ABOUT WOMEN AND MEN:
THE RELEVANCE OF SEX DIFFERENCES IN CARDIOVASCULAR DISEASES

Over vrouwen en mannen:
De relevantie van geslachtsverschillen bij
hart- en vaatziekten

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About Women And Men: the relevance of sex differences In cardiovascular diseases

ISBN: 978-94-6458-761-6
Layout: Egied Simons
Printing: Ridderprint | www.ridderprint.nl

Acknowledgements
Financial support by the Dutch Heart Foundation for the publication of this thesis is gratefully acknowledged.

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Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de
rector magnificus

Prof.dr. A.L. Bredenoord

en volgens besluit van het College voor Promoties.
De openbare verdediging zal plaatsvinden op

dinsdag 10 januari 2023

om 13.00 uur

door

Michelle Schreuder

geboren te Arnhem.

Erasmus University Rotterdam

Promotiecommissie:

Promotor:	Prof.dr.ir. H. Boersma
Overige leden:	Prof.dr. B.C.P. Koch Prof.dr. F.H. Rutten Prof.dr. A.H.E.M. Maas
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1

General introduction

INTRODUCTION

Cardiovascular disease (CVD) is the collective name for diseases affecting the heart or blood vessels, of which many are related to atherosclerosis. According to the American Heart Association, CVD includes the following diseases: myocardial infarction (MI), stroke, heart failure, arrhythmia and heart valve problems.(1)

For both sexes, cardiovascular disease (CVD) is the leading cause of death globally.(2) In The Netherlands, in 2021, 18,168 men and 18,411 women died of CVD, whereas 139,501 men and 94,307 were hospitalized for CVD.(3) The difference in mortality/hospitalization ratio between men and women is indicative for differences in pathophysiology and disease course between both sexes. For example, ischemic heart disease is a more common cause of death in men, whereas heart failure is more dominant in women.(3) Also, men have shorter life-expectancy than women, which implies that women more often experience the longer-term sequelae of CVD.(3) The sex difference in CVD, however, is more complex, and cannot be reduced to a simple black and white phenomenon.

Sex vs Gender

In the medical literature, ''sex'' refers to biological attributes in humans, and is primarily associated with physical and physiological features, such as chromosomes and reproductive anatomy. In addition to "sex ", there is ''gender'', which refers to socially constructed roles and behaviors, which influences how people act and interact.(4) Biological sex and social gender are no synonyms, although women (sex) are often linked with feminine (gender) characteristics, whereas men are often linked with masculine characteristics.(5) The research that is described in this thesis is predominantly focused on sex-differences with respect to aspects of CVD. However, sometimes it is difficult to dissect between sex and gender. For example adverse drug reactions can be both related to sex- and gender-related factors

In 1991, Dr. Bernadine Healy was the first to describe a sex and gender bias in diagnosis and treatment of CVD commenting on a study which showed that women have a poorer prognosis after myocardial infarction than men. She called this the Yentl syndrome, which is described as ''Once a woman showed that she was just like a man, by having severe coronary artery disease or a myocardial infarction, then she was treated as a man''.(6) Sex- and gender related factors that influence the prevention, diagnosis and treatment of CVD can be both patient and health care provider related. Examples of patient-related such factors are delay in seeking care, discontinuation of treatment, and experiencing adverse drug reactions. Examples of factors that are related to the health care provider include delays in CVD diagnosis and treatment, and withholding treatment due to suspected side effects.

Differences between women and men with respect to CVD manifest in three main domains: *risk factors, symptoms and treatment* are addressed in this thesis.

Risk factors

Traditional CVD risk factors include dyslipidemia, hypertension, diabetes and smoking. Although these apply to women and men, there are relevant differences between both sexes concerning these traditional risk factors. For example, studies reported differences between women and men in LDL-C concentrations across age, with women having higher LDL-C levels until young adulthood and then again after menopause.(10,11) On the other hand, the prevalence of hypertension is lower in women until menopause after which, especially systolic blood pressure, rises more sharply compared to men.(12) Also, differences are observed in the detrimental effects of specific risk factors, for instance smoking (13) and diabetes mellitus (14) have a stronger impact on CVD in women compared to men.

Next to the traditional risk factors, there are also several women-specific CVD risk factors. For example, disorders of pregnancy such as preeclampsia and gestational diabetes are related with increased risk of CVD at a later age.(7-11) Also, women have a significant increase in the risk for CVD after menopause independent of their age of menopausal transition.(12)

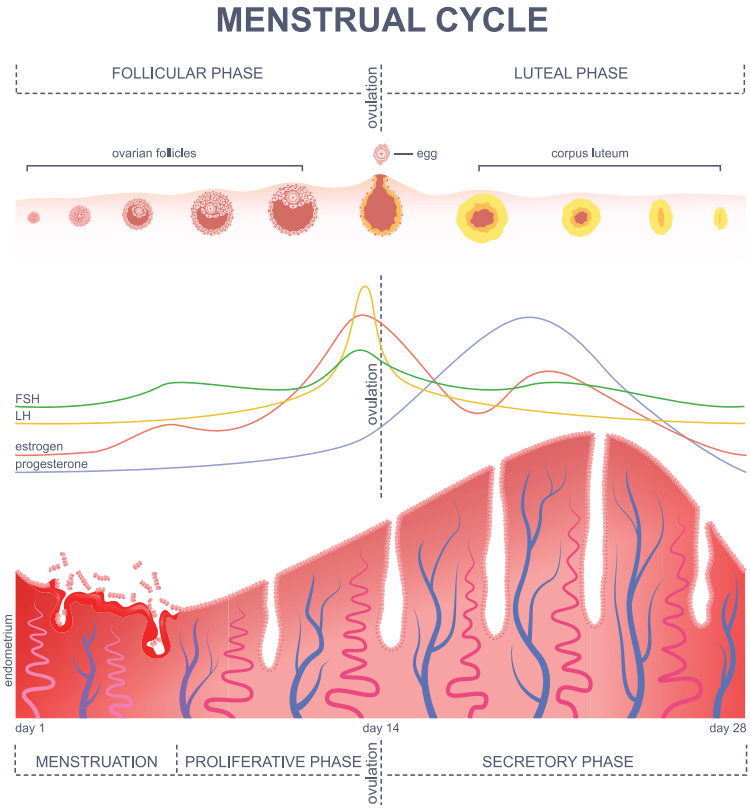
This suggests that sex hormones play a role in the sex disparity in CVD. Estradiol stimulates angiogenesis and vascular remodeling via proliferation and migration of both endothelial cells and vascular smooth muscle cells.(13) Therefore, both biological hormonal changes during menopause, but also the use of hormonal contraception or hormone replacement therapy might influence cardiovascular risk.(14)

Symptoms

Sex differences are reported with respect to symptoms that are associated with myocardial infarction (MI). Studies reported that women often have atypical clinical symptoms such as nausea, back pain and palpitations, while men are more likely to experience chest pain.(15, 16) Studies also showed the influence of hormonal changes in women on the risk of MI. Women were at relatively high risk during their menses, when their estradiol levels are low, suggesting a cardioprotective effect of estradiol.(17, 18) In the presentation of arrhythmias, sex differences are described as well. Women with atrial fibrillation are more likely to be symptomatic than men, with palpitations and fear/anxiety as most common symptoms.(19) Regarding supraventricular tachycardia, it has been reported that episodes of palpitations occur significantly more often during the late luteal phase (just before menstruation) of the menstrual cycle as compared to the late follicular phase (just after menstruation). Hormones were measured and an inverse correlation was found between serum estradiol and supraventricular tachycardia episodes. (20)

Fluctuations of endogenous female hormones occur naturally during the menstrual cycle. In the follicular phase, serum estradiol levels rise with the peak at ovulation. After ovulation estradiol levels drop, followed by a (second) rise of estradiol and progesterone levels during the mid-luteal phase, with again a decrease at the end of the menstrual cycle.(21) These hormonal changes make the menstrual cycle a suitable model to gain insight in the relation

between endogenous female hormones and CVD in women. Against this background, *The Cycle Study* that is part of this thesis investigated the influence of the menstrual cycle on reported chest symptoms in young women.



Treatment

Several sex-specific differences have been identified in the pharmacological management of CVD. Regarding pharmacokinetics, there are sex differences in drug metabolizing enzymes cytochrome P450, which is more active in men than women, while CYP2D6 is more active in women than in men. (22, 23) Also, physiological factors such as women having more body fat, smaller body weight, lower glomerular filtration rate and different gastric motility might hypothetically lead to sex differences in the clinical effectiveness of drugs.(22, 24-26) Although clinically significant differences in therapeutic response based on sex disparity in pharmacokinetics seem to be rare,(27) fewer women than men are included in clinical trials on drug therapies, which makes drawing conclusion on efficacy and safety in women more complex.(28) Moreover, gender-related factors can also have its effect on pharmacotherapy, such as women experiencing more adverse drug reactions leading to drug discontinuation but also prescribers giving different or less aggressive drugs to women than men.(29-32) Therefore, more insight is needed into both sex and gender differences for efficacy and

safety of cardiovascular drugs in order to improve clinical outcomes in women with CVD and provide sex-specific recommendations if needed. For that reason, sex-specific analyses on efficacy and safety of the cardiovascular drugs ACE-inhibitors, P2Y12 inhibitors, and the lipid lowering therapies statins and PCSK9-inhibitors are performed in this thesis. Eventually, systematic meta-analyses are needed in order to determine whether sex-specific treatment with cardiovascular drugs are needed.

Aim and outline of this thesis

In order to gain more insight into sex differences in CVD, this thesis focuses on the previously mentioned domains of risk factors, symptoms and treatment. This thesis has two aims: 1) to study the prevalence of cardiac symptoms in different phases of the menstrual cycle and 2) to study the efficacy and safety of cardiovascular medication in women and men from an epidemiological point of view.

In Part A, the effect of sex on symptoms are studied by gaining more insight in the influence of the menstrual cycle on cardiac symptoms. The evidence on the influence of menstruation on heart rate and tachycardia is first summarized (**Chapter 2**) followed by a case report on a patient who suffered from menstruation-related angina pectoris and eventually had a spontaneous coronary artery dissection (**Chapter 3**). In **Chapter 4**, the results of *The Cycle Study* are presented in which women reported chest symptoms during one menstrual cycle.

Then, in part B of this thesis, the sex-specific effects of cardiovascular risk factors and treatment are investigated by performance of sex-specific analyses on the efficacy and safety of cardiovascular drugs. In **Chapter 5** we studied the temporal evolution of cardiac biomarkers in women and men with HF with reduced ejection fraction**. Chapter 6** focuses on sex- and age-specific efficacy of the ACE-inhibitor perindopril in three randomized clinical trials that included patients with different vascular diseases. In **Chapter 7**, the sex differences in adverse events of angiotensin-converting enzyme inhibitors are analyzed. **Chapter 8** assesses the efficacy and safety of dual antiplatelet therapy with P2Y12 inhibitor ticagrelor and clopidogrel vs. prasugrel and clopidogrel in women and men with CHD in a meta-analysis. **Chapter 9** and **Chapter 10** focus on lipid lowering therapies in patients with familial hypercholesterolemia. In **Chapter 9** sex-specific responses to statin therapy are studied and **Chapter 10** shows sex-specific data in real-world data of patients treated with PCSK9-inhibitors.

In Part C of this thesis, relevance of sex and gender-sensitive clinical practice and research is examined. In **Chapter 11**, the preference for a female or male general practitioner is determined in both female and male patients. **Chapter 12** focuses on availability of sex-specific data in the late breaking pharmacological randomized controlled trials of the three biggest cardiovascular conferences in 2010 and 2017.

Lastly, in Part D the most important findings from this thesis are discussed separately for all parts followed by strengths, limitations and future perspectives.

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A

The Menstrual Cycle and Cardiac Symptoms

2

Supraventricular Tachycardia and the menstrual cycle

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Published in ***Case Reports in Women's Health***
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6861643/

HIGHLIGHTS

- The influence of the menstrual cycle on the occurrence of arrhythmia is still understudied.
- Episodes of arrhythmia might occur more frequently in the premenstrual phase.
- Taking the menstrual cycle into account when scheduling diagnostic tests might lead to more accurate diagnoses.

Over the menstrual period, various conditions such as migraine, asthma or epilepsy can be exacerbated by the variations in hormone levels. (1) Female sex hormones have a multitude of effects on the cardiovascular system through several mechanisms, ranging from estradiol-induced vasodilation associated with fluctuations of the blood pressure during the menstrual cycle to increased elasticity of aortic smooth muscle cells after incubation of estradiol and progesterone. (2, 3) Although it is known that both estrogen and progesteron have electrophysiological properties, only a few studies have assessed the effect of the menstrual cycle on arrhythmia. In general, women less often develop ventricular arrhythmia than men; however, they have an increased risk of long-QT-induced torsades de pointes and long-QT associated drug induced ventricular arrythmia. (4) Clinically significant variations of QT interval duration have been linked to the menstrual cycle and sex hormones fluctuations, so an association between menstrual cycle phase and occurrence of ventricular tachycardia would be quite possible. (5) However, to our knowledge, no studies have been published on this topic.

This editorial gives a brief overview of the current knowledge of the effect of changing ovarian hormone levels across the menstrual cycle in women with supraventricular tachycardia (SVT) and its possible diagnostic and therapeutic consequences..

The menstrual cycle can be divided in several phases. The first phase, starting with the first day of menstruation, is known as the follicular phase, when estradiol and progesterone levels are low. Mid-cycle, at ovulation, estradiol shows a sharp surge but progesterone is still low. Finally, in the premenstrual or luteal phase, estradiol and progesterone levels are initially high but then decrease (so levels are low again at the next menstruation).

Both estradiol and progesterone influence heart rate in women, via several pathways. It is reported that estradiol has a direct negative chronotropic effect by suppressing T-type calcium channels and by its influence on the cardiac autonomic nervous system.(6, 7) Progesterone, on the other hand, activates the renin-angiotensin system, leading to fluid retention and consequently an increase in circulating blood volume and increased heart rate. (8)

A study of 49 healthy premenopausal women with a regular menstrual cycle found a significantly lower average heart rate (−2.33 bpm), but an increased heart rate variability, during the follicular (menstrual) phase compared with the luteal (premenstrual) phase. This implies that estradiol and progesterone fluctuations affect cardiac autonomic regulation.(9)

Based on these results, one might expect most episodes of tachycardia to occur during the premenstrual luteal phase. Indeed, in a study of 26 premenopausal women with a regular menstrual cycle and paroxysmal SVT, who underwent weekly 48 -h ambulatory electrocardiographic monitoring during one menstrual cycle, significantly more episodes of paroxysmal SVT were recorded in the premenstrual days than in the menstrual days. Moreover, an inverse correlation between frequency and duration of episodes of paroxysmal SVT and estradiol level was found. (10) In a study of 42 premenopausal women with

symptomatic paroxysmal SVT, 40 % of the patients reported a clustering of SVT episodes in the premenstrual period (11) Moreover, this study showed that the cyclic increased sensitivity for episodes of SVT has clinical consequences for diagnostic testing. All women underwent diagnostic electrophysiological testing, including provocation with isoproterenol, which was performed to induce episodes of SVT. First, electrophysiological tests were performed mid-cycle. Six patients in whom episodes of SVT were not inducible during the initial test underwent a second electrophysiological test in the premenstrual period. All six women who initially had a negative electrophysiological mid-cycle test had induced episodes of paroxysmal SVT during the repeat test in the premenstrual phase. Therefore, performing electrophysiological procedures in women with SVT in their premenstrual period may lead to more accurate diagnosis. (11)

The influence of the menstrual cycle on the occurrence of arrhythmia has been investigated in only a few studies, with small samples. As indicated above, taking the menstrual cycle into account when scheduling diagnostic tests such as ambulatory electrocardiographic (ECG) monitoring and electrophysiological tests might lead to more accurate diagnoses. It is recommended that ECG monitoring be performed during the premenstrual phase, as the occurrence of arrhythmias is highest when estradiol levels are low and progesterone levels are high. If premenstrual-related arrhythmia is diagnosed, it would be interesting to investigate whether treatment can be tailored around the menstrual phase. Research is needed to evaluate whether adjusting the dosage of antiarrhythmic drugs in different phases of the menstrual cycle will lead to less symptomatic arrhythmia in premenopausal women. Another option would be to learn more about the effect of continuous estradiol treatment by testing if the oral contraceptive pill (without the often-used week of interruption) decreases the number of episodes of SVT. However, the most exciting direction will be to reveal the precise pathways by which sex hormones affect SVT and to modulate these in a more sophisticated fashion, which might lead to new antiarrhythmic treatment options, not only for premenopausal women but also for postmenopausal women and men.

Contributors

M.M. Schreuder contributed to the literature search and wrote the first draft of the manuscript. M. Sunamura contributed to the literature search and revision of the manuscript. J.E. Roeters van Lennep contributed to the literature search and revision of the manuscript.

Conflict of interest

The author has no conflict of interest regarding the publication of this editorial.

Funding

No funding was sought or secured in relation to this editorial.

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3

Catamenial chest pain and spontaneous coronary artery dissection

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Published in ***Case Reports in Women's Health***
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6861643/

ABSTRACT

Spontaneous coronary artery dissection (SCAD) is a rare cause of myocardial infarction, presenting mostly in healthy, young women. The exact pathogenesis is still poorly understood. A 45-year old woman presented with a ST-elevation myocardial infarction, caused by SCAD of the mid left anterior descending coronary artery. In the six years prior to this event, she frequently experienced chest pain coinciding with her menstruation.

INTRODUCTION

Spontaneous coronary artery dissection (SCAD) is a rare cause of myocardial infarction (MI), presenting mostly in healthy, young women. The exact incidence of SCAD is unknown, but it is estimated to be around 25% of all MIs amongst women <60 years.(1) SCAD is not associated with atherosclerosis or trauma and is not iatrogenic.(2) The dissection may occur in either the intima, media or adventitia of the coronary artery wall. It is an underdiagnosed condition and is often missed on a coronary angiogram.(3)
In this case report, we present a woman with SCAD, who experienced chest pain related to her menstrual cycle prior to this event.

CASE PRESENTATION

A 43-year-old woman with perimenstrual, episodic chest pain and exertional dyspnea was referred to the cardiology outpatient clinic for cardiac evaluation of suspected coronary artery disease. These chest pains were normally retrosternal, dull and cramping, sometimes with radiation to the throat. They occurred a few days before, during or a few days after the menstruation and would last between 5-30 minutes.

She had always been healthy, had had one uncomplicated pregnancy of twins and used no medications. The patient was obese (body mass index: 32,6 kg/m2), had normal blood pressure (111/73 mmHg), and normal lipid levels (low density lipid cholesterol: 3,0 mmol/L). Furthermore, she did not smoke and had no first-degree family members with cardiovascular disease before the age of 60 years.

She had a normal 12-lead resting electrocardiogram (ECG) and troponin levels were not elevated. Cardiac ultrasound showed normal cardiac wall motion, normal left- and right-ventricle function and no valve abnormalities. Ergometer stress testing showed no signs of coronary insufficiency. Maximal load was 177 watt (121% predicted), with a heart rate of 173 beats per minute (98% predicted). The conclusion of the cardiologist was that cardiac ischemia, due to obstructive coronary artery disease, was unlikely and the origin of her chest pain was either due to small-vessel disease without clinical consequences, or was stress-related. She was referred back to her general practitioner.

Noteworthy was that the episodes of chest pain always occurred during or a couple of days before or after the menstruation. Her menstruations had always been regular, with a duration of vaginal blood loss of 5-10 days. The patient had had severe perimenstrual symptoms, including fluid retention, constipation and migraines since her menarche.

Six months after the cardiac evaluation, the patient was admitted to the emergency department with severe chest pain, radiating to her jaw, back and neck with nausea. The pain started two days after menstruation began. The character of the pain was similar to previous episodes; however, it was more intense and did not subside.

A 12-lead ECG (figure 1) showed sinus rhythm at a rate of 77 beats per min and a normal QRS-axis. ST-elevations were observed in leads II, III, aVF, V2-V5, indicative of an acute anterolateral MI. In the ambulance, she was treated according to the ST-elevation myocardial infarction protocol with aspirin 500 mg, ticagrelor 180 mg and intravenous heparin 5000 IU. Subsequently, ST-elevations resolved completely. At the hospital coronary angiogram (CAG) was performed (figure 2). This CAG showed a mid-left anterior descending artery (LAD) lesion, suspected for an intramural hematoma due to SCAD. Furthermore, the coronary arteries seemed to be normal. Coronary vasospasm was ruled out with intracoronary nitroglycerin injection. Percutaneous coronary intervention (PCI) was not performed because of absence of a coronary occlusion, normal coronary flow (Thrombolysis in Myocardial Infarction III), resolution of symptoms and ECG abnormalities during CAG. Moreover, in SCAD a PCI could cause worsening of the dissection. Aspirin 80 mg, once daily and fraxiparin 5700 IU, twice daily were started and the patient was discharged. Repeat CAG after 6 weeks showed spontaneous healing of the SCAD lesion.

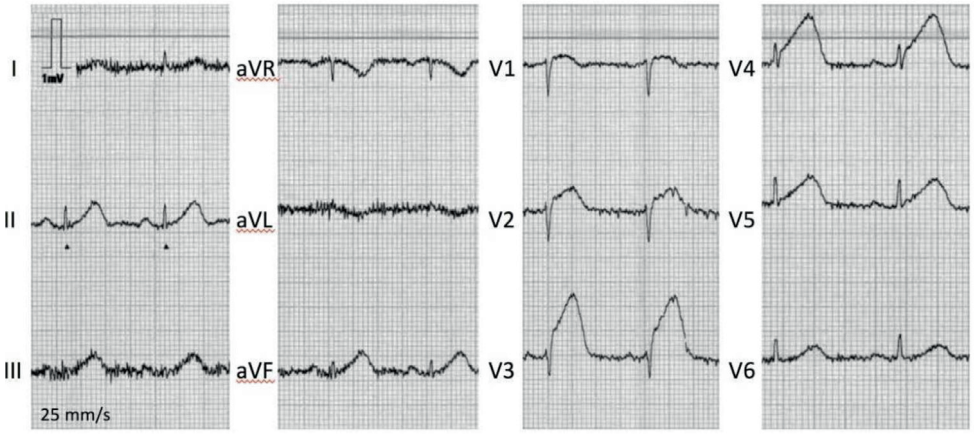

Figure 1. 12-lead ECG in ambulance showing ST-elevations in II, III, aVF, and V1-V5.

A CT scan of carotid and renal arteries and total aorta was performed to assess fibromuscular dysplasia (FMD) as a cause of SCAD. The CT-scan showed abnormalities of the left renal artery, suggestive of FMD. Also mild dilatation of the ascending aorta was found (37 mm, 95th percentile of normal). Therefore, the patient was referred to the clinical geneticist to test for mutations related to vascular connective tissue disorders. These were not found. However, absence of genetic mutations(4) does not exclude FMD, as many related mutations are still unknown.

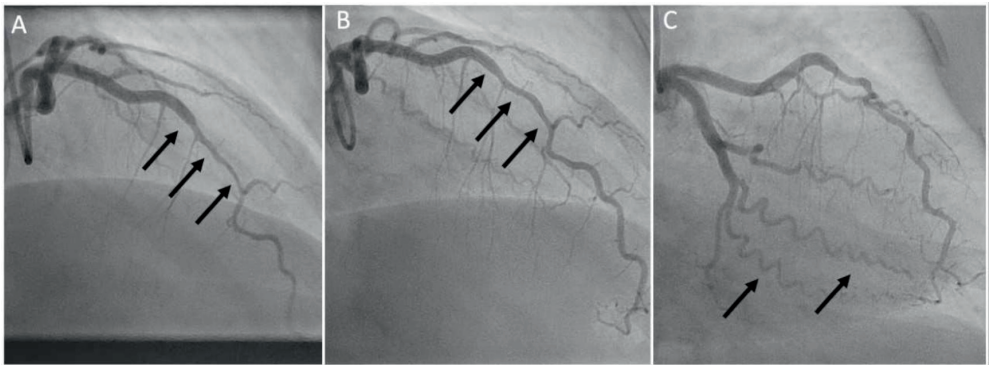

Figure 2. CAG of presented patient. Panel A: a type 2 spontaneous coronary artery dissection (SCAD) within the mid segment of the left anterior descending artery (LAD) at hospital admission with an acute anteroseptal ST-elevation myocardial infarction. Panel B: spontaneous healing of the mid segment of the LAD, 6 weeks after initial presentation. Panel C: typical tortuosity in the coronary arteries often observed patients with SCAD.

After discharge the patient was referred to cardiac rehabilitation which she completed in two months. Even though she recovered well, she kept experiencing mild catamenial chest pains, mostly in rest, at night. To alleviate the pain she was prescribed sublingual nitroglycerin.

Table 1 provides a timeline of the events in this case.

Table 1. Timeline of events.

Time	Event
Since the patient's menarche	Since the patient's menarche, at the age of 11 years, the patient has experienced perimenstrual symptoms. In the previous decade the patient has had multiple episodes of catamenial chest pains, varying in intensity.
Six months prior to the spontaneous coronary artery dissection (SCAD)	Cardiac evaluation. Electrocardiogram showed no abnormalities, the ergometer test showed no signs of cardiac ischemia and cardiac ultrasound showed normal left and right ventricle function and no valve anomalies.
SCAD	Admitted to the emergency room for severe chest pain. Electrocardiogram showed an acute anterolateral ST-elevation myocardial infarction due to a spontaneous dissection of the mid left anterior descending artery and intramural hematoma diagnosed by coronary angiography.
6 weeks after SCAD	Hospital admission for coronary angiography to re-examine the left anterior descending artery dissection, showing the mid-left anterior descending artery had healed well after the SCAD.
Two months after SCAD	CT showed abnormalities of the left renal artery suspect for fibromuscular dysplasia, and mild dilatation of the ascending aorta (37 mm; 95th percentile).

DISCUSSION

We describe a woman with SCAD, who experienced chest pain that coincided with menstruation. The patient's previous catamenial chest pains were similar to the chest pain she experienced when she had her SCAD, although milder. Recurrent chest pains before the start of menstrual bleeding both before and after experiencing a SCAD have been described earlier, in the setting of variant angina or vasospastic angina (6), and as prodromal to SCAD. (7) There is a lack of evidence for a correlation between catamenial chest pains and SCAD, and so further research is necessary, for example a retrospective study with women who have had a SCAD before or a follow-up study of women with catamenial chest pains.

Low estrogen levels have been associated with cardiovascular disease such as coronary heart disease, migraine and strokes.(8) In small observational studies it has also been reported that women have an increased risk of developing chest pain, cardiac ischemia and other vascular-related symptoms around the time of the menstruation, when estrogen levels are low.(7)

The patient presented in this case report is suspected to have had FMD, which is related to SCAD. As more than 90% of FMD patients is female, it is likely that sex hormones play a role in the process of developing FMD.(9) However, the pathways in which female sex hormones, such as estrogen, contribute to the development of FMD have not been identified.(10)

There are some limitations to our presentation of the case. The reporting of the episodes of catamenial chest pain was subjective, and there were no recordings of any cardiac abnormalities prior to or during the menstruation. Moreover, ischemia might be missed due to the timing of the cardiac diagnostics as they were not performed during her menstruation when she experiences most complaints.

CONCLUSION

This case report adds to the literature because it discusses in detail the course of catamenial chest pains preceding SCAD. By presenting this case, our aim is to create more awareness for the cardiovascular risk of women with catamenial chest pain, as they might have an increased risk for SCAD. These patients might require extra surveillance when reaching the (peri)menopause, as this could increase their risk for cardiac ischemia due to decreasing estrogen levels. Moreover, it is important to take catamenial cardiac symptoms seriously and time diagnostic tests according to the period of the menstrual cycle when the patient experiences most complaints.

LEARNING POINTS

- It is important to take catamenial chest pain seriously, as it might be of diagnostic use.
- Diagnostic tests should be planned and timed according to the menstrual cycle, as chances are lower of missing something because this is the time most symptoms occur.

Contributors
Zainab Al Fatly collected patient information and wrote the manuscript. Famke L.M. Beckers collected patient information and wrote the manuscript. Krischan D. Sjauw provided patient information and the radiological images. Jeanine E. Roeters van Lennep provided critical feedback and contributed to the drafting of the manuscript. M. M. Schreuder wrote the manuscript.

Conflict of Interest
The authors declare that they have no conflict of interest regarding the publication of this case report.

Funding
No funding from an external source supported the publication of this case report.

Patient Consent
Obtained.

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4

The influence of the Menstrual Cycle on Chest Symptoms

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Submitted

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Sex-specific effects of cardiovascular risk factors and treatment

5

Sex-specific temporal evolution of cardiac biomarkers in patients with Heart Failure with Reduced Ejection Fraction

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International Journal of Cardiology
https://pubmed.ncbi.nlm.nih.gov/33940096/

ABSTRACT

BACKGROUND: We aimed to assess differences in clinical characteristics, prognosis, and the temporal evolution of circulating biomarkers in male and female patients with HFrEF.

METHODS: We included 250 patients (66 women) with chronic heart failure (CHF) between 2011 and 2013 and performed trimonthly blood sampling during a median follow-up of 2.2 years [median (IQR) of 8 (5–10) urine and 9 (5–10) plasma samples per patient]. After completion of follow-up we measured 8 biomarkers. The primary endpoint (PE) was the composite of cardiac death, cardiac transplantation, left ventricular assist device implantation, and hospitalization due to acute or worsened CHF. Joint models were used to determine whether there were differences in the temporal patterns of the biomarkers between men and women as the PE approached.

RESULTS: A total of 66 patients reached the PE of which 52 (78.8%) were male and 14 (21.2%) were female. The temporal patterns of all studied biomarkers were associated with the PE, and overall showed disadvantageous changes as the PE approached. For NT-proBNP, HsTnT, and CRP, women showed higher levels over the entire follow-up duration and concomitant numerically higher hazard ratios [NT-proBNP: women: HR(95%CI) 7.57 (3.17-21.93), men: HR(95%CI) 3.14 (2.09-4.79), p for interaction = 0.104, HsTnT: women: HR(95%CI) 6.38 (2.18-22.46), men: HR(95%CI) 4.91 (2.58-9.39), p for interaction = 0.704, CRP: women: HR(95%CI) 7.48 (3.43-19.53), men: HR(95%CI) 3.29 [2.27 - 5.44], p for interaction = 0.106). In contrast, temporal patterns of glomerular and tubular renal markers showed similar associations with the PE in men and women.

CONCLUSION: Although interaction terms are not statistically significant, the associations of temporal patterns of NT-proBNP, HsTnT, and CRP appear more outspoken in women than in men with HFrEF, whereas associations seem similar for temporal patterns of creatinine, eGFR, Cystatin C, KIM-1 and NAG. Larger studies are needed to confirm these potential sex differences.

Highlights

- Associations of temporal patterns of NT-proBNP, HsTnT, and CRP appear more outspoken in women than in men with HFrEF
- Associations seem similar for temporal patterns of creatinine, eGFR, Cystatin C, KIM-1 and NAG in women and men with HFrEF
- More research is warranted before any sex-specific clinical recommendations can be made based on changes in biomarkers.

INTRODUCTION

Evidence on differences between men and women affected by heart failure (HF) continues to accumulate.(1) Age at HF diagnosis is higher in women and symptoms may differ.(2, 3) Women are more often affected by HF with preserved ejection fraction (HFpEF) than HF with reduced ejection fraction (HFrEF) (4, 5). In conjunction, risk factors play different roles in both sexes: diabetes mellitus,(6) hypertension (7) and obesity (8) are prominent in women with HF, while in men coronary artery disease prevails.(9) These differences suggest that sex is an important aspect to consider during diagnosis, management and treatment of HF.

Although women more often present with HFpEF, this does not preclude that HFrEF is an important problem in women as well. In the large ESC Heart Failure Long-Term registry, women constituted over 20% of patients with ejection fraction <40% , and over 30% of patients with ejection fraction <50%. (10) Yet, to date, studies performing sex-specific analyses in HFrEF patients are scarce. A recent study showed an independent survival benefit in women compared to men.(11) However, the underlying pathophysiological mechanisms for this difference in survival has not yet been elucidated and warrant further investigation.

Circulating biochemical markers (biomarkers) related to inflammation, cardiac remodeling, and cardiomyocyte conditions have been found to be associated with adverse cardiac outcomes in HF patients.(12, 13) These biomarkers represent underlying biological processes and thus carry potential to unveil and explain differences in HF pathophysiology between men and women; even those that may not be clinically apparent. Herewith they may also contribute to explaining differences in survival between men and women with HFrEF. Serial biomarker measurements are especially interesting in this context, as they may expose potential differences in the temporal evolution of HF mechanisms in men and women.

With the current investigation, we aimed to assess differences in clinical characteristics, prognosis, and the temporal evolution of circulating biomarkers (of wall stress, myocardial injury, inflammation, and glomerular and tubular renal function) in male and female patients with HFrEF.

METHODS

Study design

The design of the Bio-SHiFT study has been published in detail elsewhere.(14, 15) In brief, the Bio-SHiFT study is a prospective, observational study consisting of patients with stable CHF carried out at the Erasmus MC, University Medical Center, Rotterdam, Netherlands, and Northwest Clinics, Alkmaar, Netherlands. From October 2011 to June 2013, during the first inclusion round of Bio-SHiFT, 263 patients were enrolled. The main inclusion criteria were age ≥18 years, capability of understanding and signing informed consent and diagnosis of CHF ≥3 months ago according to European Society of Cardiology guidelines.(16) A total of 250 (95%) patients had HFrEF, and they were available for the current analysis. At baseline, blood- and urine sampling was performed and study follow-up visits with repeated sampling were planned every 3 months (±1 month was allowed), until a maximum of 10 study follow-up visits were completed. A medical evaluation was performed with a short questionnaire and samples were obtained during each study follow-up visit.

The study was approved by the medical ethics committee of the Erasmus MC, and conducted according to the Declaration of Helsinki. Written informed consent was obtained in all participants. The study is registered at ClinicalTrials.gov (NCT01851538).

Baseline assessment

We collected information on CHF-related symptoms and New York Heart Association (NYHA) class, CHF etiology, cardiovascular risk factors, medical history and medical treatment. Also, systolic blood pressure, heart rate, body mass index and left ventricular ejection fraction (LVEF) as measured by echocardiography were determined at baseline.

Biomarker measurements

Plasma and urine samples were collected at baseline and at each follow-up visit, and were processed and stored at a temperature of -80 within 2 hours after blood collection. When applicable, samples were transported to the central laboratory (Erasmus MC, Rotterdam, the Netherlands) under controlled conditions (at a temperature of -80°C) and stored until batch analysis was performed. Laboratory personnel was blinded for clinical data.

NT-proBNP, HsTNT, and CRP were measured in stored serum samples. Plasma NT-proBNP was analyzed using an electrochemiluminescence immunoassay (Elecsys 2010; Roche Diagnostics, Indianapolis, IN), which measures concentrations ranging from 5 to 35000 ng/L. Cardiac troponin T was also measured using an electrochemiluminescence immunoassay (Elecsys 2010 immunoassay analyzer; Roche Diagnostics, Indianapolis, IN) which measures concentrations ranging from 3 to 10000 ng/L. CRP was measured using an immunoturbidimetric assay (Roche Hitachi 912 chemistry analyzer; Roche, Basel, Switzerland). Measurement of renal biomarkers in plasma and urine samples was performed at HaemoScan BV (Groningen, Netherlands).

Creatinine was determined by a colorometric test by the Jaffe's reaction. Plasma was used undiluted, urine was diluted ten times in water (LLD: plasma 0,14 mg/dl, urine: 1.56 mg/ml). CysC was determined in plasma, diluted 2000 times in 0,1%BSA/PBS buffer, by ELISA (R&D systems, Minneapolis, MN) (LLD: 0.1066 µg/mL). KIM-1 was determined in urine, diluted 50% in 0,1% BSA/PBS buffer, by ELISA (R&D systems, Minneapolis, MN, USA) (LLD: 0.146 ng/mL). NAG was determined using a substrate p-nitrophenyl N-acetyl-β-D-glucosaminidase at pH 4.5 (Sigma, St Louis, MO, USA) (LLD: 0.485 U/L). All urinary biomarkers were normalized to urinary creatinine concentrations to correct for concentration or dilution of urine.

GFR was determined by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation that has been validated in HF patients.(17) Patients were categorized using National Kidney Foundation–Kidney Disease Outcome Quality Initiative (K/DOQI) clinical practice guidelines. (18)

Follow-up and adverse events

Because of the batch laboratory analysis after completion of follow-up, results of the biomarker assays were not available to treating physicians at the time of the outpatient visits. As such, this was an observational study, all patients were treated according to prevailing ESC guidelines and the biomarker measurements performed for this study did not alter usual patient care.

Patients were followed at the outpatient clinic every 3 months with a maximum of 10 follow-up visits per patient. The follow-up visit consisted of a short medical evaluation, during which all medication changes and adverse cardiovascular events since the previous visit were reported and blood and urine samples were collected. The primary endpoint (PE) was the composite of cardiac death, cardiac transplantation, left ventricular assist device implantation, and hospitalization due to acute or worsened CHF, whichever occurred first during follow-up.

Statistical analysis

Normality of continuous variables, including biomarker concentrations, was assessed by the Kolmogorov-Smirnov test. Normally-distributed continuous variables were reported as means and standard deviations, non-normally distributed continuous variables as medians and interquartile ranges (IQRs). In case of skewed distributions, continuous variables were logarithmically transformed (log base 2) for further analysis. All biomarker values were transformed in this way. Categorical variables were reported as numbers and percentages.

Univariate cox regression was performed to investigate whether there was an association between baseline characteristics and biomarker levels and the PE. Unadjusted hazard ratios (HRs) were reported with 95% confidence intervals (CIs) per two fold increase in biomarker

level. We stratified for sex. Interaction terms between sex and the biomarkers of interest were added to the models to determine potential differences between men and women.

We used linear mixed effect models to describe the average temporal pattern of each biomarker for men and women with and without a PE during study follow-up. To estimate the associations between repeated biomarker measurements and the hazard of PE, we applied joint modeling (JM) analyses, which combine linear mixed effect models for temporal evolution of the repeated measurements with relative risk models for the time-to-event data. By using the JM technique, analyses inherently accounted for different follow-up durations between patients.(19) For the joint models, unadjusted HRs and corresponding CIs, per doubling of the biomarker level at a given follow-up time, were reported.

Analyses were performed in SPSS and R package JM Bayes(20). All statistical tests were two-tailed. P-values <0.05 were considered statistically significant.

RESULTS

Baseline characteristics

A total of 66 (26.4%) were women. Baseline characteristics of the study patients, stratified by sex, are described in Table 1. Women and men had similar mean age (6.7±13.3 vs. 66.7±12.5). Men more often had ischemic etiology of HF (53.8% vs 25.8, P = 0.012) while women more often had hypertensive etiology (19.7% vs. 9.8%, P = 0.036). Men were more likely to have a history of myocardial infarction (42.9% vs. 21.2%, P = 0.004), PCI (36.4% vs. 21.2%, P = 0.021), and CABG (20.1% vs. 7.6%, P = 0.019). Mean BMI was higher in men (27.9 ± 4.6 vs. 26.1± 4.5, P = 0.009), and men more often had known hypercholesterolemia (39.7% vs. 27.3%, P = 0.020) and were more likely to have ever smoked than women (67.4% vs. 43.9%, P = 0.003). No clinically relevant differences in mean LVEF were present between the sexes.

Table 1. Baseline characteristics

	N = 250 patients	Female (n = 66)	Male (n = 184)	p-value
Demographical characteristics				
Age, years (mean ± SD)	66.7 (12.7)	66.7 (13.3)	66.7 (12.5)	0.68
Caucasian ethnicity, n (%)	231 (92.4)	61 (92.4)	170 (92.4)	0.65
Clinical characteristics				
BMI, kg/m^2 (mean ± SD)	27.4 (4.7)	26.1 (4.5)	27.9 (4.6)	0.009
Heart rate, beat/min (mean ± SD)	67.1 (11.7)	69.4 (11.6)	66.3 (11.6)	0.066
SBP, mmHg (mean ± SD)	121.6 (20.6)	122 (22.0)	121.4 (20.1)	0.85
DBP, mmHg (mean ± SD)	72.2 (10.9)	72.5 (11.2)	72.1 (10.8)	0.85
Features HF				
Duration of HF, years	6.3 (5.6)	3.7 (0.92-7.4)	5.1 (2.1-10.2)	0.103
NYHA class I or II / III or IV, n (%)	188 (75.2) / 62 (24.8)	49 (74.2)/ 17 (25.8)	139 (75.5)/ 45 (24.5)	0.83
LVEF, % (mean ± SD)	30.3 (9.6)	29.3 (10.5)	30.8 (9.2)	0.47
Biomarker levels				
NT-proBNP (pmol/L)*	133.2 (44.9-274.4)	108.9 (46.2-251.9)	138.5 (44.9-283.9)	0.64
HsTnT (ng/L)*	17.7 (9.3-32.8)	11.7 (7.2-27.7)	19.6 (10.7-36.7)	0.002
CRP (mg/L)*	2.2 (0.9-4.9)	2.3 (0.9-4.9)	2.2 (0.9-4.9)	0.78
Creatinine (mg/dL)	1.2 (1.0-1.5)	1.2 (0.9-1.5)	1.2 (1.0-1.5)	0.66
eGFR (mg/dL)	58.4 (41.7-76.7)	47.5 (36.1-65.1)	62.5 (36.1-65.1)	<0.001
KIM1	488.6 (246.6 – 935.2)	447.7 (234.6-738.6)	544.6 (258.5-941.5)	0.25
Cystatin C, mg/L	0.73 (0.6-1.0)	0.7 (0.5-0.9)	0.7 (0.6-1.0)	0.15
Etiology of HF (n, %)				
Ischemic heart disease	116 (46.4)	17 (25.8)	99 (53.8)	0.012
Hypertension	31 (12.4)	13 (19.7)	18 (9.8)	0.036
Secondary to valvular heart disease	10 (4.0)	3 (4.5)	7 (3.8)	0.79
Cardiomyopathy	63 (25.2)	19 (28.8)	44 (23.9)	0.43
Dilated	49 (19.6)	13 (19.7)	36 (19.6)	0.98
Hypertrophic	7 (2.8)	2 (3.0)	5 (2.7)	0.90
Non compaction	4 (1.6)	2 (3.0)	2 (1.1)	0.28
Unclassified	3 (1.2)	2 (3.0)	1 (0.5)	0.11
Unknown	18 (7.2)	9 (13.6)	9 (4.9)	0.018
Other	3 (1.2)	1 (1.5)	2 (1.0)	0.32

	N = 250 patients	Female (n = 66)	Male (n = 184)	p-value
Medical history, n (%)				
Myocardial infarction	93 (37.2)	14 (21.2)	79 (42.9)	0.004
PCI	81 (32.4)	14 (21.2)	67 (36.4)	0.021
CABG	42 (16.8)	5 (7.6)	37 (20.1)	0.019
Valvular heart disease	127 (50.8)	36 (54.5)	91 (49.5)	0.57
Atrial fibrillation	96 (38.4)	19 (28.8)	77 (41.8)	0.18
ICD	146 (58.4)	33 (50.00	113 (61.4)	0.11
CRT	77 (30.8)	19 (28.8)	58 (31.5)	0.69
Pacemaker	40 (16.0)	10 (15.2)	30 (16.3)	0.25
CVA	38 (15.2)	8 (12.1)	30 (16.3)	0.73
Chronic renal failure	131 (52.4)	37 (56.1)	94 (51.1)	0.71
Diabetes mellitus	77 (30.8)	19 (28.8)	58 (31.5)	0.68
Known hypercholesterolemia	91 (36.4)	18 (27.3)	73 (39.7)	0.020
Hypertension	113 (45.2)	27 (40.9)	86 (46.7)	0.37
Intoxication, n (%)				
Alcohol consumption (>1 U/d)	104 (41.6)	23 (34.8)	81 (44.0)	0.24
Smoking				
Ever	153 (61.2)	29 (43.9)	124 (67.4)	0.018
Current	26 (10.4)	11 (16.7)	15 (8.2)	0.003
Medication use, n (%)				
ACE-I or ARB	235 (94.0)	63 (95.5)	172 (93.5)	0.21
Aldosterone antagonist	174 (69.6)	47 (71.2)	127 (69.0)	0.063
Diuretic	227 (90.8)	62 (93.9)	165 (89.7)	0.30
β-Blocker	225 (90.0)	58 (87.9)	167 (90.8)	0.95

Values are mean ± SD, n (%), or median (interquartile range)*. ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; BMI, body mass index; CABG, coronary artery bypass grafting; CRT, cardiac resynchronization therapy; CVA, cerebrovascular accident; SBP, systolic blood pressure; DPB, diastolic blood pressure; HF, heart failure; ICD, implantable cardioverter defibrillator; IQR, interquartile range; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention

At baseline, HsTnT level was higher in men than in women [median (IQR): 19.6 ng/L (10.7-36.7) vs. 11.7 ng/L (7.2-27.7)]. Median eGFR was lower in women [median (IQR): 47.5 (IQR: 36.1-65.1) vs 62.5 mg/dL (IQR: 36.1-65.1, respectively]. For the other biomarkers, baseline levels were similar between women and men.

Follow-up and incidence of the PE

During a median follow-up of 2.2 years , a total of 1910 plasma samples (505 in 66 women and 1405 in 184 men) were collected and analyzed. A median (interquartile range, IQR) of 8 (5–10) urine and 9 (5–10) plasma samples were collected per patient. Median number of plasma samples collected per person was similar in women and men, whereas there was a slight difference in the median number of urine samples collected [median (IQR): women; 9 (IQR:5-10), men; 8 (IQR:5-10)]. During 2.2 (IQR:1.4-2.5) years, a total of 66/250 (26.4%) patients reached the PE of which 52 (78.8%) were male and 14 (21.2%) were female (log-rank, p = 0.28).

Associations between clinical characteristics and the PE

In women, age [HR (95%CI) 1.07 (1.01-1.12]), diabetes mellitus [HR (95%CI) 3.06 (1.06-8.87]) and PCI [HR (95%CI) 4.08 (1.43-11.67]) were associated with the PE, while in men these associations did not reach statistical significance. In men, MI [HR (95%CI) 1.81 (1.04-3.15]), valvular heart disease [HR (95%CI) 2.34 (1.29-4.25]) and chronic renal failure [HR (95%CI) 1.94 (1.07-3.53]) were associated with the PE, while in women these associations did not reach statistical significance. However, interaction terms with sex were only significant for PCI (p for interaction=0.018) and valvular heart disease (p for interaction=0.031). (Supplemental table 1)

Associations between NT-proBNP, HsTnT, CRP, and the PE

Baseline NT-proBNP was positively associated with the PE in both sexes. Differences in temporal patterns between patients with and without the PE were similar for men and women, with rising levels as the PE approached in both sexes (Figure 1A). However, NT-proBNP levels appeared higher over the full time-course in women experiencing the PE than in men experiencing the PE. This was reflected by the HRs entailed by the serially measured NTproBNP levels, which were numerically but not significantly higher in women [HR (95%CI): women; 7.57 (3.17- 21.93), men; 3.14 (2.09- 4.79), p for interaction = 0.104] (Table 2).

Table 2. Associations between cardiac and renal biomarkers, and the PE.

	All patients		Women		Men		P for interaction
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	
NT-proBNP							
Baseline level*	1.02 (1.02-1.03)	<0.001	1.02 (1.01-1.03)	<0.001	1.02 (1.02-1.03)	<0.001	0.261
Temporal evolution**	3.61 (2.49-5.37)	<0.001	7.57 (3.17-21.93)	<0.001	3.14 (2.09- 4.79)	<0.001	0.104
HsTnT							
Baseline level*	1.11 (1.06-1.16)	<0.001	1.26 (1.11-1.42)	<0.001	1.09 (1.03-1.15)	0.001	0.038
Temporal evolution**	5.85 (3.33-9.58)	<0.001	6.38 (2.18- 22.46)	0.001	4.91 (2.58-9.39)	<0.001	0.704
CRP							
Baseline level*	1.26 (1.06-1.50)	0.008	2.42 (1.40-4.20)	0.002	1.17 (0.95-1.45)	0.137	0.011
Temporal evolution**	3.95 (2.71-6.12)	<0.001	7.48 (3.43-19.53)	<0.001	3.29 (2.27 - 5.44)	<0.001	0.106
Creatinine							
Baseline level†	1.04 (0.99-1.09)	0.148	1.07 (0.96-1.19)	0.205	1.03 (0.97-1.09)	0.343	0.588
Temporal evolution**	1.15 (1.03-1.29)	0.012	1.12 (0.90-1.36)	0.278	1.13 (1.01-1.28)	0.038	0.925
eGFR							
Baseline level†	1.03 (0.99-1.07)	0.164	1.08 (0.99-1.17)	0.074	1.03 (0.98-1.08)	0.307	0.362
Temporal evolution**	1.10 (1.01-1.21)	0.028	1.19 (1.00-1.48)	0.048	1.14 (1.02-1.26)	0.028	0.679
Cystatin C							
Baseline level†	1.09 (1.04-1.14)	<0.001	1.11 (1.01-1.23)	0.029	1.08 (1.02-1.13)	0.002	0.598
Temporal evolution**	2.52 (1.89-3.50)	<0.001	1.90 (1.46-2.63)	<0.001	2.76 (2.01-3.98)	<0.001	0.111
NAG							
Baseline level*	1.07 (1.04-1.09)	<0.001	1.05 (1.01-1.09)	0.023	1.08 (1.05-1.12)	<0.001	0.248
Temporal evolution**	1.07 (1.02-1.13)	0.004	1.05 (0.97-1.15)	0.220	1.07 (1.00-1.13)	0.047	0.787
KIM							
Baseline level*	1.02 (1.00-1.04)	0.063	1.01 (0.97-1.04)	0.557	1.02 (1.00-1.04)	0.084	0.763
Temporal evolution**	1.08 (1.04-1.12)	<0.001	1.25 (1.02-1.62)	<0.001	1.06 (1.02-1.09)	0.01	0.209

*Hazard ratios and 95% CI are given per 10 units increase.
**Hazard ratios and 95% CI are given per doubling.
† Hazard ratios and 95% CI are given per 20% increase of creatinine, cystatin C and 20% decrease of eGF

For HsTnT, the association between baseline levels and the PE was stronger for women than for men [HR (95%CI) 1.26 (1.11-1.42), and [HR (95%CI) 1.09 (1.03-1.15), respectively; p for interaction = 0.038)]. Likewise, although levels rose in both sexes as the PE grew near, the difference in level at any moment in time between those with and those without the PE appeared larger in women than in men, although this difference was not statistically significant (Figure 1B). Again, this was reflected by the HRs entailed by the serially measured HsTnT levels [HR (95%CI): women; 6.38 (2.18-22.46), men; 4.91 (2.58-9.38); p for interaction = 0.704] (Table 2, Figure 1B).

Similar results were found for CRP. The association between baseline levels and the PE was stronger for women than for men [HR (95%CI) 2.42 (1.40-4.20), and HR (95%CI) 1.17 (0.95-1.45), respectively; p for interaction = 0.011] (Table 2, Figure 1C). Women showed a greater incline in CRP than men as they approached the PE. The temporal evolution of CRP level was associated with the PE in both sexes, but relative risk was numerically higher in women [HR (95%CI): women; 7.48 (3.43-19.53) , men; 3.29 (2.27-5.44); p for interaction = 0.106] (Table 2).

Associations between glomerular and tubular renal markers and the PE

The association between baseline levels of creatinine and the PE was similar in men and women [HR (95%CI): women; 1.07 (0.96-1.19), men; 1.03 (0.97-1.09); p for interaction = 0.588]. The temporal evolution was significantly associated with the PE only in men, but the effect estimate was of similar magnitude in women and not significantly different from that in men [HR (95%CI): men; 1.13 (1.01-1.28), women; 1.12 (0.90-1.36); p for interaction = 0.925] (Table 2, Figure 1D).

The association between baseline levels of eGFR was similar in men and women. (Table 2, Figure 1E) The temporal evolution of eGFR was associated with the PE in both sexes, and did not show relevant sex differences [HR (95%CI): women; 1.19 (1.00-1.48), men; 1.14 (1.02-1.26); p for interaction = 0.679]. Levels of Cystatin C at baseline were related to the PE in both sexes (Table 2, Figure 1F). Repeatedly measured cystatin C showed similar temporal patterns in men and women, with slightly higher risk of PE in men compared to women [HR (95%CI): women; 1.90 (1.46-2.63), men; 2.76 (2.01-3.98); p for interaction = 0.111] (Table 2).

With regard to NAG, baseline levels were associated with the PE without differences in the associations between men and women (Table 2, Figure 1G). The temporal evolution of NAG was associated with the PE in men [HR(95%CI) 1.07 (1.00-1.13), p = 0.047]. In women the risk estimate again was of similar magnitude but failed to reach statistical significance [HR(95%CI) 1.05 (0.97-1.15), p for interaction= 0.22] (Table 2).

For KIM, the baseline levels were not associated with the PE with no sex differences. (Table 2, Figure 1H) In both sexes, the temporal evolution of KIM was associated with the PE, but the association appeared somewhat stronger in women [HR(95%CI): women; 1.25 (1.02-1.62), men; 1.06 (1.02-1.09); p for interaction= 0.209] (Table 2).

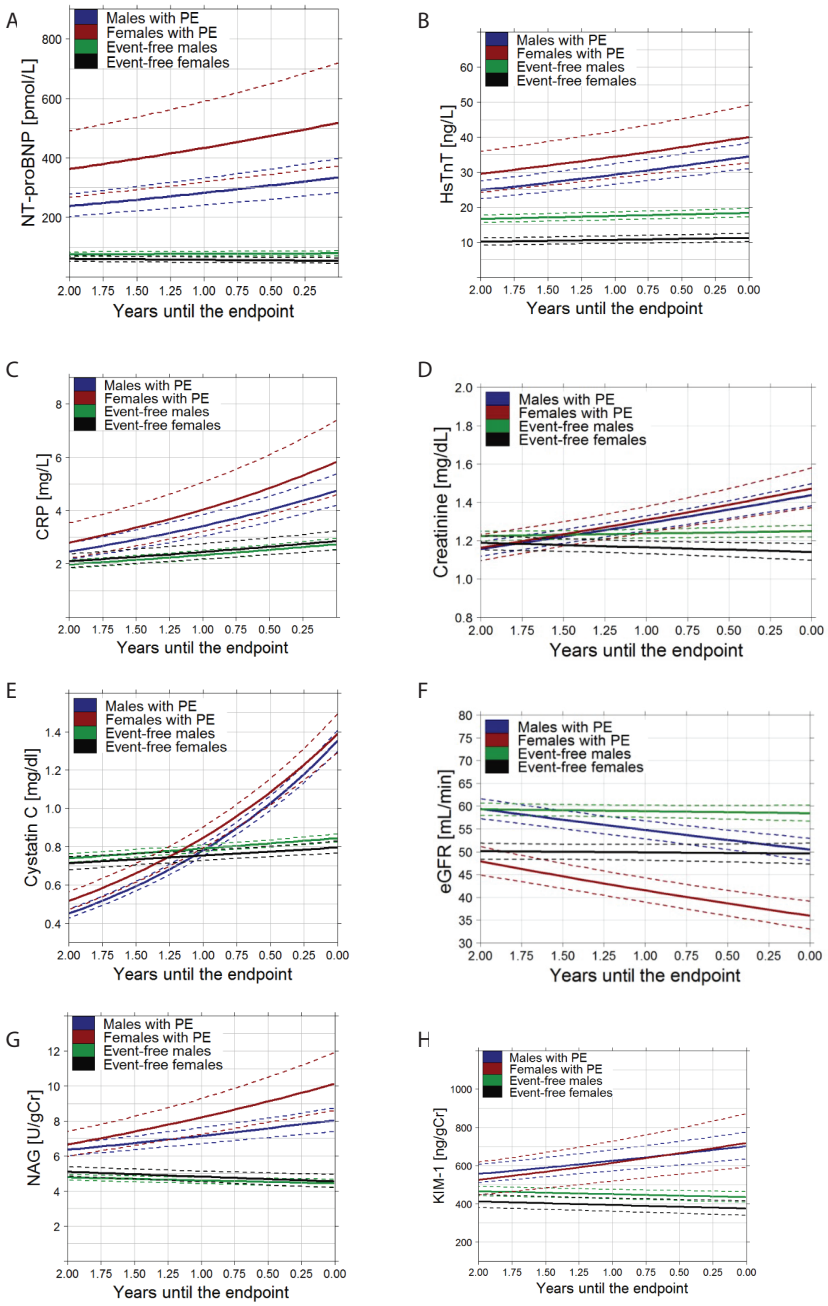

Fig. 1. Average evolution of circulating biomarkers during follow-up. Patients who reached the study endpoint are presented as a solid red line, and endpoint-free patients as a solid blue line. Dashed lines represent the 95% confidence interval. X-axis represents the time from baseline (left part of the x-axis), and time remaining to the event (patients who experienced incident events) or last sample moment (patients who remained event-free; right part of the x-axis). Biomarker levels are presented on the y-axis. (a) NT-proBNP (pmol/L). (b) hsTnT (ng/L). (c) CRP (mg/L). (d) Creatinine (mg/dL). (e) Cystatin C (mg/dL). (f) eGFR (mL/min). (g) NAG (U/gCr). (h) KIM-1 (ng/gCr). PE, primary endpoint.

DISCUSSION

In this cohort of 250 patients with HFrEF with a median follow-up time of 2.2 (IQR:1.4-2.5) years, the cumulative incidence of the PE was 28.3% in men and 21.2% in women although age at baseline was similar, confirming better prognosis in women with HF. Baseline levels of HsTnT and CRP were significantly stronger associated with the PE in women than in men. The temporal patterns of all studied biomarkers were associated with the PE, and overall showed disadvantageous changes as the PE approached. For NT-proBNP, HsTnT, and CRP, changes in temporal patterns appeared more outspoken in women than in men as the PE grew near, with higher levels over the entire follow-up duration and concomitant numerically higher hazard ratios. However, these differences did not reach statistical significance. Temporal patterns of glomerular and tubular renal markers showed similar associations with the PE in men and women.

Differences between men and women in the epidemiology of HF are most apparent when the type of HF is considered (1). In general, women are more often affected by HFpEF, and men by HFrEF. Nevertheless, over 20% of outpatients with HFrEF also consists of women (10). To date, only one study has examined sex difference in clinical characteristics and in survival in HFrEF patients. They observed that women had higher prevalence of risk factors including obesity, higher systolic blood pressure, and higher heart rate, but were less likely than men to have comorbidities, except for hypertension. Women had lower mortality than men [HR(95%CI): women; 0.68 (0.62-0.74), p<0.001], but more symptoms and worse quality of life. (11)

Moreover, few studies are available on sex differences in circulating biomarkers in heart failure patients, and in particular in HFrEF patients. Meyer et al examined HF patients with the full continuum of LVEF included in the Coordinating study evaluating Outcomes of Advising and Counseling in Heart failure (COACH). They determined biomarkers in 567 patients (38% women) shortly before discharge following a heart failure hospitalization. (21) Several biomarkers reflecting inflammation, remodeling and renal function were significantly lower in women, suggesting differences in biological disease expression, etiology and influence of comorbidities. Also, while NTpro-BNP did not differ between men and women at baseline, it showed different predictive value in women and men for 3-year all-cause mortality. This was also observed for several other biomarkers, albeit less explicitly.

Our study extends these findings by examining differences in temporal evolution of circulating biomarkers between men and women with HF, and moreover it is the first to focus specifically on HFrEF. While median baseline NT-proBNP level was similar in men and women, rise in level was more outspoken in women as the PE approached. Differences in sex hormones may contribute to these findings. Previous research has shown that women with hormone replacement therapy (HRT) have higher NT-proBNP levels than women without HRT, suggesting a stimulating effect of estrogen on natriuretic peptides that may in part also explain sex differences. (22) It should be noted however that given the relatively high age

of our study population and the limited use of hormone therapy in the Netherlands, other mechanisms are probably also at play here.

The association of Hs-TnT with clinical outcome was also stronger in women than in men in our study, although men had higher baseline Hs-TnT levels than women. The latter has recently also been shown by Lew et al.(23) Sex-related differences in body composition (24, 25), differences in anatomy leading to variation of the cardiac mass and coronary artery size (26) and cardiac remodeling related to sex hormones have been suggested to underlie these differences in troponin levels. (27)

How above-described mechanisms could also lead to more explicit temporal biomarker changes in women remains to be elucidated. In this context, previous research has demonstrated that estrogen receptor activation leads to reduction in necrotic and/or apoptotic cell death in animal models. Thus, apoptosis rate may be higher in men, which could potentially result in more unfavorable cardiac remodeling directly after ischemic injury. (28, 29) Such differences in the remodeling process may in part explain why biomarkers associated with cardiac remodeling including NT-proBNP and hsTnT show different patterns in men and women experiencing adverse clinical events

In our study, the association of CRP with clinical outcome was stronger in women than in men as well. Studies in the general population point towards higher CRP levels in women compared to men (30). As there is a strong correlation between CRP levels and subcutaneous fat, these higher levels could in part be explained by women having more subcutaneous, but not visceral, fat compared to men (31, 32). Further to these differences, an unfavorable temporal evolution of inflammatory status as signified by CRP, might have stronger consequences for clinical outcome in women than in men, in line with the known stronger impact on HF evolution carried by factors such as diabetes mellitus in women (33).

For clinical settings, the above findings imply that increasing levels of NT-proBNP, hsTnT and CRP over time may carry stronger predictive value for major adverse cardiovascular events in women compared to men with HFrEF. Therefore, levels of these biomarkers might need to be evaluated according to sex during clinical follow-up, and any consequences for estimation of prognosis based on changes in these biomarkers should also be evaluated according to sex. However, before any specific clinical recommendations can be made about subsequent timing or adaptation of therapy based on changes in biomarkers, trials on multiple-biomarker guided therapy which focus on both men and women are warranted.

In contrast with the sex differences we found for aforementioned markers, we found no differences between men and women in levels of glomerular and tubular markers, nor in the associations of renal markers with clinical outcome. An exception was baseline eGFR, which was lower in women than in men. It has previously been demonstrated that in general eGFR is lower in women than men with HF.(21) The hypothesis has been raised that men have a higher renal functional reserve to compensate for the loss of glomeruli during aging.(34, 35)

This suggests that eGFR is a less sensitive marker for HF in men than women. Recently, a study was published showing that Cystatin C is a gender-neutral glomerular rate biomarker that is preferred to eGFR.(36) In order to prevent underestimation of renal dysfunction in men with HF, use of Cystatin C as a glomerular rate biomarker should be considered as well. (36) Previous studies on sex differences in tubular renal markers in HF patients are scarce.

Some aspects of our study warrant consideration. Firstly, our study was not originally designed to examine sex differences, and consequently statistical power for this investigation was limited. Studies with larger sample size are needed to confirm our results. Furthermore, only limited molecular biological research is currently available on the effect of sex differences on proteins involved in wall stress, myocyte injury, inflammation and renal function. Such knowledge however is necessary to fully understand the biological processes underlying clinical epidemiological sex differences observed in these biomarkers.

In conclusion, this study demonstrates for the first time that the associations of temporal patterns of NT-proBNP, HsTnT, and CRP appear more outspoken in women than in men with HFrEF, whereas associations are similar for temporal patterns of eGFR, Cystatin C, NAG and KIM-1. Additional studies with larger sample sizes are warranted in order to confirm these findings, while molecular biology studies are needed to further unravel underlying mechanisms.

Conflict of interest

All authors declare no conflict of interest.

Author contribution

MMS, AS, IK and EB conceived the study. AS performed the data analysis and interpretation of data. MMS drafted the article. MMS and AS wrote the manuscript with support of EB, JRvL and IK. All authors revised it critically for important intellectual content.

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APPENDIX

Table 1. Association between clinical characteristics and the primary endpoint[2] stratified per sex

	Women		Men		
	HR	**95% CI**	**HR**	**95%CI**	**p for interaction**
Age	1.07	1.01-1.12	1.01	0.99-1.03	0.20
Race	0.045	0-1249.61	ref	ref	0.92
BMI	0.97	0.85-1.11	0.99	0.93-1.05	0.77
Heart Rate	1.02	0.97-1.06	1.02	0.99-1.04	0.97
SBP	1.00	0.97-1.02	0.98	0.97-1.00	0.50
DBP	0.97	0.93-1.02	0.97	0.95-1.00	0.97
Duration HF	1.00	0.91-1.10	1.07	1.03-1.12	0.16
NYHA class					
NYHA 1	ref	ref	ref	ref	0.72
NYHA 2	3.28	0.39-27.33	3.44	1.41-8.42	0.99
NYHA 3	10.25	1.26-83.59	6.32	2.56-15.62	0.69
NYHA 12vs34 (3/4)	4.14	1.45-11.9	2.73	1.57-4.75	0.52
LVEF	0.97	0.89-1.07	0.98	0.93-1.03	0.87
Etiology**					
IHD	2.34	0.81-6.77	1.20	0.69-2.08	0.29
HT	0.66	0.15-2.96	1.10	0.47-2.59	0.57
VALVHD	3.09	0.69-13.90	1.55	0.48-4.98	0.43
CMP	0.41	0.09-1.85	0.86	0.44-1.67	0.38
Type of CMP					
DCMP	0.34	0.05-2.64	0.74	0.35-1.57	0.46
HCMP	x	x	3.18	0.99-10.21	x
NCCMP	x	x	x	X	x
UNCCMP	2.76	0.36-21.31	x	X	X
Other	0.65	0.09-5.04	1.45	0.45-4.66	0.55
Medical History					
MI	0.94	0.26-3.39	1.81	1.04-3.15	0.35
PCI	4.08	1.43-11.67	0.96	0.55-1.69	0.018
CABG	0.84	0.11-6.24	1.09	0.56-2.12	0.81
Valvular heart disease	0.62	0.22-1.76	2.34	1.29-4.25	0.031
AF	1.98	0.69-5.67	1.33	0.77-2.31	0.44
ICD	1.55	0.52-4.63	1.20	0.68-2.15	0.67
CRT	0.50	0.14-1.81	0.92	0.51-1.66	0.45

	Women		Men		
	HR	95% CI	HR	95%CI	p for interaction
Pacemaker	1.41	0.38-5.26	1.04	0.50-2.15	0.63
CVA	1.03	0.23-4.68	1.60	0.82-3.12	0.64
Chronic renal failure	3.20	0.89-11.48	1.94	1.07-3.53	0.50
DM	3.06	1.06-8.87	1.62	0.93-2.81	0.34
Hypercholsterolemia	1.09	0.34-3.48	1.38	0.79-2.42	0.70
Hypertension	1.55	0.54-4.43	1.12	0.65-1.95	2.37
Alcohol consumption	1.22	0.42-3.51	1.80	1.00-3.22	0.19
Smoking ever/current	1.10	0.37-3.29	1.47	0.71-3.01	0.65
ACE-1 inhibitor/ARB	0.53	0.07-4.06	0.35	0.15-0.81	0.66
Aldosteron antagonist	0.62	0.21-1.85	1.71	0.88-3.33	0.12
Diuretics	0.73	0.10-5.59	6.54	0.90-47.35	0.13
Beta-blocker	0.25	0.08-0.82	0.86	0.34-2.16	0.14

ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; BMI, body mass index; CABG, coronary artery bypass grafting; CMP, cardiomyopathy; CRT, cardiac resynchronization therapy; CVA, cerebrovascular accident; DCMP, dilated cardiomyopathy; DPB, diastolic blood pressure; HCMP, hypertensive cardiomyopathy; HF, heart failure; HT, hypertension; ICD, implantable cardioverter defibrillator; IHD, ischemic heart disease; IQR, interquartile range; LVEF, left ventricular ejection fraction; NCCMP, non compaction cardiomyopathy; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; UNCCMP, unclassified cardiomyopathy; VALVHD, valvular heart disease.

* Composite of cardiac death, cardiac transplantation, left ventricular assist device implantation, and hospitalization due to acute or worsened chronic heart failure

** Some could not be tested because of paucity of events

6

The effect of age on blood pressure response by 4-week treatment perindopril: A pooled sex-specific analysis of the EUROPA PROGRESS and ADVANCE trials

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Published in ***Clinical Translational Science***
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ABSTRACT

Previous studies showed that postmenopausal women are more likely to have poorly controlled hypertension than men of the same age. Whether this is caused by inadequate treatment or poor response to antihypertensive agents remains unknown. The aim of this study is to analyze treatment response to the most potent renin angiotensin aldosterone system (RAAS) inhibitor perindopril in different age categories in women and men. Individual patient data were used from the combined European Trial on Reduction of Cardiac Events With Perindopril (EUROPA), Perindopril Protection Against Recurrent Stroke Study (PROGRESS), and Action in Diabetes and Vascular disease: Preterax and Diamicron-MR Controlled Evaluation (ADVANCE) trials, which include patients with vascular disease (n = 29,463). We studied the relative and absolute changes in systolic blood pressure (SBP) and diastolic blood pressure (DBP) during a 4-week run-in phase in which all patients were treated with the perindopril-based treatment in different age categories. In total, 8366 women and 21,097 men were included in the analysis. Women greater than 65 years of age showed a significantly smaller blood pressure reduction after perindopril treatment (2.8 mmHg [95% confidence interval {CI} = 0.1–5.5] less reduction compared to women ≤45 years, p = 0.039). In men, the SBP reduction after perindopril in patients greater than 55–65 and greater than 65 years was lower compared to the age category less than or equal to 45 years (adjusted mean difference >55–65: 2.8 mmHg [95% CI = 1.8–3.7], p < 0.001, >65: 3.7 mmHg [95% CI = 2.7–4.7], p < 0.001). A trend of less blood pressure reduction was seen with ageing in both men and women (p < 0.001). To conclude, we observed that in both women and men the perindopril leads to less SBP reduction with increasing age, whereas the DBP reduction increases with age. More research is needed to determine whether it would be beneficial to use age-adjusted perindopril dosages.

Study Highlights

- What is the current knowledge on the topic?
  Previous animal studies have shown that the response to antihypertensive treatment targeting the RAAS might be different after reproductive senescence.
- What question did this study address?
  Are there differences in perindopril-based treatment response to RAAS inhibitor perindopril in different age categories in women and men?
- What does this study add to our knowledge?
  In both women and men, the effects of perindopril on SBP decrease and on DBP increase with age.
- How might this change clinical pharmacology or translational science
  More research is needed to find out whether it would be beneficial to use age-adjusted perindopril dosages in isolated systolic hypertension

INTRODUCTION

Premenopausal women typically have lower blood pressure than age-matched men. (1) Studies have shown that aging in men and women is accompanied by an increase in blood pressure, and that this age-related increase is more prominent in women after menopause. (2) As a result, the prevalence of hypertension in postmenopausal women is higher than in age-matched men. (3) Moreover, postmenopausal women are more likely to have poorly controlled hypertension than men. (3) Whether this is caused by inadequate treatment or poor response to antihypertensive agents remains unknown.

Renin angiotensin aldosterone system (RAAS) inhibitors, such as angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs) are a mainstay treatment for hypertension. In recent years, animal studies have provided strong evidence that sex- and age-related differences exist in the RAAS. (4) For example, sex chromosomes and sex hormones are known to modulate the depressor/pressor balance of the RAAS with female mice having greater expression of the depressor components of the RAAS (e.g., angiotensin type 2 receptor and angiotensin converting enzyme 2). Consequently, females of reproductive age are less sensitive to the vasopressor effects of angiotensin II than age-matched males (5) and aging reproductively senescent females.(4) In humans, the acute infusion of angiotensin II has similar effects on blood pressure between women and men. However, when given an ARB, the depressor response is more rapid in premenopausal women as compared to men. (6) Therefore, the response to antihypertensive treatment targeting the RAAS might be different after menopause. Earlier sex-specific analyses of RAAS inhibitors compared men and women and did not take menopausal status in account.(7)

As a result of above described differences in RAAS, the short-term response of ACEi on blood pressure might differ between women and men in relation to age. To evaluate this hypothesis, we performed a proof-of-principal study based on the 4-week run-in phase of three large randomized controlled trials of the ACEi perindopril in cardiovascular (CV) patients: the European Trial on Reduction of Cardiac Events With Perindopril (EUROPA), Perindopril Protection Against Recurrent Stroke Study (PROGRESS) and Action in Diabetes and Vascular disease: preterAx and diamicroN-MR Controlled Evaluation (ADVANCE).(8-10)

METHODS

Patients and material

EUROPA, PROGRESS and ADVANCE studied the effectiveness of perindopril to reduce CV outcomes in patients with diabetes mellitus type 2 or established CV disease (CVD). (8-10), EUROPA included patients with stable coronary heart disease, PROGRESS studied patients with a history of stroke or transient ischemic attack (TIA) and ADVANCE enrolled patients with type 2 diabetes. In all three trials, potentially eligible patients entered a pre-randomization run-in phase of 4-6 weeks during which they received open-label perindopril. For the current study, we only used the blood pressure data that were obtained during this run-in. The dosage of perindopril and the comedication varied between the trials: EUROPA studied perindopril 4 mg/day for two days followed by 8 mg/day for two weeks; PROGRESS studied perindopril 2 mg/day for two weeks followed by 4mg/day for two weeks, ADVANCE studied a fixed dose combination of perindopril 2 mg/day plus indipamide 0.625 mg/day. The combined dataset has been used previously and confirmed the consistency of the treatment benefit of perindopril within patients at different level of risk but with the same underlying disease (vascular disease). Heterogeneity of the treatment effect of perindopril has been studied previously within these cohorts as well as on pharmacological levels, where perindopril is one of the more potent ACE-inhibitors in terms of bradykinin release (11-13), which makes it the most relevant to study.

Data analysis and presentation

Continuous baseline characteristics are presented as mean values ± one standard deviation (SD), whereas categorical characteristics are presented as numbers and percentages. Differences between women and men, as well as differences between age categories were studied by Student's T-tests and linear trend tests for continuous data, and by chi-square tests for categorical data.

Information on menopausal (hormonal) status in women was not systematically collected. Alternatively, we used the women's (baseline) age to estimate menopausal (hormonal) status. We considered the following age-strata: ≤45 years, >45-55 years, 56-65 years and >65 years. According to the US National Institute of Health,(14) these thresholds correspond with most common start (45 years) and end (55 years) of the menopausal transition, and with a definite (late) postmenopausal status (65 years). Univariable and multivariable linear regression analyses were applied to study changes in systolic (SBP) and diastolic blood pressure (DBP) during the run-in phase in relation to sex and age. In multivariable analyses, we adjusted for trial of origin and CV risk factors, including diabetes, stroke/TIA and history of CVD (among other factors). We report crude and adjusted mean changes with corresponding 95% confidence interval (CI).

IBM SPSS statistics 25 was used for the analyses. A 2-sided p value <0.05 was considered as significant.

RESULTS

In total, 8366 women and 21097 men were included in the analysis. We observed significant differences in baseline characteristics in relation to age with respect to blood pressure, CV risk factors, cardiovascular history and medication in both sexes (Table S1). In women and men, the prevalence of hypertension and diabetes increased with age, while the prevalence of smoking and previous CVD was not age-related. Platelet inhibitors, beta blockers and lipid lowering agents were more often used by younger patients, while calcium blockers were more frequently used by the elderly (Table S1).

Women

In women, pre-treatment SBP showed a significant increasing trend with age, from a mean of 134.7 mmHg in patients ≤45 years to 137.7, 143.3 and 148.5 mmHg in those aged >45-55,>55-65 and >65 respectively (P-value for trend <0.001) (Table 1). An inverse trend with age was observed for pre-treatment DBP (Table 1).

In unadjusted analyses, a significant SBP reduction after the run-in period with perindopril was observed in all age categories, which was numerically smallest in patients ≤45 years (mean change -6.1 mmHg (-5.3%)) and largest in those >45-55 years (mean change -8.5 mmHg (-7.3%)), however the differences between the age categories were not significant. Also, we found no consistent, significant (linear) trend for SBP reduction after perindopril treatment in relation to age (P-value trend test=0.425) (Table 1). After multivariable adjustment for potential confounders, we observed a significant positive linear trend for both absolute and relative SBP reduction in relation to age (P-value trend test < 0.001) meaning that the perindopril response on SBP decreases with age.

In unadjusted analyses, the DBP response to perindopril showed a similar pattern to SBP, with numerically smallest change in patients ≤45 years (mean change -2.7 mmHg,-2.3%) compared to patients >45-55 years (-4.3 mmHg,-3.6%) , patients >55-65 years (-3.6 mmHg, -3.0%) and >65 years (-3.4 mmHg, -2.8%)), but without significant intergroup differences. After multivariable adjustment, we observed a negative significant (linear) trend (P for trend <0.001) meaning that the response on DBP increases with age. (Table 1)

Table 1. Systolic and Diastolic Blood Pressure response after 4-week perindopril-based treatment in women and men in different age categories.

		Women						
Metric	**Age groups, years**	**Mean (SD) baseline value**	**Unadjusted mean (95% CI) difference**	**P-value trend test**	**P-value for comparison with the reference**	**Adjusted mean difference (95% CI) ***	**P-value adjusted trend test**	**P-value for comparison with the reference**
SBP pretreatment, mmHg	≤45	134.7(17.8)	-ref-	<0.001	-ref-	-ref-	<0.001	
	>45-55	137.7(19.3)	3.0 (-0.6, 6.7)		0.105	2.6 (-0.6, 6.2)		0.104
	>55-65	143.3(19.8)	8.6 (5.1, 12.1)		<0.001	7.6 (4.3, 10.8)		<0.001
	>65	148.5(21.3)	13.9 (10.4, 17.3)		<0.001	12.2 (8.9, 15.5)		<0.001
DBP pretreatment, mmHg	≤45	84.5 (11.4)	-ref-	<0.001	-ref-	-ref-	<0.001	
	>45-55	83.8 (10.3)	-0.8 (-2.7, 1.1)		0.427	0.2 (-1.6, 1.9)		0.848
	>55-65	81.9 (10.3)	-2.6 (-4.4, -0.8)		0.004	-1.0 (-2.7, 0.7)		0.240
	>65	80.3 (10.7)	-4.2 (-6.0, -2.4)		<0.001	-3.0 (-4.7, -1.3)		0.001
Delta SBP, mmHg	≤45	-6.1 (13.7)	-ref-	0.425	-ref-	-ref-	<0.001	
	>45-55	-8.5 (16.2)	-2.4 (-5.6, 0.8)		0.139	-1.5 (-4.3, 1.2)		0.275
	>55-65	-8.2 (17.1)	-2.1 (-5.2, 0.9)		0.169	0.7 (-1.9, 3.4)		0.594
	>65	-8.4 (18.8)	-2.4 (-5.4, 0.7)		0.127	2.8 (0.1, 5.5)		0.039
Delta SBP (%)	≤45	-5.3 (10.8)	-ref-	0.958	-ref-	-ref-	<0.001	
	>45-55	-7.3 (12.8)	-2.0 (-4.4, 0.4)		0.098	-1.5 (-3.6, 0.7)		0.175
	>55-65	-6.9 (13.0)	-1.6 (-3.9, 0.7)		0.166	0.2 (-1.8, 2.3)		0.842
	>65	-6.9 (13.9)	-1.6 (-3.9, 0.7)		0.163	1.7 (-0.3, 3.8)		0.101
Delta DBP, mmHg	≤45	-2.7 (10.0)	-ref-	0.145	-ref-	-ref-	<0.001	-ref-
	>45-55	-4.3 (8,9)	-1.6 (-3.3, 0.1)		0.065	-2.1 (-3.5, -0.6)		0.006
	>55-65	-3.6 (9.5)	-1.0 (-2.6, 0.7)		0.245	-2.5 (-3.9, -1.1)		0.001
	>65	-3.4 (9.7)	-0.8 (-2.4, 0.8)		0.343	-3.2 (-4.6, -1.8)		<0.001
Delta DBP, %	≤45	-2.3 (8.0)	-ref-	0.018	-ref-	-ref-	<0.001	-ref-
	>45-55	-3.6 (7.1)	-1.3 (-2.6, 0.0)		0.056	-1.6 (-2.8, -0.5)		0.005
	>55-65	-3.0 (7.3)	-0.6 (-1.9, 0.6)		0.308	-1.8 (-2.9, -0.8)		0.001
	>65	-2.8 (7.2)	-0.4 (-1.6, 0.8)		0.513	-2.4 (-3.5, -1.3)		<0.001

*Adjusted for hypertension, diabetes mellitus, smoking, previous myocardial infarction, previous revascularization, previous stroke, previous transient ischemic attach/stroke, mean systolic blood pressure, mean diastolic blood pressure, platelet inhibitors, betablockers, calcium blockers, lipid lowering agents, type of study (EUROPA, PROGRESS, ADVANCE)

SD = standard deviation

EUROPA = European Trial on Reduction of Cardiac Events With Perindopril, PROGRESS = Perindopril Protection Against Recurrent Stroke Study , ADVANCE = Action in Diabetes and Vascular disease: Preterax and Diamicron-MR Controlled Evaluation

Men						
Mean (SD) baseline value	**Unadjusted mean (95% CI) difference**	**P-value trend test**	**P-value for comparison with the reference**	**Adjusted mean difference (95% CI) ***	**P-value adjusted trend test**	**P-value for comparison with the reference**
130.7 (14.3)	-ref-	<0.001	-ref-	-ref-	<0.001	-ref-
134.9 (15.8)	4.2 (2.9, 5.5)		<0.001	2.4 (1.2, 3.6)		<0.001
140.5 (18.0)	9.9 (8.6, -11.1)		<0.001	6.2 (5.0, 7.3)		<0.001
145.2 (19.0)	14.6 (13.3, 15.8)		<0.001	9.8 (8.6, 11.0)		<0.001
83.1 (9.0)	-ref-	<0.001	-ref-	-ref-	<0.001	-ref-
84.0 (9.4)	0.9 (0.2, 1.6)		0.013	0.4 (-0.3, 1.0)		0.268
83.1 (9.7)	0.1 (-0.6, 0.7)		0.874	-0.7 (-1.4, -0.1)		0.024
81.1 (10.0)	-2.0 (-2.7, -1.3)		<0.001	-3.2 (-3.9, -2.6)		<0.001
-8.4 (12.5)	-ref-	0.601	-ref-	-ref-	<0.001	-ref-
-8.6 (14.2)	-0.2 (-1.4, 0.9)		0.697	0.8 (-0.2, 1.8)		0.129
-8.0 (15.6)	0.4 (-0.7, 1.5)		0.451	2.8 (1.8, 3.7)		<0.001
-8.6 (16.5)	-0.2 (-1.3, 0.9)		0.704	3.7 (2.7, 4.7)		<0.001
-7.4 (10.4)	-ref-	0.218	-ref-	-ref-	<0.001	-ref-
-7.5 (11.6)	-0.1 (-1.0, -0.8)		0.834	0.5 (-0.3, 1.3)		0.205
-6.7 (12.0)	0.7 (-0.2, 1.5)		0.128	2.1 (1.3, 2.8)		<0.001
-7.1 (12.5)	0.3 (-0.6, 1.1)		0.495	2.7 (1.9, 3.5)		<0.001
-4.6 (8.6)	-ref-	0.002	-ref-	-ref-	<0.001	-ref-
-4.4 (9.0)	0.2 (-0.4, 0.9)		0.500	0.3 (-0.2, 0.9)		0.239
-3.7 (8.9)	0.9 (0.2, 1.5)		0.006	0.2 (-0.4, 0.7)		0.522
-3.9 (9.2)	0.7 (0.1, 1.4)		0.022	-1.3 (-1.9, -0.7)		<0.001
-4.0 (7.2)	-ref-	<0.001	-ref-	-ref-	<0.001	-ref-
-3.8 (7.4)	0.3 (-0.3, 0.8)		0.314	0.3 (-0.2, 0.7)		0.226
-3.1 (6.9)	1.0 (0.5, 1.5)		<0.001	0.3 (-0.2, 0.7)		0.255
-3.1 (7.0)	0.9 (0.4, 1.4)		<0.001	-0.9 (-1.3, -0.4)		<0.001

Men

In men, pre-treatment SBP and DBP showed similar trend as in women, with a significant increasing trend for SBP with age, from a mean of 130.7 mmHg in patients ≤45 years to 134.9 and 145.2 mmHg in those >45-55 and >65, respectively (P-value for trend <0.001) and pre-treatment DBP showing an inverse trend with age. (Table 1)

In unadjusted analyses, a significant SBP reduction after the run-in period with perindopril was observed in all age categories, which was numerically smallest in patients >55-65 years (-8.0 mmHg, -6.7%) and largest in those >45-55 years (-8.6 mmHg, -7.5%) with no significant intergroup differences (Table 1). After multivariable adjustment, we observed a positive significant (linear) trend for SBP reduction in relation to age (P<0.001), meaning that the response on SBP decreases with age (Table 1).

The DBP response to perindopril in the univariate analyses showed a linear pattern over age, with numerically smallest change in patients >55-65 years (-3.7 mmHg, -3.1%) and largest in patients ≤45 years (-4.6 mmHg, -4.0%) (P-value for trend 0.002) (Table 1). The multivariate analyses showed a significant negative (linear) trend over age (P for trend < 0.001) meaning that DBP response increases with age (Table 1).

DISCUSSION

This study of 29459 patients treated with perindopril for 4-6 weeks is the largest study so far studying the blood pressure response over age for women and men. Elderly patients had higher pre-treatment SBP, whereas perindopril-induced SBP reductions declined with age. In contrast, elderly patients had lower pre-treatment DBP, while DBP reductions increased with age. After adjustment for potential confounders, we found no relevant differences in blood pressure response between women and men.

Previous research has shown that SBP increases linearly with age, due to arterial and arteriole stiffness, which is also seen in our study population.(15) DBP is known to have a varying pattern with aging: a systematic rise is seen from until the age of ~50 years, whereas thereafter DBP slowly declines with age, which we also observed in our study population. (16)

In women, the menopausal transition leads to additional significant increases in arterial pressure. (17) Genetic factors affecting RAAS and eNOS, environmental factors such as BMI, cholesterol and obesity and hormonal changes are thought to contribute to the increase in BP in menopause. (18) The drop in estrogen during menopause leads to vascular changes, which has been shown before to occur during the menstrual cycle as well: in the luteal phase, when estradiol levels are highest, blood pressure is lower compared to the follicular phase. (19)

In addition, previous animal studies have shown that estrogen causes increased expression of angiotensinogen and renin and downregulates angiotensinogen converting enzyme (ACE). This leads to a decrease in plasma angiotensin II, which has a decrease in blood pressure as a result.(20-22)

This hypothesis has been proven in human studies as well. Serum ACE activity was lower in normotensive pregnant women, who have increased estrogen levels, as compared to non-pregnant women. (23) Also, hormone replacement therapy (HRT) in postmenopausal women is correlated to higher ACE activity compared to postmenopausal women not using HRT.(24)

However, our study shows that these differences in ACE activity in women at older age do not lead to a different response to the 4-6 week treatment of perindopril compared to premenopausal women. We showed, that, women and men ≤45 years have lower SBP before treatment and higher the absolute SBP reduction compared to the age group >65 years. In women, this could imply that physiological differences are subtle and overcome by pharmacological intervention. In men, more research is needed to find out the less responsiveness to perindopril above the age of 55 years. However, it has to be taken into account that the absolute and relative differences found in the different age categories were small and might not of clinical relevance for the individual. Nevertheless, even small changes in blood pressure (response) can be relevant on population level.

In general, menopausal status should be taken into account when studying drug effects in women, considering major differences regarding pharmacokinetics (for instance body composition) and pharmacodynamics (for instance RAAS activity). Previous evidence suggested that age affects ACE-inhibitor response in female mice,(4) however we observed that the 4-week perindopril response in SBP declines with age in women and the DBP response increases with age in both men and women. Also, decreasing testosterone levels are known to reduce ACE-activity as well (25), so more research is needed in this field to find out whether this could be the leading cause of older men showing less SBP reduction after treatment with ACEi.

Limitations

The findings of this study have to be seen in light of some limitations. First, EUROPA, PROGRESS and ADVANCE enrolled different types of patients, whereas various doses of perindopril were studied, whether or not in combination with other agents that influence blood pressure, including thiazide diuretics. These between-trial variations might somewhat complicate the interpretation of our findings. However, noteworthy, differences in clinical phenotypes and treatment regimens were the same in all age categories and do, therefore, most likely, not explain the differences we found. Indeed, accounting for the trial of origin in the multivariable regression models did not alter our findings and conclusions.

Second, our analysis included a total of 8366 women, which, although substantial, was lower than the number of men (N=21097). It is a well-known phenomenon that fewer women than men are enrolled in cardiovascular trials. Without going into detail, the clinical phenotype studied is one of the reasons why.(26) Indeed, we found variations in the percentage of women that were enrolled in EUROPA (15%), PROGRESS (30%) and ADVANCE (43%). Since our findings were homogeneous across the trials, we feel justified to obtain pooled estimates, also in the various age-strata in women. Nevertheless, the obtained estimates in women are less certain than in men, because of the smaller numbers.

Third, information on pre-, peri- and postmenopausal state was not systematically collected at the study entry visits. Alternatively, for our analyses, we used the women's (baseline) age to estimate menopausal (hormonal) status. Although, most likely, most women ≤45 years were premenopausal en those >55 years postmenopausal, we acknowledge the lack of precision of our definition; however, this is a common issue since the exact transition can be difficult to define and depends on the remembrance of the patients. Also, most women that we studied had established vascular disease. In view of the relation between menopausal status and (cardio)vascular disease, we appreciate that the label ''premenopausal'' for all women ≤45 years can be questioned.(27)

Conclusion

To conclude, we observed that in both women and men the perindopril response on SBP decreases with age and DBP response increases with age. More research is needed to determine whether this is caused by changing levels of sex hormones in women and men and whether it would be beneficial to use age-adjusted perindopril dosages especially in isolated systolic hypertension as commonly seen in elderly.

Acknowledgements

Our analyses are based on the individual patient data of the EUROPA, PROGRESS and ADVANCE trials, which we obtained by courtesy of Servier.

Author contributions

M.M.S., K.M.M.C., J.V., E.B., and J.R.v.L. wrote the manuscript. J.V. designed the research. M.M.S. and J.B. performed the research and analyzed the data.

Conflicts of interest

All authors declared no competing interests for this work.

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APPENDIX

Table S1. Sex-specific baseline characteristics with statistical testing between age categories

		A1: ≤45 years		A2: >45-55 years	
		F	M	F	M
Patient characteristics (n.%)	n=29463	N=138 (1.6)	N=858 (4.1)	N=874 (10.4)	N=3822 (18.1)
Hypertension (n, %)	54.1%	62 (44.9)	208 (24.2)	471 (53.9)	1408 (36.8)
Diabetes (n, %)	45.5%	10 (7.2)	53 (6.2)	313 (35.8)	689 (18.0)
Smoking (n, %)	16.2%	31 (22.5)	245 (28.6)	154 (17.6)	1026 (26.8)
Previous MI (n, %)	32.8%	53 (38.4)	543 (63.3)	256 (29.3)	1962 (51.3)
Previous revascularization (n, %)		35 (25.4)	356 (41.5)	204 (23.3)	1645 (43.0)
Previous TIA/stroke (n, %)	27%	67 (48.6)	155 (18.1)	329 (37.6)	776 (20.3)
Platelet inhibitors (n, %)	70.8%	107 (77.5)	754 (87.9)	620 (70.9)	3290 (86.1)
Betablockers (n, %)	38.8%	61 (44.2)	495 (57.7)	368 (42.1)	2100 (54.9)
Calcium blockers (n, %)	33.3%	39 (28.3)	201 (23.4)	286 (32.7)	1131 (29.6)
Lipid lowering agents (n, %)	39.5%	57 (41.3)	479 (55.8)	336 (38.4)	1927 (50.4)
Study (n, %)					
EUROPA		73 (52.9)	704 (82.1)	258 (29.5)	2913 (76.2)
PROGRESS		65 (47.1)	154 (17.9)	281 (32.1)	662 (17.3)
ADVANCE		0	0	335 (38.3)	247 (6.5)

MI = myoardial infarction. TIA = transient ischemic attack. EUROPA = European Trial on Reduction of Cardiac Events With Perindopril. PROGRESS = Perindopril Protection Against Recurrent Stroke Study . ADVANCE = Action in Diabetes and Vascular disease: Preterax and Diamicron-MR Controlled Evaluati

A3: >55-65 years		A4: >65 years		P-value
F	M	F	M	
N=3327 (39.8)	N=7985 (37.8)	N=4027 (48.1)	N=8432 (40.0)	
2251 (67.7)	3983 (49.9)	2849 (70.7)	4707 (55.8)	M: P<0.001 F: P<0.001
2242 (67.4)	3347 (41.9)	2659 (66.0)	4090 (48.5)	M: P<0.001 F: P<0.001
416 (12.5)	1625 (20.4)	291 (7.2)	976 (11.6)	M: P<0.001 F: P<0.001
540 (16.2)	2959 (37.1)	672 (16.7)	2686 (31.9)	M: P<0.001 F: P<0.001
435 (13.1)	2495 (31.2)	491 (12.2)	2166 (25.7)	M: P<0.001 F: P<0.001
912 (27.4)	2024 (25.3)	1192 (29.6)	2490 (29.5)	M: P<0.001 F: P<0.001
1846 (55.5)	5974 (74.8)	2324 (57.7)	5952 (70.6)	M: P<0.001 F: P<0.001
1003 (30.1)	3289 (41.2)	1191 (29.6)	2911 (34.5)	M: P<0.001 F: P<0.001
1164 (35.0)	2691 (33.7)	1405 (34.9)	2899 (34.4)	M: P<0.001 F: P=0.243
1183 (35.6)	3484 (43.6)	1317 (32.7)	2845 (33.7)	M: P<0.001 F: P=0.001
660 (19.8) 608 (18.3) 2059 (61.9)	3779 (47.3) 1549 (19.4) 2657 (33.3)	700 (17.4) 898 (22.3) 2429 (60.3)	3131 (37.1) 1888 (22.4) 3413 (40.5)	M: P<0.001 F: P<0.001

7

Sex differences in Reported Adverse Drug Reactions to Angiotensin-Converting Enzyme Inhibitors

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Published in ***JAMA Network Open***
https://pubmed.ncbi.nlm.nih.gov/35442456/

ABSTRACT

This cross-sectional study investigates differences by sex in reporting of adverse drug reactions associated with angiotensin-converting enzyme inhibitors combining global and prescription-corrected databases.

Introduction

Sex differences in adverse drug reactions (ADRs) of angiotensin-converting enzyme inhibitors (ACEIs) remain poorly understood due to lack of sex-specific ADR data from clinical trials(1). Post-marketing pharmacovigilance data, containing highly structured and detailed ADR information, can play an important role here. However, these data are often not corrected for prescription numbers and therefore cannot separate sex differences in ADR risk from sex differences in prescription rates. To investigate whether women report more ACEI-related ADRs than men after correction for sex-specific prescription and describe sex differences in reported ADR types, we combined data from the global pharmacovigilance database VigiBase and the prescription-corrected Dutch pharmacovigilance database Lareb.

Methods

We studied all ADR reports submitted by patients and health care professionals between 1980 and January 2020 for VigiBase and 2003 and January 2021 for Lareb that included information on sex. Drug name, patient sex and age, and detailed ADR classification were extracted. Outcomes were number of reports by sex and type of ADR classified according to MedDRA hierarchy. Dutch prescription data were obtained from the Medical Product Information Project database. Sex-specific reporting rates of ADRs per 100 000 individuals were calculated by dividing the total number of reports by the total number of individuals. We used rate differences and incidence rate ratios to investigate whether sex differences in ADR incidence were statistically significant. We calculated and compared the ADR type-specific number of and absolute difference in reports (see Supplementary Methods for more details).

Results

VigiBase included 227 482 ACEI-related ADR reports (53% women), and Lareb included 3903 reports (52% women). Most reports came from individuals aged 45 to 64 years (98 339 individuals [42.5%]). After Lareb data were corrected for sex-specific prescription rates, the ADR reporting rate per 100 000 individuals was 25 reports in women and 18 reports in men, for an absolute rate difference of 6 reports (95% CI, 4 to 7 reports) per 100 000 individuals. Women had a 1.31-fold higher reporting rate of ADRs (95% CI, 1.27-1.35) compared with men. Cough and angioedema were the most frequently reported ADRs among women and men in VigiBase and Lareb (Table). Women outnumbered men in 19 of 27 ADR categories,

with most reports with more women in respiratory, gastrointestinal, and general disorders categories and reports with more men in skin and subcutaneous tissue, kidney and urinary, and reproductive system and breast tissue disorder categories (Figure, A). Figure, B-G, shows a more detailed breakdown across ADR types within 3 categories with the largest excess of female reports (B-D) and male reports (E-G).

Table 1. Ten most commonly reported adverse drug reactions at MedDRA preferred term level in the global database VigiBase and the Dutch database Lareb, stratified by sex

	Vigibase		Lareb	
	Women	Men	Women	Men
1	Cough (n = 10,909)	Cough (n = 7701)	Angio-oedema (n = 199)	Angio-oedema (n = 153)
2	Angio-oedema (n = 3441)	Angio-oedema (n = 6634)	Cough (n = 163)	Cough (n = 124)
3	Dizziness (n = 2509)	Acute kidney injury (n = 2830)	Therapeutic response unexpected (n = 70)	Therapeutic response unexpected (n = 91)
4	Drug hypersensitivity (n = 2323)	Hyperkalaemia (n 2159)	Dizziness (n = 51)	Dizziness (n = 49)
5	Headache (n = 1965)	Dizziness (n = 2056)	Headache (n = 51)	Pruritus (n = 45)
6	Nausea (n = 1810)	Hypotension (n = 1949)	Alopecia (n = 44)	Erectile dysfunction (n = 37)
7	Acute kidney injury (n = 1793)	Dyspnoea (n = 1540)	Dyspnoea (n = 42)	Fatigue (n = 36)
8	Dyspnoea (n = 1723)	Pruritus (n = 1309	Nausea (n = 39)	Myalgia (n = 29)
9	Drug ineffective (N = 1605)	Drug ineffective (n = 1272)	Paraesthesia (n = 37)	Headache (n = 29)
10	Pruritus (n = 1456)	Headache (n = 1213)	Rash (n = 35)	Muscle spasms (n = 27)

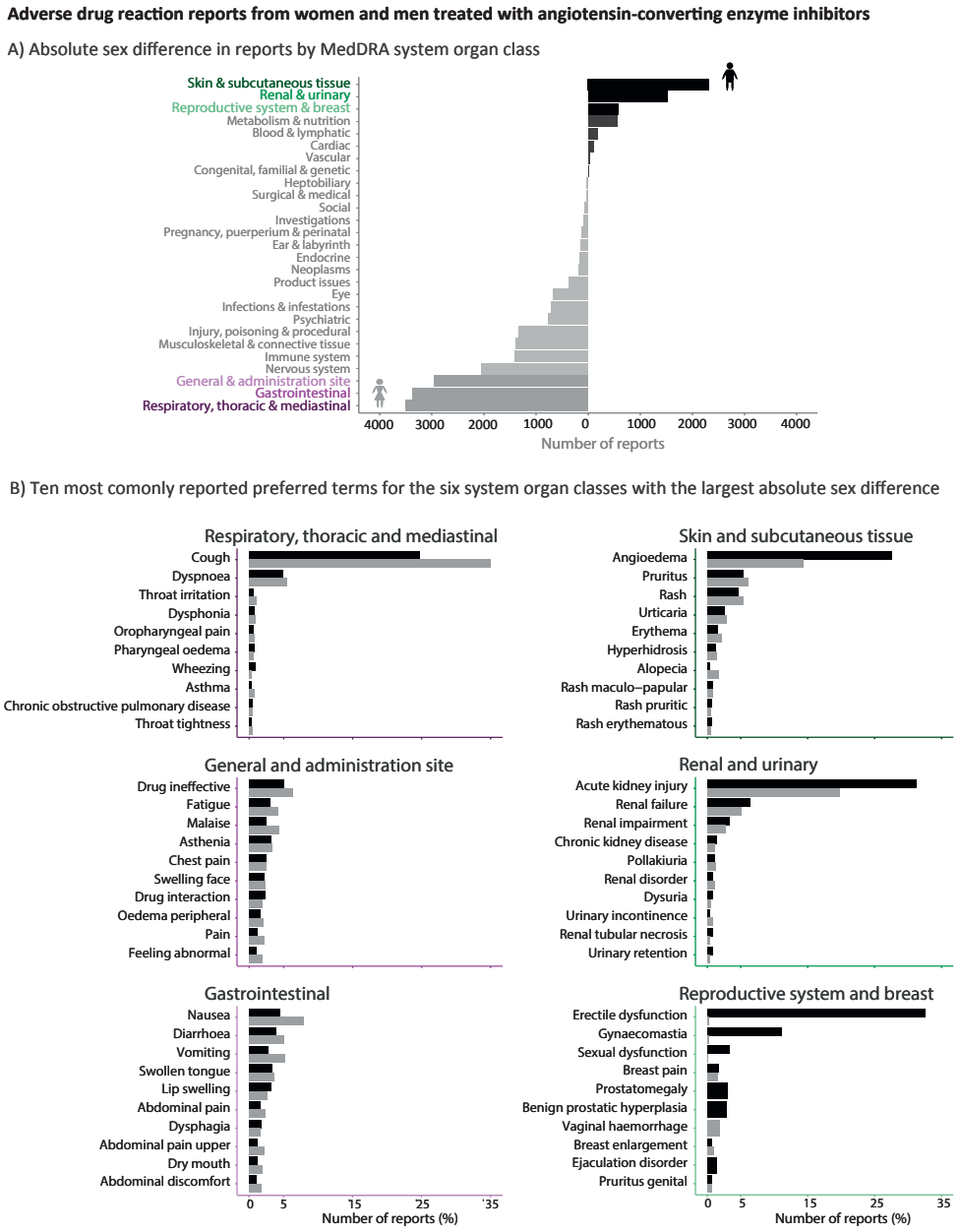

Figure 1 A) Absolute sex difference in number of adverse drug reaction reports in Vigibase per system organ class; B) ten most commonly reported preferred term-level adverse drug reactions for the six system organ classes with the largest sex difference

DISCUSSION

These findings are in line with a previous study suggesting women experience more ADRs than men(2). The 1.31-fold higher ADR incidence in women compared with men is large considering that ACEIs comprise one of the first-line treatments of choice for cardiovascular conditions common in women and men, such as hypertension (3). Given that ADRs play an important role in adherence(4) and failure to reach guideline-recommended target doses, sex-stratified comparison trials equally powered for women and men are needed to explore whether different dosages or ACEI alternatives are associated with decreased ADR risk. These studies should give priority to ADRs associated with the greatest differences in adherence, which our study and previous literature(5) suggest may differ between the sexes. Importantly, we may have underestimated ADR incidence owing to underreporting(6). Our 95% CIs may be artificially narrow because we could not account for in-person clustering of reports. In addition, our findings need validation in specific settings given that country-specific prescription practices or comorbidities may be associated with ADR risk and reporting differences.

Our study provides evidence for sex differences in ACEI-related ADRs, with women reporting more ADRs and different types of ADRs compared with men. These findings suggest the need for further studies to elucidate mechanisms underlying women's higher reporting rates and optimal treatment strategies for women and men.

Acknowledgement section

Funding/support

This work was supported by the Dutch CardioVascular Alliance (2020B004) and an ERC Consolidator grant (UCARE, 866478).

Role of the funder statement

The funder had no role in design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Access to data and data analysis

SB had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Originality of content

The authors verify that all information and materials in the manuscript are original.

Conflict of Interest Disclosures

None reported.

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APPENDIX

SUPPLEMENTARY METHODS

Study databases

We used pharmacovigilance data from the global database VigiBase(1) and the Dutch database Lareb(2). We obtained Dutch prescription data from the Genees- en hulpmiddelen Informatie Project (GIP) database(3).

Vigibase

VigiBase collects ADR reports shared between member countries of the WHO Programme for International Drug Monitoring, submitted by both healthcare professionals and, in some countries, directly from patients. Reports can also be submitted by manufacturing pharmaceutical companies. For the current study, we used all reports on ACEIs collected between their introduction to the market in the 1980s and January 2020. Reports without information on sex were excluded and suspected duplicate reports were removed using VigiMatch(4), the duplicate detection method developed at the Uppsala Monitoring Centre.

We extracted detailed ADR data for the five individual ACEI medications with the largest number of serious ADR reports and five with the largest number of non-serious ADR reports. We extracted the name of the drug, sex of the person who experienced the ADR, seriousness of the ADR, and the complete classification of the ADR type according to MedDRA. The ADR reports were classified as serious if they resulted in death, were life-threatening, caused or prolonged hospitalisation, resulted in permanent disability, caused congenital anomalies or birth defects, or resulted in other medically important conditions. We also extracted the number of ADR reports per age group.

Lareb and GIP database

The Lareb collects ADR reports from patients, healthcare professionals and marketing Authorisation Holders in the Netherlands. The GIP database tracks the number of people that use certain medications in the Netherlands based on claims from 24 health insurance companies. Together, these companies cover almost 17 million people, which is close to the entire population of the Netherlands. It covers all medications insured by the standard medical care insurance, which each person living and working in the Netherlands must have by law(3).

For the current study, we extracted all ACEI-reports collected by the Lareb between 1 January 2003 and 1 January 2021 because GIP data was not available before 2003. Reports without information on sex or from patients younger than 25 years were excluded because these were unlikely to suffer from cardiovascular disease. Reports submitted by pharmaceutical industry were also excluded as it could not be certified if these derived from

patients treated in the Netherlands. We extracted detailed ADR information for all ACEI-related reports that fell within the selected time period. We extracted the name of the drug, sex and age of the person who experienced the ADR, and the classification of the ADR type according to MedDRA. We extracted the number of individual users that were prescribe ACEIs stratified by year, sex, and 10-year age categories.

Statistical analysis

We calculated the sex-specific total number of reports stratified by ADR preferred term code according to the MedDRA system. This is a hierarchical system that groups similar ADR types together at several levels of detail, with the Preferred Term (PT) level being most detailed level available and the System Organ Classes (SOC) level being least detailed. To compare ADR types between the sexes, the absolute sex difference in number of reports for each primary SOC was calculated. Results are given as numbers with percentages or bar graphs.

The sex-specific number of ADRs per 100,000 users was calculated by dividing the total number of ADR reports by the total number of prescriptions for each sex separately. We considered this to be an incidence rate, as the number of cases (ADRs) could be larger than the number of people at risk (prescriptions). To test whether the difference in ADR incidence was statistically significant, we calculated the rate difference and incidence rate ratio with 95% confidence interval. A p-value < 0.05 was considered statistically significant.

All analyses were performed in R (R Core Team, Vienna, Austria).

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8

Efficacy and Safety of Ticagrelor, and Prasugrel in Subjects with Coronary Heart Disease treated with Dual Antiplatelet Therapy – a sex-specific systematic review and meta-analysis

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Published in ***Journal of American Heart Association***
https://pubmed.ncbi.nlm.nih.gov/32063118/

ABSTRACT

BACKGROUND

Sex differences in efficacy and safety of dual antiplatelet therapy remain uncertain, because of the underrepresentation of women in cardiovascular trials. The aim of this study was to perform a sex-specific analysis of the pooled efficacy and safety data of clinical trials comparing a high potent $P2Y_{12}$ inhibitor + aspirin with clopidogrel + aspirin in patients with Acute Coronary Syndrome (ACS)..

METHODS AND RESULTS

A systematic literature search was performed. Randomized clinical trials that compared patients following percutaneous coronary intervention/acute coronary syndrome who were taking high potent P2Y12 inhibitors+aspirin versus clopidogrel+aspirin were selected. Random effects estimates were calculated and relative risks with 95% CIs on efficacy and safety end points were determined per sex. We included 6 randomized clinical trials comparing prasugrel/ticagrelor versus clopidogrel in 43 990 patients (13 030 women), with a median follow-up time of 1.06 years.

Women and men had similar relative risk (RR) reduction for major cardiovascular events (women: RR, 0.89 [95% CI, 0.80–1.00; men: RR, 0.84 [95% CI, 0.79–0.91) (P for interaction=0.39). Regarding safety, women and men had similar risk of major bleeding by high-potency dual antiplatelet therapy (RR, 1.18 [95% CI, 0.98–1.41] versus RR, 1.03 [95% CI, 0.93–1.14]) (P for interaction=0.20).

CONCLUSION

The small and statistically insignificant difference in efficacy and safety estimates of high-potency dual antiplatelet therapy between women and men following percutaneous coronary intervention/acute coronary syndrome do not justify differential dual antiplatelet therapy treatment for both sexes.

What is new:

- Women are less likely to be treated with high potent $P2Y_{12}$ inhibitors prasugrel/ticagrelor than men in clinical practice
- Sex-specific additional risk for cardiovascular endpoints and bleeding of prasugrel/ticagrelor compared to clopidogrel is lacking

What the study adds:

- We showed that there are no significant sex differences in efficacy and safety of the high potent $P2Y_{12}$ inhibitors prasugrel/ticagrelor compared to clopidogrel
- This should lead the way to prescribing guideline recommended high potent DAPT in both men and women.

ABBREVIATIONS

CAD	coronary artery disease
DAPT	dual antiplatelet therapy
RCT	randomized controlled trial
ACS	acute coronary syndrome
PCI	percutaneous coronary intervention
MACE	major adverse cardiovascular event
GUSTO	Global Utilization Of Streptokinase And Tpa For Occluded Arteries
BARC	Bleeding Academic Research Consortium
TIMI	Thrombolysis in Myocardial Infarction
P + A	prasugrel + aspirin
T + A	ticagrelor + aspirin
C + A	clopidogrel + aspirin
RR	relative risk
CI	confidence interval
NNT	numbers needed to treat
NNH	numbers needed to harm
HPR	high platelet reactivity

INTRODUCTION

Current guidelines for the management of patients with coronary artery disease (CAD) recommend the use of dual antiplatelet therapy (DAPT), a combination of aspirin and an oral inhibitor of the platelet $P2Y_{12}$ receptor, to reduce coronary thrombosis and mortality in patients who experienced an acute coronary syndrome (ACS) or who underwent a percutaneous coronary intervention (PCI). Although DAPT is effective in decreasing thrombotic complications in these patients, the therapy increases the risk of bleeding complications. Therefore, risk assessment balancing thrombotic vs bleeding risk is warranted before DAPT is considered. (1)

The next generation $P2Y_{12}$ inhibitor prasugrel has a more rapid onset of action than clopidogrel due to more efficient metabolic activations (2) and led to reduction of ischemic events compared to clopidogrel.(3) Later, ticagrelor was developed which reversibly inhibits the $P2Y_{12}$ receptor, so the effects can be reversed more easily and not being a prodrug, leading to a faster onset of action because it does not require conversion to an active metabolite. (4, 5) A large clinical trial also showed a higher efficacy of ticagrelor in reduction of ischemic events and stent thrombosis compared to clopidogrel. (6)

Therefore, the high potent $P2Y_{12}$ inhibitors ticagrelor or prasugrel in combination with aspirin are currently recommended as first choice therapy in patients with ACS. (1)

The latest update of The European Society of Cardiology guidelines on DAPT in patients with CAD states that there is ''no convincing evidence for a gender-related difference in the efficacy and safety of currently available DAPT type or duration across studies''. (1) However, taking into account that the typical women to men ratio in these trials is 1:4, analyses stratified by sex – if published – are underpowered and therefore sex differences in efficacy and safety of DAPT remain uncertain. (7) Also, registries have shown that women are less likely to be treated with high potent $P2Y_{12}$ inhibitors than men in clinical practice. (8)

Currently, it is more and more recognized that efficacy and safety of drugs may differ between men and women. As women have in general lower body weight, a higher fat/water balance and a lower clearance as well as different hormonal composition, pharmacokinetics and pharmacodynamics can be affected.(9-11) Therefore, in order to be able to provide sex- and gender-specific guideline recommendations it is important to verify whether efficacy and safety is equal for specific drugs, especially when these are prescribed to a large number of both male and female patients.

The aim of this study was to perform sex-specific analyses of the pooled efficacy and safety data of trials comparing high potent DAPT prasugrel/ticagrelor against clopidogrel in patients with ACS with or without PCI.

METHODS

Our protocol is published on PROSPERO (ID: CRD42018082179).
The authors declare that all supporting data are available within the article (and its online supplementary files).

Literature search

We developed a search strategy to identify randomized controlled trials investigating the efficacy and safety of Aspirin and $P2Y_{12}$ inhibitors compared to aspirin, aspirin + placebo or clopidogrel + aspirin in patients with CAD. We performed a systematic literature search in MEDLINE Ovid, EMBASE, and the Cochrane Central Register of Controlled trials (latest search performed: June 2018). For the full search strategies, see Table S1. Besides, reference lists from eligible trials were reviewed to identify potentially relevant trials.

Population

We considered studies of participants who were assigned to DAPT for cardiovascular prevention following PCI with or without coronary stent, or after admission for ACS. Studies focusing on the use of DAPT in patients undergoing coronary artery bypass graft (CABG) surgery were excluded, as the efficacy and safety of DAPT in these subjects is complex and depending on pre-treatment with PCI.(12)

Inclusion and exclusion criteria

Studies were eligible if they fulfilled the following criteria (a) original full text article (b) randomized controlled trials (RCT) or double-blind, single-blind, or open-label design (c) DAPT treatment as secondary prevention after either PCI following documented CAD, or a diagnosis with CAD with a high risk of events e.g. previous MI (d) DAPT treatment > 1 month (e) analysis on both cardiovascular outcomes and adverse events was performed (f) ≥50 participants in intervention and control group, and (g) population ≥18 years old. Language was restricted to English.

For our study the regimen of DAPT were limited to the following combinations: ticagrelor + aspirin (T+A) and prasugrel + aspirin (P+A) vs clopidogrel + aspirin. Studies analyzing the effect of cangrelor and elinogrel were excluded as these are administered intravenously when oral drugs are contraindicated and therefore the duration of use of these agents is generally limited.

Studies were excluded if: (a) the population had other (cardiovascular) disease than ACS, (b) DAPT was intended as primary cardiovascular prevention, and (c) the population was non-human.

If more than one published article was available from the same trial, the article with the most detailed information regarding cardiovascular outcomes and adverse events was included.

See Table S2 for the full overview of the in- and exclusion criteria.

Data extraction

A systematic two-step screening of literature was performed by two independent reviewers (RB & LV). First the title- and abstract screening was performed, after which full-text screening ensued. Disagreements during the title/abstract and full-text screening about whether to include a study were resolved by discussion with a third investigator (MS) to reach consensus.

Of the included trials, the following relevant data were extracted: trial name, first author, journal, publication year, country, the blinding method which was applied, treatment of intervention and control-arms, demographic characteristics (indication, duration of follow-up, sample size), age and sex. Efficacy and safety endpoints were extracted, if reported, for women and men separately.

If data of the included trials was not available, we requested both efficacy and safety endpoints per sex by contacting the corresponding author.

The risk of bias in the included trials for the meta-analysis was assessed with the Cochrane Collaboration's tool.(13) (Table 1 and Table S3) This tool consists of six domains of bias in which different aspects are covered. The risk per aspect was categorized by the reviewers as low, unclear or high.

	AUTHOR	YEAR, PUBLICATION	COUNTRY	TRIAL	YEAR, BASELINE	POPULATION*	AGE (years)	SAMPLE SIZE (n=)	REVASCULAR-IZATION*
1	C.P. Cannon	2007	UK (multicentre trial)	DISPERSE-2(14)	2004	NSTE-ACS	ticagrelor: 64, clopidogrel 62	948 316 ♀ 632 ♂	PCI
2	L. Wallentin	2009	US (multicentre trial)	PLATO(6)	2006	ACS	ticagrelor: 61, clopidogrel: 61	18624 5288 ♀ 13336 ♂	PCI with DES or BMS
3	S. Saito	2014	Japan	PRASFIT – ACS(15)	2010	ACS	prasugrel: 65.4, clopidogrel: 65.1	1363 289 ♀ 1074 ♂	PCI WITH BMS OR DES
4	T. Cuisset	2017	France	TOPIC, 2017(16)	2014	ACS	ticagrelor/prasugrel: 59.6, clopidogrel: 60.6	646 114 ♀ 532 ♂	PCI
5	M.T. Roe	2012	US (multicentre)	TRILOGY ACS(17)	2008	NSTEMI or UA	prasugrel: 66, clopidogrel: 66	9326 3650 ♀ 5676 ♂	NO
6	S. Wiviott	2007	France (multicentre)	TRITON-TIMI 38(3)	2004	ACS	prasugrel: 74, clopidogrel: 74	13608 3523 ♀ 10085♂	PCI with DES or BMS

Table 1. Description of included trials in the meta-analysis*Indication: Acute Coronary Syndrome (ACS), non-ST-elevation myocardial infarction (NSTEMI), Unstable Angina (UA). Revascularization: Percutaneous coronary intervention (PCI), Drug-eluting Stent (DES), Bare-metal stent (BMS). Efficacy endpoints: All-cause mortality (ACM), Cardiovascular mortality (CVM), Myocardial infarction (MI), Stent-thrombosis (ST), Cerebrovascular accident (CVA), UR (unplanned revascularization), MACE (Major Cardiovascular Event).
**The median follow-up was not mentioned, therefore we used the weighed mean follow-up of the intervention and control group.

FOLLOW-UP (median)	FOLLOW-UP START RELATED TO EVENT	INTERVENTION	CONTROL	EFFICACY ENDPOINTS	BLEEDING CLASSIFICATION	COCHRANE COLLABORATION TOOL, RISK OF BIAS
56 days	Not specifically reported	TICAGRELOR + ASPIRIN	CLOPIDOGREL + ASPIRIN	MI, ACM, STROKE, severe recurrent ischemia	TIMI	Low
279 days	Directly after PCI	TICAGRELOR + ASPIRIN	CLOPIDOGREL + ASPIRIN	ACM, CVM, MI, CVA, ST	TIMI + GUSTO / PLATO DEFINED TIMI BLEEDING.	Low
210,5 days **	When scheduled for PCI	PRASUGREL + ASPIRIN	CLOPIDOGREL + ASPIRIN	MACE: CVM, non-fatal MI and STROKE	TIMI	Low
359 days	1 month after PCI	PRASUGREL / TICAGRELOR + ASPIRIN	CLOPIDOGREL + ASPIRIN	MACE: CVM, UR, STROKE	BARC	Low
17 months	Within 10 days after index event	PRASUGREL + ASPIRIN	CLOPIDOGREL + ASPIRIN	MACE: CVM, non-fatal MI and STROKE	TIMI / GUSTO	Low
14,5 months	When scheduled for PCI	PRASUGREL + ASPIRIN	CLOPIDOGREL + ASPIRIN	MACE: ACM, CVM, MI , ST	TIMI	Low

Efficacy and safety endpoints

The primary efficacy endpoint was Major Cardiovascular Event (MACE). For the definition of MACE per included trial, see Table S4. The secondary efficacy endpoints were all-cause mortality, cardiovascular mortality, myocardial infarction, stroke and stent thrombosis.

The primary safety endpoint was defined as major bleeding, based on the Thrombolysis in Myocardial Infarction (TIMI) bleeding criteria 1, Bleeding Academic Research Consortium (BARC) 2,3 and 5 or Global Utilization Of Streptokinase And TPA For Occluded Arteries (GUSTO) bleeding criteria 1.(18-20) The secondary safety endpoint was defined as minor bleeding, based on the (TIMI) bleeding criteria 2.

Statistical analyses

Potential sex differences in efficacy and safety of potent $P2Y_{12}$ inhibitors (prasugrel or ticagrelor) + aspirin vs clopidogrel + aspirin were determined by extracting MACE endpoints and major bleeding for women and men separately from the selected trials. The pooled relative risks (RR) for efficacy and safety endpoints and 95% confidence intervals (CIs) were then estimated per sex with a random effect model computed based on the DerSimonian and Laird method.(21) Under the null-hypothesis, the difference in $\ln(RR_{pooled})$ between women and men follows (approximately) a normal distribution. We therefore calculated the statistic Z = difference in $\ln(RR_{pooled})$ / standard error, which we then compared with the standard normal distribution to reveal the level of significance.

The pooled absolute risk reduction was determined as follows. First, for each trial, the absolute risks in treatment and control arms were calculated as the number of patients with an endpoint event divided by the corresponding sample size. Then, the absolute risk reduction was defined as the difference in absolute risk in the treatment arm minus control. Finally, trial estimates were pooled using the inverse of the variance of the absolute risk reductions as weighing factor. Numbers needed to treat/harm (NNT/NNH) were calculated for the differences in absolute risk, based on the weighed median duration of follow-up of all trials.

Statistical analyses were performed in STATA (version 14, StataCorp LLC) and in R. For the STATA scripts, see Table S5. All tests were 2-sided, with significance defined as a P value of <0.05.

Heterogeneity

Heterogeneity between studies was assessed based on the Q-statistic and quantified by I^2 statistic. Moreover, a 95% prediction interval was determined in order to report heterogeneity between studies better.(22-24) Small-study effects were assessed using contoured Funnel Plots and tested by the Egger's test.(25)

RESULTS

Characteristics of the RCT's

Twelve trials were found eligible for inclusion in our meta-analysis. Five trials reported their outcomes for women and men separately in the original publications, sub-analyses or in previously published systematic-reviews and meta-analyses. (Figure 1) One of the corresponding authors of the remaining trials who were contacted for their efficacy and safety outcomes stratified by sex provided the required sex-specific data. Three investigators declined to perform the additional analyses requested, due to low capacity in staff, and two authors did not respond to our requests.

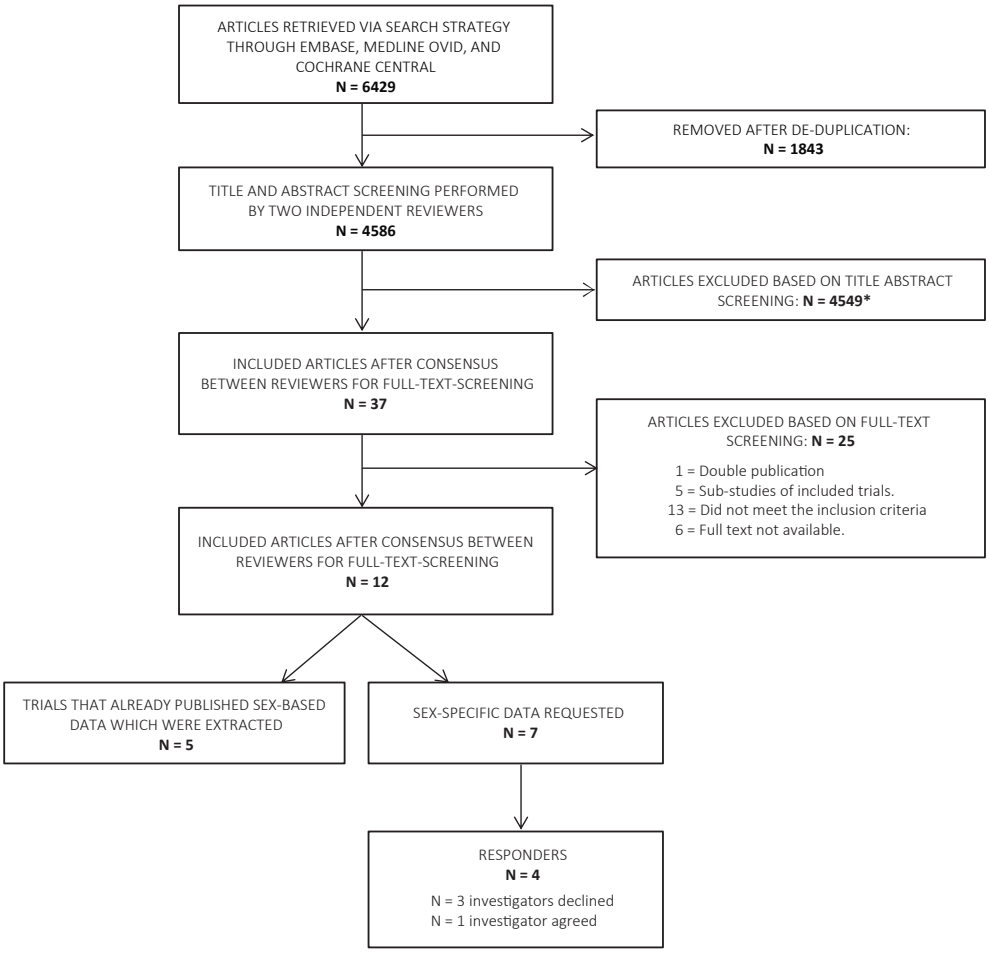

Figure 1. Flow-chart describing the screening- and selection process. * See Table S2 for the appropriate exclusion reasons for the title- and abstract screening

Thus, six trials with in total 13,030 (30%) female and 30,960 (70%) male participants were included in our meta-analysis.

Key characteristics of these trials are presented in Table 1. The weighed median follow-up time was 1.06 years. The population of the PLATO trial, PRASFIT-ACS, TOPIC and TRITON-TIMI 38 consisted of ACS patients, whereas DISPERSE-2 enrolled exclusively patients with non-ST-segment elevation ACS and TRILOGY ACS included only patients with NSTEMI (non-ST-segment-elevation myocardial infarction or unstable angina. All trials enrolled patients who underwent revascularization, except for the TRILOGY ACS trial, in which patients were only eligible if they received medical treatment without revascularization after the index event. In 3 trials prasugrel was used as high potent $P2Y_{12}$ inhibitor, in 2 trials ticagrelor and in 1 trial prasugrel or ticagrelor. Of the DISPERSE-2 trial, the 90 mg ticagrelor dosage group was included as treatment group.

Quality assessment

The quality assessment is presented in Table S3. All included trials scored low on selection bias, performance bias, detection bias, attrition bias and reporting bias. Therefore all have been evaluated as having low risk of bias. The most prevalent potential risk of bias was because studies did not clearly indicate the allocation concealment.

Efficacy outcomes

High potent $P2Y_{12}$ inhibitor (prasugrel or ticagrelor) + aspirin was associated with showed an additional reduction in MACE compared to clopidogrel + aspirin (RR 0.87 and 95% CI [0.80 to 0.94]; $p < 0.001$). (Table 2) Women and men had similar relative risk reduction (women: RR 0.89 and 95% CI [0.80 – 1.00]; men: RR 0.84 and 95% CI [0.79 - 0.91], p for interaction = 0.39). (Table 3, Figure 2 and 3) The number needed to treat (NNT) with high potency DAPT vs clopidogrel + aspirin to prevent one major cardiovascular event was 88 for women and 55 for men based on a weighed median duration of treatment of 1.06 years. (Table 4)

Table 2. Efficacy and Safety analysis of high potent P2Y12i + Aspirin vs. Clopidogrel + Aspirin

ENDPOINTS	RR (95% CI)	EVENTS INTERVENTION	EVENTS CONTROL	p value
MACE				
HIGH POTENT P2Y12 INHIBITOR + ASPIRIN vs. *CLOPIDOGREL + ASPIRIN*	0.87 (0.80 - 0.94)	2211/21828	2540/21754	< 0.001
MAJOR BLEEDING				
HIGH POTENT P2Y12 INHIBITOR + ASPIRIN vs. *CLOPIDOGREL + ASPIRIN*	1.06 (0.97 – 1.17)	901/22078	842/21998	0.184

Table 3. Sex-specific Efficacy and Safety analysis of high potent P2Y12i + Aspirin vs. Clopidogrel + Aspirin

EFFICACY AND SAFETY ANALYSIS BASED ON HIGH POTENT DAPT vs. CLOPIDOGREL + ASPIRIN							
ENDPOINTS	**FEMALE**			**MALE**			
	RR (95% CI)	**EVENTS INTER-VENTION**	**EVENTS CONTROL**	**RR (95% CI)**	**EVENTS INTER-VENTION**	**EVENTS CONTROL**	**SEX INTER-ACTION**
Major Cardiovascular Event*	0.91 (0.83 – 1.00)	737/6497	818/6543	0.85 (0.80 – 0.91)	1474/15410	1722/15277	P = 0,24
All-cause mortality	0.91 (0.79 - 1.05)	360/6530	396/6574	0.86 (0.77 – 0.95)	630/15620	732/15503	P = 0,53
Cardiovascular Mortality	0.88 (0.76 – 1.03)	294/6530	333/6574	0.85 (0.76 – 0.96)	516/15620	603/15503	P = 0,72
Myocardial infarction	0.88 (0.78 – 1.00)	455/6530	520/6574	0.82 (0.74 – 0.93)	991/15620	1201/15503	P = 0,41
Stent thrombosis**	0.52 (0.23 – 1.16)	24/6307	51/6369	0.56 (0.44 – 0.70)	111/15416	197/15286	P = 0,86
Stroke***	1.03 (0.78 - 1.37)	100/6497	98/6551	1.02 (0.82 – 1.26)	178/15512	174/15392	P = 0.96

*TOPIC was not included because they did not report a MACE endpoint

DISPERSE-2 was not included because they did not report a stent thrombosis endpoint, TOPIC ticagrelor and PRASFIT were not included because there were no stent thrombosis events during follow-up*TOPIC ticagrelor was not included because there were no stroke events during follow-up. Stroke was defined as either ischemic stroke (TOPIC, TRITON TIMI 38 and PRASFIT-ACS) or ischemic/hemorrhagic stroke (DISPERSE-2, TRILOGY ACS and PLATO).

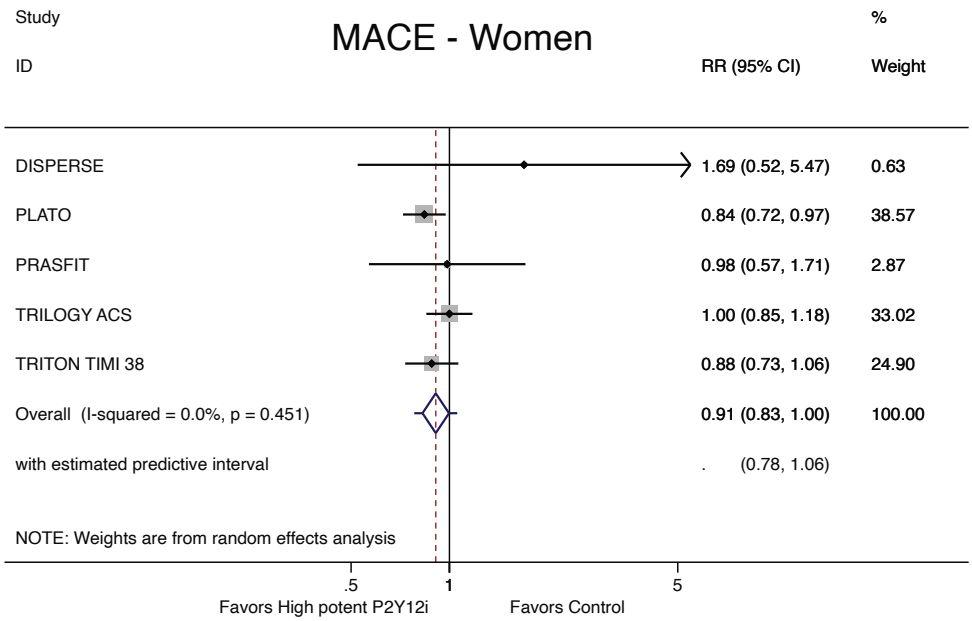

Figure 2. The relative risk of major cardiovascular events in women treated with a high potent P2Y12 inhibitor (prasugrel/ticagrelor) vs. clopidogrel

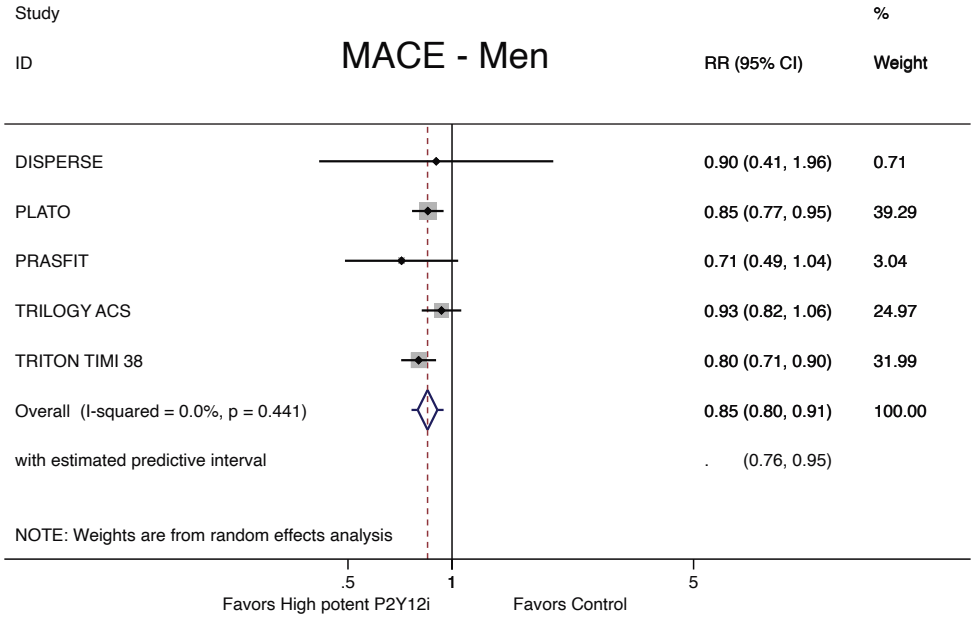

Figure 3. The relative risk of major cardiovascular events in men treated with a high potent P2Y12 inhibitor (prasugrel/ticagrelor) vs. clopidogrel

Table 4. Pooled absolute event rates and Numbers needed to treat(a)/harm(b) with high potent P2Y12i + A vs. C + A.

	High potent P2Y12i (%)	Control (%)	absolute risk difference (%)	NNT/NNH
MACE				
women	11,1	11.9	0,8	131
men	9,3	11,1	1,8	58
All-cause mortality				
women	4,8	5,1	0,3	364
men	3,1	3,7	0,6	191
CVM				
women	4,0	4,3	0,3	424
men	2,4	2,8	0,4	232
Myocardial infarction				
women	6,9	7,7	0,8	114
men	6,5	7,8	1,3	74
Stent Thrombosis				
women	0,06	1,3	1,2	140
men	0,6	1	0,4	256
Stroke*				
women	1,4	0,4	1	96
men	1	1,1	0,1	5912
Major bleeding				
women	2,8	2,6	0,2	541
men	2,6	2,6	0,04	2474
Minor Bleeding				
women	2,6	1,8	0,8	911
men	2,6	2,9	0,3	268

***DISPERSE-2, TRILOGY ACS and PLATO defined stroke as either ischemic or hemorrhagic.**

Our secondary efficacy endpoints (all-cause mortality, cardiovascular mortality, myocardial infarction, stent thrombosis and stroke) also did not show any significant difference between women and men. (Figures S1-S10) The statistics of all efficacy endpoints are summarized in Table 3. Regarding the absolute numbers, women compared to men showed less absolute risk reduction in all-cause mortality (0.3% vs 0.6%), cardiovascular mortality (0.3 vs 0.4), myocardial infarction (0.8% vs 1.3%) and stent thrombosis (1.15% vs 1.22%). (Table 4) Also, the absolute risks for the efficacy endpoints were slightly higher in women than men on high potent $P2Y_{12}$ inhibitor, except for stent thrombosis and stroke. (Table 4)

Safety outcome

Risk for major bleeding in patients treated with high potent $P2Y_{12}$ inhibitor + aspirin compared to clopidogrel + aspirin was not significantly increased (RR: 1.06 and 95% CI [0.97 – 1.17], p = 0.2] (Table 2). Also, no differences between women and men were observed regarding major bleeding in patients randomized to high potent DAPT vs clopidogrel + aspirin (women: RR 1.18 and 95% CI [0.98 – 1.41]; men: RR 1.03 and 95% CI [0.93 – 1.14], p for interaction = 0.2. (Table 3, Figure 4 and 5)

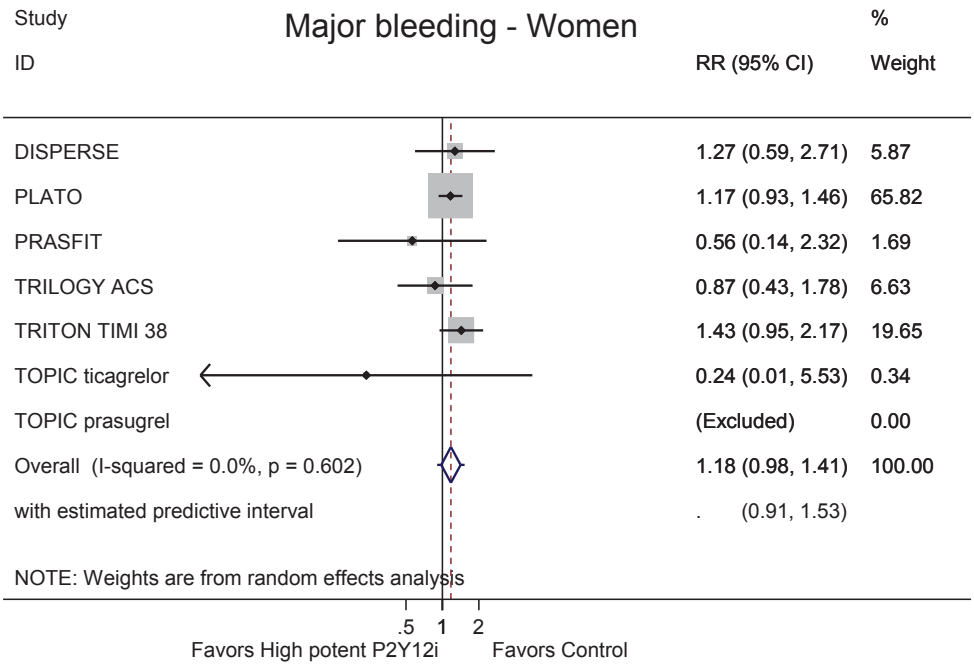

Figure 4. The relative risk of major bleeding in women treated with a high potent P2Y12 inhibitor (prasugrel/ticagrelor) vs. clopidogrel

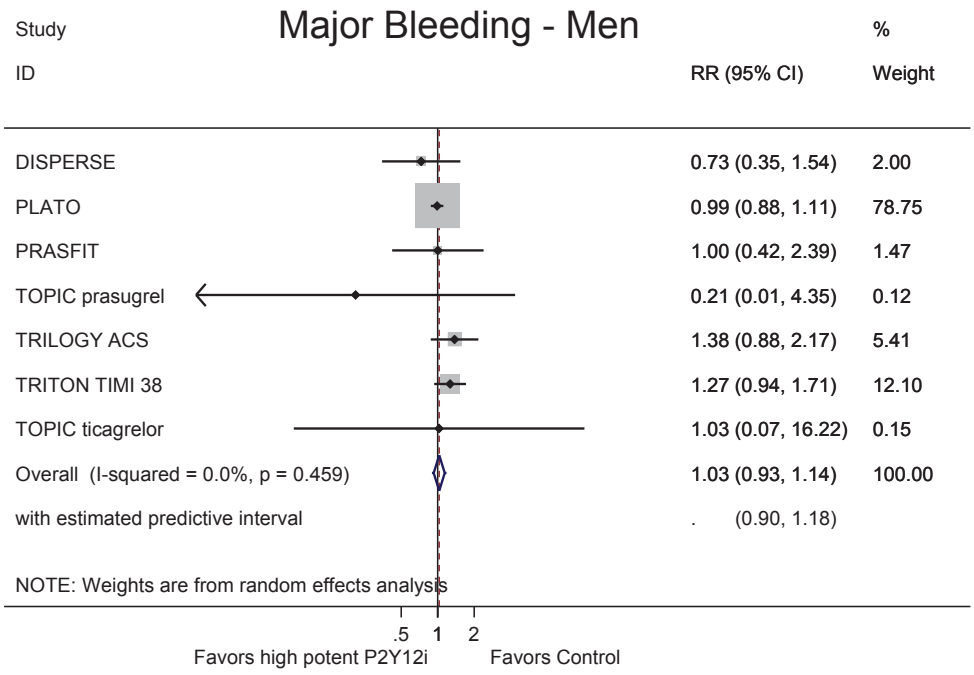

Figure 5. The relative risk of major bleeding in men treated with a high potent P2Y12 inhibitor (prasugrel/ticagrelor) vs. clopidogrel

Adding prasugrel or ticagrelor to aspirin instead of clopidogrel is associated with an increased risk of major bleeding of 0.2% in women and 0.04% in men. This results in a number needed to harm (NNH) for high potent DAPT treatment of 538 women vs 2489 men based on a weighed median duration of treatment of 1.05 years. (Table 4)

Minor bleedings were also showed no sex differences (Table 3, Figures S11 and S12). Regarding the absolute numbers, the additional risks for minor bleeding in men using high potent $P2Y_{12}$ inhibitor + aspirin were slightly higher compared to women (0.8% vs. 0.3%). (Table 4)

Heterogeneity

Some heterogeneity was found in the efficacy endpoint of myocardial infarction in men between studies for myocardial infarction in men (I^2=29,2%, Q statistic p = 0.205) and stent thrombosis in women (I^2=49,3%, Q statistic p = 0.1) with prediction intervals slightly exceeding the confidence interval of the pooled effect. However, the Egger's test showed no indication for small-study effects. (Figures S13-S28)

DISCUSSION

Our systematic review and meta-analysis show that efficacy and safety of high potent DAPT (prasugrel or ticragelor in combination with aspirin) compared to clopidogrel + aspirin in patients with ACS is similar in both men and women. No sex difference was observed in additional reduction of major cardiovascular events or increase of bleeding risk in patients randomized to high potent DAPT vs clopidogrel + aspirin. However, women randomized to aspirin + clopidogrel had 1.3% higher MACE risk and 1.1% lower risk of major bleeds, so that the differences in absolute treatment effects between women and men were negligibly small. Hence, our study supports similar DAPT management in both sexes.

Sex differences in response to antiplatelet therapy

It has currently been acknowledged that poor response to clopidogrel can be explained by increased platelet reactivity.(26, 27) In vitro studies showed that women have increased platelet reactivity compared to men, however the underlying mechanism of this sex difference is not completely understood. It has been suggested that it is caused by higher levels of estrogen in women that lead to increased platelet-to-platelet aggregation, (28, 29) increased platelet adhesion to fibrinogen (30) and platelet interaction with leukocytes (31).

A sub analysis of the Assessment of Dual AntiPlatelet Therapy with Drug-Eluting Stents (ADAPT-DES) study (8448 patients (25.6% women who underwent a PCI)) compared the risk for stent thrombosis and bleeding in patients with high platelet reactivity (HPR) vs patients without HPR, stratified by sex. They found that both men and women with HPR have an increased risk of stent thrombosis, but only in women with HPR a significantly lower risk of bleeding was observed. (32) Also, they observed that HPR was more prevalent in women than men (51.7% versus 39.6%; P<0.0001), which might explain sex differences in response to treatment with clopidogrel.

However, a sex-specific meta-analysis of 5 trials of 79,613 patients (30% women) compared clopidogrel + aspirin vs aspirin monotherapy in patients with CVD and found that DAPT was slightly less effective in prevention of CVD in women, but no significant sex differences in efficacy to prevent major cardiovascular events or safety depicted as major bleeding.(33) Another meta-analysis focusing on short- vs long-term DAPT treatment in men and women, including 6 randomized trials, concluded that short-term treatment lead to similar rates of MACE as long-term treatment but lower risk of bleeding with no sex differences observed.

High potent $P2Y_{12}$ inhibitors prasugrel, ticagrelor and cangrelor have a stronger antiplatelet action and therefore are effective also in patients with HPR. Two sex-specific meta-analyses assessing the efficacy and safety of high-potent DAPT were previously published. Lau et al. included seven trials involving 87,840 patients (24,494 women) with CAD and found no sex differences for MACE or major bleeding.(34) However, in this meta-analysis, 3 trials assessing cangrelor were included and the effect of cangrelor, prasugrel and

ticagrelor was pooled, while in our meta-analysis, we excluded trials assessing cangrelor because this drug is intravenously administered and only prescribed in the first 48 hours following PCI.

A less extensive meta-analysis compared to the current study, was published by Zaccardi et al. consisting of three trials with 24,844 patients (7232 women) testing prasugrel vs clopidogrel or placebo and one trial with 18,624 participants (5288 women) treated by ticagrelor vs clopidogrel. No significant differences were found for cardiovascular or bleeding events in the prasugrel or ticagrelor subgroups.(35)

Therefore, our results are in line with these meta-analyses but add to the current literature that it contains the largest number of studies and patients treated with high potent DAPT according to the recommendations of the current guideline who are treated >1 year. The importance of our meta-analysis is that with our results the guidelines statement that no relevant sex differences in efficacy and safety of DAPT exist, can be validated.

Management of men and women with ACS

Women have worse cardiovascular outcomes than men after ACS. (36, 37) Underlying causes for this are women's higher age when suffering from ACS and women having more comorbidities than men, such as diabetes, hypertension and renal failure.(36) Also, differences in the management of women with ACS has been suggested as a reason for worse clinical outcomes. Multiple registry studies showed that women with ACS are less likely to be treated according to the guidelines.(8, 37-39) The SWEDEHEART registry previously showed that women with STEMI are less likely to be given reperfusion therapy.(40) Moreover, DAPT is more often prescribed in men than women with ACS. When DAPT was prescribed in women, the low-intensity $P2Y_{12}$ inhibitor clopidogrel was more frequently used in women compared to men, while the more effective high potent $P2Y_{12}$ inhibitor prasugrel was preferred in men.(41)

The most likely reason for this undertreatment is the hypothetical concern for higher risk of bleeding in women.(42, 43) Regarding milder forms of bleeding it should be noted that access site hematomas occur more often in women than men (22% vs 5.8%, P<0.0001).(44) However, we showed no evidence for an increased risk of major bleeding in women. Therefore, more research on bleeding avoidance strategies is warranted to reduce access site hematomas, especially in women, but it is unjustified to treat women different or less aggressively with DAPT on the long-term due to risk for major bleedings.

Moreover, in the 2 years following PCI both physician recommended disruption (mostly due to bleeding) and non-recommended disruption of DAPT (due to patient noncompliance) were more common in women than in men (59.1% vs 55.9%, p = 0.007).(41, 45) The impact of DAPT cessation was similar in women and men, with disruption significantly associated with ischemic and bleeding events in both sexes.(45, 46) Therefore, it is important to resume DAPT after cessation in order to prevent cardiovascular events in the long-term in both sexes.

Study Strengths and Limitations

Our meta-analysis included all contemporary studies using guideline recommended high potency DAPT. Treatment in control groups was homogeneous (clopidogrel + aspirin), and we reported an average follow-up of at least 1 years, thus describing the longer-term effects of high potency DAPT in women and men.

Limitations are that we found inter-trial variations in study design, study population, follow-up duration, percentage of women included, dosage of prasugrel/ticagrelor and definition of MACE and stroke endpoints. Also, it has to be noted that our results are based on RCT data, in which the included patients are not fully reflecting patients with ACS in real life. In particular, women are less likely to be representative as they develop cardiovascular disease at a later age then men and might thus exceed the upper age limit determined by the RCT. (47) Also, women with cardiovascular disease in general have more comorbidities than men, which can lead to exclusion from a RCT. (48) Last, our study has added only received sex-specific data from one extra trial that was not presented before, however the sex-specific stroke data of the trials have not been published before in a meta-analysis. (34)

CONCLUSION

No significant sex differences in efficacy and safety of the high potent $P2Y_{12}$ inhibitors were observed and therefore there is no reason to treat women and men differently. Our meta-analysis can be used to substantiate the essential evidence that sex-specific recommendations regarding the use of high potent DAPT are unjustified. Therefore, this should lead the way to implementation of prescribing guideline-recommended DAPT in both men and women.

Funding

The project was funded by the Dutch Heart Foundation. There are no relations with industry.

Conflicts of interest:

Dr. Roeters van Lennep reports grants from Dutch Heart Foundation, grants from Amryt, during the conduct of the study;
Dr. Versmissen reports grants from Dutch Heart Foundation, during the conduct of the study;
Dr. Kavousi reports grants from Dutch Heart Foundation, during the conduct of the study;
Prof. Boersma reports grants from Dutch Heart Foundation, during the conduct of the study;
Dr. Visser reports grants from Dutch Heart Foundation, during the conduct of the study;
Ms. Schreuder reports grants from Dutch Heart Foundation, during the conduct of the study;
Prof. Roos-Hesselink reports grants from Dutch Heart Foundation, during the conduct of the study

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APPENDIX

SUPPLEMENTARY FILES

Table S1: Syntax Electronic Databases

Provided in the table down below are the syntax used for the different electronic databases. All results were imported into EndNote. After de-duplication the screening process was started.

Table 1. Database syntax used for the respective electronic databases accessible via Erasmus MC network.

Embase.com	('dual antiplatelet therapy'/de OR (((dual OR combin*) NEAR/3 (antiplatelet* OR anti-platelet*)) OR dapt):ab,ti OR (('acetylsalicylic acid'/exp OR 'acetylsalicylic acid plus clopidogrel'/de OR (acetylsalicyl* OR acetyl-salicyl* OR aspirin):ab,ti) AND ('purinergic p2y receptor antagonist'/exp OR (cangrelor OR clopidogrel OR elinogrel OR prasugrel OR regrelor OR ticagrelor OR ticlopidine OR ((P2Y*) NEAR/3 (antagonist* OR inhibitor*))):ab,ti))) AND ('coronary artery disease'/exp OR 'ischemic heart disease'/de OR (((myocard* OR coronar*) NEAR/3 (disease* OR infarct* OR syndrom* OR acute* OR ischem* OR ischaem* OR obstruct*)) OR angina OR ((heart OR cardiac*) NEAR/3 (infarct* OR ischem* OR ischaem*))):ab,ti) AND ('adverse drug reaction'/exp OR 'side effect'/exp OR adverse:lnk OR 'bleeding'/exp OR (adverse* OR side-effect* OR bleeding OR hemorrhag* OR haemorrhag* OR (blood NEAR/3 (loss OR effusion))):ab,ti) AND ('Controlled clinical trial'/exp OR 'Crossover procedure'/de OR 'Double-blind procedure'/de OR 'Single-blind procedure'/de OR (random* OR factorial* OR crossover* OR (cross NEXT/1 over*) OR placebo* OR ((doubl* OR singl*) NEXT/1 blind*) OR assign* OR allocat* OR volunteer* OR trial OR groups):ab,ti) NOT ([animals]/lim NOT [humans]/lim) NOT ([Conference Abstract]/lim OR [Letter]/lim OR [Note]/lim OR [Editorial]/lim) AND [english]/lim
Medline Ovid	(exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/ OR (statin* OR simvastatin OR rosuvastatin OR pravastatin OR pitavastatin OR lovastatin OR atorvastatin OR fluvastatin OR ((hmg OR hydroxymethylglutaryl) ADJ3 (coa OR coenzyme-A) ADJ3 inhibitor*)).ab,ti.) AND (exp Coronary Artery Disease/ OR exp Myocardial Ischemia/ OR (((myocard* OR coronar*) ADJ3 (disease* OR infarct* OR syndrom* OR acute* OR ischem* OR ischaem* OR obstruct*)) OR angina OR ((heart OR cardiac*) ADJ3 (infarct* OR ischem* OR ischaem*))).ab,ti.) AND (Drug-Related Side Effects and Adverse Reactions/ OR "adverse effects".fs. OR exp Hemorrhage/ OR (adverse* OR side-effect* OR bleeding OR hemorrhag* OR haemorrhag* OR (blood ADJ3 (loss OR effusion))).ab,ti.) AND (Exp Controlled clinical trial/ OR "Double-Blind Method"/ OR "Single-Blind Method"/ OR "Random Allocation"/ OR (random* OR factorial* OR crossover* OR cross over* OR placebo* OR ((doubl* OR singl*) ADJ blind*) OR assign* OR allocat* OR volunteer* OR trial OR groups).ab,ti.) NOT (Animals/ NOT Humans/) NOT (letter OR news OR comment OR editorial OR congresses OR abstracts).pt. AND english.la.
Cochrane CENTRAL	((statin* OR simvastatin OR rosuvastatin OR pravastatin OR pitavastatin OR lovastatin OR atorvastatin OR fluvastatin OR ((hmg OR hydroxymethylglutaryl) NEAR/3 (coa OR coenzyme-A) NEAR/3 inhibitor*)):ab,ti) AND ((((myocard* OR coronar*) NEAR/3 (disease* OR infarct* OR syndrom* OR acute* OR ischem* OR ischaem* OR obstruct*)) OR angina OR ((heart OR cardiac*) NEAR/3 (infarct* OR ischem* OR ischaem*))):ab,ti) AND ((adverse* OR side-effect* OR bleeding OR hemorrhag* OR haemorrhag* OR (blood NEAR/3 (loss OR effusion))):ab,ti)

Table S2: Selection criteria used during title-/abstract- and full-text screening.

Selection Criteria
Inclusion Criteria: Subjects with ACS treated with dual antiplatelet therapy (DAPT), which includes the use of Aspirin and P2Y12-receptor antagonists (prasugrel/ticagrelor) as a form of secondary prevention.
Population: At least 18 years of age Secondary prevention Patients with acute coronary syndrome (STEMI, NSTEMI, myocardial infarction, or unstable angina pectoris) Patients were treated for coronary heart disease with revascularization either: percutaneous coronary intervention (PCI) + stent placement
Study Type: Double blind, randomized controlled trials, single-blind randomized controlled trials, and open-label studies. Original article Published as full text article Written in English language > 50 patients per group
Exclusion Criteria: All other indications not covering ACS Primary prevention studies. Non-human studies (e.g. animal studies)

Table S3: Cochrane Collaboration's Tool

TRIAL	SELECTION BIAS						
	RANDOM SEQUENCE GENERATION	ALLOCATION CONCEALMENT	PERFORMANCE BIAS	DETECTION BIAS	ATTRITION BIAS	REPORTING BIAS	OTHER BIAS
DISPERSE -2	LOW	LOW	LOW	LOW	LOW	LOW	LOW
PLATO	LOW	UNCLEAR	LOW	LOW	LOW	LOW	LOW
PRASFIT ACS	LOW	UNCLEAR	LOW	LOW	LOW	LOW	HIGH
TOPIC	LOW	UNCLEAR	LOW	LOW	LOW	LOW	LOW
TRILOGY ACS	LOW	LOW	LOW	LOW	LOW	LOW	LOW
TRITON TIMI 38	LOW	LOW	LOW/UNCLEAR	LOW	LOW	LOW	LOW

Table S4: Overview of primary efficacy endpoints per included trial.

TRIAL	PRIMARY EFFICACY ENDPOINT
DISPERSE – 2	Composite of CVM, MI (fatal and non-fatal) and stroke
PLATO	Composite of CVM, MI and stroke
PRASFIT – ACS	Incidence of MACE at 24 weeks: composite of: CVM, non-fatal MI, nonfatal ischemic stroke
TOPIC	Composite of: CVM, unplanned hospitalization leading to urgent coronary revascularization, stroke, and bleeding episodes as defined by the BARC classification > 2 at 1 year after ACS.
TRILOGY ACS	Composite of: CVM, non-fatal MI, and non-fatal stroke.
TRITON – TIMI 38	Composite of: CVM, non-fatal MI, and non-fatal stroke.

Efficacy endpoints: Cardiovascular mortality (CVM), Myocardial infarction (MI), Major adverse cardiovascular events (MACE)

Table S5: Overview of syntax used in STATATM

To generate an RR in STATA the following code was used:	gen rr=(mi/ni)/(mc/nc)
To generate the log RR:	gen logrr=log(rr)
To generate the standard error of the log RR:	gen selogrr=sqrt(1/mi-1/ni+1/mc-1/nc)
To generate the log lower confidence interval:	gen loglci=logrr-1.96*selogrr
To generate the log upper confidence interval:	gen loguci=logrr+1.96*selogrr
To re-calculate the log	gen lci=exp(loglci)
To perform the meta-analysis the metan command was used. We performed a fixed effects model, seconded by a random effects model. The model was separated by gender and sorted per trial included.	*metan mi nmi mc nmc, rr random rfdist label(namevar=trial) xlabel (0.5,1,5) xtitle() favours (Favors High Potent DAPT # Favors Control) boxsca(30)*
To calculate the funnel plot the data of each trial were pooled into one group and entered into STATA, after which the log RR and standard error of the log RR were calculated. Using the confunnel command, a contour enhanced funnel plot can be plotted. The Egger's test for small study effects was calculated with the metabias command.	confunnel _ES _selogES metabias _ES _selogES, egger

Table S6: Overview of excluded articles based on title- and abstract screening.

ANTICOAGULANT STUDIES EXCLUSION BASED ON: ANTIPLATELET THERAPIES OR ANTICOAGULANTS THERAPIES SUCH AS CANGRELOR (N=19), ELINOGREL (N = 6), GLYCOPROTEINS (N= 74), HEPARIN (N = 258), TICLOPIDINE (N=46), AND THROMBOLYTICS.	N = 739
CARDIOVASCULAR DISEASE EXCLUSION BASED ON: ATRIAL FIBRILLATION STUDIES (N=82), HEART FAILURE (N= 29), HEART VALVE (N=27), PERIPHERAL ARTERIAL DISEASE (N=42), AND CORONARY ARTERY BYPASS GRAFT (N=74)	N = 254
CEREBROVASCULAR STUDIES EXCLUSION BASED ON: CEREBROVASCULAR STUDIES E.G. STROKE.	N = 172
CHILDREN STUDIES EXCLUSION BASED ON INCLUSION CRITERIA.	N = 1
OTHER MEDICATION EXCLUSION BASED ON: CILOSTAZOL (N=50), MONOTHERAPEUTIC STUDIES (N=6), PROTONPUMP INHIBITORS (N=72), STATINS (N=77), TRIPLE THERAPY (N=29).	N = 234
STUDY DESIGN EXCLUSION BASED ON: NO DAPT STUDIES (N=323), NO RCT (N=1229), PRIMARY PREVENTION (N=7), STUDY DESIGN (N=26), SYSTEMTIC REVIEWS (N=117), TITLE AND ABSTRACT (N=169), DOUBLES (N=6), FOLLOW-UP STUDIES (N=2), NO ABSTRACT (N=10), SUBSTUDIES (N=33)	N = 1922
PHARMACOLOGY EXCLUSION BASED ON: PHARAMCODYNAMIC OR PHARMACOKINETIC STUDIES (N=131), PLATELET REACTIVITY STUDIES (N=70)	N = 201
STENT STUDIES EXCLUSION BASED ON: TYPE OF DAPT OR TRIAL FOCUS ON DAPT.	N = 1026

Due to overflow of the flow-chart excluded articles are noted here separately. Each row is described by a main topic, under which the excluded subtopics (n =) are described. The right column provides the total amount of excluded articles per main-topic.

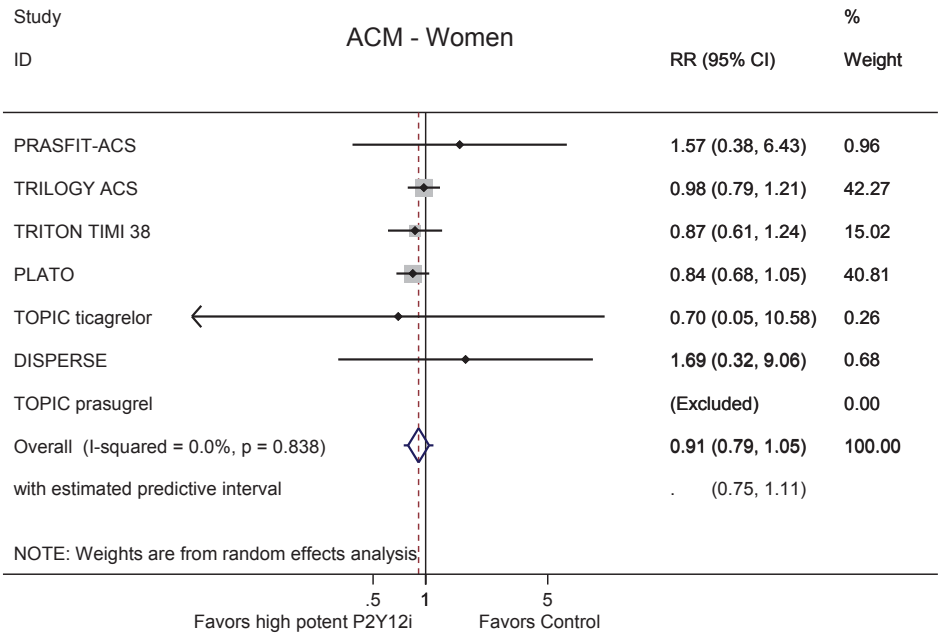


Fig S1. The relative risk of all-cause mortality in women treated with a high potent P2Y12 inhibitor (prasugrel/ticagrelor) vs. clopidogrel

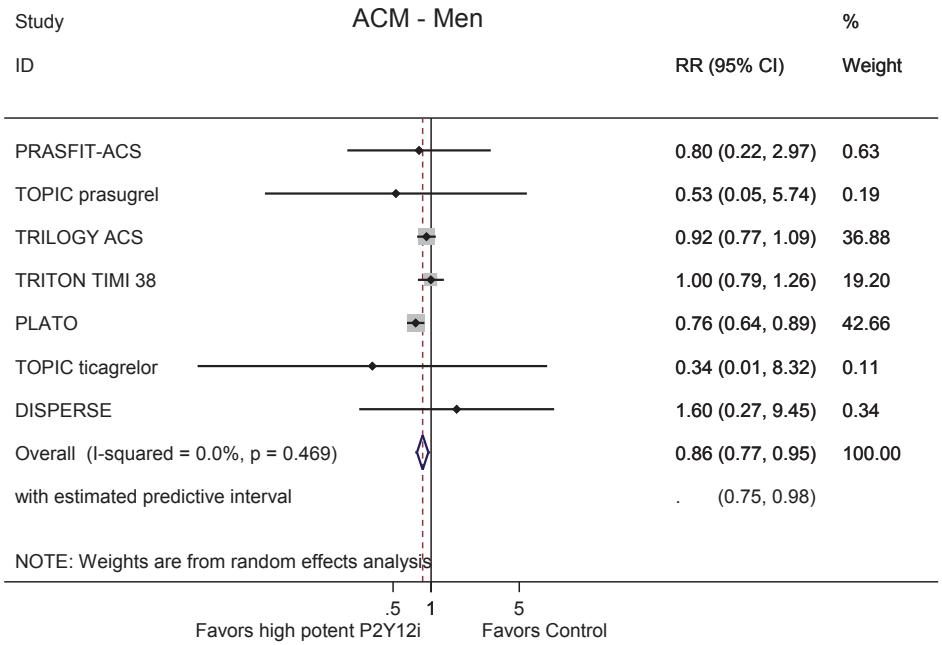


Fig S2. The relative risk of all-cause mortality in men treated with a high potent P2Y12 inhibitor (prasugrel/ticagrelor) vs. clopidogrel

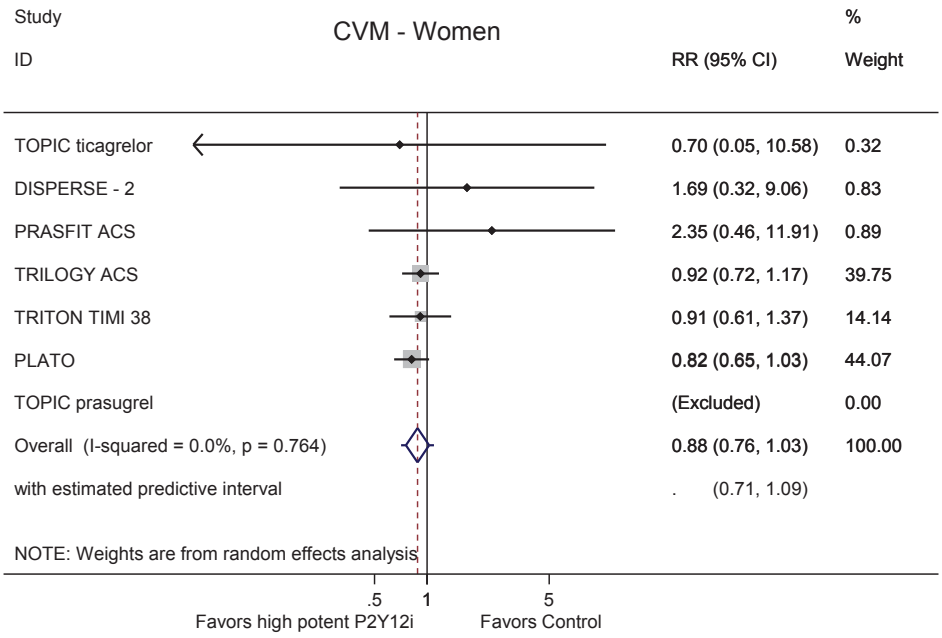


Fig S3. The relative risk of cardiovascular mortality in women treated with a high potent P2Y12 inhibitor (prasugrel/ticagrelor) vs. clopidogrel

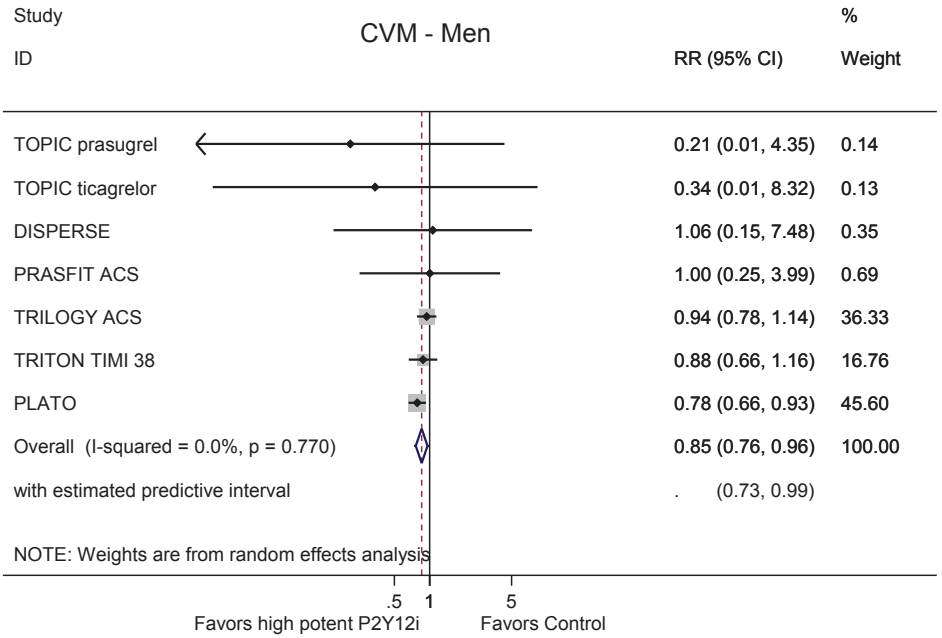


Fig S4. The relative risk of cardiovascular mortality in men treated with a high potent P2Y12 inhibitor (prasugrel/ticagrelor) vs. clopidogrel

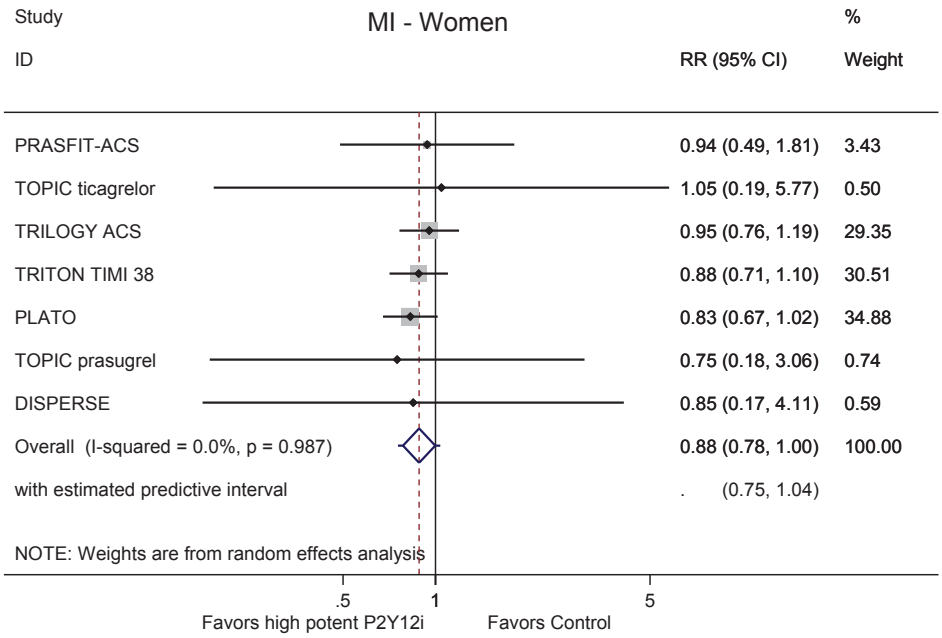


Fig S5. The relative risk of myocardial infarction in women treated with a high potent P2Y12 inhibitor (prasugrel/ticagrelor) vs. clopidogrel

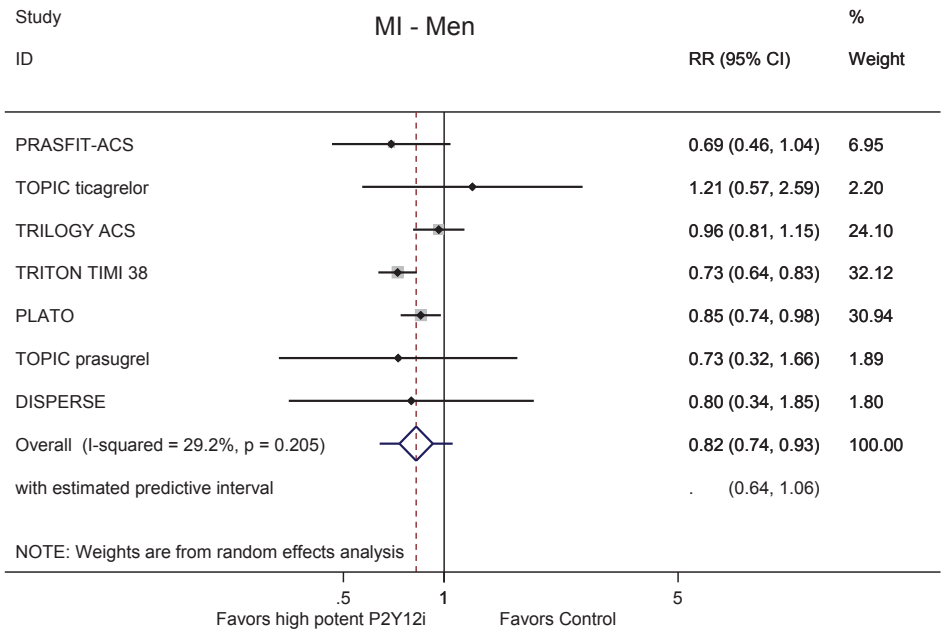


Fig S6. The relative risk of myocardial infarction in men treated with a high potent P2Y12 inhibitor (prasugrel/ticagrelor) vs. clopidogrel

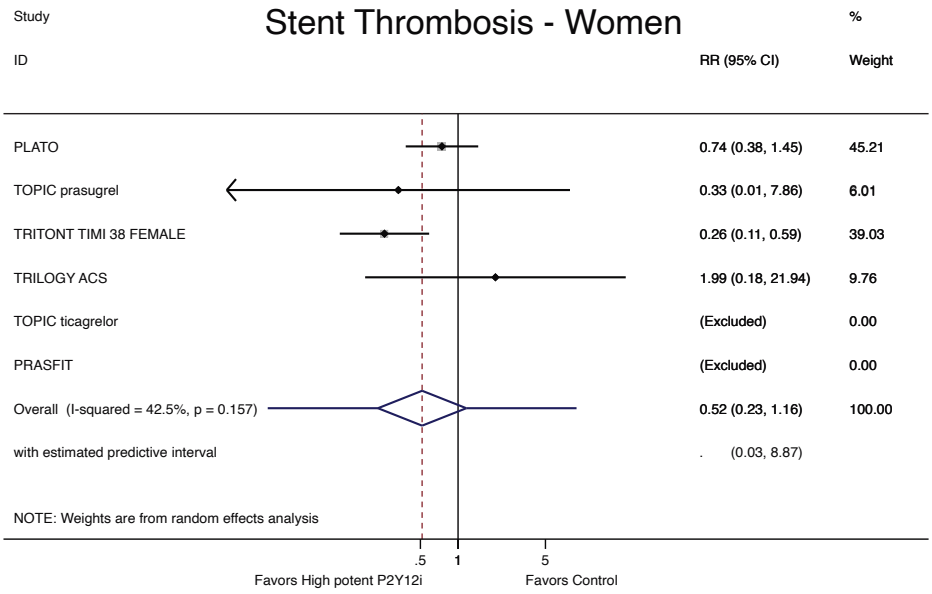


Fig S7. The relative risk of stent thrombosis in women treated with a high potent P2Y12 inhibitor (prasugrel/ticagrelor) vs. clopidogrel
TOPIC ticagrelor and PRASFIT ACS were excluded because there were no events during follow-up. DISPERSE-2 was excluded because there was no stent thrombosis endpoint reported.

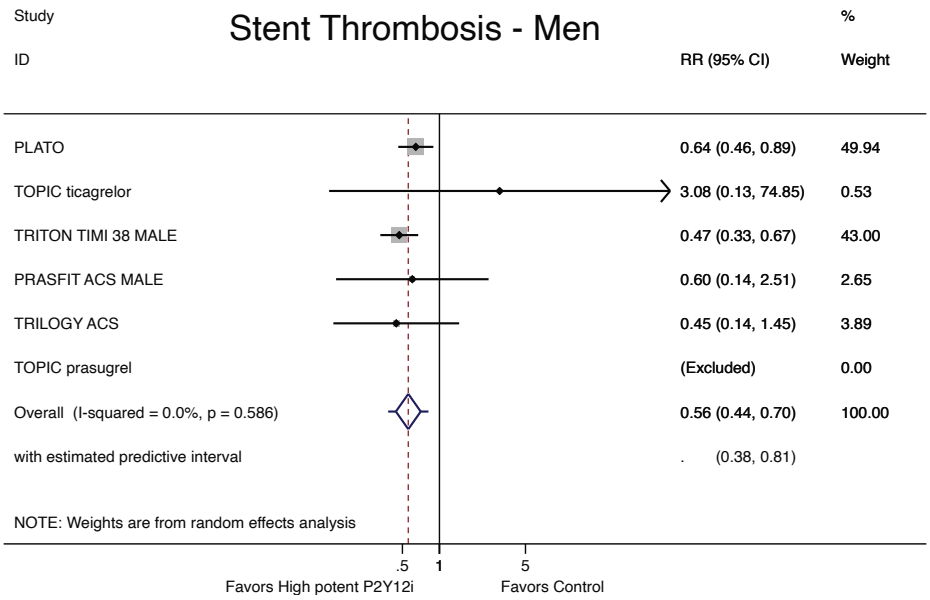


Fig S8. The relative risk of stent thrombosis in men treated with a high potent P2Y12 inhibitor (prasugrel/ticagrelor) vs. clopidogrel
aTOPIC prasugrel was excluded because there were no events during follow-up. DISPERSE-2 was excluded because there was no stent thrombosis endpoint reported.

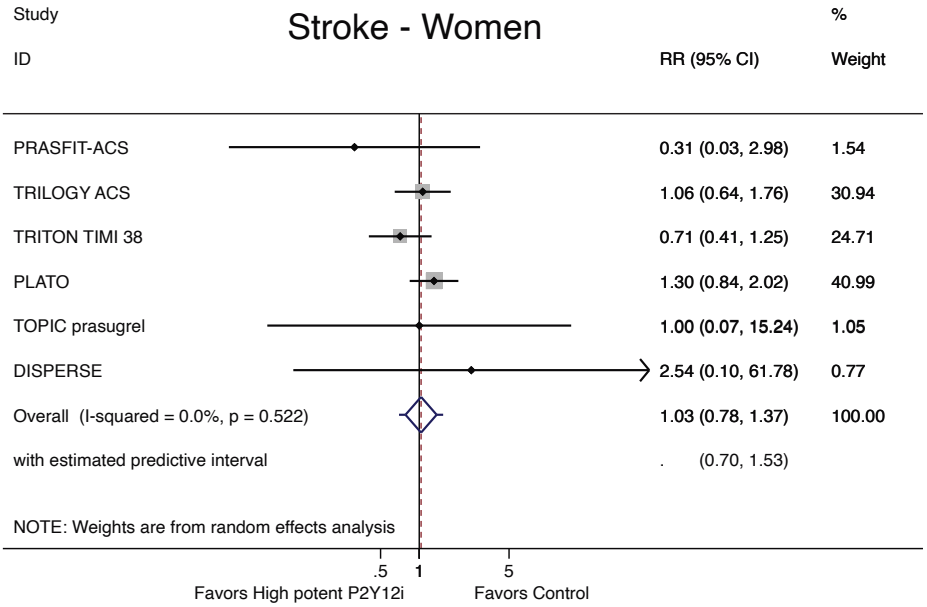


Fig S9. The relative risk of stroke in women treated with a high potent P2Y12 inhibitor (prasugrel/ticagrelor) vs. clopidogrel
TOPIC ticagrelor was excluded because there were no events during follow-up.
DISPERSE-2, TRILOGY ACS and PLATO defined stroke as either ischemic or hemorrhagic.

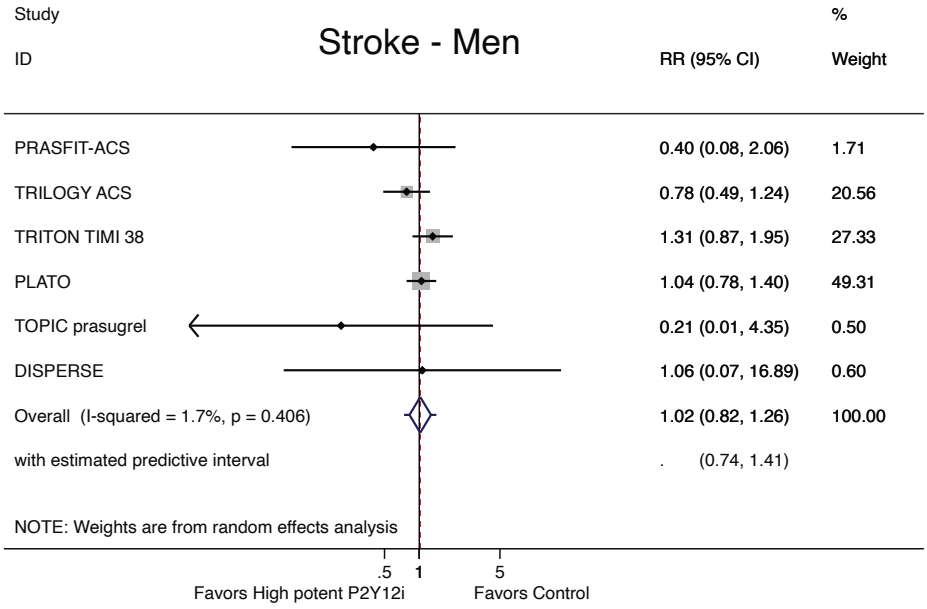


Fig S10. The relative risk of stroke in men treated with a high potent P2Y12 inhibitor (prasugrel/ticagrelor) vs. clopidogrel
TOPIC ticagrelor was excluded because there were no events during follow-up.
DISPERSE-2, TRILOGY ACS and PLATO defined stroke as either ischemic or hemorrhagic.

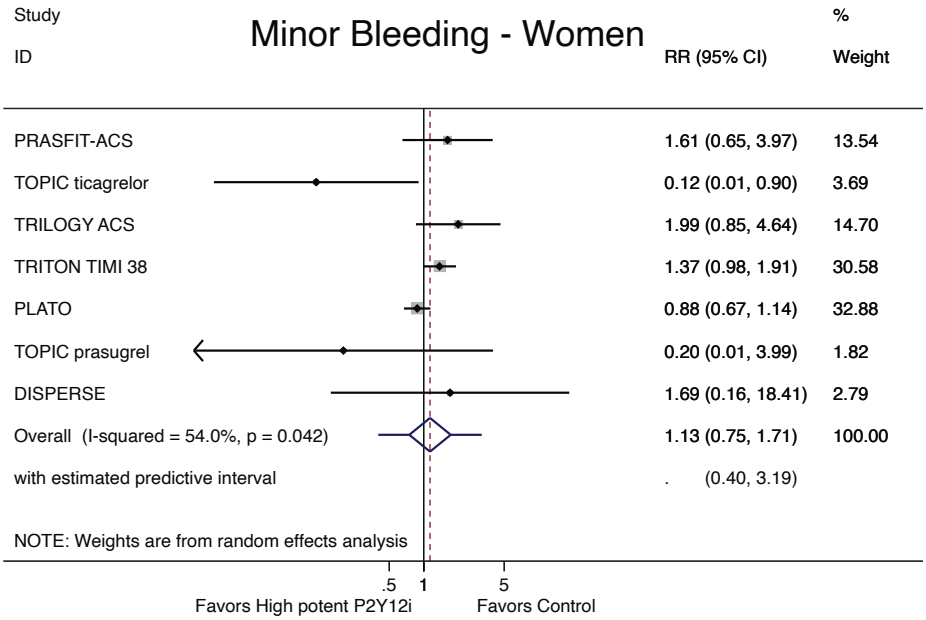


Fig S11. The relative risk of minor bleeding in women treated with a high potent P2Y12 inhibitor (prasugrel/ticagrelor) vs. clopidogrel

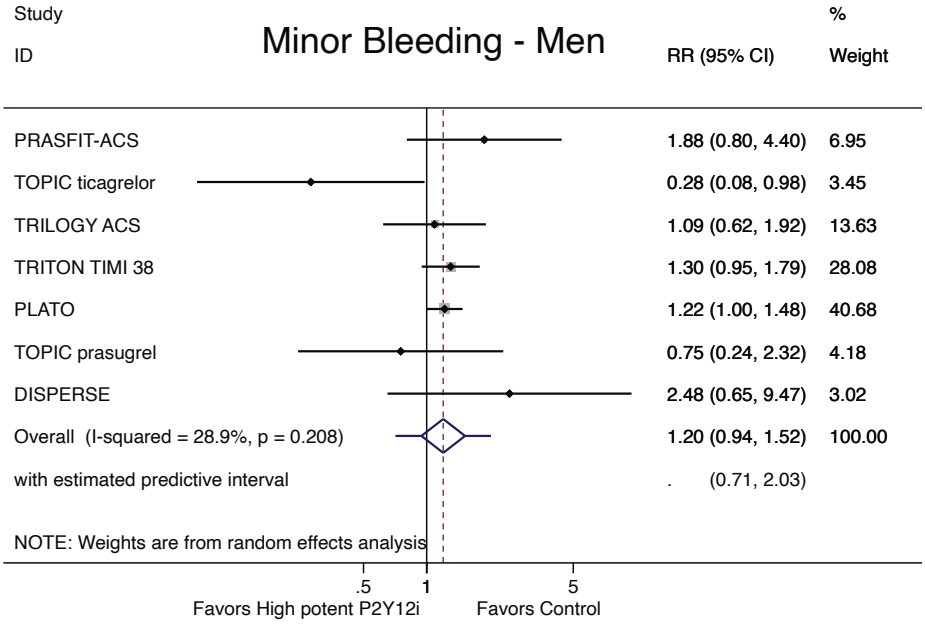
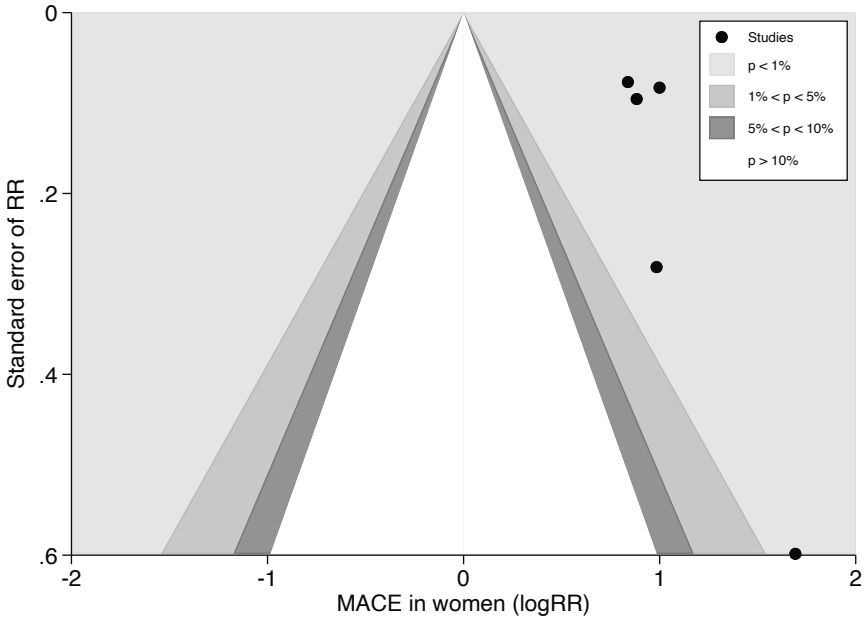
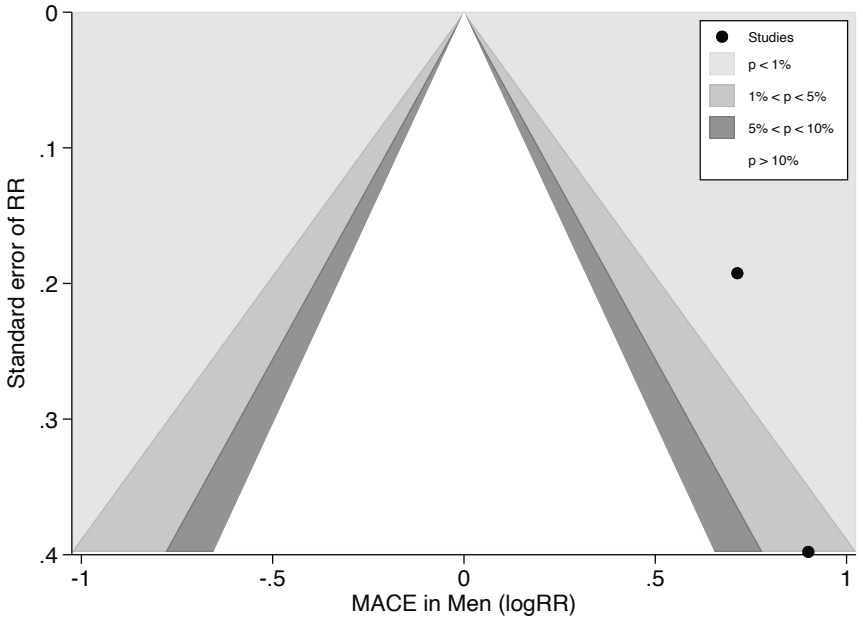


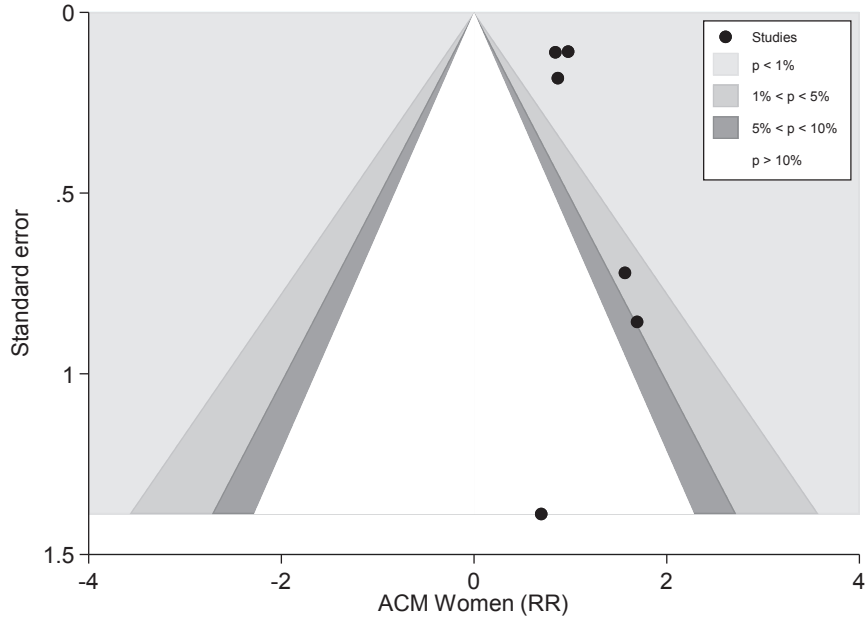
Fig S12. The relative risk of minor bleeding in men treated with a high potent P2Y12 inhibitor (prasugrel/ticagrelor) vs. clopidogrel



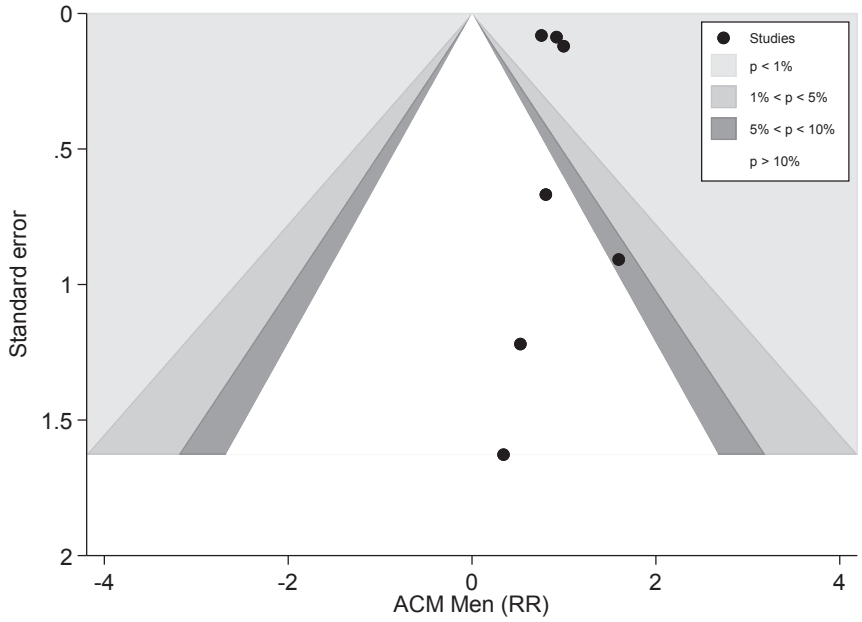
Test of H0: no small-study effects P = 0.270
Fig S13. Contour enhanced funnel plot of MACE in women



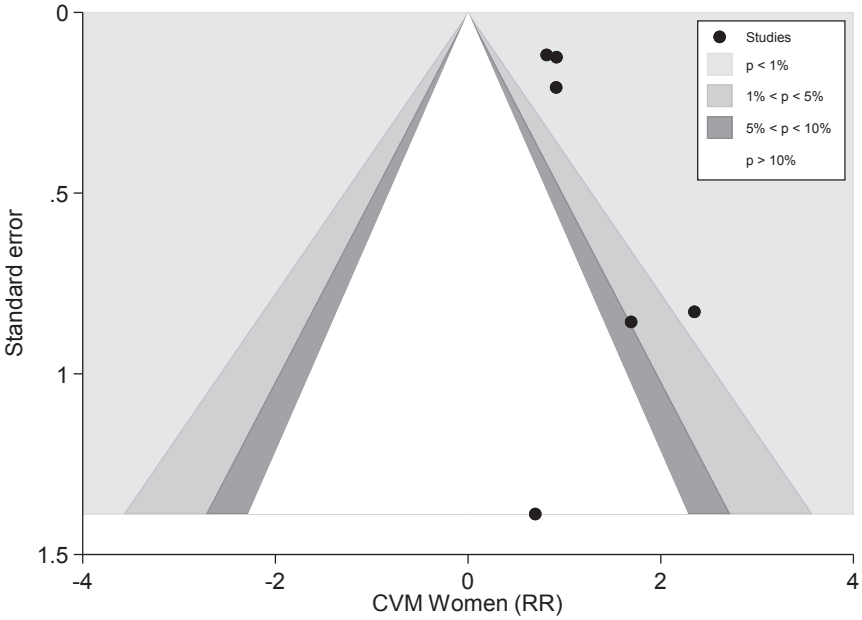
Test of H0: no small-study effects P = 0.826
Fig S14. Contour enhanced funnel plot of MACE in men



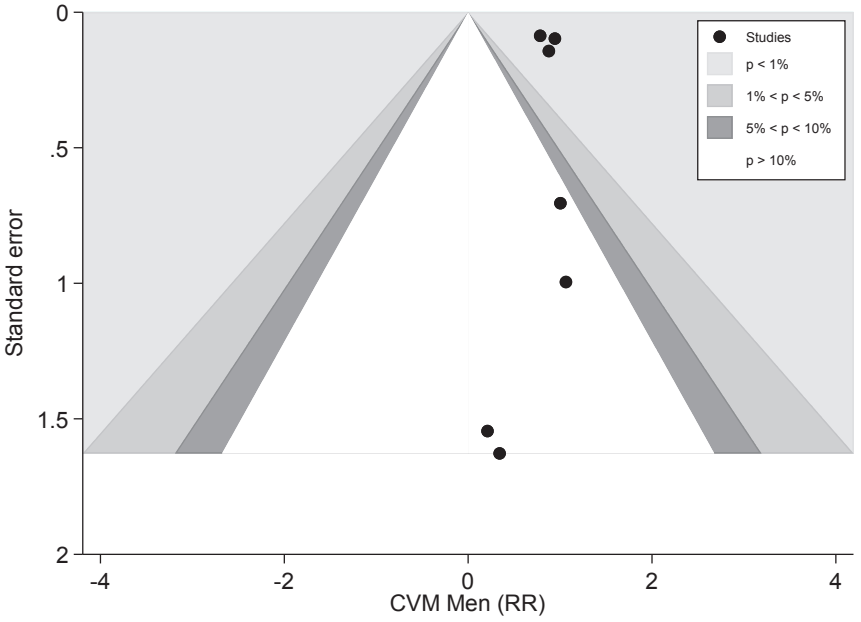
Test of H0: no small-study effects P = 0.271
Fig S15. Contour enhanced funnel plot of ACM in women



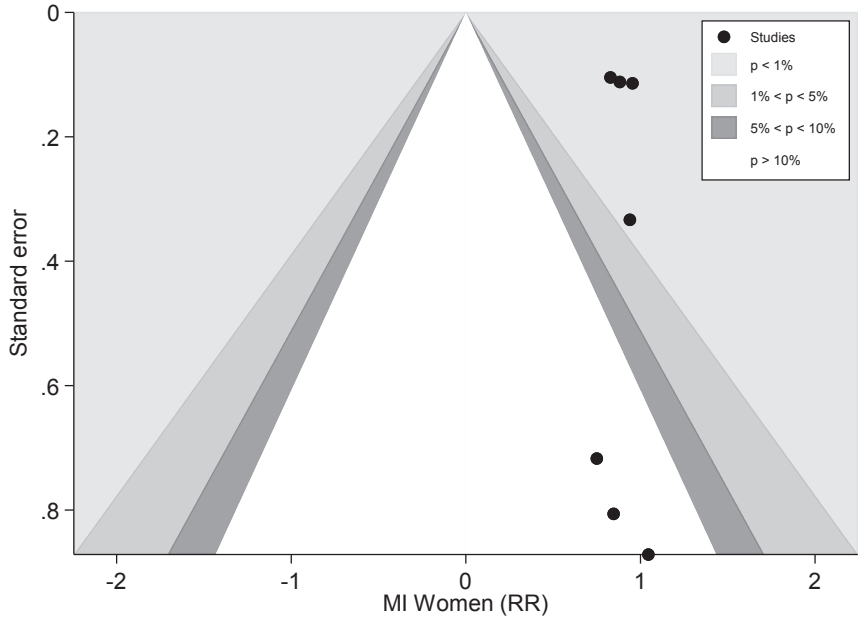
Test of H0: no small-study effects P = 0.779
Fig S16. Contour enhanced funnel plot of ACM in men



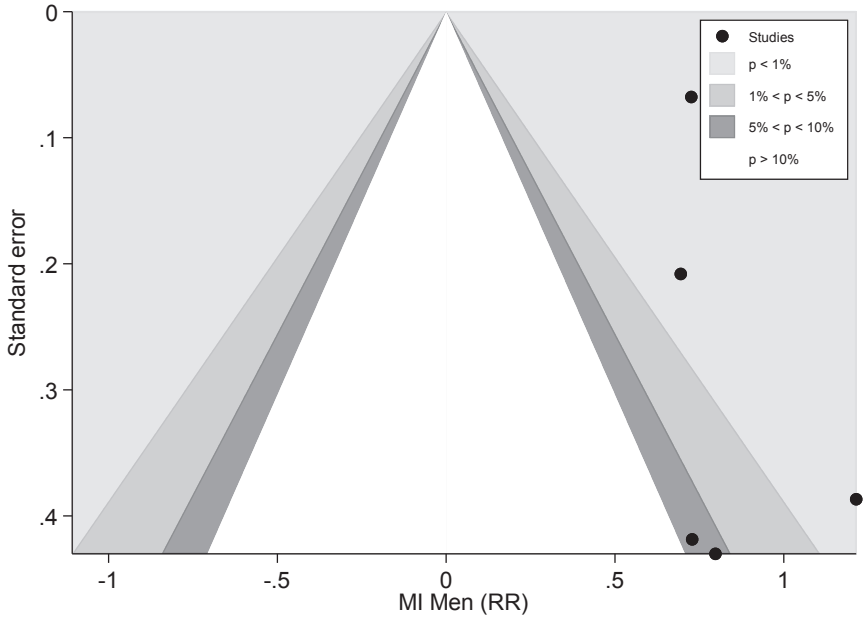
Test of H0: no small-study effects P = 0.125
Fig S17. Contour enhanced funnel plot of CVM in women



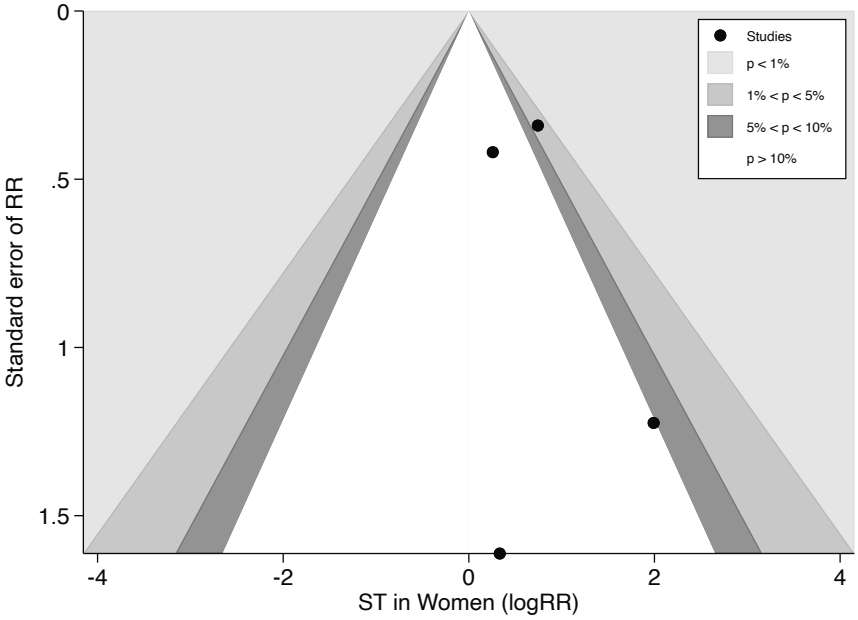
Test of H0: no small-study effects P = 0.878
Fig S18. Contour enhanced funnel plot of CVM in men



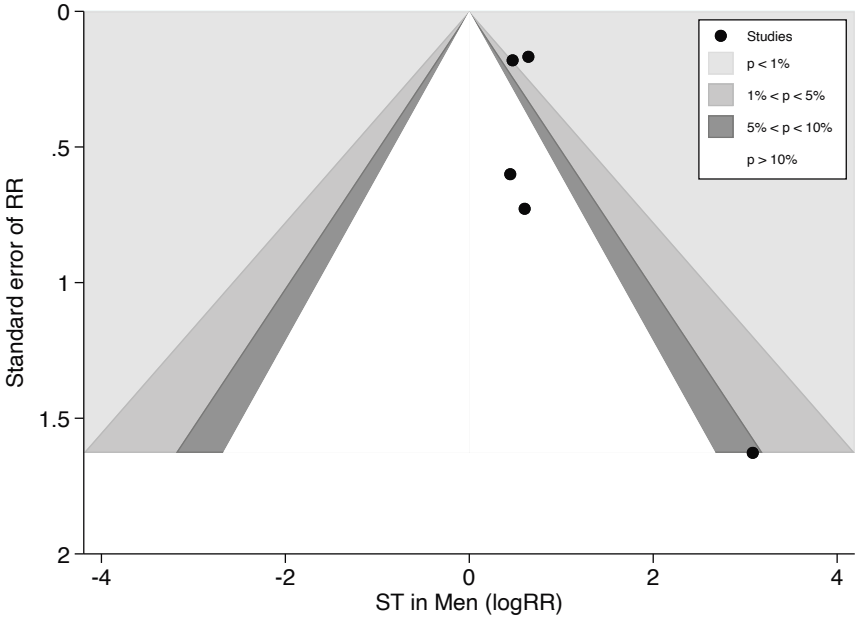
Test of H0: no small-study effects P = 0.864
Fig S19. Contour enhanced funnel plot of MI in women



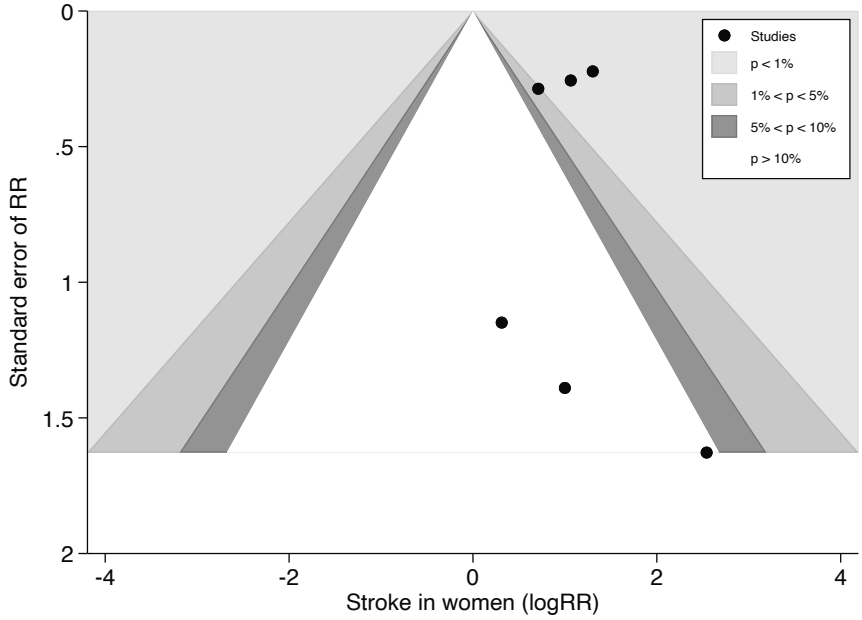
Test of H0: no small-study effects P = 0.747
Fig S20. Contour enhanced funnel plot of MI in men



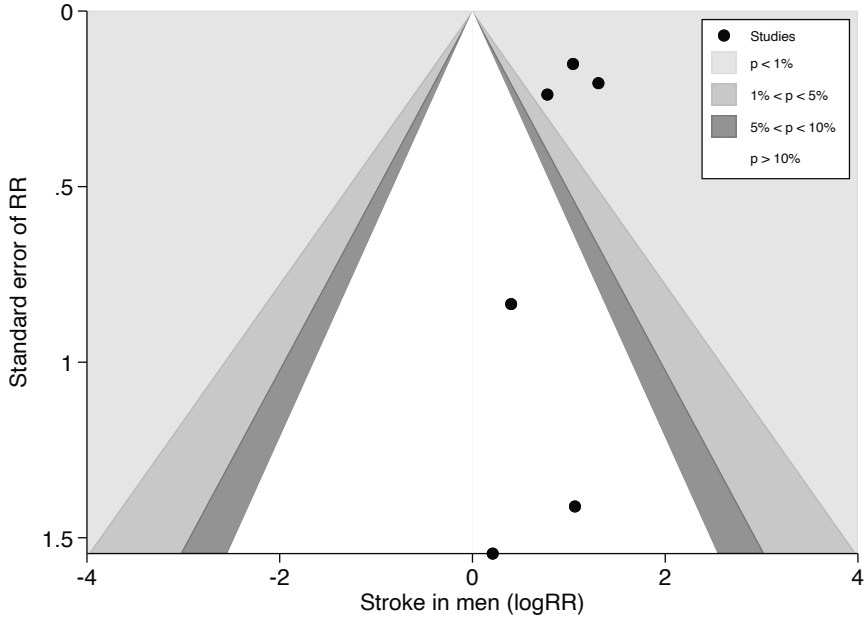
Test of H0: no small-study effects P = 0.648
Fig S21. Contour enhanced funnel plot of ST in women



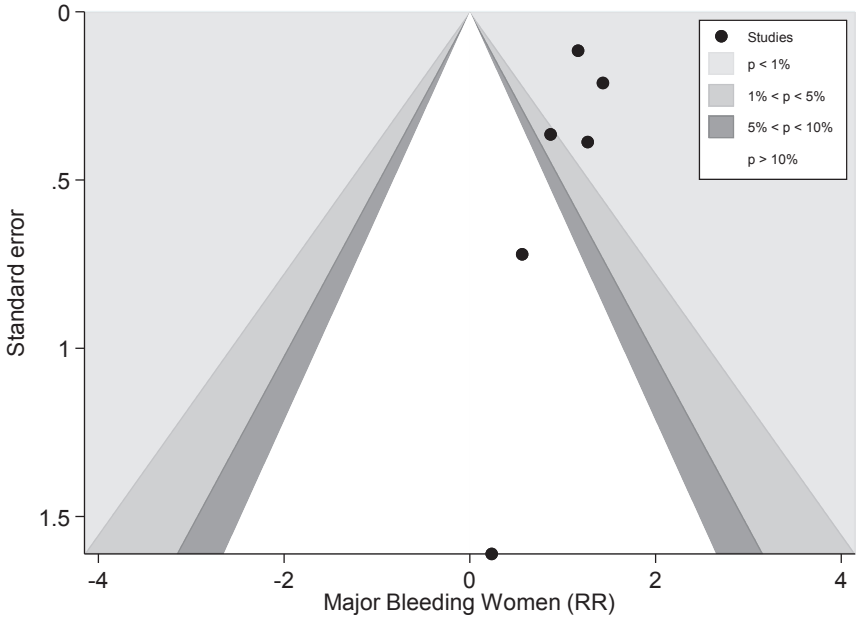
Test of H0: no small-study effects P = 0.352
Fig S22. Contour enhanced funnel plot of ST in men



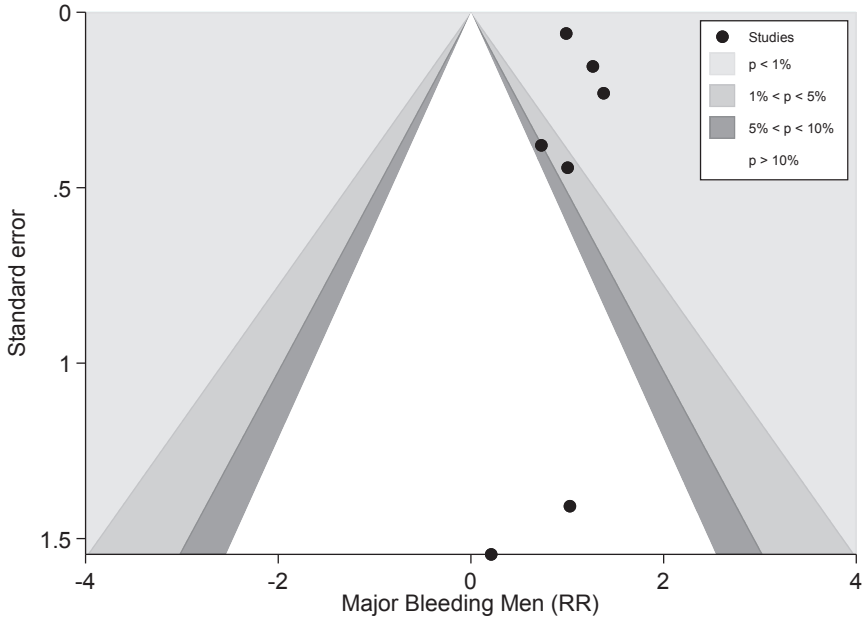
Test of H0: no small-study effects
Fig S23. Contour enhanced funnel plot of stroke in women



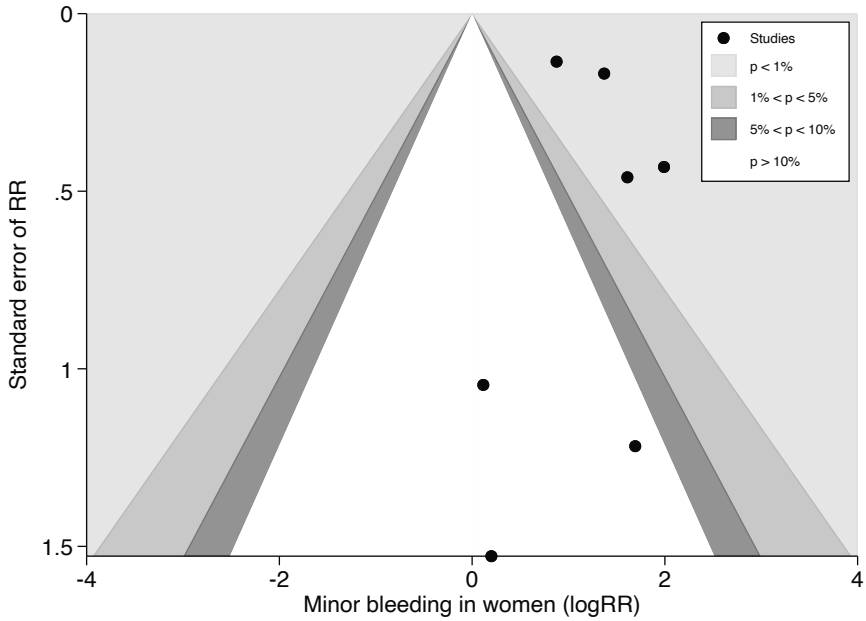
Test of H0: no small-study effects P = 0.416
Fig S24. Contour enhanced funnel plot of stroke in women



Test of H0: no small-study effects P = 0.366
Fig S25. Contour enhanced funnel plot of major bleeding in women

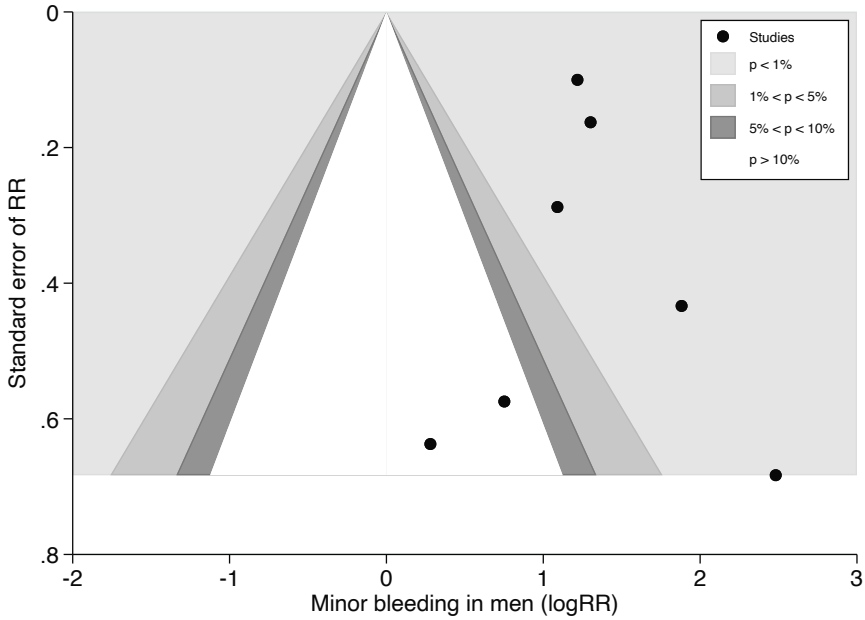


Test of H0: no small-study effects P = 0.745
Fig S26. Contour enhanced funnel plot of major bleeding in men



Test of H0: no small-study effects P = 0.632

Fig S27. Contour enhanced funnel plot of minor bleeding in women



Test of H0: no small-study effects P = 0.829

Fig S28. Contour enhanced funnel plot of minor bleeding in men

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LDL Cholesterol Targets Rarely Achieved in FH Patients: a sex-specific analysis

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Submitted

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Adverse Events Associated With PCSK9 Inhibitors: A Real-World Experience

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Published in ***Clinical Pharmacology and Therapeutics***
https://pubmed.ncbi.nlm.nih.gov/30053327/

ABSTRACT

In randomized clinical trials (RCTs) pro-protein convertase subtilisin/kexin 9 (PCSK9) inhibitors showed a favorable safety profile, however "real-world" data on adverse events (AEs) is scarce. Three datasets, a hospital registry (n=164) and two Pharmacovigilance databases, Lareb (n=149) and VigiLyze (n=15,554), reporting AEs attributed to PCSK9 inhibitors (alirocumab or evolocumab) prescribed in clinical practice were analyzed. In the hospital registry 41.5% of the patients reported any AE, most often injection-site reactions (33.8%) and influenza like illness (27.9%). Twelve patients (7%) discontinued PCSK9 inhibitor treatment. Most common AE reported in the Lareb and VigiLyze database was myalgia (12.8% and 8.3% respectively). No clinically relevant differences in gender or between drugs were observed. No specific subgroup of patients could be identified at risk of developing AEs. During follow-up, AEs resolved in most patients (71.1%). In real-world setting, PCSK9 inhibitors are well tolerated with an overall safety profile comparable to RCTs.

STUDY HIGHLIGHTS

What is the current knowledge on the topic?

RCTs assessing clinical effects of PCSK9 inhibitors alirocumab and evolocumab showed a favorable safety profile with a low rate of AEs. Most common reported AEs in RCTs are nasopharyngitis, upper respiratory tract infection, influenza like illness, myalgia, back pain, arthralgia, headache and ISRs.

What question did this study address?

What are (most common) AEs associated with the use of the PCSK9 inhibitors alirocumab and evolocumab prescribed in a real-world setting?

What does this study add to our knowledge?

In real-world setting, PCSK9 inhibitors are well tolerated with an overall safety profile comparable to RCTs. Most common AEs are influenza like illness, nasopharyngitis, myalgia and ISRs which often resolve over time. No clinical relevant differences in gender or between drugs were observed. No specific subgroup of patients could be identified at risk of developing AEs.

How might this change clinical pharmacology or translational science?

Safety monitoring of PCSK9 inhibitors is indispensable to assess long-term effects and reactions occurring in specific subgroups of patients. Therefore, health care providers should contribute to report to pharmacovigilance.

INTRODUCTION

High LDL-cholesterol (LDL-C) levels are associated with risk of cardiovascular disease (CVD).(1) Lipid-lowering therapy (LLT) including statins and ezetimibe proved to be very effective in lowering CVD events.(2) Cardiovascular prevention guidelines provide recommendations for optimal LDL-C levels for patients at high risk of CVD.(3) However, despite maximum tolerated LLT, only a minority of these patients reach the desired LDL-C targets.(4)

Pro-protein convertase subtilisin/kexin 9 (PCSK9) has been identified as a new player within the lipid metabolism.(5) PCSK9 binds to the LDL-receptor and promotes its lysosomal degradation, hence increasing LDL-C plasma levels.(6) People with hereditary high PCSK9 levels have a higher risk of cardiovascular events, whereas the opposite is true for people with hereditary low PCSK9 compared to the general population.(7)

Monoclonal antibodies binding PCSK9 have been successfully developed as a new class of LLT.(6) In 2015, two PCSK9 inhibitors (alirocumab and evolocumab) have been approved by the Food and Drug Administration (FDA) and European Medicines Agency (EMA). In multiple large randomized placebo controlled trials PCSK9 inhibitors showed reductions of LDL-C levels up to 60% and recently also a decrease in cardiovascular outcomes.(8, 9)

According to current literature alirocumab and evolocumab have a favorable safety profile and are generally well tolerated.(10) However, real-word data on adverse events (AEs) of PCSK9 inhibitors prescribed outside clinical trials is scarce. At present, real-world observational studies are considered indispensable to provide complementary information to RCTs especially about AEs as these studies involve a large and diverse population of patients in a real-world setting beyond the rather homogenous group of patients who participated in RCTs. This allows for detection of rare complications, long-term effects and reactions occurring in specific subgroups of patients.(11)

The aim of this study is to assess the main AEs reported by patients using PCSK9 inhibitors alirocumab and evolocumab in clinical practice.

RESULTS

Baseline characteristics per database are shown in Table 1 and supplementary tables S1-S3 for data on alirocumab and evolocumab separately.

Table 1. Patient characteristics

Characteristics	EMC, n=164*	Lareb, n=149	VigiLyze, n=15,554
Age (y), median (IQR)	58 (48-65)	63 (56-69)	
Age groups, n (%)			
0-17 years	0 (0)	0 (0.0)	8 (0.1)†
18-44 years	24 (15)	5 (3.4)	289 (1.9)
45-64 years	91 (56)	71 (47.7)	4,210 (27.1)
65-74 years	46 (28)	56 (37.6)	4,835 (31.1)
≥ 75 years	3 (2)	8 (5.4)	2,670 (17.2)
Age unknown, n (%)	0 (0)	9 (6)***	3,542 (22.8)
Gender, n (%)			
Male	90 (55)	70 (47)	5,975 (38.4)
Female	74 (45)	78 (52)	8,772 (56.4)
Unknown	0 (0)	1 (1)	807 (5.2)
BMI (kg/m^2), median (IQR)	27.4 (24.4-30.2)		
Diabetes mellitus, n (%)	29 (18)		
Hypertension, n (%)	75 (46)		
Ever smoker, n (%)	78 (48)		
Current smoker, n (%)	24 (15)		
History of CVD, n (%)	108 (66)		
Familial hypercholesterolemia, n (%)	148 (90)		
Heterozygous	98 (60)		
Homozygous**	7 (4)		
Clinical	43 (26)		
Lipid lowering therapy, n (%)			
Statin use	100 (61)		
High Intensity	63 (38)		
Moderate Intensity	30 (18)		
Low Intensity	7 (4)		
Ezetimibe	164 (100)		
Ezetimibe monotherapy	64 (39)		
LDL cholesterol (mmol/L), median (IQR)	4.28 (3.34 -5.14)		

*Baseline characteristics before starting PCSK9 inhibitor
**Double heterozygous LDLR/APOB gene mutation (n=1) , compound heterozygous LDLR gene mutation (n=6)
***One patient was reported to be 114 years old, which was put as missing value.
†These reports are considered either incorrectly documented or concerning off-label use

EMC Hospital Registry

Of the 183 patients registered in the database, 19 were excluded; 10 lacked follow-up data, eight participated in PCSK9 trials and one patient had missing baseline data. Therefore, 164 patients were included in the current analysis (Table 1). The median age was 58 (IQR 48-65) years, 55% were male. The majority of patients (90%) was diagnosed with FH. 66% of the patients had a history of CVD. All patients used LLT, however more than a third of the patients (39%) used ezetimibe monotherapy because of statin intolerance. Baseline median LDL-C was 4.28 mmol/L (166 mg/dL). Alirocumab and evolocumab were used by 49.4% and 50.6% of the patients respectively. There was no difference between baseline characteristics of patients using alirocumab and evolocumab (Table S1).

Lareb Database

Of the 152 reports in the database, 149 reports were included in the analysis (Table 1). Main reasons for exclusion were AEs not related to PCSK9 inhibitors (Figure S1). The median age of the patients in the reports was 63 (IQR 56-69) years. In 52% of the reports the patients were women, 47% men and in 1% gender was not reported. In 43 reports the patients used alirocumab and 110 evolocumab (Table S2). Age and sex distribution was similar between both groups.

VigiLyze Database

The VigiLyze database contained 15,554 reports of AEs associated with PCSK9 inhibitors. In most reports (31.1%) the patients were 65-74 years, 56.4% of the reports concerned women, 38.4% men and in 5.2% gender was not reported. A total of 4,650 reports concerned alirocumab and 10,931 evolocumab (Table S3). Age and sex distribution was similar between both groups.

Adverse events

Most common AEs are presented in Table 2 and supplementary tables S4-S6 for data on alirocumab and evolocumab separately.

Table 2. Overall frequencies of adverse events for both PCSK9 inhibitors with gender differences

ERASMUS MC	Total (n=68*)	OR (95% CI) Male vs Female	**Lareb**	Total (n=149)
Any TEAE, n (%)	68 (100.0)	0.58 (0.31-1.09)**	Any TEAE, n (%)	149 (100.0)
1 event	37 (54.4)		1 event	51 (34.2)
2 events	21 (30.9)		2 events	41 (27.5)
≥3 events	10 (14.7)		≥3 events	61 (38.3)
Events, median (IQR)	1.0 (1.0-2.0)		Events, median (IQR)	2.0 (1.0-3.0)
Total no. of TEAEs reported	116		Total no. of TEAEs reported	375
TEAEs leading to discontinuation	11 (16.2)		TEAEs leading to discontinuation	60 (40.3)
TEAEs leading to death	0 (0.0)		TEAEs leading to death	1 (0.7)
Most common (≥4%) TEAEs, n (%)			Most common (≥4%) TEAEs, n (%)	
Influenza like illness	19 (27.9)	0.56 (0.19-1.66)	Myalgia	19 (12.8)
Injection-site haematoma	13 (19.1)	0.43 (0.12-1.56)	Influenza like illness	14 (9.4)
Nasopharyngitis	11 (16.2)	0.52 (0.16-2.25)	Fatigue	12 (8.1)
Abdominal discomfort	8 (11.8)	2.04 (0.45-9.31)	Headache	12 (8.1)
Myalgia	7 (10.3)	0.41 (0.07-2.30)	Arthralgia	10 (6.7)
Cognitive disorder	6 (8.8)	2.43 (0.41-14.25)	Dyspnoea	9 (6.0)
Fatigue	6 (8.8)	2.43 (0.41-14.25)	Nausea	9 (6.0)
Headache	6 (8.8)	0.53 (0.09-3.13)	Malaise	8 (5.4)
Injection-site pain	6 (8.8)	1.14 (0.21-6.08)	Muscle spasms	8 (5.4)
Injection-site swelling	6 (8.8)	2.43 (0.41-14.25)	Pain in extremity	8 (5.4)
Rash	4 (5.9)	0.36 (0.04-3.60)	Diarrhoea	6 (4.0)
			Dizziness	6 (4.0)
Injection-site reactions, n (%)	23(33.8)	0.62 (0.22-1.71)	Injection-site reactions, n (%)	3 (2.0)
Injection-site haematoma	13 (19.1)	0.43 (0.12-1.56)	Injection-site haematoma	1 (0.7)
Injection-site pain	6 (8.8)	1.14 (0.21-6.08)	Injection-site haemorrhage	1 (0.7)
Injection-site swelling	6 (8.8)	2.43 (0.41-14.25)	Injection-site swelling	1 (0.7)
Injection-site erythema	2 (2.9)	1.13 (0.07-18.8)		
Injection-site infection	1 (1.5)			

TEAE, treatment-emergent adverse event. OR, odds ratio. 95% CI, Confidence Interval.
Significant results are set in bold.
*Only patients with adverse events at follow-up 1. Total patients n=164.
**Odds ratio calculated on total population of males and females with and without adverse events.

OR (95% CI) Male vs Female	**VigiLyze**	Total (n=15,554)	OR (95% CI) Male vs Female
	Any TEAE, n (%)	15,554 (100.0)	
	Total no. of TEAEs reported	29,956	
	TEAEs leading to discontinuation	N/A	
	TEAEs leading to death	N/A	
	Most common (≥4%) TEAEs, n (%)		
1.63 (0.62-4.32)	Myalgia	1,287 (8.3)	1.11 (0.99-1.25)
2.15 (0.69-6.77)	Drug dose omission	1,151 (7.4)	**0.87 (0.77-0.99)**
1.13 (0.35-3.67)	Injection-site pain	959 (6.2)	**0.55 (0.48-0.65)**
0.20 (0.04-0.95)	Influenza like illness	818 (5.3)	1.06 (0.91-1.23)
1.73 (0.47-6.42)	Back pain	816 (5.2)	0.95 (0.82-1.09)
0.13 (0.02-1.04)	Arthralgia	789 (5.1)	1.01 (0.87-1.17)
0.54 (0.13-2.24)	Fatigue	764 (4.9)	0.92 (0.79-1.06)
0.35 (0.07-1.81)	Pain in extremity	755 (4.9)	**0.77 (0.66-0.90)**
0.65 (0.15-2.84)	Muscle spasms	719 (4.6)	**0.81 (0.69-0.95)**
0.35 (0.07-1.81)	Pain	703 (4.5)	**0.66 (0.56-0.78)**
0.54 (0.10-3.07)	Headache	651 (4.2)	**0.72 (0.61-0.86)**
0.54 (0.10-3.07)			
2.27 (0.20-25.53)	Injection-site reactions (≥1.0%), n (%)	3291 (21.2)	**0.55 (0.50-0.60)**
	Injection-site pain	959 (6.2)	**0.55 (0.48-0.65)**
	Injection-site bruising	526 (3.4)	**0.56 (0.46-0.67)**
	Injection-site haemorrhage	373 (2.4)	**0.72 (0.58-0.89)**
	Injection-site erythema	268 (1.7)	**0.49 (0.37-0.65)**
	Injection-site swelling	229 (1.5)	**0.61 (0.45-0.81)**
	Injection-site pruritus	152 (1.0)	**0.42 (0.29-0.62)**

EMC Hospital Registry

At first follow-up 68 (41.5%) patients reported ≥ 1 AEs. A total of 116 events were reported with most patients reporting one event (54.4%) (Table 2). Most common AEs were influenza like illness (27.9%), nasopharyngitis (16.2%), abdominal discomfort (11.8%) and myalgia (10.3%). 23 patients (33.8%) reported ≥ 1 injection-site reactions (ISRs), most commonly injection-site haematoma. No significant sex differences in AEs were observed.

The percentage of patients reporting AEs were similar for the alirocumab group and the evolocumab group (43.2% and 39.8% respectively) (Table S4). Influenza like illness was the most reported AE for both alirocumab and evolocumab (28.6% and 27.3%, respectively). AE profile did not significantly differ between alirocumab and evolocumab.

Lareb Database

A total of 149 reports, containing 375 suspected AEs were collected. Most reports contained ≥ 3 AEs (38%) (Table 2). The most common reported AEs were myalgia (12.8%), influenza like illness (9.4%), fatigue (8.1%) and headache (8.1%). ISRs were infrequently reported, in 2.0% of the reports.

No significant differences in sex were observed, except for headache reported less frequent in reports concerning men compared to women (OR 0.20, 95% CI [0.04-0.95]; p=0.042). The overall AE profile for alirocumab and evolocumab was similar (Table S5).

VigiLyze Database

A total of 15,554 reports, containing 29,956 suspected AEs were collected (Table 2). Most common documented AEs were myalgia (8.3%), influenza like illness (5.3%), back pain (5.2%) and arthralgia (5.1%). ISRs were frequently reported (21.2%), most often injection-site pain (6.2%). Significantly more reports concerned women than men, for the AEs pain in extremity (p<0.001), muscle spasms (p=0.010), pain (p<0.001), headache (p<0.001), diarrhoea (p=0.002), nausea (p<0.001) and the overall total of ISRs (p<0.001). Drug dose omission (7.4%) was not considered a drug-related AE that was relevant for this study.

Myalgia was the most reported AE for both alirocumab and evolocumab (9.4% and 7.8%, respectively) (Table S6). Back pain was reported nearly three times as frequent for evolocumab (6.4%) compared to alirocumab (2.4%). ISRs were reported at a similar rate (21.6% vs 21.3%).

Predictors and time course of AEs

In the EMC hospital registry we analyzed for possible predictors of AEs, such as sex, statin use or a very low LDL-C. Univariate logistic regression analyses did not show any significant predictors for AEs, in particularvery low LDL-C and statin intolerance (Table 3).

Table 3. Univariate logistic regression of possible predictors of adverse events at follow-up 1

	OR (95% CI)	*P*-value
Age	0.98 (0.96-1.01)	0.202
Gender (Male)	0.58 (0.31-1.09)	0.091
BMI	0.99 (0.92-1.07)	0.740
Hypertension (Yes)	1.34 (0.72-2.50)	0.356
Current Smoker (Yes)	0.63 (0.25-1.57)	0.320
Diabetes melltius (Yes)	1.00 (0.44-2.25)	0.992
History of CVD (Yes)	1.44 (0.74-2.80)	0.283
Familial hypercholesterolemia (FH) (Yes)	0.90 (0.32-2.56)	0.845
FH – Genetic mutation (Yes)	1.46 (0.70-3.04)	0.318
Statin use (Yes)	1.18 (0.62-2.23)	0.618
Statin intensity (High vs Low+Mod)	1.68 (0.73-3.88)	0.225
LDL-C at baseline	1.05 (0.88-1.24)	0.590
LDL-C at follow-up 1	1.14 (0.94-1.38)	0.187
LDL-C <0.5 mmol/L* at follow-up 1	1.83 (0.47-7.07)	0.383
PCSK9 inhibitor (EVO vs ALI)	0.87 (0.47-1.62)	0.654

*0.5 mmol/L = 19.3 mg/dl

To study the time course of reported AEs we compared the reported AEs at first, second and third follow-up visit (Table 4). Of the 164 patients with a first follow-up visit, 131 had a second follow-up visit and 94 a third follow-up visit. Nearly 60% of patients who reported AEs at first follow-up, also had AEs at the second follow-up visit. Notably, the majority (74%) of these patients reported different AEs at first and second follow-up visit. For 40.4% of the patients with AEs at first follow-up, AEs resolved at second follow-up. However, 22.8% of the patients without AEs at first follow-up developed new AEs at second follow-up. Compared to first follow-up visit, AEs resolved in 71.1% at third follow-up.

Table 4. Comparison of adverse events occurrence at follow-up

		Follow-up 2 (n=131)		**Follow-up 3 (n=94)**	
		AEs	**No AEs**	**AEs**	**No AEs**
Follow-up 1	AEs	**31** 59.6%	**21** 40.4%	**11** 28.9%	**27** 71.1%
	No AEs	**18** 22.8%	**61** 77.2%	**7** 12.5%	**49** 87.5%
Follow-up 2	AEs			**11** 33.3%	**22** 66.7%
	No AEs			**7** 11.5%	**54** 88.5%

FU1 vs FU2: McNemar's p=0.749; FU2 vs FU3: McNemar's p=0.009;
FU1 vs FU3: McNemar's p=0.001

Drug discontinuation

In the EMC hospital registry 12 patients (7%), 5 patients using alirocumab and 7 evolocumab, discontinued PCSK9 inhibitor treatment; 11 because of AEs and 1 due to non-response. The majority (67%) of patients who stopped treatment was female and 42% reported ≥ 3 events. 24 AEs were reported by 11 patients most often influenza like illness (50%), cognitive disorders (25%), abdominal discomfort (17%), fatigue (17%) and malaise (17%) (Table S7). ISRs did not lead to discontinuation of drug therapy. Notably, most patients with these AEs continued treatment.

In the Lareb database, in 60 reports (40%) the patients discontinued treatment due to AEs; in 12 reports (20%) the patients were using alirocumab and in 48 reports (80%) evolocumab. In line with the hospital registry, in most reports the patients discontinued treatment due to ≥3 AEs (57%) and ISRs were not associated with discontinuation (Table S7). For alirocumab discontinuation was higher in women compared to men (67% vs 33%), whereas the women to men ratio was similar for those who stopped evolocumab treatment. The main reason for drug discontinuation was myalgia; in patients with myalgia 100% of alirocumab users and 70% of evolocumab users discontinued therapy (Figure 1).

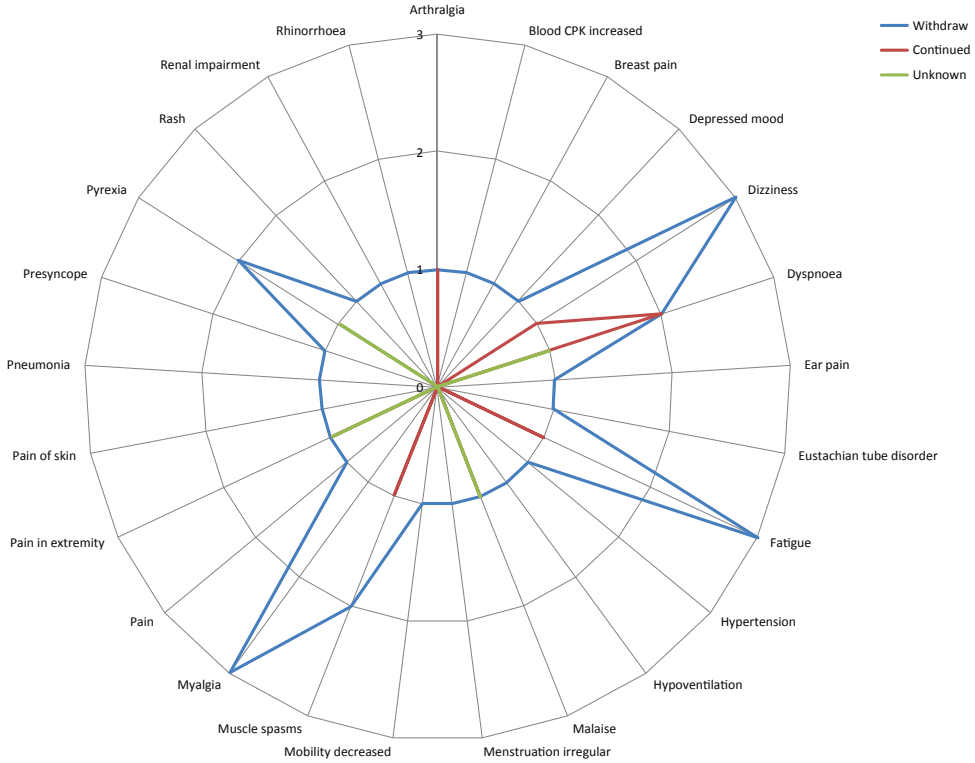

Fig 1a. Drug action taken per reported AE by patients who discontinued alirocumab compared to patients who continued or for whom drug action was unknown

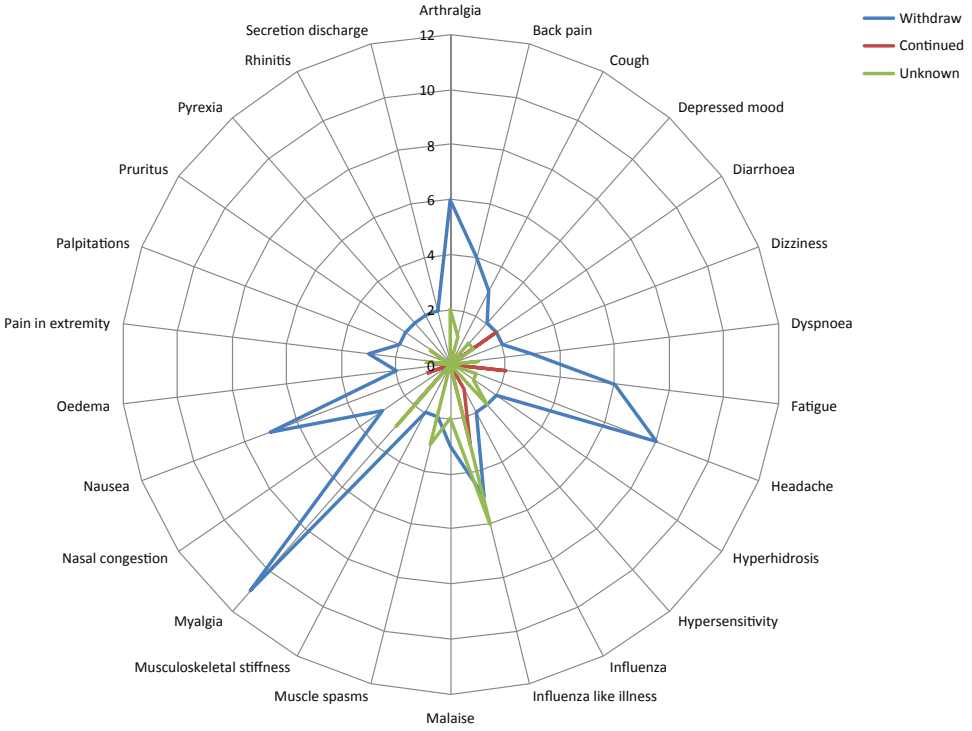

Fig 1b. Drug action taken per reported AE by patients who discontinued evolocumab compared to patients who continued or for whom drug action was unknown

DISCUSSION

In an analysis of three different registries (one hospital registry and two pharmacovigilance databases) we showed that the most reported AEs associated with PCSK9 inhibitors prescribed in clinical setting were influenza like illness, nasopharyngitis, myalgia and ISRs, with no significant difference between alirocumab and evolocumab and between sexes. In the hospital registry, no specific category of patients could be identified at increased risk of developing AEs, the AEs were usually mild, during follow-up most AEs resolved and rate of drug discontinuation was infrequent.

RCTs assessing clinical effects of PCSK9 inhibitors showed a favorable safety profile with a low rate of AEs. Most common reported AEs in RCTs are nasopharyngitis, upper respiratory tract infection, influenza like illness, myalgia, back pain, arthralgia, headache and ISRs.(10, 12, 13) Most meta-analyses of published RCTs showed no significant difference in AE occurrence, serious AEs or specific AEs between the PCSK9 inhibitors and control arms (placebo or ezetimibe).(10, 14, 15) Real-world data on AEs is limited. Five studies, including our previous work, published data of AEs associated with PCSK9 inhibitors in a limited number of patients.(16-20) These previous studies described a similar set of AEs associated with PCSK9 inhibitors in 15%-39% of the patients. The method of acquisition of AEs was often not described in detail, only Saborowski et al. indicated that AEs were acquired by self-reported questionnaires available in 31 of 38 patients (82%).(20) Compared to these studies, we observed a higher rate of AEs of 41.5% in our population. An explanation for this difference could be that in our registry, patients were systematically questioned about AE specifically attributed to PCSK9 inhibitors at every visit.

AEs related to monoclonal antibodies (mAbs) can be distinguished in non-specific AEs and AEs specifically related to the mAb target, for example infections with infliximab due to reduced activity of immune cells.(21) The use of mAbs can lead to an immune response and even immunogenicity such as the development of neutralizing antibodies, depending on the type of mAb.(21) The effect of a mAb on the immune system can range from immune suppression to immune stimulation leading to a wide variety of AEs.[22] The cytokine-mediated type alpha immune response is likely to be the main mechanism for common AEs associated with mAbs such as flu-like symptoms and ISRs.(23)

Alirocumab and evolocumab are fully humanized, which substantially reduces the risk of immunogenicity.(21) The use of PCSK9 inhibitors is not related to target-specific AEs. Very low LDL-C levels achieved with PCSK9 inhibitors were not significantly associated with an increase in overall AE rates(24, 25) or neurocognitive AEs(26, 27). Moreover, levels of vitamin E, steroid or gonadal hormones were not affected in patients using PCSK9 inhibitors even at very low LDL-C levels of <0.4 mmol/L (15 mg/dL).(28)

In RCTs, among the most reported AEs were nasopharyngitis (5.9%-12.2%) and influenza (2.1%-7.3%) in patients randomized to PCSK9 inhibitors.(10, 12, 13) In our study, in the

EMC registry influenza like illness and nasopharyngitis were reported by 27.9 % and 16.2% respectively and often resolved during follow-up. Influenza like illness was also among the most frequent reported reactions in both the Lareb and VigiLyze database.

ISRs were reported by 3.1%-7.4% of patients randomized to PCSK9 inhibitors and in general occurred more often in patients randomized to a PCSK9 inhibitor compared to placebo.(10, 12, 13) Overall ISRs in RCTs were mild and transient and did not lead to drug discontinuation. In this analysis, in the EMC registry ISRs were reported more frequently (33.8%) compared to RCTs, were also mild and not leading to drug discontinuation. Remarkably, ISRs were reported frequently (21.2% of the reports) in the VigiLyze database as opposed to the Lareb database (2% of the reports), which might be explained by differences in the types of information source between different countries.

In RCTs, myalgia was reported by 3.5-7.2% of patients randomized to a PCSK9 inhibitor. (10, 12, 13) No significant differences were observed in myalgia between PCSK9 inhibitor and comparator arm.(10, 14, 15) In the EMC hospital registry myalgia was reported in 10.3% which is more compared to RCTs. In both the Lareb and the VigiLyze database myalgia was the most commonly reported AE and in case of Lareb this was also a major reason for drug discontinuation. As mentioned before, the number of reports in these databases reflect reporting behavior and not incidence on a suspected AE. We do not have a conclusive explanation for the differences concerning myalgia between the RCTs and the hospital registry. A possible pathogenic mechanism of the development of myalgia as a result of the use of a PCSK9 inhibitor is unclear.

Two meta-analyses showed that the use of PCSK9 inhibitors was associated with a significantly increased incidence of neurocognitive AEs compared to controls.(29, 30) These results raised initial concern about the effect of PCSK9 inhibitors and led to a recommendation of the FDA in 2014 to perform a long-term trial prospectively evaluating neurocognitive function.(31) The Evaluating PCSK9 Binding antiBody Influence oN coGnitive HeAlth in High cardiovascular Risk Subjects (EBBINGHAUS) study, prospectively assessed cognitive function using formal tests and showed no effect on cognitive function in patients randomized to evolocumab compared to placebo.(26) Moreover, no significant differences in neurocognitive AE rates were found between alirocumab vs controls.(27) Finally a recent meta-analysis including a larger number of trials, showed no significant differences between PCSK9 inhibitor and control arm on neurocognitive outcomes.

In our study, cognitive disorders were reported more frequently (3.7%) than in RCTs and were one of the main reasons for drug discontinuation. An explanation could be that in contrast to the placebo-controlled trials, patients were unblinded to treatment and were aware of possible negative cognitive effects attributed to PCSK9 inhibitors via the media. Cognitive AEs reported were mainly mental dullness and forgetfulness and were nonspecific. No formal screening tools have been used in these patients.

Until now, it is not known whether the reported adverse events are caused by the PCSK9 inhibition or are specific for the monoclonal antibody that is administered. A novel PCSK9-

based therapy is inclisiran, a small interfering RNA which inhibits translation of the PCSK9 protein. A phase 2 trial studied showed a maximum LDL-C decrease of 41.9% after a single-dose of 500 mg and 52.6% after two-dose of 500 mg. (32) The most common adverse events of inclisiran were comparable to those of PCSK9 monoclonal antibodies, namely myalgia, headache, fatigue, nasopharyngitis, back pain, hypertension, diarrhea, and dizziness. The overall adverse event rate in the patients that received inclisiran was similar to the patients that received placebo. (10, 12, 32)

We assessed both a hospital registry as well as two pharmacovigilance databases containing spontaneous AE reports. Pharmacovigilance databases in general contain fewer reports of non-serious AEs or AEs not associated with drug discontinuation because of the threshold to report. It is known that women are at higher risk of developing AEs(33) and more often report to pharmacovigilance centers compared to men(34). In our study we found that women represented 52% of Lareb and 56% of VigiLyze reports. In the Netherlands 42% of all patients using PCSK9 inhibitors were female(35) leading to a AE report ratio of 1.23 supporting that women report AEs more than men. This is in line with the women to men ratio of AE reports of 1.18 observed in the hospital registry.

To our knowledge, this is the largest in-depth study of AEs of PCSK9 inhibitors prescribed in a clinical setting to date. Our study has several strengths. First, in the EMC hospital registry, the treating healthcare professional enquired about AEs at every visit and only AEs considered to be directly related to the use of PCSK9 inhibitor were included. Therefore we consider that reporting bias is prevented as much as possible. We provide data up to a follow-up duration of 42 weeks which provides insight on how AEs develop over time. As we combined different data sources utilizing different methods of AE monitoring a complete overview of possible AEs is provided. General limitations of using real-world data such as selection bias, confounding, the lack of a control group and variable physician-scheduled appointments, also apply for our study.[11] Specific limitations are that the power of the EMC hospital registry was too low to detect significant differences in AEs between sexes. A limitation of the Lareb and VigiLyze data was that the amount of available information varied between cases. Moreover, this is a single country study, except for the VigiLyze data, and experience with these agents is limited.

In conclusion, in a real-world setting, PCSK9 inhibitors are well tolerated. Most common AEs are influenza like illness, nasopharyngitis, myalgia and ISRs which often resolve over time. ISRs are mild and don't lead to drug discontinuation. However, despite these findings cost-effectiveness has still to be taken in account regarding both FH and non-FH patients.(36) Long-term safety monitoring of PCSK9 inhibitors prescribed in clinical practice to a diverse population is indispensable to discover new or rare AEs and to assess AE risk in specific subgroups. All health care professionals prescribing these medications should contribute to monitor AEs by reporting these to pharmacovigilance agencies and if possible by collecting long-term data in a local, national and ultimately an international database.

METHODS

Patients and study design

Three different data sources were analyzed: 1) the Erasmus Medical Centre (EMC) hospital registry, 2) the Netherlands Pharmacovigilance Centre Lareb database(37) and 3) VigiLyze(38) pharmacovigilance database maintained by the World Health Organization (WHO) collaborating center for international drug monitoring UMC (Uppsala Monitoring Centre in Sweden).

EMC Hospital Registry

Full details of this registry have been published before.(17) Briefly, patients with hypercholesterolemia, mostly patients with FH, not reaching target LDL-C levels despite maximally tolerated statin and ezetimibe therapy who were eligible for treatment with PCSK9 inhibitors, were recruited from the outpatient clinic in a tertiary university hospital setting. All patients fulfilled the Dutch criteria for reimbursement of PCSK9 inhibitors.(39)

Patients started with a PCSK9 inhibitor (evolocumab 140mg subcutaneously every two weeks [HeFH] or 420mg subcutaneously every two weeks [HoFH] or alirocumab 75mg or 150mg subcutaneously every two weeks [HeFH]) between June 2015 and November 2017, as part of clinical care. There was no preference for alirocumab or evolocumab. All patients had at least two PCSK9 inhibitor subcutaneous injections between baseline and on-treatment measurements. Only patients of whom at least one follow-up visit was available were included in the analysis. Patients who participated in a PCSK9 trial were excluded from analysis.

Baseline date was defined as the date when the first injection of the PCSK9 inhibitor was administered. Routine laboratory investigations were performed before and after start of PCSK9 inhibitor to monitor treatment effects. Patients had regular appointments for follow-up at six weeks, 18 weeks and 42 weeks at the outpatient clinic. Adverse events, including injection-site reactions (ISRs) and adherence to LLT were systematically discussed during each consultation. Only PCSK9 inhibitor-related AEs were included, defined as AEs not present prior to start of PCSK9 inhibitor therapy, or an already present symptom that changed or worsened following treatment. Adverse events were classified using Medical Dictionary for Regulatory Activities (MedDRA) terms. One patient may report multiple events. Clinical data such as age, sex, body mass index (BMI), diabetes mellitus, hypertension, history of CVD, familial hypercholesterolemia, LLT, laboratory values and AEs were collected from patients' files and entered into a database.

According to the Medical Ethical Research Committee, this study (MEC-2016-698) was not subject to the Medical Research involving Human Subjects Act. We only used data of patients, who provided written consent for research and anonymous publication of their clinical information.

Lareb Database

The Netherlands Pharmacovigilance Centre Lareb(37) identifies risks associated with the use of drugs in daily practice in the Netherlands. This database contains individual case safety reports of suspected AEs reported by health care professionals, manufacturers, patients or others. The submitted reports are reviewed case-by-case by Lareb and AEs are defined with the use of MedDRA terms. One single report may refer to multiple AEs. It must be emphasized, that the number of reports reflect reporting behavior and not the incidence of a reaction. Furthermore, it must be noted that the likelihood of a causal relationship can differ between cases, since the aim is to collect all reports of suspicions of AEs and reports may be incomplete concerning the provided information. The database was accessed on September 26, 2017 and contained all AE reports for alirocumab and evolocumab since its inception.

VigiLyze Database

VigiLyze(38) contains individual case safety reports of suspected AEs collected by national drug authorities in over 110 countries, including Lareb data. Similar to the Lareb database one single report may refer to multiple AEs, the number of reports reflect reporting behavior and not the incidence of a reaction, and causality is not ensured. Collection of data is, due to e.g. differing national legislation and policies, heterogeneous between different countries. The database was accessed on November 21, 2017 and contained the dataset from inception to November 19, 2017 of all AE reports on alirocumab and evolocumab.

Statistical Analysis

Dichotomous variables are reported as numbers and percentages. Continuous variables are presented as mean ± standard deviation (SD) or median and interquartile range (IQR). Normality of data was assessed by visually exploring the distribution in normal plots, checking for skewness and using The Shapiro-Wilk test. Differences between categorical variables were evaluated using Chi-square or Fisher's exact test as appropriate. Differences between numeric variables were evaluated using student *t*-test or Mann-Whitney U test as appropriate. Sex differences were assessed using odds ratios [OR], which were obtained using binary logistic regression. Covariates were analyzed using univariate logistic regression to determine possible predictors. McNemar's test was performed to assess asymmetry in the distribution of AE occurrence during follow-up. For all tests, a *P*-value below 0.05 was considered statistically significant. Data were analyzed using IBM SPSS Statistics for Windows, version 21. When individual cases were not available for analysis, SAS Statistics v.9.4 was used to obtain odds ratios from counts.

DISCLAIMER

The authors are indebted to the national pharmacovigilance centers that contributed data to the worldwide database, maintained by the World Health Organization (WHO) collaborating center for international drug monitoring UMC (Uppsala Monitoring Centre in Sweden). The opinions and conclusions, however, are not those of the various centers, nor of the UMC in Sweden. The information originates from a variety of sources, and the likelihood that the suspected AEs are drug-related can vary between cases.

ACKNOWLEDGEMENTS

The authors would like to thank K.A. Steward for carefully scanning through patients' files and data entry in the EMC hospital registry. All authors approved the final version of the submitted manuscript.

AUTHOR CONTRIBUTIONS

M.T.G., and J.E.R. wrote the manuscript; M.T.G., A.H.G.M., M.M.S., J.M.H.G., H.B., and J.E.R. made critical revisions to the manuscript; M.T.G., A.H.G.M., J.M.H.G., and J.E.R. designed the research; M.T.G., A.H.G.M., J.M.H.G., and J.E.R. performed the research; M.T.G., A.H.G.M., H.B., and J.E.R. analyzed the data.

CONFLICT OF INTEREST

J.E. Roeters van Lennep reports personal fees from AKCEA, grants from AMRYT, paid to the institution, outside the submitted work. A.M.H. Galema-Boers reports personal fees from Sanofi-Aventis Netherlands B.V. for publication of her thesis and Amgen for presentation at congress, outside the submitted work. All other authors declared that there is no conflict of interest regarding the publication of this article.

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APPENDIX

Table S1a. Baseline patient characteristics for EMC database split by drug

Characteristics	Alirocumab, n=81	Evolocumab, n=83	*P*-value
Age (y), median (IQR)	58.0 (49.5-66.0)	58.0 (48.0 – 65.0)	0.313
Gender, n (%)			0.649
Male	43 (53)	47 (57)	
Female	38 (47)	36 (43)	
BMI (kg/m^2), mean (±SD)	27.8 (±4.7)	27.4 (±3.6)	0.583
Diabetes mellitus, n (%)	14 (17)	15 (18)	0.895
Hypertension, n (%)	35 (43)	40 (48)	0.522
Ever smoker, n (%)	36 (44)	42 (51)	0.415
Current smoker, n (%)	11 (14)	13 (16)	0.709
History of CVD, n (%)	52 (64)	56 (68)	0.659
Familial hypercholesterolemia, n (%)	76 (94)	72 (87)	0.127
Heterozygous	48 (59)	50 (60)	
Homozygous	1 (1)*	6 (7)**	
Clinical	27 (33)	16 (19)	
Lipid lowering therapy, n (%)			
Statin use	49 (61)	51 (61)	0.901
High Intensity	27 (33)	36 (43)	
Moderate Intensity	16 (20)	14 (17)	
Low Intensity	6 (7)	1 (1)	
Ezetimibe	81 (100)	83 (100)	
Ezetimibe monotherapy	32 (40)	32 (39)	
LDL cholesterol (mmol/L), median (IQR)	4.22 (3.45-5.00)	4.40 (3.16-5.68)	0.986

* double heterozygous LDLR/APOB gene mutation (n=1)
** compound heterozygous LDLR gene mutation (n=6)

Table S1b. Patient characteristics for Lareb database split by drug

Characteristics	Alirocumab, n=43	Evolocumab, n=110
Age (y), median (IQR)	60 (53-66)	64 (56-69)
Age unknown, n (%)	4 (9)	6 (5)
Gender, n (%)		
Male	20 (47)	54 (49)
Female	23 (53)	55 (50)
Unknown	0 (0)	1 (1)

Table S1c. Patient characteristics for VigiLyze database split by drug

Characteristics	Alirocumab, n=4,650	Evolocumab, n=10,931
Age groups, n (%)		
0-17 years*	1 (0.0)	7 (0.1)
18-44 years	84 (1.8)	205 (1.9)
45-64 years	1,101 (23.7)	3,120 (28.5)
65-74 years	1,438 (30.9)	3,400 (31.1)
≥ 75 years	756 (16.3)	1,919 (17.6)
Unknown	1,270 (27.3)	2,280 (20.9)
Gender, n (%)		
Male	1,832 (39.4)	4,148 (37.9)
Female	2,614 (56.2)	6,179 (56.5)
Unknown	204 (4.4)	604 (5.5)

*These reports are considered either incorrect or due to off-label use

Table S2a. Adverse events with percentages for total population and cohort with adverse events split by PCSK9 inhibitor for EMC database

EMC	Total (n=164)	Alirocumab (n=81)	Evolocumab (n=83)
Any TEAE, n (%)	68 (41.5)	35 (43.2)	33 (39.8)
No adverse events	96 (58.5)	46 (56.8)	50 (60.2)
1 event	36 (22.0)	19 (23.5)	18 (21.7)
2 events	22 (13.4)	9 (11.1)	12 (14.5)
≥3 events	10 (6.1)	7 (8.6)	3 (3.6)
Events, median (IQR)	0.0 (0.0-1.0)	0.0 (0.0-1.0)	0.0 (0.0-1.0)
Total no. of TEAEs reported	116 (100.0)	61 (52.6)	55 (47.4)
TEAEs leading to discontinuation	11 (6.7)	5 (6.2)	6 (7.2)
TEAEs leading to death	0 (0.0)	0 (0.0)	0 (0.0)
Most common (≥4%) TEAEs, n (%)			
Influenza like illness	19 (11.6)	10 (12.3)	9 (10.1)
Injection-site haematoma	13 (7.9)	8 (9.9)	5 (6.0)
Nasopharyngitis	11 (6.7)	5 (6.2)	6 (7.2)
Abdominal discomfort	8 (4.9)	3 (3.7)	5 (6.0)
Myalgia	7 (4.3)	5 (6.2)	2 (2.4)
Cognitive disorder	6 (3.7)	4 (4.9)	2 (2.4)
Fatigue	6 (3.7)	2 (2.5)	4 (4.8)
Headache	6 (3.7)	2 (2.5)	4 (4.8)
Injection-site pain	6 (3.7)	3 (3.7)	3 (3.6)
Injection-site swelling	6 (3.7)	4 (4.9)	2 (2.4)
Rash	4 (2.4)	1 (1.2)	3 (3.6)
Injection-site reactions, n (%)	23 (14.0)	13 (16.0)	10 (12.0)
Injection-site haematoma	13 (7.9)	8 (9.9)	5 (6.0)
Injection-site pain	6 (3.7)	3 (3.7)	3 (3.6)
Injection-site swelling	6 (3.7)	4 (4.9)	2 (2.4)
Injection-site erythema	2 (1.2)	1 (1.2)	1 (1.2)
Injection-site infection	1 (0.6)	1 (1.2)	0 (0.0)

*Only patients with adverse events at follow-up 1.

Total (n=68*)	Alirocumab (n=35)*	Evolocumab (n=33)*	*P*-value
68 (100.0)	35 (100.0)	33 (100.0)	0.654
37 (54.4)	19 (54.3)	18 (54.5)	
21 (30.9)	9 (25.7)	12 (36.4)	
10 (14.7)	7 (20.0)	3 (9.1)	
1.0 (1.0-2.0)	1.0 (1.0-2.0)	1.0 (1.0-2.0)	
116 (100.0)	61 (52.6)	55 (47.4)	
11 (16.2)	5 (14.3)	6 (18.2)	
0 (0.0)	0 (0.0)	0 (0.0)	
19 (27.9)	10 (28.6)	9 (27.3)	0.905
13 (19.1)	8 (22.9)	5 (15.2)	0.419
11 (16.2)	5 (14.3)	6 (18.2)	0.663
8 (11.8)	3 (8.6)	5 (15.2)	0.471
7 (10.3)	5 (14.3)	2 (6.1)	0.429
6 (8.8)	4 (11.4)	2 (6.1)	0.674
6 (8.8)	2 (5.7)	4 (12.1)	0.421
6 (8.8)	2 (5.7)	4 (12.1)	0.421
6 (8.8)	3 (8.6)	3 (9.1)	1.000
6 (8.8)	4 (11.4)	2 (6.1)	0.674
4 (5.9)	1 (2.9)	3 (9.1)	0.349
23 (33.8)	13 (37.1)	10 (30.3)	0.551
13 (19.1)	8 (22.9)	5 (15.2)	0.419
6 (8.8)	3 (8.6)	3 (9.1)	1.000
6 (8.8)	4 (11.4)	2 (6.1)	0.674
2 (2.9)	1 (2.9)	1 (3.0)	1.000
1 (1.5)	1 (2.9)	0 (0.0)	1.000

Table S2b. Adverse events split by PCSK9 inhibitor for Lareb database

Lareb	Total (n=149)*	Alirocumab (n=43)	Evolocumab (n=110)
Any TEAE, n (%)	149 (100.0)	70 (100.0)	78 (100.0)
1 event	51 (34.2)	13 (30.2)	38 (34.5)
2 events	41 (27.5)	13 (30.2)	32 (29.1)
≥3 events	61 (38.3)	17 (39.5)	40 (36.4)
Events, median (IQR)	2.0 (1.0-3.0)	2.0 (1.0-3.0)	2.0 (1.0-3.0)
Total no. of TEAEs reported	375	106 (27.7)	277 (72.3)
TEAE leading to discontinuation	60 (40.3)	12 (27.9)	48 (43.6)
TEAE leading to death	1 (0.7)	0 (0.0)	1 (0.9)
Most common (≥4%) TEAEs, n (%)			
Myalgia	19 (12.8)	3 (7.0)	16 (14.5)
Influenza like illness	14 (9.4)*	3 (7.0)	14 (12.7)
Fatigue	12 (8.1)	4 (9.3)	8 (7.3)
Headache	12 (8.1)	3 (7.0)	9 (8.2)
Arthralgia	10 (6.7)	2 (4.7)	8 (7.3)
Dyspnoea	9 (6.0)	5 (11.6)	4 (3.6)
Nausea	9 (6.0)	1 (2.3)	8 (7.3)
Malaise	8 (5.4)	3 (7.0)	5 (4.5)
Muscle spasms	8 (5.4)	3 (7.0)	5 (4.5)
Pain in extremity	8 (5.4)	3 (7.0)	5 (4.5)
Diarrhoea	6 (4.0)	1 (2.3)	5 (4.5)
Dizziness	6 (4.0)	4 (9.3)	2 (1.8)
Injection-site reactions, n (%)	3 (2.0)	1 (2.3)	2 (1.8)
Injection-site haematoma	1 (0.7)	0 (0.0)	1 (0.9)
Injection-site haemorrhage	1 (0.7)	0 (0.0)	1 (0.9)
Injection-site swelling	1 (0.7)	1 (0.9)	0 (0.0)

*Four patients reported same adverse events for both drugs

Table S2c. Adverse events split by PCSK9 inhibitor for VigiLyze database

VigiLyze – Total	Total (n=15,554)*	Alirocumab (n=4,650)	Evolocumab (n=10,931)
Any TEAE, n (%)	15,554 (100.0)	4,650 (100.0)	10,931 (100.0)
Total no. of TEAEs reported	29,956	8,982	21,030
Most common (≥4%) TEAEs, n (%)			
Myalgia	1,287 (8.3)	438 (9.4)	850 (7.8)
Drug dose omission	1,151 (7.4)	59 (1.3)	1,092 (10.0)
Injection-site pain	959 (6.2)	197 (4.2)	763 (7.0)
Influenza like illness	818 (5.3)	267 (5.7)	556 (5.1)
Back pain	816 (5.2)	113 (2.4)	705 (6.4)
Arthralgia	789 (5.1)	279 (6.0)	514 (4.7)
Fatigue	764 (4.9)	257 (5.5)	508 (4.6)
Pain in extremity	755 (4.9)	243 (5.2)	516 (4.7)
Muscle spasms	719 (4.6)	291 (6.3)	429 (3.9)
Pain	703 (4.5)	247 (5.3)	456 (4.2)
Headache	651 (4.2)	188 (4.0)	464 (4.2)
Injection-site reactions (≥1.0%), n (%)	3,291 (21.2)	1,005 (21.6)	2,326 (21.3)
Injection-site pain	959 (6.2)	197 (4.2)	763 (7.0)
Injection-site bruising	526 (3.4)	130 (2.8)	397 (3.6)
Injection-site haemorrhage	373 (2.4)	109 (2.3)	264 (2.4)
Injection-site erythema	268 (1.7)	128 (2.8)	144 (1.3)
Injection-site swelling	229 (1.5)	84 (1.8)	146 (1.3)
Injection-site pruritus	152 (1.0)	82 (1.8)	73 (0.7)

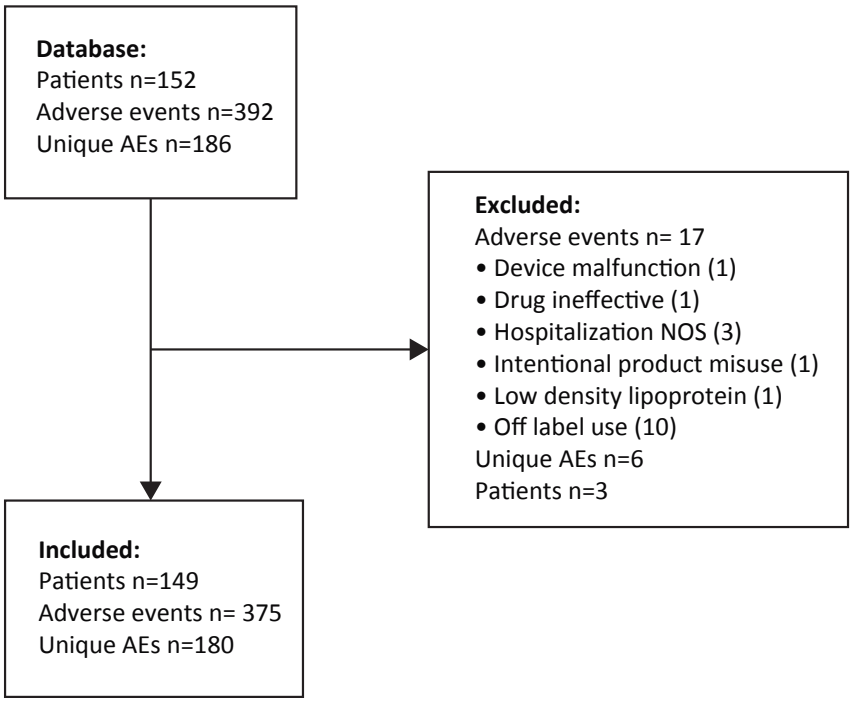
*Twenty seven patients reported (same) adverse events for both drugs.

Table S3. Drug discontinuation

EMC	Drug Discontinued (n=12)	Lareb	Drug Discontinued (n=60)
TEAEs, n (%)	11 (90)*	**TEAEs, n (%)**	60 (100)
0 event	1 (8)	0 event	0 (0)
1 event	4 (33)	1 event	13 (22)
2 events	2 (17)	2 events	13 (22)
≥3 events	5 (42)	≥3 events	34 (57)
Events, median (IQR)	2.0 (1.0-3.0)	**Events, median (IQR)**	3.0 (2.0-4.0)
No. of reported AEs	25	**No. of reported AEs**	179
Gender, n (%)		**Gender, n (%)**	
Male	4 (33)	Male	29 (48)
Female	8 (67)	Female	31 (52)
PCSK9 inhibitor, n (%)		PCSK9 inhibitor, n (%)	
Alirocumab	5 (42)	Alirocumab	12 (20)
Evolocumab	7 (58)	Evolocumab	48 (80)
TEAEs leading to discontinuation (≥5%), n (%)		**TEAEs leading to discontinuation (≥5%), n (%)**	
Influenza like illness	6 (50)	Myalgia	11 (18)
Cognitive disorder	3 (25)	Headache	8 (13)
Abdominal discomfort	2 (17)	Nausea	7 (12)
Fatigue	2 (17)	Arthralgia	6 (10)
Malaise	2 (17)	Fatigue	6 (10)
Arthralgia	1 (8)	Influenza like illness	5 (8)
Dizziness	1 (8)	Back pain	4 (7)
Dyspnoea	1 (8)	Cough	3 (5)
Epistaxis	1 (8)	Dizziness	3 (5)
Eye infection	1 (8)	Dyspnoea	3 (5)
Myalgia	1 (8)	Fatigue	3 (5)
Pruritus	1 (8)	Malaise	3 (5)
Syncope	1 (8)	Myalgia	3 (5)
Visual impairment	1 (8)	Nasal congestion	3 (5)
Weight decreased	1 (8)	Pain in extremity	3 (5)

*One patient discontinued drug due to non-response.

Figure S1. Flowchart of patient inclusion and exclusion for the Lareb database



C

Relevance of sex-sensitive clinical practice and research

11

Huisarts man of vrouw – heeft de patiënt voorkeur?

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Published in ***Nederlandse Tijdschrift voor Geneeskunde***
https://pubmed.ncbi.nlm.nih.gov/30676707/

SAMENVATTING

Doel
Onderzoeken of en bij welke problemen patiënten een voorkeur hebben voor een mannelijke of een vrouwelijke huisarts.

Opzet
Vragenlijstonderzoek

Methode
In totaal kregen 24,430 patiënten die geregistreerd staan in het Zorgpanel van de Patiëntenfederatie Nederland een e-mail toegestuurd met een vragenlijst. De vragenlijst bestond uit 50 vragen die waren opgedeeld in verschillende thema's, zoals het contact met de huisarts, het verschil tussen een mannelijke en een vrouwelijke huisarts, gevoelige onderwerpen en vrije artsenkeuze.

Resultaten
De vragenlijst werd ingevuld door 7019 patiënten van wie 26,7% aangaf dat er verschillen zijn tussen mannelijke en vrouwelijke huisartsen. Empathische werkwijzen werden vaker toegeschreven aan vrouwelijke huisartsen. Vrouwen hebben vaker liever een huisarts van het eigen geslacht dan mannen (38,9 vs. 12,8%), vooral voor problemen over seksualiteit en intieme lichaamsdelen. Psychologische klachten bespreken patiënten vaker liever met een vrouwelijke dan een mannelijke huisarts (16,3 vs. 4,4%). Schaamte om een klacht te bespreken met de huisarts en schaamte bij lichamelijk onderzoek vanwege een arts van het andere geslacht kwamen vaker voor bij vrouwen dan bij mannen ($p < 0,001$), maar nemen af met de leeftijd. Van de respondenten gaf 8% aan dat zij weleens een huisartsbezoek hadden uitgesteld omdat zij ertegenop zagen om een klacht te bespreken met een huisarts van het andere geslacht.

Conclusie
Het merendeel van de respondenten denkt dat er geen verschil is tussen vrouwelijke en mannelijke huisartsen. Vrouwen voelen vaker gêne bij de huisarts, maar dit gevoel neemt af met de leeftijd. Om te voorkomen dat patiënten hun huisartsbezoek onnodig uitstellen door schaamte, is het van belang om te weten of de patiënt een voorkeur heeft voor een vrouwelijke of mannelijke huisarts.

Kernpunten

- Er zijn verschillen tussen vrouwelijke en mannelijke artsen in de zorg die zij bieden, in hoe patiënten die zorg ervaren en in de gezondheidsuitkomsten.
- Dit onderzoek laat zien dat ongeveer een kwart van de patiënten een voorkeur heeft voor een vrouwelijke of mannelijke huisarts.
- De voorkeur voor een huisarts van het eigen geslacht is het grootst bij patiënten met problemen over seksualiteit en intieme lichaamsdelen.
- Dit onderzoek laat zien dat 8% van de patiënten weleens een huisartsbezoek heeft uitgesteld omdat zij ertegenop zagen om een klacht te bespreken met een huisarts van het andere geslacht.

ABSTRACT

Objective
To determine whether and when patients prefer a female or male general practitioner (GP).

Design
Questionnaire survey

Method
A total of 24,430 patients registered in the Care Panel [zorgpanel] of the Dutch patient federation [Patiëntenfederatie Nederland] received an e-mail with a questionnaire. The questionnaire consisted of 50 questions divided in different themes such as contact with GPs, differences between male and female GPs, sensitive topics and free choice of doctors.

Results
The questionnaire was completed by 7,019 patients of whom 26.7% indicated that there are differences between female and male GPs. Empathic practices were more often attributed to female GPs. Women more often prefer a GP of their own sex than men (38.9% vs 12.8%), especially for problems involving sexuality and private body parts. Patients prefer to discuss psychological symptoms with a female rather than a male GP (16.3% vs 4.4%). Embarrassment to discuss symptoms with a GP and embarrassment regarding physical examination by doctors of the opposite sex were more common in women than in men ($p < 0.001$) but decreased with age. 8% of the respondents indicated that they had occasionally postponed a GP consultation because they were reluctant to discuss a symptom with a GP of the opposite sex.

Conclusion
The majority of respondents feel there is no difference between female and male GPs. Women tend to feel embarrassed more often at the GP but this feeling decreases with age. To prevent patients from unnecessarily delaying their GP visits, it is important to know whether the patient prefers a female or a male GP.

INTRODUCTIE

Het zou niet moeten uitmaken: een mannelijke of een vrouwelijke arts. Ze hebben immers dezelfde opleiding doorlopen. Toch toont onderzoek aan dat er verschillen bestaan tussen mannelijke en vrouwelijke artsen in de zorg die zij bieden en hoe patiënten die zorg beleven. Vrouwelijke artsen bieden vaker preventieve zorg aan,[1-6] houden zich beter aan richtlijnen,[7-9] luisteren beter naar patiënten,[10,11] en bieden meer psychosociale steun dan hun mannelijke collega's.[11] Ook doen zij meer moeite voor een gelijkwaardige positie tussen arts en patiënt, moedigen zij de patiënt aan om verder te vertellen en nemen zij meer tijd voor hun patiënt.[12] Op hun beurt vertellen patiënten meer tijdens afspraken met vrouwelijke dokters.[13] Dit onderscheid tussen mannelijke en vrouwelijke artsen betreft een genderverschil. Anders dan sekse, dat biologische en lichamelijke verschillen tussen mannen en vrouwen aanduidt, gaat gender over culturele en sociale verschillen die mannelijkheid en vrouwelijkheid definieren.. Heersende normen in onze maatschappij over vrouwelijkheid en mannelijkheid werken door in de interactie tussen arts en patiënt in de spreekkamer.

Tegen deze achtergrond lijkt de vervrouwelijking van het beroep arts goed nieuws. In de periode 2005-2016 steeg het percentage vrouwelijke artsen van 32% naar 46%.[14] Momenteel zijn mannelijke artsen nog in de meerderheid, maar dit zal snel veranderen: 67,8% van de artsen in opleiding en 66% van de geneeskundestudenten is vrouw.[15] Een nadeel van deze ontwikkeling is dat in de toekomst mogelijk een dusdanig tekort aan mannelijke artsen ontstaat dat het binnen bepaalde vakgebieden niet langer mogelijk is om tegemoet te komen aan de wens van patiënten die een voorkeur voor een mannelijke arts hebben.

Tegenwoordig zijn we er ons steeds meer van bewust dat gender van invloed is op allerlei facetten van onze dagelijks ervaring. Toch is er weinig onderzoek gedaan naar de voorkeur van patiënten voor vrouwelijke of mannelijke artsen. Wij onderzochten of patiënten een mannelijke of een vrouwelijke huisarts prefereren, of die voorkeur verschilt tussen vrouwelijke en mannelijke patiënten, en of de aard van de klacht van invloed is op hun voorkeur. Om erachter te komen wat aan een eventuele geslachtsvoorkeur ten grondslag ligt, wilden we weten welke eigenschappen patiënten toekennen aan mannelijke en vrouwelijke huisartsen.

METHODE

Onderzoekspopulatie en meetinstrument

In totaal kregen 24,430 patiënten die geregistreerd staan in het Zorgpanel van de Patiëntenfederatie Nederland een e-mail toegestuurd met een vragenlijst over hun voorkeur voor een mannelijke of vrouwelijke huisarts. Tevens werd een link naar de vragenlijst opgenomen in de nieuwsbrief van het tijdschrift *Libelle* en op de websites van *Libelle* en Patiëntenfederatie Nederland geplaatst. De vragenlijst bestond uit 50 vragen die waren opgedeeld in verschillende thema's, zoals het contact met de huisarts, het verschil tussen een mannelijke en een vrouwelijke huisarts, gevoelige onderwerpen en vrije artsenkeuze. De volledige vragenlijst staat in een supplement op www.ntvg.nl/D3146.

Statistische analyses

Wij analyseerden de gegevens met beschrijvende statistiek met behulp van SPSS Statistics versie 24 (IBM Corp., Armonk, VS). We stratificeerden de resultaten naar geslacht en naar verschillende leeftijdscategorieën. Eventuele verschillen in antwoorden tussen mannelijke en vrouwelijke respondenten werden getoetst met de χ^2-toets. Wij vermeldden alleen relevante verschillen. De resultaten zijn weergegeven in percentages van de respondenten.

RESULTATEN

De vragenlijst werd ingevuld door 7019 personen (56% vrouw) van wie 92% de enquête opende via de e-mail van Patiëntenfederatie Nederland en de overige 8% via de link op de websites. De mediane leeftijd van de respondenten was 65 jaar (interkwartielafstand: 57-71) en er deden relatief veel hoogopgeleiden mee (45,3%). De respondenten waren evenredig verdeeld over de provincies. In totaal had 32,6% van de respondenten een vrouwelijke en 46,5% een mannelijke huisarts; 20,9% van de respondenten gaf aan dat het geslacht van de huisarts onbekend was. Het aantal huisartsbezoeken in het afgelopen jaar liep uiteen van 0 tot en met > 10 keer; de grootste groep (47,8%) bezocht de huisarts in het afgelopen jaar 1-3 keer (Tabel 1).

Tabel 1. Karaktereigenschappen passend bij geslacht

Eigenschappen	Vrouwen (n=3917, 56%)	Mannen (n=3078, 44%)	Totaal* (n=7019)
Leeftijd (jr), mediaan (IQR)	61 (53-68)	68 (63-77)	65 (57-71)
Leeftijdsgroepen, n (%)			
0-17 jaar	4 (0.1)	2 (0.1)	6 (0.1)
18-44 jaar	398 (10.2)	54 (1.8)	454 (6.5)
45-64 jaar	2008 (51.3)	888 (28.8)	2908 (41.4)
65-74 jaar	1187 (30.3)	1560 (50.7)	2753 (39.2)
≥ 75 jaar	257 (6.6)	546 (17.7)	807 (11.5)
Leeftijd onbekend, n (%)	63 (1.6)	28 (0.9)	92 (1.3)
Opleidingsniveau			
laag opgeleid, n (%)	369 (9.4)	330 (10.7)	703 (10)
middelbaar opgeleid, n (%)	1811 (46.2)	1128 (36.6)	2943 (41.9)
hoog opgeleid, n (%)	1530 (39.1)	1479 (48.1)	3024 (43.1)
onbekend, n (%)	207 (5.3)	141 (4.6)	350 (5)
Geslacht eigen huisarts			
Vrouw, n (%)	1366 (34.9)	915 (29.7)	2289 (32.6)
Man, n (%)	1736 (44.3)	1515 (49.2)	3262 (46.5)
Onbekend, n (%)	815 (20.8)	648 (21.1)	1469 (20.9)
Aantal contacten huisarts afgelopen jaar			
0 keer, n (%)	253 (6.5)	196 (6.4)	449 (6.4)
1-3 keer, n (%)	1773 (45.3)	1569 (51.0)	3357 (47.8)
4-10 keer, n (%)	1454 (37.1)	1060 (34.4)	2519 (35.9)
Vaker dan 10 keer, n (%)	428 (10.9)	240 (7.8)	671 (9.6)
Onbekend, n (%)	9 (0.2)	13 (0.4)	23 (0.3)

*24 deelnemers gaven aan anders te zijn dan een man of vrouw

WERKWIJZEN

Op de vraag of u denkt dat er een verschil is tussen mannelijke en vrouwelijke huisartsen, antwoordde het merendeel (73,3%) van de respondenten dat het geslacht van de huisarts er niet toe doet. Van de respondenten die dachten dat er wél een verschil is, was 64,5% vrouw en 35,3% man. Op de vraag of bepaalde werkwijzen meer bij een vrouwelijke of een mannelijke huisarts passen, antwoordde de meerderheid van de respondenten dat dit niet niet het geval is. Respondenten die aangaven dat dit wél het geval is, schreven empathische werkwijzen als 'zich goed kunnen inleven in de patiënt' en 'persoonlijke benadering' vaker toe aan vrouwelijke huisartsen (Tabel 2). Daarentegen werd de werkwijze 'zich autoritair opstellen' vaker toegedicht aan mannelijke huisartsen. Er waren geen stastisch significante verschillen in de antwoorden tussen mannelijke en vrouwelijke respondenten.

Tabel 2. Karaktereigenschappen meer passend bij een vrouwelijke of mannelijke huisarts

Eigenschappen	Past bij vrouwelijke huisarts (%)	Past bij mannelijke huisarts (%)	Geen verschil (%)
Goed luisteren naar de klachten en vragen van een patiënt	20.0	4.9	75.1
Goed de tijd nemen voor de patiënt	17.5	5.0	77.5
Zich goed kunnen inleven in de patiënt	26.3	4.5	69.2
Klachten serieus nemen	13.4	5.1	81.5
Moeite doen om de situatie van de patiënt te begrijpen	21.7	5.5	72.8
Samen met de patiënt tot een diagnose en plan voor de behandeling komen	13.5	5.5	81.1
Persoonlijke benadering	22.7	4.9	72.5
Meer ervaring hebben	2.0	8.2	89.9
Kennis van zaken hebben	4.0	4.3	91.7
Daadkrachtig handelen	9.0	10.6	80.5
Zich autoritair opstellen	5.3	25.0	69.7
Meer diagnostische onderzoeken aanvragen	9.1	6.0	84.9
Snel medicatie voorschrijven	3.9	9.8	86.3
Snel doorverwijzen	8.1	6.4	85.5

Specifieke problemen

Op de vraag of er onderwerpen of klachten zijn die u liever met een mannelijke huisarts bespreekt, antwoordde 12,8% van de mannen en 8,4% van de vrouwen 'ja' ($p < 0,001$). Deze mannen gaven aan dat zij problemen over seksualiteit en intieme lichaamsdelen liever met een mannelijke huisarts bespraken (Tabel 3). Op de vraag of er onderwerpen of klachten zijn die u liever met een vrouwelijke huisarts bespreekt, gaf 6,9% van de mannen en 38,9% van de vrouwen een bevestigend antwoord ($p < 0,001$). Deze vrouwen gaven aan dat zij problemen over seksualiteit, intieme lichaamsdelen en de overgang liever met een vrouwelijke huisarts bespraken (Tabel 3).

Tabel 3. Voorkeur vrouwelijke of mannelijke huisartsen bij bepaalde onderwerpen.

Onderwerp te bespreken	Liever met vrouwelijke huisarts (%)	Liever met mannelijke huisarts (%)	Geen voorkeur (%)
Vrouwen:			
Menstruatie	37.0	1.8	61.2
Menopause	34.7	2.1	63.2
Zwangerschap	26.2	1.8	72.0
Anticonceptie	18.8	2.1	79.1
Vruchtbaarheid	24.6	2.0	73.4
Seksualiteit	43.5	2.0	54.4
Geslachtsdelen	38.8	2.1	59.1
(vermoeden van) SOA	27.6	2.3	70.1
Psychologische klachten	19.1	4.4	76.5
Mannen:			
Vruchtbaarheid	5.1	6.5	88.3
Seksualiteit	6.3	16.5	77.1
Geslachtsdelen	5.2	12.4	82.4
(vermoeden van) SOA	4.1	10.8	85.0
Psychologische klachten	12.7	4.5	82.8

Een aanzienlijk deel van de respondenten die aanvankelijk aangaven dat er geen verschil is tussen mannelijke en vrouwelijke huisartsen, had toch een voorkeur voor een huisarts van het eigen geslacht bij bepaalde onderwerpen, zoals problemen over seksualiteit en intieme lichaamsdelen.(Tabel 3) Respondenten prefereerden vaker een vrouwelijke huisarts boven een mannelijke huisarts bij psychologische problemen, zoals relatieproblemen, overspannenheid en psychische klachten (16,3 vs. 4,4%; p = <0,001).

Schaamte

Schaamte om een klacht te bespreken met de huisarts kwam vaker voor bij vrouwelijke dan bij mannelijke respondenten (21,1 vs. 9,1%; p < 0,001). Deze gêne was voor beide groepen leeftijdsgebonden en nam af met de leeftijd (figuur 1A). Het opleidingsniveau had geen invloed op het gevoel van schaamte. Schaamte kwam vaker voor onder respondenten die de huisarts in het afgelopen jaar vaker hadden bezocht (figuur 1B).

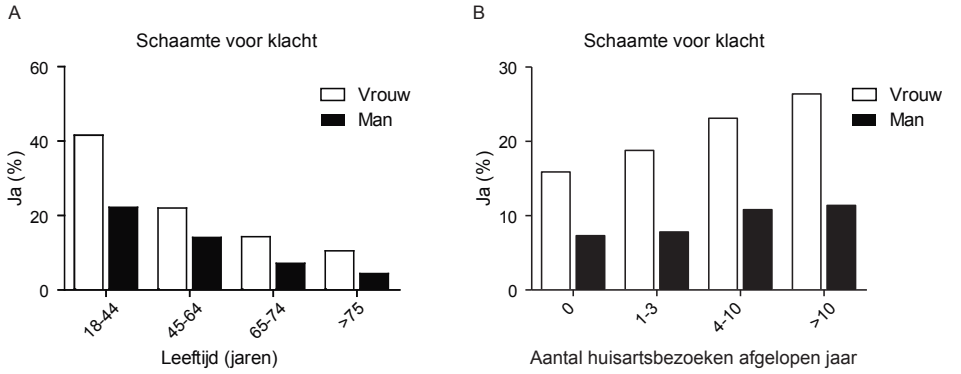

Fig 1. Percentage vrouwen en mannen per leeftijdscategorie (A) en aantal huisartsbezoeken afgelopen jaar (B) dat zich wel eens schaamt voor een klacht

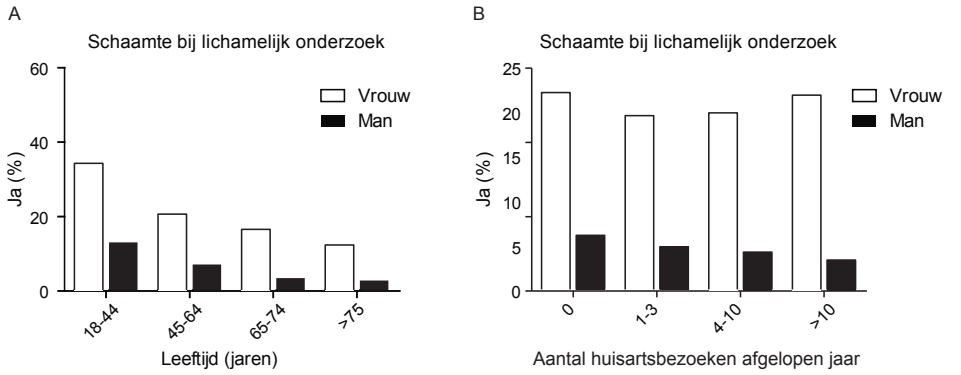

Fig 2. Percentage vrouwen en mannen per leeftijdscategorie (A) en aantal huisartsbezoeken afgelopen jaar (B) dat aangeeft er moeite mee te hebben als een arts van het andere geslacht borts(en), buik, billen of geslachtsdelen ziet bij lichamelijk onderzoek

Vrouwen gaven vaker aan dat zij er moeite mee hebben als een arts van het andere geslacht lichamelijk onderzoek uitvoert waarbij hun borsten, buik, billen of geslachtsdelen te zien zijn, vergeleken met mannen (20,2 vs. 4,7%; $p < 0,001$). Dit ongemak werd het vaakst gerapporteerd door respondenten van 18-44 jaar en het minst door respondenten ≥ 75 jaar (figuur 2A). Onder mannelijke respondenten nam de schaamte bij lichamelijk onderzoek af naarmate zij de huisarts in het afgelopen jaar vaker hadden bezocht (figuur 2B). Voor vrouwen vonden wij daarentegen geen relatie tussen schaamte bij lichamelijk onderzoek en het aantal huisartsbezoeken.

Van de respondenten gaf 8% aan dat zij weleens een huisartsbezoek hadden uitgesteld omdat zij ertegenop zagen om een klacht te bespreken met een huisarts van het andere geslacht. Uitstel van een huisartsbezoek vanwege schaamte kwam frequenter voor bij vrouwen dan bij mannen (11,8 vs. 3,5%; $p < 0,001$), nam af met leeftijd en nam juist toe met het aantal huisartsbezoeken in het afgelopen jaar (figuur 3A en 3B).

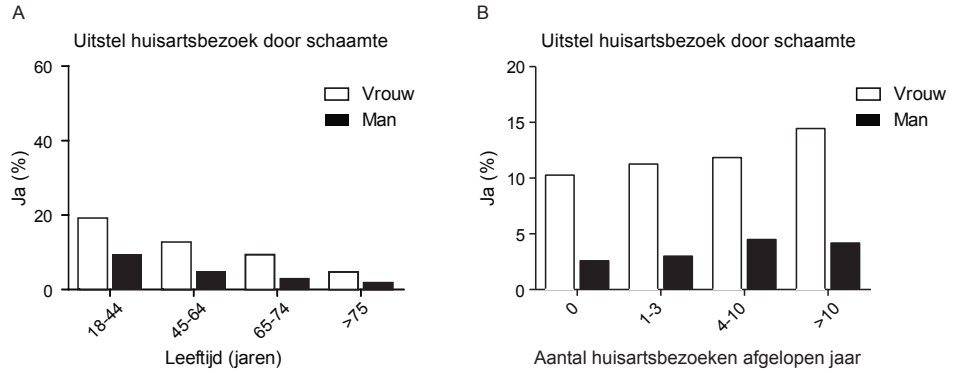

Fig 3. Percentage vrouwen en mannen per leeftijdscategorie (A) en aantal huisartsbezoeken afgelopen jaar (B) dat hun huisartsbezoek uitstelt omdat ze er wegens het geslacht van de huisarts tegenop zagen bepaalde klachten ter sprake te brengen

Vrije artsenkeuze

De meeste respondenten (68,1%) gaven aan dat zij in hun huisartsenpraktijk kunnen kiezen voor een mannelijke of vrouwelijke huisarts. Een eventuele voorkeur voor een mannelijke of vrouwelijke huisarts werd door de meeste respondenten (85,4%) echter nooit uitgesproken, terwijl de meerderheid (61,9%) zich er wel van bewust is dat zij een vrije artsenkeuze heeft.

Beschouwing

Sekse en gender doen ertoe in de zorg. Ondanks dat de meerderheid van de respondenten in eerste instantie zegt dat het geslacht van de huisarts niet uitmaakt, blijkt dit bij doorvragen wel degelijk het geval te zijn. Zowel mannen als vrouwen bespreken gevoelige onderwerpen, zoals problemen over seksualiteit en intieme lichaamsdelen, liever met een arts van het

eigen geslacht. Klachten en vragen over de psychische gezondheid bespreekt een deel van de mannelijke en vrouwelijke respondenten juist liever met een vrouw.

Respondenten gaven aan dat empathische werkwijzen als 'zich goed kunnen inleven in de patiënt' en 'persoonlijke benadering' meer bij een vrouwelijke huisarts past, terwijl een mannelijke huisarts vaker als autoritair werd gezien. Schaamte om een klacht te bespreken met de huisarts of schaamte bij lichamelijk onderzoek vanwege een arts van het andere geslacht is leeftijdsafhankelijk en komt vaker voor bij vrouwen. Bij 11,8% van de vrouwen en bij 3,5% van de mannen leidt schaamte zelfs tot uitstel van het huisartsbezoek.

Vergelijking met eerder onderzoek

Onze resultaten komen overeen met die van eerdere onderzoeken naar de voorkeur van vrouwen voor het geslacht van de arts bij gynaecologische klachten. Een aanzienlijk deel van de vrouwen (33,9-86,4%) heeft een duidelijke voorkeur voor een vrouwelijke gynaecoloog.[16-21] Ook ervaren vrouwen vaginaal onderzoek als gênanter bij een mannelijke dan bij een vrouwelijke arts.[22,23] Bij mannen is de voorkeur voor een uroloog van het eigen geslacht minder uitgesproken: 42,8% van de mannen heeft liever een mannelijke uroloog, 53,8% heeft geen voorkeur en 3,4% heeft liever een vrouwelijke uroloog.[24,25] Van de mannen die een urogenitaal of rectaal onderzoek ondergingen bleek respectievelijk 51,5 en 38,5% een voorkeur te hebben voor een mannelijke arts.[26] Patiënten vertellen meer over hun psychische klachten aan vrouwelijke dan aan mannelijke artsen omdat de communicatiestijl van vrouwelijke artsen meer uitnodigend blijkt te zijn voor patiënten voor het delen van psychische problemen. .[11,13]

Sterke en zwakke punten

Een sterk punt van ons onderzoek is het grote aantal respondenten. Voor zover wij weten is het gegeven dat patiënten hun huisartsbezoek uitstellen door schaamte niet eerder aangetoond. Een tekortkoming van onze studie is dat er relatief weinig laagopgeleiden en patiënten < 45 jaar deelnamen. Ook hebben wij de respondenten niet gevraagd naar hun etnische achtergrond. Derhalve zijn er beperkingen voor de generaliseerbaarheid van onze resultaten.

Consequenties voor de praktijk

Het is verontrustend dat schaamte om een klacht te bespreken met een huisarts van het andere geslacht een drempel vormt waardoor patiënten soms hun huisartsbezoek uitstellen. Vooral vrouwen van 18-44 jaar ervaren schaamte bij een mannelijke huisarts. Ondanks het relatief hoge opleidingsniveau – en dus ogenschijnlijke mondigheid – van de respondenten ervoeren veel van hen deze drempel. Het uitstellen van een huisartsbezoek kan leiden tot een 'patient's delay'. Het is belangrijk dat huisartsen zich ervan bewust zijn dat – voornamelijk vrouwelijke – patiënten hun bezoek onnodig uitstellen. Toekomstig

onderzoek, waarbij niet alleen naar leeftijd en opleidingsniveau, maar ook naar etnische achtergrond, religie en seksuele voorkeur wordt gekeken, is nodig om te achterhalen bij welke specifieke patiënten dit probleem het grootst is.

Ons onderzoek laat zien dat een aanzienlijk deel van de patiënten een verschil ervaart tussen mannelijke en vrouwelijke artsen. Hoewel die ervaring niets zegt over een objectief verschil in kundigheid tussen mannelijke en vrouwelijke artsen, moet ze niet onderschat worden: de ervaring kan gevolgen hebben voor hoe snel patiënten een afspraak maken bij de huisarts. Het geslacht van de huisarts is daardoor van invloed op de zorg die de arts levert. De aangetoonde verschillen hebben echter geen invloed op de patiënttevredenheid. Het blijkt namelijk dat patiënten vrouwelijke artsen niet meer waarderen, aangezien patiënten verwachten dat vrouwelijke artsen empatisch en patiëntgericht zijn, juist omdat ze vrouw zijn.[27] Een empathische mannelijke arts wordt zelfs meer gewaardeerd dan een empathische vrouwelijke arts.

Recentelijk hebben Amerikaans onderzoekers gekeken naar meetbare gezondheidsuitkomsten van patiënten die behandeld werden door een vrouwelijke of een mannelijke internist.[28] Patiënten die behandeld werden door een mannelijke internist hadden een hoger risico op een heropname en op overlijden dan patiënten die zorg kregen van een vrouwelijke internist. Een ander Amerikaans onderzoek liet zien dat vrouwen die een hartinfarct hebben doorgemaakt een lagere overlevingskans hadden als zij behandeld werden door een mannelijke arts.[29]

Om te voorkomen dat genderverschillen de kwaliteit van de zorg benadelen, is het belangrijk dat artsen weten welke invloed zij – bewust en onbewust – hebben op de patiënt. Hoe kunnen vrouwelijke patiënten uitgenodigd worden om naar een arts te stappen als zij problemen hebben waar zij zich voor schamen? Een goed begin is het implementeren van het thema ‘gender in de gezondheidszorg’ in de geneeskundeopleiding. Daarnaast is het bespreekbaar maken van de eventuele invloed van het geslacht van de huisarts op de patiënt aan te raden. Patiënten zou gevraagd kunnen worden of ze een voorkeur hebben voor een vrouwelijke of mannelijke arts, zodat hier vervolgens rekening mee gehouden kan worden. Tot slot is het van belang dat wordt onderzocht of vrouwen inderdaad betere dokters zijn en – als dat zo is – hoe dat komt.

Genderverschillen zullen niet verdwijnen en moeten daarom juist erkend worden. Als de positieve en negatieve kenmerken van mannelijke en vrouwelijke artsen bekender worden, is er ook ruimte voor artsen om van elkaar te leren om zo de zorg te verbeteren.

CONCLUSIE

Het is belangrijk dat verschillen tussen vrouwelijke en mannelijke huisartsen erkend worden. Door deze verschillen hebben vooral vrouwen, maar ook mannen, vaker een voorkeur voor een vrouwelijke arts. Vooral jongere vrouwen schamen zich voor hun klachten en bij lichamelijk onderzoek, wat kan leiden tot het ongewenst uitstellen van een bezoek aan de huisarts. Ondanks dat een deel van de patiënten bepaalde problemen liever met een vrouwelijke of mannelijke huisarts bespreekt, geven zij dit bijna nooit aan bij de zorgverlener. Om te voorkomen dat patiënten hun huisartsbezoek onnodig uitstellen door schaamte, is het van belang om te weten of de patiënt een voorkeur heeft voor een vrouwelijke of een mannelijke huisarts.

Conflict of interest and financial support:
Potential conflicts of interest have been reported for this article. ICMJE forms provided by the authors are available online along with the full text of this article.

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12

Reporting of sex-specific outcomes of trials of intervention in cardiovascular disease: has there been progress?

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Published in ***Maturitas***
https://pubmed.ncbi.nlm.nih.gov/33358200/

ABSTRACT

In the past decade, the leading international cardiology societies have released statements that emphasize the importance of sex-specific reporting of the findings of clinical trials in cardiovascular research. To find out whether this has led to improvement, we compared sex-specific reporting of efficacy and safety outcomes for trials of cardiovascular drug interventions presented at the major clinical trials sessions of the European Society of Cardiology (ESC), American Heart Association (AHA) and the American College of Cardiology (ACC) before and after publication of these statements. We found that sex-specific efficacy and safety outcomes of the most influential cardiovascular intervention trials are still not systematically presented.

Key words
Sex-specific – Cardiovascular research – Clinical Trial

INTRODUCTION

All patients, women and men, expect medication to be both safe and effective. Women and men differ not only biologically ("sex") but also socio-cultural and behavioral differences exist ("gender"). As both sex and gender influence the safety and efficacy of medication, it is important that prior to approval of a drug a sufficient number of (representative) women are included in preregistration phase 1-3 trials.-

As individual trials are usually underpowered to analyze outcomes for men and women separately, pooled data and meta-analyses are required to assess sex-specific effects and adverse drug events (ADE) of individual drugs. Obviously, availability of sex-specific data then is a pre-requisite. In the past decade, the leading international cardiology societies European Society of Cardiology (ESC), American Heart Association (AHA) and the American College of Cardiology (ACC) have released statements that emphasize the importance of sex-specific reporting of clinical trial findings.(1-3) We wondered if the presentation of sex-specific efficacy- and ADE data in cardiovascular trial reports has improved since then. Therefore, we compared sex-specific reporting of efficacy and safety outcomes in cardiovascular drug intervention trials presented at the major clinical trials sessions of the ESC, AHA and ACC prior and after these published statements.

Methods

We reviewed the full-text main results manuscripts of pharmacologica randmized controlled trials (RCTs) presented at the major clinical trials sessions (the "Hotline sessions" of the conference of the European Society of Cardiology (ESC) or the "Late Breaking Clinical Trials" of the American Heart Association (AHA) and the American College of Cardiology (ACC)) of 2010 reperesenting the era before awareness for gender specific medicine and 2017 as year in knowledge about the importance of presenting data for men and women seperatetely should be standard. Moreover we chose this year as we would assume that all data of the presented study will be published within 2 years.We retrieved reported data on sex-specific reporting, which we defined as primary efficacy and safety (ADE) endpoints stratified per sex. RCTs that only report treatment effects adjusted for sex in a statistical model were considered as not presenting sex-specific results, as these data are insufficient for meta-analyses based on pooled data.

RESULTS

Baseline characteristics

In total, 29 cardiovascular drug RCTs were presented in 2010 and 34 in 2017 and were mainly published in the high-impact journals The Lancet, The New England Journal of Medicine, European Heart Journal, Journal of American Medical Association and Circulation. All trial reports presented data on efficacy and safety, except 2 (5,6%) of the 2010 trials. Women constituted (a mean of) 32.8% and 33.4% of the included patients in 2010 and 2017, respectively. The treatment population of the included RCTs was mostly patients with coronary artery disease (51.7% of the trials in 2010 vs 44.1% of the trials in 2017). (Table 1, Online Table 1)

Table 1. Characteristics of cardiovascular pharmacological trials of the Hotline Sessions / Late Breaking Trials of the ESC, AHA and ACC performing sex-specific analyses on efficacy endpoints and safety endpoints in 2010 vs 2017. European Society of Cardiology (ESC), American Heart Association (AHA), American College of Cardiology (ACC)

Characteristics	2010		2017	
Number of studies, n (%)				
ESC	13		11	
AHA	8		17	
ACC	8		6	
total	29		34	
Women, (mean %)				
ESC	31.9		37.3	
AHA	31.5		26.4	
ACC	36.5		34.9	
total	32.8		33.0	
Cardiovascular field, n (%)	**n**	**%**	**n**	**%**
Heart failure	5	17.2	-	
ACS / CAD / CVD	15	51.7	15	44.1
Hypercholesterolemia	-		3	8.8
Atrial Fibrillation	4	13.8	8	23.5
Cardiothoracic surgery	1	3.4	1	2.9
Other	4	13.8	8	20.6
Journal, n (%)	**n**	**%**	**n**	**%**
NEJM	9	31.0	13	38.2
EHJ	2	6.9	4	11.8
JAMA	4	13.8	3	8.8
Circulation	5	17.2	4	11.8
Lancet	3	10.3	3	8.8
JACC	4	13.8	3	8.8

Characteristics	2010		2017	
Other	2	6.9	4	11.8
Authors*	**n**	**%**	**n**	**%**
First author female, n (%)	3	13.0	3	8.8
Last author female, n (%)	1	4.3	2	5.9
Sex-specific reporting				
Efficacy endpoints (nr. of journals)	11	37.9	8	23.5
Lancet	2		-	
EHJ	1		-	
JAMA	1		-	
NEJM	4		5	
Circulation	1		1	
JACC	2		1	
Other	-		1	
Safety endpoints	3	11.1	3	8.8
Lancet	1		1	
EHJ				
JAMA	1			
NEJM	1		2	
Circulation				
JACC				
Other				

*RCTs with group of authors were excluded

Sex-specific reporting of efficacy and safety endpoints

Sex-specific efficacy endpoints were reported in 34.5% and 23.5% of the main publications of the trials that were presented in 2010 and 2017, respectively, whereas sex-specific safety outcomes were reported in 11.1% and 8.6%. Among the publishing journals of the articles we reviewed, The New England Journal of Medicine published the highest number of papers reporting sex-specific efficacy and safety endpoints. A total of 2 (3.2%) of the trials had a woman as first or last author. We were not able to analyze a possible relation between the sex of the first/last author and the reporting of sex-stratified outcomes because there were too few females. (Table 1)

DISCUSSION

Although since 2010 awareness of the importance of sex and gender in cardiovascular disease has increased, this has not led to an improvement of sex-specific presentation of efficacy and safety outcomes in reports of cardiovascular drug trials between 2010 and 2017.

Role of the publishing journals

The Lancet was the first journal to adopt a policy for sex and gender analysis including the enrollment of women in clinical trials and separate reporting of data by sex. Currently, several author and reviewer guidelines addressing the importance of analyses stratified by sex and gender have been developed: the updated International Committee of Medical Journal Editors (ICMJE) recommendations and the Sex and Gender Equity in Research (SAGER) guidelines, which are endorsed by a growing number of journals ’including the EHJ, JAMA, NEJM, Circulation and JACC. Circulation also explicitly mentions in author instructions that sex-specific data should be provided.

Already in 2007, a systematic protocol to evaluate the quality of evidence on sex in clinical guidelines was initiated by Keuken et al.(4) However, due to lack of available data it is almost not feasible to employ this procedure. This was encountered recently when the Canadian guideline for the management for ST-elevated myocardial infarction tried to follow this protocol and experienced that required data were not available.(5) For heart failure patients, a sex-specific sub analysis of the PARAGON HF was carried out in which fewer hospitalizations were seen in women compared to men who were treated with sacubitril-valsartan. This addresses again the importance of presenting data for women and men separately in order to reveal differences in cardiovascular therapies.(6)

In 2015 the FDA began ‘’Snapshots’’, a website consisting of information on differences of novel drug efficacy and side effects among different demographic groups, including sex. However, Snapshots does not include results of any dugs approved before 2015, and we therefore strongly encourage Snapshots to also accept RCTs on drugs that were approved earlier in order to make more sex-specific data available.(7)

CONCLUSION

It can be concluded that, despite the specific recommendations and guidelines for reporting sex-specific data, the sex-specific efficacy and safety outcomes of the most influential cardiovascular intervention trials are still not systematically presented. As these trials are the most important source of evidence for clinical guidelines, improvement in reporting of sex-specific data is essential to enable sex-specific recommendations in the future. Therefore, researchers, scientific societies organizing cardiovascular conferences and publishing journals should verify that sex-specific reporting is secured.

Contributors

M.M. Schreuder contributed to the analysis of the results and to the writing of the manuscript.
E. Boersma contributed to the analysis of the results and to the writing of the manuscript.
M. Kavousi contributed to the writing of the manuscript.
L.E. Visser contributed to the writing of the manuscript.
J.W. Roos-Hesselink contributed to the writing of the manuscript.
J. Versmissen contributed to the writing of the manuscript.
J.E. Roeters van Lennep contributed to the design and implementation of the research.

Conflict of Interests

Outside the submitted work, J.E. Roeters van Lennep reports to have received honorary fees and grants from Akcea and Amryt. All other authors declare no competing interests.

Funding

Our study was funded by the Dutch Heart foundation (2016t098).

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APPENDIX

Online Table 1. Characteristics of the pharmacological randomized controlled trials presented at the Hot Line Sessions/Late Breaking Trials of the European Society of Cardiology (ESC). American Heart Association (AHA) and the American College of Cardiology (ACC) in 2010 and 2017

	ESC 2010				
	Trial	**Cardiovascular domain**	**Journal**	**Study Phase**	**Placebo controlled**
1	**PEARL-HF**	Heart Failure	European Journal of Heart Failure	2	yes
2	**SHIFT**	Heart Failure	The LANCET	3	yes
3	**ALPHA OMEGA**	Acute Coronary Syndrome/ Myocardial Infraction	The New England Journal of Medicine	n.a.	yes
4	**HEBEIII**	Acute Coronary Syndrome/ Myocardial Infraction	European Heart Journal	2	no
5	**INNOVATE PCI**	Acute Coronary Syndrome/ Myocardial Infraction	Circulation	2	no
8	**Atoll**	Acute Coronary Syndrome/ Myocardial Infraction	The LANCET	3	no
9	**ISAR REACT 3A**	Acute Coronary Syndrome/ Myocardial Infraction	European Heart Journal	4	no
10	**E5555**	Angina/CAD	Circulation	2	yes
12	**AVERROES**	Atrial Fibrillation	The New England Journal of Medicine	3	no
13	**EINSTEIN DVT**	Deep Venous Thrombosis	The New England Journal of Medicine	3	no
14	**ANTIPAF**	Atrial Fibrillation	Circulation	3	yes
15	**FUTURA OASIS 8**	Acute Coronary Syndrome/ Myocardial Infraction	JAMA	4	no
16	**COPPS**	Cardiothoracic surgery	Circulation	3	yes
	ESC: 2017				
	Trial	Cardiovascular Field	Journal	Study Phase	Placebo controlled
1	**CASTLE-AF**	Atrial Fibrillation	J Community Hosp Intern Med Perspect	4	no
2	**CANTOS**	Acute Coronary Syndrome/ Myocardial Infarction	The New England Journal of Medicine	3	yes
3	**COMPASS**	ASCVD	The New England Journal of Medicine	3	yes
4	**DETO2X-AMI**	Acute Coronary Syndrome/ Myocardial Infarction	The New England Journal of Medicine	3	no
5	**EMANATE**	Atrial Fibrillation	European Heart Journal	4	no
6	**IMPACT-AF**	Atrial Fibrillation	The LANCET	n.a.	no
7	**ORION 1**	Hypercholesterolemia	The New England Journal of Medicine	2	yes
8	**PRECISION-ABPM**	Angina/CAD	European Heart Journal	4	yes
9	**SIOVAC**	Cardiothoracuc Surgery	European Heart Journal	4	yes
10	**HPS3/TIMI55 REVEAL**	ASCVD	The New England Journal of Medicine	3	yes

Men (n)	Women (n)	Women (%)	Sex-specific efficacy endpoint	Sex-specific safety endpoint	Prevalence corrected estimate women(1)	Comments
63	42	40.0	No	No	0.8	15% HFPEF. 85% HREF
4970	1535	23.6	No	No	0.4	HFREF
3783	1054	21.8	No	No	0.7	Type myocardial infarction not described
412	117	22.1	No	No	0.7	STEMI
804	236	22.7	No	No	0.7	Type myocardial infarction not described
712	198	21.8	Yes	Yes	0.7	STEMI
3098	902	22.6	Yes	Yes	0.7	Type myocardial infarction not described
548	172	23.9	No	No	0.6	
3277	2322	41.5	Yes	Yes	1.2	
2653	1992	42.9	No	No		
249	176	41.4	No	No	1.2	
1375	651	32.1	Yes	Yes	1.0	Type myocardial infarction not described
230	106	31.5	No	No		

Men (n)	Women (n)	Women (%)	Sex-specific efficacy endpoint	Sex-specific safety endpoint	Prevalence corrected estimate women(1)	Comments
311	52	14.3	Yes	No	0.4	
7474	2587	25.7	No	No	0.8	55% STEMI. 34% NSTEMI. 11% unknown
21375	6020	22.0	Yes	Yes		
4606	2023	30.5	No	No	0.9	44.5% STEMI, 31% NSTEMI,, 24.5% other cardiac diagnosis
2927	1450	33.1	No	No	0.9	
1202	1079	47.3	No	No	1.3	
323	174	35.0	No	No		
205	239	53.8	No	No	1.3	
46	154	77.0	No	No		
25534	4915	16.1	No	No		

AHA: 2010

	Trial	Cardiovascular Field	Journal	Study Phase	Placebo controlled	Men (n)
1	**ACT**	Angina Pectoris/CAD	Circulation	n.a.	no	1416
2	**ASCEND HF**	Heart Failure	NEJM	3	yes	4616
3	**DEFINE**	Angina Pectoris/CAD	The New England Journal of Medicine	3	yes	1247
4	**EMPHASIS-HF**	Heart Failure	Journal of the American College of Cardiology	3	no	2127
5	**GRAVITAS**	Acute Coronary Syndrome/ Myocardial Infarction	JAMA	3	yes	1911
6	**P-OM3**	Atrial Fibrillation	JAMA	4	yes	746
7	**ROCKET AF**	Atrial Fibrillation	The New England Journal of Medicine	3	yes	8601
8	**TIM-HF**	Heart Failure	Circulation	3	no	577

AHA: 2017

	Trial	Cardiovascular Field	Journal	Study Phase	Placebo controlled	Men (n)
1	**DACAB**	Acute Coronary Syndrome/ Myocardial Infarction	JAMA	4	no	409
2	**PRESERVE**	Acute Coronary Syndrome/ Myocardial Infarction	NEJM	3	yes	9342
3	**BRUISE CONTROL-2**	Atrial Fibrillation	European Heart Journal	4	no	479
4	**ABRIDGE J**	Atrial Fibrillation	JAMA	?	no	331
5	**REAL-CAD**	Angina pectoris/CAD	Circulation	n.a.	no	10253
6	**FOURIER**	Angina pectoris/CAD	Circulation	3	yes	17544
7	**CANTOS**	Angina pectoris/CAD	The Lancet	3	yes	7100
8	**CANVAS**	Diabetes	Circulation	4	yes	6509
9	**EXSCEL**	Diabetes	The New England Journal of Medicine	n.a.	no	9149
10	**EMPA-REG OUTCOME**	Diabetes	Circulation	3	yes	n/a
11	**COMPASS**	Angina pectoris/CAD	The New England Journal of Medicine	3	yes	21375
12	**RE-DUAL PCI**	Atrial Fibrillation	The New England Journal of Medicine	3	no	2664
13	**POISE-2 PCI**	Angina pectoris/CAD	Annals of Internal Medicine	3	yes	5283
14	**GEMINI-ACS-1**	Acute Coronary Syndrome/ Myocardial Infarction	The Lancet	2	no	2275
15	**PRAGUE-18**	Acute Coronary Syndrome/ Myocardial Infarction	JACC	4	no	928
16	**TNT-POAF**	Cardiothoracic Surgery	Heart rhythm	1	yes	90
17	**PROPEL**	Peripheral Artery Disease	JAMA	3	yes	128

Women (n)	**Women (%)**	**Sex-specific efficacy endpoint**	**Sex-specific safety endpoint**	**Prevalence corrected estimate women(1)**	**Comments**
892	38.6	yes	no	0.9	
2391	34.1	yes	x	0.6	HFREF/HFPEF rate not described
376	23.2			0.5	
610	22.3			0.4	HFREF
889	31.8			1.0	Type myocardial infarction not described
580	43.7	yes	no	1.2	
5663	39.7			1.1	
133	18.7	no	-	0.4	HREF

Women (n)	Women (%)	Sex-specific efficacy endpoint	**Sex-specific safety endpoint**	**Prevalence corrected estimate women (1)**	**Comments**
91	18.2	no	no	0.6	NSTEMI and stable/unstable AP
644	6.4	no	no	0.2	Type myocardial infarction not described
183	27.6	no	no	0.8	
111	25.1	-	yes	0.7	
2160	17.4	yes	no	0.4	
4807	21.5	no	-	0.5	
2434	25.5	yes	no	0.6	
3633	35.8	no	no		
5603	38.0	yes	no		
n/a		no	no		
6020	22.0	yes	no	0.5	
825	23.6	no	no	0.7	
4727	47.2	no	no	1.1	
762	25.1	no	yes	0.8	49% STEMI 40% NSTEMI. 1% unknown
302	24.6	yes	no	0.7	90% STEMI. 5% NSTEMI. 5% unknown
40	30.8	no	no		
82	39.0	no	-		

ACC: 2010

	Trial	Cardiovascular Field	Journal	Study Phase	Placebo controlled
1	**ACCORD Lipid**	Diabetes	The New England Journal of Medicine	3	yes
2	**ACCORD BP**	Diabetes	The New England Journal of Medicine	3	yes
3	**NAVIGATOR**	Angina Pectoris/CAD	The New England Journal of Medicine	n.a.	no
4	**INVEST**	Angina Pectoris/CAD	JAMA	4	no
5	**SORT OUT III**	Angina Pectoris/CAD	The Lancet	3	no
6	**PLATO**	Acute Coronary Syndrome/ Myocardial Infarction	JACC	3	no
7	**JETSTENT**	Acute Coronary Syndrome/ Myocardial Infarction	JACC	4	no

ACC: 2017

	Trial	Cardiovascular Field	Journal	Study Phase	Placebo controlled
1	**FOURIER**	Angina Pectoris/CAD	The New England Journal of Medicine	3	yes
2	**SPIRE 1 and SPIRE 2**	Hypercholesterolemia	The New England Journal of Medicine	3	yes
3	**ABSORB III**	Angina Pectoris/CAD	JACC	n.a.	no
4	**RE-CIRCUIT**	Atrial Fibrillation	The New England Journal of Medicine	4	no
5	**ARISTOTLE**	Atrial Fibrillation	JACC	3	no
6	**GIFT of Warfarin**	Deep Venous Thrombosis	JAMA	3	no

Mozaffarian D. Benjamin EJ. Go AS. et al. Heart Disease and Stroke Statistics-2016 Update: A Report From the American Heart Association. Circulation. 2016 Jan 26;133(4):e38-e360. p. 296
ASCVD= Atherosclerotic Cardiovascular Disease
HFPEF = Heart Failure with Preserved Ejection Fraction
HFREF = Heart Failure with Reduced Ejection Fraction
STEMI = ST Elevated Myocardial Infarction
NSTEMI = Non-ST Elevated Myocardial Infarction
CAD = Coronary Artery Disease

Men (n)	Women (n)	Women (%)	Sex-specific efficacy endpoint	Sex-specific safety endpoint	Prevalence corrected estimate women(1)	Comments
3824	1694	30.7	yes	no		
2475	2258	47.7	yes	no		
4595	4711	50.6	yes	no	1.2	
2945	3455	54.0	no	no	1.3	
4112	1564	27.6	yes	no	0.6	
995	266	21.1	yes	no	0.6	38% STEMI. 43% NSTEMI. 19% unknown
394	107	21.4	no	no	0.6	STEMI

Men (n)	Women (n)	Women (%)	Sex-specific efficacy endpoint	Sex-specific safety endpoint	Prevalence corrected estimate women(1)	Comments
20795	6769	24.6	yes	yes	0.6	
n/a	n/a		no	no		
1415	593	29.5	yes	no	0.7	
475	160	25.2	yes	no	0.7	
3590	2234	38.4	no	no	1.1	
579	1018	63.7	no	no		

D

Epilogue

SUMMARY, GENERAL DISCUSSION AND FUTURE PERSPECTIVES

Although awareness of the importance of sex and gender in cardiovascular disease (CVD) has increased in the last few decades, a better understanding of how these factors affect risk factors, clinical manifestation and drug responses is still required in order to optimize prevention and management of CVD in both women and men.

This thesis consists of three parts, the first part assesses the influence of fluctuating sex hormones on the prevalence of cardiac symptoms, using the menstrual cycle as a model. The second part evaluates sex-specific effects of cardiovascular risk factors and treatment with a special focus on efficacy and safety of the most common cardiovascular drugs. The last part describes the relevance of sex and gender- in clinical practice and research. The main findings of the studies will be discussed and interpreted in this chapter, followed by recommendations for clinical implications and suggestions for further research.

Part A - The Menstrual Cycle and Cardiac Symptoms

In **Chapter 1**, we reviewed the literature of how female sex hormones influence the symptoms of women with supraventricular tachycardia (SVT) and whether episodes of arrhythmia might be more prevalent in the premenstrual phase compared to other days of the menstrual cycle. When translating this to clinical practice, this would mean that women might present at the general practitioner of cardiologist with menstruation-related symptoms such as palpitations, which should be recognized as a potential symptom of SVT. Besides, it should be considered in the future that diagnostic tests for arrhythmias in women are scheduled in the days of the menstrual cycle in which women have most complaints, as this might lead to more accurate diagnoses.

Chapter 2 describes the case of a 45-year-old woman with an ST-elevation myocardial infarction, caused by SCAD of the mid left anterior descending coronary artery. In the six years prior to this event, she frequently experienced chest pain coinciding with menstruation. The case report highlights the importance of investigating catamenial chest pain. We suggest that when a patient reports catamenial chest pain, diagnostic tests should be planned and timed according to the menstrual cycle phase. Finally in **Chapter 3**, we showed in *The Cycle study*, a prospective cross-sectional study, of 175 women who reported chest symptoms that symptoms of palpitations or angina-like symptoms were more often reported during menstruation than on the other days of the menstrual cycle showing that the menstrual cycle is a factor which is associated with chest symptoms

In conclusion, from part A of this thesis we learned that it is important to recognize menstrual cycle-related cardiac symptoms during history taking and examination of women with suspected CVD, as it can contribute to the improvement of diagnosis and treatment of CVD in women.

There are still many questions unanswered for which future research is required. Female sex hormones such as estradiol and progesterone affect the cardiovascular system via multiple pathways ranging from direct effects on the cardiac myocyte and nitric oxide synthesis in the endothelium but also indirectly because of cyclic variations in blood pressure and lipid levels. However, which exact mechanism is related to specific cardiac complaints remains to be unraveled. With *The Cycle Study* we focused on subjective symptoms in a heterogeneous population. For future research it will be interesting to assess if objective measurements of arrhythmia by event recorders can be related to specific phases of the menstrual cycle and if this can be confirmed by measurement of estradiol and progesterone levels.

Part B - Sex-specific effects of cardiovascular risk factors and treatment

Chapter 4 reports a sex-specific analysis of the temporal evolution of circulating biomarkers in 250 patients (66 women) with heart failure with reduced ejection fraction (HFrEF). In total 66 patients had reached the primary endpoint consisting of a cardiac event or hospitalization in the follow-up time of two years. Although we found no significant sex differences in the association of the primary endpoints with the circulating biomarkers, NT-proBNP, HsTnT, and CRP levels appear more outspoken associated in the temporal evolution of women who reached the primary endpoint. This suggests that increasing levels of these biomarkers are more worrisome in women than men with HFrEF. However, future studies with larger sample sizes with sex-specific analyses are needed to confirm our observations.

In **Chapter 5** we analyzed the sex-specific effect of angiotensin converting enzyme (ACE) inhibition on blood pressure by studying the response of perindopril-based treatment in 8366 women and 21,097 men with CVD. We observed no sex differences in absolute and relative systolic and diastolic blood pressure reduction after a 4-week treatment with perindopril. Interestingly, we found that increasing age led to a significantly lower blood pressure response to perindopril treatment in both men and women. Therefore, future studies are needed to assess whether the dosage of ACE inhibitors should be adjusted to age for both women and men.

In **Chapter 6,** we present a sex-based analysis of adverse drug reactions (ADR) reports of the Dutch (LAREB) and global (VIGILISE) pharmacovigilance database to determine the number and type of ACE inhibitors related ADRs in women and men. The reported incidence of ADR was 31% higher in women than in men. Moreover, women report particularly respiratory, thoracic and mediastinal ADRs, while men predominantly report more skin and subcutaneous tissue ADRs. We attempted to perform a systematic review and meta-analysis to assess efficacy and safety of ACE inhibitors in placebo-controlled trials of patients with CVD. However, none of the relevant trials reported sex-stratified results. Our study stresses the importance of reporting efficacy and especially safety of ACE inhibitors for women and men separately. The underlying pathogenesis of ACE-inhibitor induced ADRs in women

and men is unknown. Future studies are needed to elucidate these pathways in order to optimize the treatment strategies of ACE inhibitors for women and men.

We showed no differences in the efficacy (major cardiovascular events) and safety (major bleedings) of prasugrel and ticagrelor between the sexes in a sex-specific systematic review and meta-analysis (**Chapter 7**) on the efficacy and safety of high potent P2Y12 inhibitors prasugrel and ticagrelor in 13,030 women and 30,960 men with coronary heart disease (CHD) treated with dual antiplatelet therapy. In current practice, women are treated less often with guideline-recommended dual antiplatelet therapy. Our results can help to substantiate that there is no reason to treat women and men with CHD differently in this respect. In **Chapter 8**, statin treatment in 1,713 women and 1,465 men with Familial Hypercholesterolemia (FH) was evaluated, which showed that only the minority of FH patients (26.9% of the women and 28.9% of the men) reached their LDL-C target. The most reported reason for not reaching the LDL-C target in both sexes was that they received the maximum dose of lipid-lowering therapy. However, we observed that women more frequently not reached their LDL-C treatment goal because of ADR of lipid lowering therapy than men. This emphasizes the importance taking ADRs into account in clinical practice, as it might lead to suboptimal treatment of FH patients, especially in women and if statin therapy is insufficient, PCSK9-inhibitors should be considered.

In **Chapter 9**, we studied ADRs of PCSK9 antibodies (alirocumab or evolocumab) in a real-world data set consisting of three datasets: a hospital registry, and a national and the international pharmacovigilance database. Our main finding was that ADRs of these drugs in clinical setting were comparable to clinical trials. We observed no sex differences and concluded that PCSK9 antibodies are well tolerated in both sexes in clinical practice.

Concluding, from part B of this thesis we learned that the efficacy of the ACE inhibitor perindopril and also of high potent P2Y12 inhibitors (prasugrel and ticagrelor) is not different between sexes. Concerning the safety of CVD medication, we found that high potent P2Y12 inhibitors do not lead to more bleedings in women than in men, implying that it is not justified to treat women with a less potent P2Y12 inhibitor than men. For statin treatment and ACE inhibitors, women were more likely to report ADRs compared to men, and in case of ACE inhibitors the ADRs were also different between the sexes. On the other hand, we observed no sex differences in ADRs for PCSK9 inhibitors. Sex-stratified analyses for efficacy and safety are important for clinical practice. Not only the observation of sex differences, but also the absence of differences in efficacy and safety between men and women are essential to report. In view of our data, clinical treatment guidelines in the cardiovascular domain should no longer provide uniform, but rather sex and gender-sensitive recommendations.

Part C - Sex-specific effects of cardiovascular risk factors and treatment

In **Chapter 10** we evaluated with a questionnaire survey if and for what kind of symptoms patients prefer a female or male general practitioner (GP). A total of 7,019 people filled in

the questionnaire, which showed that women more often prefer a GP of their own sex than men (38.9% vs 12.8%), in particular for symptoms involving sexuality or private body parts. Moreover, patients more willingly discussed psychological symptoms with a female GP than a male GP (16.3% vs 4.4%). A small group of patients (8%) even stated that their GP being of the opposite sex was a reason for them to postpone their GP appointment, however this was higher in women < 45 yrs of which almost 20% reported to postpone an appointment because they feared to discuss symptoms with a male GP. This study demonstrates that, although most patients do not prefer a GP of a specific sex, there is a subgroup, consisting mostly of younger women, who experience embarrassment especially for more intimate or psychological problems towards a GP of the opposite sex. Therefore, it is important that it is acknowledged that sometimes patients have a specific preference for a female or male GP in order to prevent unnecessary delay of doctor consultations.

Finally in **Chaper 11**, we describe the reporting of sex-specific efficacy and safety outcomes in randomized clinical trials (RCTs) of pharmacological interventions for CVD presented at the major clinical trials sessions of the European Society of Cardiology (ESC), American Heart Association (AHA) and the American College of Cardiology (ACC) in 2010 compared to 2017. To our disappointment, we observed over time even a decrease in reporting per sex of both the efficacy (34.5 % in 2010 and 23.5 % in 2017) and safety outcomes (11.1 % 2010 and 8.6 % in 2017). This observation showed that in the most influential cardiovascular intervention trials, sex-specific results of efficacy and safety outcomes are still underreported. Therefore, researchers, scientific societies organizing cardiovascular conferences and publishing journals should verify that sex-specific reporting of clinical trials is secured.

What is already known?

- Female sex hormones affect the cardiovascular system by different pathways
- Women report more adverse drug reactions
- Sex-specific data on cardiovascular drugs is insufficiently reported in older cardiovascular trials

What does this thesis add?

- Women report symptoms such as chest pain and palpitations more often just before or during menstruation compared to other days of the menstrual cycle
- Efficacy outcomes of perindopril, high potent P2Y12 inhibitors and statins are similar in women and men
- Women more often report ADRs of ACE inhibitors than men; the type of side effects is also different. ADRs with respect to PCSK9 inhibitors are similar in both sexes
- Women with FH have higher pre-treatment LDL-C levels than men, but are less likely to be treated with high intensity statins, which might be because of ADRs.
- For patients, especially women, the sex of their general practitioner is important when they have intimate of psychological symptoms and can even lead to postponing their consultation
- During 2010-2017 no progress was observed in the sex-specific presentation of clinical trial results at major cardiology congresses

Recommendation for clinical practice/future research

- The menstrual cycle- should be taken into account during history taking and examining of premenopausal women who present with cardiac symptoms
- In depth studies are needed to study why ACE inhibitors lead to more and different ADRs in women and men
- Both women and men should be treated equally with high potent P2Y12 inhibitors after percutaneous coronary intervention or acute coronary syndrome
- As women with FH have higher LDL-C levels than men, high intensity statins should be first choice treatment, but the occurrence of ADRs should be taken into account
- All cardiovascular trials should present efficacy and safety data stratified by sex

NEDERLANDSE SAMENVATTING

Tegenwoordig wordt er meer aandacht besteed aan sekseverschillen in de epidemiologie en behandeling van hart- en vaatziekten (HVZ). Hoewel de bewustwording van man/vrouw-verschillen bij hart- en vaatziekten de afgelopen tien jaar aanzienlijk is toegenomen, moeten er nog veel uitdagingen worden aangegaan om het diagnostische proces en de behandeling van HVZ bij vrouwen en mannen te verbeteren en te optimaliseren. Dit proefschrift bestaat uit drie delen. Het eerste deel beoordeelt de invloed van fluctuerende geslachtshormonen op de prevalentie van hartklachten, waarbij de menstruatiecyclus als model wordt gebruikt om dit te onderzoeken. Het tweede deel van dit proefschrift evalueert geslachts-specifieke effecten van cardiovasculaire risicofactoren en behandeling met speciale aandacht voor de werkzaamheid en veiligheid van de meest voorkomende cardiovasculaire geneesmiddelen. Het laatste deel van dit proefschrift beschrijft de relevantie van seksegevoelige klinische praktijk en onderzoek.

In **deel A** van dit proefschrift wilden we met een inzicht geven in de invloed van vrouwelijke geslachtshormonen op hartsymptomen. In **Hoofdstuk 2** hebben we waargenomen dat episodes van aritmie meer voorkomen in de premenstruele fase dan op andere dagen van de menstruatiecyclus aan de hand van de meest recente literatuur over menstruatie en supraventriculaire tachycardie. De invloed van de menstruatiecyclus op het optreden van aritmie is echter slechts in enkele onderzoeken met kleine steekproeven onderzocht. In **Hoofdstuk 3** wordt de casus beschreven van een 45-jarige vrouw met een hartinfarct veroorzaakt door een spontane coronaire arteriedissectie (SCAD). Voorafgaand aan deze gebeurtenis had ze gedurende meerdere jaren menstruatie-gerelateerde pijn op de borst en ook haar SCAD-voorval vond plaats twee dagen nadat haar menstruatie was begonnen. **Hoofdstuk 4** is een prospectieve cross-sectionele studie waarin 175 vrouwen met subjectieve symptomen van hartkloppingen of pijn op de borst symptomen werd gevraagd om een dagboek bij te houden gedurende twee menstruatiecycli waarin ze hun symptomen en menstruatie bijhielden. We zagen dat vrouwen meer kans hadden op hartklachten tijdens de menstruatie in vergelijking met de andere dagen van de menstruatiecyclus. Hiermee hebben we laten zien dat de herkenning van thoracale symptomen die verband houden met de menstruatiecyclus is dus belangrijk voor zowel de patiënt als de zorgverleners en er moet rekening mee worden gehouden bij de anamnese en het onderzoek van vrouwen met verdenking op hart- en vaatziekten.

In **deel B** van dit proefschrift hebben we ons gericht op sekseverschillen in cardiovasculaire geneesmiddelen. Een geslachts-specifieke analyse van de temporele evolutie van circulerende biomarkers bij 250 patiënten (66 vrouwen) met hartfalen met verminderde ejectiefractie (HFrEF) tussen 2011 en 2013 wordt besproken in **Hoofdstuk 5.** Tijdens de

follow-up tijd bereikten 66 patiënten de primaire eindpunt (hartdood, harttransplantatie, implantatie van een steunhart en ziekenhuisopname als gevolg van acuut of verergerd hartfalen), waarvan 78,8% mannen waren. Hoewel de interactieterm niet significant was, lijken de associaties van de primaire eindpunten met de temporele patronen van NT-proBNP, HsTnT en CRP meer uitgesproken bij vrouwen dan bij mannen met HFrEF, wat betekent dat verhoogde waardes een slechtere prognose geven bij vrouwen dan bij mannen. **Hoofdstuk 6** is een geslachts-specifieke analyse van de relatieve en absolute veranderingen in systolische bloeddruk (SBP) en diastolische bloeddruk (DBP) tijdens een perindopril-gebaseerde behandeling van 4 weken bij 8,366 vrouwen en 21,097 mannen met vasculaire ziekte. We zagen geen significante sekseverschillen in bloeddrukrespons, maar toenemende leeftijd leidde tot minder respons op perindopril behandeling bij zowel mannen als vrouwen. Daarom is meer onderzoek nodig om te bepalen of het nuttig zou zijn om voor leeftijd aangepaste perindopril doseringen te gebruiken. In **Hoofdstuk 7** werd in een internationale en een Nederlandse geneesmiddelendatabase met bijwerkingen gebruikt om sekseverschillen in het aantal en type aan angiotensine-converterende enzym (ACE)-remmer gerelateerde bijwerkingen te evalueren. De incidentie van bijwerkingen per 100,000 gebruikers was hoger bij vrouwen (24,9 bij vrouwen en 18,3 bij mannen) en vrouwen en mannen rapporteerden ook verschillende bijwerkingen. **Hoofdstuk 8** is een sekse-specifieke systematische review en meta-analyse van de werkzaamheid en veiligheid van de krachtige P2Y12-remmers prasugrel en ticagrelor bij patiënten met coronaire hartziekte die worden behandeld met dubbele plaatjesaggregatieremmers. We includeerden 6 gerandomiseerde klinische onderzoeken waarin prasugrel of ticagrelor werd vergeleken met clopidogrel bij 13,030 vrouwen en 30,960 mannen. Vrouwen en mannen hadden een vergelijkbare relatieve risicovermindering voor ernstige cardiovasculaire ziekte en een vergelijkbaar risico op ernstige bloedingen door ticagrelor of prasugrel. De effectiviteit en veiligheid van lipidenverlagende therapieën bij vrouwen en mannen werden bestudeerd in **Hoofdstuk 9** en **10**. In **Hoofdstuk 9** werden de LDL-C-spiegels gemeten van 1,713 vrouwen en 1,465 mannen met familiaire hypercholesterolemie (FH) vóór en na statinebehandeling. Vrouwen werden minder snel behandeld met een statine met hoge intensiteit, terwijl hun LDL-C vóór de behandeling significant hoger was dan bij mannen. Over het algemeen bereikte slechts een minderheid van de patiënten hun LDL-C streefwaarde, die zelfs lager waren voor vrouwen dan voor mannen (26.9% versus 28.9%). Bij zowel vrouwen als mannen was de meest voorkomende reden voor het niet bereiken van hun streefwaarde dat zij de maximale dosis statines kregen. Er was echter een sekseverschil in bijwerking, aangezien vrouwen vaker dan mannen hun LDL-C-doelstelling niet bereikten vanwege bijwerkingen of therapieontrouw. In **Hoofdstuk 10** werd een real-world dataset gebruikt bestaande uit drie datasets, een ziekenhuisregistratie en twee Geneesmiddelendatabases (8924 vrouwen en 6135 mannen) die bijwerkingen rapporteren die worden toegeschreven aan PCSK9-remmers (alirocumab of evolocumab). We vonden geen significante verschillen in bijwerkingen van PCSK9-remmers bij vrouwen en mannen.

In **deel C** worden sekseverschillen in de huisartsenpraktijk en in de rapportage van gerandomiseerde klinische onderzoeken geëvalueerd. In **Hoofdstuk 11** evalueerden we bij 7,019 patiënten of en wanneer patiënten de voorkeur geven aan een vrouwelijke of mannelijke huisarts (huisarts) met een vragenlijstonderzoek. Vrouwen gaven vaker de voorkeur aan een huisarts van hun eigen geslacht dan mannen (38.9% vs 12.8%), vooral voor problemen met seksualiteit en privé-lichaamsdelen. Ook gaven meer patiënten aan de voorkeur te geven aan een vrouwelijke arts dan aan een mannelijke huisarts voor psychische klachten. Een deel van de patiënten verklaarde zelfs al eerder een huisartsenconsult te hebben uitgesteld omdat ze hun symptoom niet wilden voorleggen aan een huisarts van het andere geslacht. **Hoofdstuk 12** richt zich op de rapportage van geslachts-specifieke effectiviteit- en veiligheidsresultaten in gerandomiseerde klinische onderzoeken van farmacologische interventies voor HVZ, gepresenteerd tijdens de belangrijkste klinische onderzoek sessies van de European Society of Cardiology (ESC), American Heart Association (AHA) en het American College of Cardiology (ACC) in 2010 en 2017. Geslachts-specifieke werkzaamheidseindpunten werden gerapporteerd voor 34.5 % van de studies in 2010 en 23.5% in 2017, en veiligheidsresultaten werden gerapporteerd per geslacht in 11.1 % van de studies in 2010 en 8.6% in 2017, wat betekent dat in de meest invloedrijke cardiovasculaire interventiestudies geslachts-specifieke uitkomsten nog steeds niet systematisch worden gepresenteerd.

LIST OF PUBLICATIONS

1 **Schreuder MM**, Sunamura M, Roeters van Lennep JE. Supraventricular tachycardia and the menstrual cycle. *Case Rep Womens Health. 2019 Oct 22;24:e00153. doi: 10.1016/j.crwh.2019.e00153.*

2 Al Fatly Z, Beckers FLM, Sjauw KD, Roeters van Lennep JE, **Schreuder MM**. Catamenial chest pain and spontaneous coronary artery dissection: A case report. *Case Rep Womens Health. 2020 Sep 28;28:e00256. doi: 10.1016/j.crwh.2020.e00256.*

3 **Schreuder MM**, Boersma E, Kavousi M, Maassen van den Brink A, Duvekot JJ, Rikmans AG, Sunamura M, Roeters van Lennep JE. The influence of the Menstrual Cycle on Chest Symptoms. *Submitted*

4 **Schreuder MM**, Schuurman A, Akkerhuis KM, Constantinescu AA, Caliskan K, van Ramshorst J, Germans T, Umans VA, Boersma E, Roeters van Lennep JE, Kardys I. Sex-specific temporal evolution of circulating biomarkers in patients with chronic heart failure with reduced ejection fraction. *Int J Cardiol. 2021 Jul 1;334:126-134. doi: 10.1016/j.ijcard.2021.04.061.*

5 **Schreuder MM**, Mirabito Colafella KM, Boersma E, Brugts JJ, Roeters van Lennep JE, Versmissen J. The effect of age on blood pressure response by 4-week treatment perindopril: A pooled sex-specific analysis of the EUROPA, PROGRESS, and ADVANCE trials. *Clin Transl Sci. 2021 Nov;14(6):2193-2199. doi: 10.1111/cts.13076.*

6 Bots SH, **Schreuder MM**, Roeters van Lennep JE, Watson S, van Puijenbroek E, Onland-Moret NC, den Ruijter HM. Sex Differences in Reported Adverse Drug Reactions to Angiotensin-Converting Enzyme Inhibitors. *JAMA Netw Open. 2022 Apr 1;5(4):e228224. doi: 10.1001/jamanetworkopen.2022.8224.*

7 **Schreuder MM**, Badal R, Boersma E, Kavousi M, Roos-Hesselink J, Versmissen J, Visser LE, Roeters van Lennep JE. Efficacy and Safety of High Potent $P2Y_{12}$ Inhibitors Prasugrel and Ticagrelor in Patients With Coronary Heart Disease Treated With Dual Antiplatelet Therapy: A Sex-Specific Systematic Review and Meta-Analysis. *J Am Heart Assoc. 2020 Feb 18;9(4):e014457. doi: 10.1161/JAHA.119.014457.*

8 **Schreuder MM**, Hamkour S, Siegers KE, Holven KB, Johansen K, van de Ree MA, Imholz B, Boersma E, Louters L, Bogsrud MP, Retterstøl K, Visseren F, Roeters van Lennep JE, Koopal C. LDL Cholesterol Targets Rarely Achieved in FH Patients: a sex-specific analysis. *Submitted.*

9 Gürgöze MT, Muller-Hansma AHG, **Schreuder MM**, Galema-Boers AMH, Boersma E, Roeters van Lennep JE. Adverse Events Associated With PCSK9 Inhibitors: A Real-World Experience. *Clin Pharmacol Ther. 2019 Feb;105(2):496-504. doi: 10.1002/cpt.1193.*

10 **Schreuder MM**, Peters L, Bhogal-Statham MJ, Meens T, Roeters van Lennep JE. Mannelijke of vrouwelijke huisarts [Male or female general practitioner; do patients have a preference?]. *Ned Tijdschr Geneeskd. 2019 Jan 14;163:D3146.*

11 **Schreuder MM**, Boersma E, Kavousi M, Visser LE, Roos-Hesselink JW, Versmissen J, Roeters van Lennep JE. Reporting of sex-specific outcomes in trials of interventions for cardiovascular disease: Has there been progress? *Maturitas. 2021 Feb;144:1-3. doi: 10.1016/j.maturitas.2020.09.007.*

PHD PORTFOLIO

Summary of PhD training and teaching activities

Name PhD student: Michelle Schreuder	PhD period: 2017-2022
Erasmus MC Department:	Promotor(s): E. Boersma
Cardiology and Vascular Medicine	Supervisor: J.E. Roeters van Lennep

1. PhD training

	Year	Workload (ECTS)
General academic skills		
Research Integrity	2018	0.3
BROK course	2018	1.5
Limesurvey and Gemstracker	2018	0.3
Biomedical English Writing and Communication	2021	2.5
Research skills		
Biostatistical Methods I: basic principals	2017	5.7
Meta-analysis	2017	0.7
Survival analysis	2017	0.6
Women's Health	2018	0.7
In-depth courses (e.g. Research school, Medical Training)		
COEUR course: Pathofysiology of Ischemic Heart Disease	2018	1.0
COEUR course: Sex and Gender in Cardiovascular Research	2018	0.5
COEUR course: Vascular Clinical Epidemiology	2019	0.4
International conferences		
European Society of Cardiology, Munich, Germany	2018	1.4
Scandinavian Atherosclerosis Conference, Humlebaek, Denmark	2018	3.3
2x European Atherosclerosis Society, Maastricht, The Netherlands and online	2019, 2021	1.7
International Society of Gender Medicine, Vienna, Austria	2019	1.9
National conferences		
Nationale Lipidendag	2019	0.3
Gender Summit	2019	1.3
HartVaat Huisartsgeneeskunde congress	2018	0.8
2x Wetenschapsdagen	2019, 2020	2.2
Sex, Gender and Pain	2019	0.3

Seminars and workshops		
3x COEUR PhD day	2017, 2019, 2021	0.9
Libin International Trainee Symposium: Research is better with Sex and Gender, Banff, Canada	2020	0.6
TED-course: public speaking	2019	0.3
Gender en Farmacologie	2018	0.8
2. Teaching activities		
Lecturing		
3x Junior Med School: Summerschool	2018, 2019, 2021	0.3
Supervision of students		
Master thesis: Ricardo Badal	2017	1.0
Master thesis: Malou Crasborn	2017	1.0
Master thesis: Janine Valk	2019	1.0
Master thesis: Janneke van Rossum	2020	1.0
Master thesis: Hannah de Jager	2021	1.0
2x Review 2nd year medical students	2017, 2019	1.0
Total		36.3

ABOUT THE AUTHOR

Michelle Schreuder was born on August 15th, 1994 in Arnhem, The Netherlands.

She graduated from the Marnix College (Gymnasium), Ede in 2012. Afterward, she was selected via the decentral selection procedure to study Medicine at the Erasmus University Rotterdam, The Netherlands. During her bachelor's degree, she participated in several research projects at the Department of Immunology and Vascular medicine.

After she finished her master thesis at the Department of Vascular medicine, she started in July 2017 as a Ph.D. Candidate under supervision of Dr. J.E. Roeters van Lennep and prof.dr.ir. E. Boersma. During this period, she worked on several national and international research projects on sex differences in cardiovascular diseases. In February 2020, she started with her clinical rotations and she obtained her medical degree in August 2022. In September 2022 she started working as a residence not in training at the Franciscus and Vlietland Hospital, Rotterdam, The Netherlands. After finishing her Ph.D., she will pursue her career as an internist.