke risicofactoren leidde niet tot betere discriminatie (onderscheiden van toekomstige zieken en niet-zieken) of calibratie (de mate

waarin het model de kans accuraat voorspelt). Hieruit hebben we geconcludeerd dat vrouwspecifieke risicofactoren geen toegevoegde waarde hebben bovenop de traditionele risicofactoren voor het voorspellen van HVZ in vrouwen.

REFERENTIES

1 Koopman C, van Dis I, Bots M, Visseren F, Vaartjes I. Hart- en vaatziekten in Nederland. In: Hart- En Vaatziekten in Nederland 2011, Cijfers Over Leefstijl- En Risicofactoren, Ziekte En Sterfte. Den Haag, Hartstichting, 2013.

LIST OF AFFILIATIONS

Yolande Appelman	Department of Cardiology, VU University Medical Center, Amsterdam, the Netherlands
Folkert W. Asselbergs	Department of Cardiology, Division of Heart and Lungs, University Medical Center Utrecht, Utrecht, the Netherlands; Institute of Cardiovascular Science, Faculty of Population Health Sciences, University College London, London, United Kingdom; Durrer Center for Cardiogenetic Research, Interuniversity Cardiology Institute Netherlands-Netherlands Heart Institute, Utrecht, the Netherlands
Barbra E. Backus	Department of Cardiology, Division of Heart and Lungs, University Medical Center Utrecht, Utrecht, the Netherlands
Jolanda M.A. Boer	National Institute for Public Health and the Environment, Bilthoven, the Netherlands
Anne Botermans	Medical student at the University Medical Center Utrecht, the Netherlands
Maarten J. Cramer	Department of Cardiology, Division of Heart and Lungs, University Medical Center Utrecht, Utrecht, the Netherlands
Pieter A. Doevendans	Department of Cardiology, Division of Heart and Lungs, University Medical Center Utrecht, Utrecht, the Netherlands
Wiek H. van Gilst	Experimental Cardiology Laboratory, University Medical Center Groningen, Groningen, the Netherlands
Yolanda van der Graaf	Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, the Netherlands
Saskia Haitjema	Experimental Cardiology Laboratory, Division of Heart and Lungs, University Medical Center Utrecht, Utrecht, the Netherlands
Pim van der Harst	Experimental Cardiology Laboratory, University Medical Center Groningen, Groningen, the Netherlands
Karel G.M. Moons	Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, the Netherlands

Hendrik M. Nathoe	Department of Cardiology, Division of Heart and Lungs, University Medical Center Utrecht, Utrecht, the Netherlands
Linda M. Peelen	Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, the Netherlands
Jean L. Rouleau	Institute of Circulatory and Respiratory Health, Canadian Institutes of Health Research, University of Montreal, Montreal, Canada
Hester M. den Ruijter	Experimental Cardiology Laboratory, Division of Heart and Lungs, University Medical Center Utrecht, Utrecht, the Netherlands
Frans H. Rutten	Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, the Netherlands
Ewoud Schuit	Julius Center for Health Sciences and Primary Care, University Medical Center, Utrecht, the Netherlands; Stanford Prevention Research Center, Stanford University, Stanford, CA, USA
A. Jacob Six	Department of Cardiology, Zuwe Hofpoort hospital, Woerden, the Netherlands
Michelle Smit	Medical student at the University Medical Center Utrecht, the Netherlands
Yvonne T. van der Schouw	Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, the Netherlands
Emmy Verheij	Medical student at the University Medical Center Utrecht, the Netherlands
W.M. Monique Verschuren	Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, the Netherlands; National Institute for Public Health and the Environment, Bilthoven, the Netherlands

LIST OF PUBLICATIONS

Manon G. van der Meer, Maarten J. Cramer, Yolanda van der Graaf, Pieter A. Doevendans, Hendrik M. Nathoe. On behalf of the SMART study group. Gender differences in long-term prognosis among patients with cardiovascular disease. *Eur J Prev Cardiol. 2014 Jan;21(1):81-9*

Manon G. van der Meer, Maarten J. Cramer, Yolanda van der Graaf, Yolande Appelman, Pieter A. Doevendans, Hendrik M.Nathoe. On behalf of the SMART study group. The impact of polyvascular disease on long-term outcome in PCI patients. *Eur J Clin Invest. 2014 Mar;44(3):231-9*

Manon G. van der Meer, Barbra E. Backus, Yolanda van der Graaf, Maarten J. Cramer, Yolande Appelman, Pieter A. Doevendans, A. Jacob Six, Hendrik M. Nathoe. The diagnostic value of clinical symptoms in women and men presenting with chest pain at the emergency department. *PLoS One. 2015 Jan 15;10(1):e0116431*

Manon G. van der Meer, Hendrik M. Nathoe, Yolanda van der Graaf, Pieter A. Doevendans, Yolande Appelman. Worse outcome in women with STEMI: a systematic review of prognostic studies. *Eur J Clin Invest. 2015 Feb;45(2):226-35*

Manon G. van der Meer, Hendrik M. Nathoe, Yolande Appelman. Sex-specific chest pain characteristics: a letter to the editor. *JAMA Intern Med. 2015; 175(4):650*

Hester M. den Ruijter*, Saskia Haitjema*, **Manon G. van der Meer**, Pim van der Harst, Jean L. Rouleau, Folkert W. Asselbergs, Wiek H. van Gilst; IMAGINE Investigators. (*shared first author) Long-term outcome in men and women after CABG; results from the IMAGINE trial. Atherosclerosis. 2015 Feb 24. *[Epub ahead of print]*

Manon G. van der Meer, Yolanda van der Graaf, Ewoud Schuit, Linda M. Peelen, W.M. Monique Verschuren, Jolanda M.A. Boer, Karel G.M. Moons, Hendrik M. Nathoe, Yolande Appelman, Yvonne T. van der Schouw. No added value of female-specific risk factors on top of traditional risk factors for the prediction of cardiovascular disease in women. *Submitted*

Manon G. van der Meer, Yolanda van der Graaf, Hendrik M. Nathoe, Pieter A. Doevendans, Barbra E. Backus, A. Jacob Six, Yolande Appelman. Interpretation of symptoms in chest pain patients is gender dependent. *Submitted*

DANKWOORD

Er zijn veel mensen die ik graag wil bedanken voor hun bijdrage aan dit proefschrift danwel voor hun interesse en betrokkenheid in de tijd dat ik hier druk mee bezig was.

Allereerst mijn promotiecommissie:
Professor Doevendans, bedankt dat u mij de gelegenheid heeft geboden om in uw team te promoveren.

Ik heb uw interesse en betrokkenheid bij onze projecten zeer gewaardeerd.
Professor van der Graaf, lieve Yolanda, ik weet niet eens waar ik moet beginnen met jou te bedanken. Jij bent in deze jaren mijn steun en toeverlaat geweest. Het is bewonderenswaardig hoeveel jij weet te combineren en (ogenschijnlijk) ook nog eens met zoveel gemak. Ondanks het feit dat jouw gezondheid je soms in de steek liet stond je werkelijk altijd voor mij klaar. Niet alleen op inhoudelijk maar ook op sociaal vlak heb je me heel veel inzichten gegeven over wat belangrijk is en wat "vliegen op de vooruit" zijn. Ik voel me bevoorrecht dat ik zo intensief met je heb mogen samenwerken en ik hoop dat ons contact nog lang stand zal houden. Geniet van je prachtige gezin en "keep strong"!

Dr. Appelman, beste Yolande, bedankt voor jouw begeleiding de afgelopen jaren. Je was altijd bereid (zelfs in vakantietijd) om mee te denken en dat heb ik zeer gewaardeerd. Jouw klinische blik was van grote waarde.

Dr. Nathoe, beste Hendrik, bedankt voor het vertrouwen om met mij het promotietraject in te gaan. Ik heb jouw begeleiding de afgelopen jaren gewaardeerd, niet alleen op wetenschappelijk maar ook klinisch vlak.

Er zijn nog een heleboel andere mensen waarmee ik heb mogen samenwerken in de afgelopen jaren:

Professor van der Schouw, lieve Yvonne, jij had genoeg vertrouwen en geduld om met mij aan onze analyse in EPIC te beginnen. Daarvoor wil ik je bedanken, maar ook voor je interesse, betrokkenheid en de fijne samenwerking. Ik vind het een grote eer dat jij de voorzitter van de leescommissie bent.

Dr. Rutten, beste Frans, ik vond het ontzettend leuk om met jou het project bij de huisartsenpost op te zetten. Het is een totaal nieuwe manier van onderzoek en mede dankzij jouw enthousiasme en betrokkenheid hebben we dit kunnen realiseren. Ik wil je hiervoor bedanken. Ook de informatieavond voor de huisartsen en het gezamenlijk begeleiden van drie studenten zijn wat mij betreft een groot succes geweest. Laten we er een prachtig artikel van maken!

Beste Dr. Six en Barbra Backus, met de data van "jullie" HEART score heb ik twee analyses mogen doen. Ik wil jullie niet alleen bedanken voor het ter beschikking stellen van de data maar ook voor jullie betrokkenheid tijdens het analyseren en schrijven van het artikel. Ik heb jullie mening erg gewaardeerd.

Beste Rutger, hoe kan ik jou genoeg bedanken... Jij was degene die keer op keer uren met mij heeft gezeten om me de beginselen van wetenschappelijke analyses en SPSS uit te leggen. Dankzij jouw geduld ben ik zover gekomen! Ik wens je al het goeds toe.

Beste Ewoud en Linda, dankzij jullie hulp en betrokkenheid heb ik de analyses in EPIC kunnen uitvoeren. Bedankt hiervoor, ik vond het een hele fijne samenwerking.

Professor Moons, beste Carl, bedankt voor je bijdrage aan EPIC.

Alle medewerkers van de RAVU: bedankt voor jullie inzet tijdens onze gezamenlijke studie naar de waarde van de anamnese voor het voorspellen van een myocardinfarct in vrouwen. Helaas is het niet gelukt om voldoende mensen te includeren om de data te kunnen analyseren. Beste Wendy, als onderzoekscoördinator van de RAVU was jij mijn vaste aanspreekpunt. Ik wil je ontzettend bedanken voor je aanhoudende inzet en de fijne samenwerking. Erg jammer dat het niet het gewenste resultaat heeft opgeleverd, maar dat heeft zeker niet aan jouw betrokkenheid gelegen. Ik hoop dat we elkaar in de toekomst nog zullen treffen. Tot slot wil ik ook graag Rene Boomars, Rob Lichtfeld, Sander Komijn, Astrid van Poppel en Kristel Brinkhoff persoonlijk bedanken voor hun betrokkenheid.

Alle medewerkers van huisartsenpost "de Gelderse Vallei" te Ede: bedankt voor jullie inzet en alle (praktische) hulp tijdens onze gezamenlijke studie over de triage van mannen en vrouwen die zich met pijn op de borst presenteren bij de HAP. Dankzij jullie is het mogelijk geweest om de bandjes terug te luisteren en alle data te extraheren en. Beste Kien, als directeur van huisartsenpost "de Gelderse Vallei" heb jij onze studie mogelijk gemaakt en daar wil ik je voor bedanken.
Verder zou ik ook graag Astrid Bos, Monique Kuunders, Alice van Veldhuizen, Tamara van den Brandt en Linda van der Ham persoonlijk bedanken voor hun inzet.

Dr. Reitsma, beste Hans, tijdens mijn promotie ben jij meerdere keren bereid geweest om (soms op heel korte termijn) hulp te bieden, bedankt hiervoor.

Dr. Asselbergs, beste Folkert, bedankt voor de samenwerking tijdens IMAGINE. Leuk dat er toch een artikel uit is voortgekomen.

Tijdens mijn promotieonderzoek heb ik meerdere studenten mogen begeleiden: Mette, Anne, Michelle, Emmy, Janita en Timion: bedankt voor de leuke samenwerking en jullie bijdrage aan dit proefschrift!

De overige leden van de leescommissie, professor Visseren, professor Pasterkamp, professor Fauser en professor Boersma, bedankt voor uw bereidheid om zitting te nemen in de beoordelingscommissie van mijn proefschrift.

Onderstaande mensen hebben niet een directe bijdrage aan het proefschrift geleverd maar wel hele prettige randvoorwaarden geschept:

Dr. Kirkels, Beste Hans, dank je wel voor jouw steun en betrokkenheid toen het tijdens mijn promotie even niet zo soepel liep. Ik heb erg veel zin om weer bij de cardiologie aan de slag te gaan.

Alle stafleden en arts-assistenten van de afdeling cardiologie in het UMC Utrecht. Bedankt voor de prettige werksfeer in de afgelopen jaren.

Stafsecretariaat cardiologie: Tamara, Sylvia, Jantine en Natasja, bedankt voor jullie onuitputtelijke hulp en gezelligheid.

Lieve SMART-lieden, lieve Lies, Loes, Ursula, Yvonne, Hetty en Harry, ik denk met een grote glimlach terug aan alle therapieadviezen maar ook aan alle gezellige momenten in jullie kantoor. Jullie zijn al die jaren een safehouse geweest waar ik heerlijk m'n hart kon luchten. Bedankt voor jullie oneindige interesse! Ik hoop jullie in de toekomst vaak te treffen.
Lieve Stan, Daniel en Remy, bedankt voor alle slechte grappen en gezelligheid tijdens het therapieadvies!

De master epidemiologie betekende opnieuw de schoolbanken in! Laurien, Irene en Maarten: dankzij jullie werd dit een stuk gezelliger! Dank hiervoor.

Arts-onderzoekers van de vasculaire geneeskunde en het Julius centrum: jullie zijn meerdere keren zo lief geweest om mij te helpen, bedankt!

Alle mede-onderzoekers bij de cardiologie: door de jaren heen was het een komen en gaan van collega's. Ik wil iedereen bedanken voor alle gezelligheid, interesse en steun. Ik kijk er naar uit dat we elkaar weer in het UMC zullen treffen!
Lieve Hermione, wij hebben zo'n 3 jaar iedere dag naast elkaar gezeten en daarbij een hoop lief en leed mogen delen. We zijn totaal andere persoonlijkheden maar vullen elkaar naar mijn idee juist goed aan.. Ik wil je bedanken voor je betrokkenheid!

Ik wil ook deze kans grijpen om de cardiologen uit het Meander te bedanken voor de geweldige tijd! Ik had me geen betere eerste baan kunnen wensen.

Lieve Diak-collega's, inmiddels is het alweer een jaar geleden dat ik bij jullie ben komen werken. Ik wil iedereen bedanken voor de goede werksfeer en collegialiteit. In het bijzonder

wil ik de roosteraars Sonja, Gerdien en Tom en opleider Alex Muller bedanken. Dankzij jullie flexibiliteit heb ik heel wat extra uren aan mijn proefschrift kunnen werken!

Mijn paranimfen, Maarten Jan en Sanne, bedankt dat jullie tijdens de verdediging aan mijn zijde willen staan!
Lieve Maarten Jan, ik heb zoveel aan jou te danken! Het begon met een wetenschappelijke stage samen met Hendrik maar voordat dit ook maar was afgerond had jij voor mij al een gesprek met Prof. Doevendans en Dr. Kirkels geregeld en zo een promotie- en opleidingsplek gereserveerd ! Je bent altijd geïnteresseerd en betrokken gebleven, ook toen je niet langer mijn co-promotor was, en dat heb ik ontzettend gewaardeerd. Van jouw politieke correctheid kan ik nog veel leren! Ik hoop dat we nog lang contact zullen houden.
Lieve San, wat ben jij een heerlijk persoon! Jij trekt totaal je eigen plan en laat je door weinig van de kaart brengen. Jouw discipline is bewonderenswaardig! Ik geniet ontzettend van jouw kijk op de wereld en ben blij dat we van collega's vrienden zijn geworden! Bedankt voor al je hulp tijdens mijn promotietraject.

Lieve familie en vrienden, het boekje is eindelijk af! Bedankt voor alle glazen wijn, interesse en steun, ik prijs mezelf gelukkig met jullie!

Lieve Tak en Minos, jullie zijn me beiden al voorgegaan! Dank voor alle "gouden tips" en belangstelling, ik koester onze vriendschap. Lieve Sieg, we zijn al maten vanaf onze 3e jaars chirurgie coschap! Ook al zien we elkaar veel te weinig: bedankt voor je altijd luisterende oor! Lieve Els, samen onze eerste baan in het Meander en sindsdien altijd contact gehouden. Dank voor je interesse!

Lieve Cos en Soof, jullie zijn er gewoonweg altijd voor mij en daar ben ik jullie heel dankbaar voor! Van de mooiste feestjes tot de meest verdrietige momenten, wij kunnen alles met elkaar delen en dat vind ik heel bijzonder! Bedankt voor alle steun en interesse. Ik hoop dat we ons leven lang samen blijven!

Lieve Christel, de jaren dat ik druk was met dit proefschrift hebben ook een hele andere lading. In die tijd werd Pieter ziek en is hij ook overleden. Ik koester de laatste maanden met elkaar en vind het bewonderenswaardig hoe jij je sindsdien redt. Ik wil je bedanken voor het feit dat je altijd voor ons klaar staat en ik blijf me verbazen over jouw kennis over alle mogelijke soorten vlekken, bloemen en planten!

Lieve Karen en Bart, we lopen de deur niet bij elkaar plat maar onze goede band is me veel waard. Jullie staan altijd voor ons klaar en daar ben ik jullie dankbaar voor.

Lieve Nien, ondanks alle verschillen zijn wij in hart en nieren zussen. Ik weet dat je er altijd voor me zal zijn en dat is een heerlijk gevoel! Ik ben er ontzettend trots op dat jij zonder te klagen zo hard werkt met zo'n prachtig resultaat en ik geniet van onze tijd samen.

Dank je wel voor je steun en interesse rondom dit proefschrift.
Lieve Chiel, ik ben je heel dankbaar dat je Nien zo gelukkig maakt en dat jullie samen zo hard kunnen lachen om elkaars onvolmaaktheden. Jij plaatst dingen in perspectief en dat kan soms hard nodig zijn! Fijn dat je nu bij ons gezin hoort.
Beiden bedankt voor het leukste dwergje ter wereld: Tobias! Ik ben erg trots dat ik zijn tante ben...

Lieve papa en mama, wat heb ik toch geboft met jullie: geen plan te gek, geen onderwerp taboe, ik kan altijd bij jullie terecht! Voor jullie oneindige interesse, trots en steun ben ik zo dankbaar! Jullie maken alles mogelijk.

Lieve Os, jij bent het kersje op de taart! Ik hoop dat we samen 100 worden. ♥

BIOGRAPHY

Manon van der Meer werd op 20 februari 1984 geboren in 's Gravenhage als tweede dochter van Felix en Marjolijn van der Meer. In de zomer van 2001 haalde ze haar diploma aan het Stedelijk Gymnasium te Leiden. Aangezien ze geen eindexamen in natuur- en scheikunde had gedaan maar wel besloot geneeskunde te willen studeren heeft ze deze vakken via het avondonderwijs van het ROC Leiden gevolgd. Hierna verhuisde ze in 2002 naar Utrecht om te starten met de studie geneeskunde. In het vijfde jaar van haar studie ontdekte ze haar liefde voor de cardiologie tijdens een coschap in het Meander Medisch Centrum te Amersfoort. Manon deed vervolgens haar semi-arts stage bij de cardiologie in het Antonius Ziekenhuis in Nieuwegein en haar wetenschappelijke stage bij dr. M.J. Cramer en dr. H.M. Nathoe in het UMC Utrecht. Na het afronden van haar studie in 2009 is ze begonnen als arts-assistent cardiologie in het Meander Medisch Centrum te Amersfoort met als opleider dr. P.J. Senden. Ze is na een jaar overgestapt naar het UMC Utrecht om daar nog 6 maanden als arts-assistent cardiologie te werken onder supervisie van opleider dr. J.H. Kirkels. In april 2011 is ze gestart met haar promotieonderzoek met als promotoren prof. dr. P.A.F.M. Doevendans en prof. dr. Y. van der Graaf en als co-promotoren dr. H.M. Nathoe en dr. Y. Appelman. Tijdens haar promotie heeft ze de post-graduate Master Epidemiologie gevolgd en was ze lid van de werkgroep Gender van de Nederlandse Vereniging voor Cardiologie. Manon is in april 2014 begonnen met de opleiding cardiologie en werkt als onderdeel van de vooropleiding met veel plezier als arts-assistent interne geneeskunde in het Diakonessenhuis Utrecht onder supervisie van dr. A.F. Muller. Ze woont samen met Oscar in Lombok, Utrecht.