Red alert for women’s heart: the urgent need for more research and knowledge on cardiovascular disease in women

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A recent report of the EuroHeart project has shown that women are still underrepresented in many cardiovascular clinical trials, while important gender differences are present within most areas of heart disease. As the burden of cardiovascular disease is increasing in middle-aged women relative to men, a more profound understanding is needed of the fundamental biological differences that exist between men and women. In the current review, we aim to address the need for more explanatory sex-specific cardiovascular research to be able to adapt existing guidelines for a better heart health in women.

Keywords: Atherosclerosis • Gender • Hormones • Risk factors • Women

Cardiovascular health needs more female-specific attention

The economic burden of cardiovascular disease (CVD) in Europe is progressively expanding with an increase in the incidence of obesity and diabetes, due to low adherence to a healthy lifestyle and poor control of CVD risk factors.¹ The risk of heart disease in women has been underestimated in the past due to the misperception that females are ‘protected’ against CVD.² Although clinical manifest CVD develops 7–10 years later in women than in men, it is the major cause of death in women older than 65 years of age (Figure 1). According to the latest World Health Organization (WHO) statistics the burden of CVD will increase further to 2030 and a large part of disability-adjusted life years (DALYs) will involve inhabitants of the Eastern and Central European Countries and in the developing countries such as Asia, Latin-America, and the Middle-East.³ In Figure 2 world-wide DALYs in women >45 years are represented according to diseases and income level. Recent data from the National Health and Nutrition Examination Surveys (NHANES) have shown that over the past two decades the prevalence of myocardial infarctions has increased in midlife (35–54 years) women, while declining in similarly aged men.⁴ Parallel with the rise in blood pressure and cholesterol levels after menopause there is almost a doubling in the prevalence of stroke among middle-aged women. As was demonstrated across Europe in the EUROASPIRE III survey,
modifiable lifestyle factors have aggravated and especially young women have taken up smoking habits and women have a higher increase in the prevalence of diabetes and hypertension than men, with its consequences for CVD incidence and prevalence.\textsuperscript{5}

In the report from the European Heart Health Strategy (Euro-Heart), it has been concluded that women are currently still under-represented in research in many important areas of cardiology.\textsuperscript{5} The mean percentage of women enrolled in cardiovascular clinical trials since 2006 was 30%, while only 50% of trials reported results by gender analysis. The latest US guidelines on CVD prevention in women include recommendations that are based on research conducted predominantly in men.\textsuperscript{7,8} Less evidence-based preventive, diagnostic, and therapeutic options for women with CVD may lead to under treatment and a lower quality of care in comparison with men. Moreover, female-specific issues related to pregnancies and hormonal changes during menopause are important in the

\begin{figure}[h]
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\includegraphics[width=\textwidth]{figure1.png}
\caption{Death rates in Europe, men and women \textless{}75 years of age; www.ehnheart.org/cdv-statistics.html, reprinted with permission from the World Health Organization.}
\end{figure}
occurrence of CVD throughout a woman’s life and will need more attention.9 The many biological differences that exist between the sexes, from basic research to responses on medical therapies, are important within the whole range of CVD and translates into socio-cultural behavioural differences (‘gender’) between men and women. A therefore more gender-specific approach to CVD is needed with specific attention to cardiovascular health in women.10 As it was emphasized in the conclusions of the EuroHeart project, this will need commitments from a broad range of researchers, medical practitioners, and European policy makers.6

Key questions concerning gender differences in cardiovascular disease

Ischaemic heart disease and stroke

Sex differences in the pathophysiology of atherosclerosis and vascular dysfunction

Combinations of inflammatory and thrombotic processes are involved in the progression of atherosclerotic disease in both men and women, whereas the role of endogenous oestrogen status in delaying the onset of atherosclerosis in women is still under debate.11–13 Inflammatory diseases, such as rheumatic disorders, are more prevalent in ageing women compared with men and may be more involved in the progression of atherosclerosis in females.14 Although atherosclerotic plaque composition changes throughout menopause transition and women have more inflammation in the coronary arteries than men, it is hypothesized that the progression of atheromas into more vulnerable plaques develops slower in women at middle age with a more diffuse pattern of atherosclerosis and outward remodelling.15–17 Plaque erosions are often seen in women with acute coronary syndromes (ACSs) at younger ages, while in men and older women the classical pattern of plaque rupture and subsequent thrombus formation is more common.18 Plaque erosions may further lead to distal embolization of microemboli and dysfunction of the microvascular coronary system. Women exhibit ACS with open coronary arteries more frequently than men.17 Further, microvascular dysfunction leading to subendocardial ischaemia in the presence of open coronary arteries may play a greater role in women than in men.20–22 In the carotid arteries, women also have a lower atheroma burden and more stable plaques than men, which may explain their more favourable outcomes for conservative treatment in symptomatic carotid stenosis.23,24 The gender differences in atherosclerotic disease progression at middle age are yet incompletely understood and will need more exploration to be translated into clinical practice.

Gender differences in cardiovascular risk factors

Data from the INTERHEART study indicate that the lower ACS prevalence among women at younger ages (<60 years) is largely explained by a lower risk factor burden.25 Although women and men share most classic CVD risk factors, the significance and the relative weighting of these factors are different.26,27 Smoking has a particularly harmful effect in young women with a 60% increased risk for ischaemic heart disease (IHD) when compared with men.28 This was not confirmed however in the INTERHEART study, possibly due to socio-cultural behaviour differences in various parts of the world. With the increase in smoking rates in younger women, not only in Europe but also in the developing countries, reinforcement of healthy lifestyle behaviour in these vulnerable age-groups becomes more important. Systolic blood pressure rises more steeply in ageing women compared with men.5,29–31 Hypertension is more prevalent in older women than in men and strongly associated with their higher prevalence of strokes, left ventricular hypertrophy, and diastolic heart failure (HF). But even moderate or borderline hypertension (<140/90 mmHg) causes more endothelial dysfunction and cardiovascular complications in females than in men.32 Type 2 diabetes has a greater risk for cardiovascular complications in women than in men. In a meta-analysis of 37 prospective cohort studies, the risk of fatal IHD was 50% higher in women with diabetes compared with men.33 The reason for this higher mortality is...
multi-factorial and related to a heavier risk factor burden, more involvement of inflammatory factors, a more diffuse atherosclerosis throughout the coronary arteries, and more small vessel disease with an often less aggressive treatment of diabetes in women.47,48,54 Further, especially in women it has been shown that type 2 diabetes is a potent, independent risk factor for HF which cannot be fully explained by coexisting cardiovascular risk factors or previous myocardial infarctions.36,37 At younger age, the prevalence of hypercholesterolaemia is lower in women compared with men, but above 65 years of age mean LDL-cholesterol is higher in women.38 Hypertriglyceridaemia and low HDL-C are more important risk factors of CVD for women than for men.39 It has to be further explored whether targeting of these lipid abnormalities may be useful in women at elevated risk. When focusing on gender aspects of the metabolic syndrome (MetS), the relative risk of insulin resistance, hypertension, and elevated hs-C-reactive protein levels is higher in women than in men.40,41

Female-specific risk factors

It has been thought for decades that the oestrogen drop during menopausal transition induces increased post-menopausal CVD risk in women, probably through harmful changes in CVD risk factors. Healthy women with a more rapid transition through menopause show a higher rate of carotid intima-media thickness progression.42 Women with an early menopause (<40 years) have a 2-years lower life expectancy compared with women with a normal or late menopause.13 Circulating oestrogens do have a regulating effect on several metabolic factors, such as lipids, inflammatory markers, and the coagulation system. They also promote a direct vasodilating effect through the α- and β-receptors in the vessel wall.43 Oestrogen causes vasodilatation by a rapid (5–20 min) activation of nitric oxide synthesis in endothelial cells. The logical consequent hypothesis that replacing endogenous estrogens by exogenous estrogens in post-menopausal women would decrease CVD risk, supported by many observational studies, could not be proved in large randomized trials.44–46 In contrast, hormone therapy (HT) has been shown to increase CVD event rate in older (>60 years) post-menopausal women and its use is not recommended for the primary and secondary prevention of CVD.47 Many hypotheses have been raised to explain the discrepant findings between observational and experimental studies, such as the age of the women and the health status of the endothelium at HT initiation. Healthy endothelium is sensitive to oestrogens, whereas endothelium damaged by atherosclerotic disease is not.48 Hormone therapy increases brachial artery blood flow in healthy post-menopausal women but not in elderly women and in women with multiple cardiovascular risk factors or manifest CVD.49 As an alternative explanation, it has been postulated that early onset atherosclerosis per se may be more important determinants of menopausal age, either through direct damage to the ovarian vasculature or indirectly through an adverse impact on the endocrine system.30,51 Recently, it has also been suggested that vasomotor symptoms (VMSs) during menopause may be crucial for sensitivity to beneficial effects of HT.52 Vasomotor symptoms have now been shown to be associated with a worse cardiovascular risk profile and also with increased coronary heart disease risk but more data are needed to evaluate this hypothesis.53,54

Although several studies have demonstrated that hormonal dysfunction in pre-menopausal women, and in particular the androgen excess as present in women with polycystic ovary syndrome (PCOS) is associated with an increased risk of atherosclerosis and IHD events, it is still unclear whether the PCOS is an independent risk factor for atherosclerosis.55,56

Evidence is increasing that pregnancy may be considered as a ‘stress-test’ for future CVD risk. Hypertensive disorders in pregnancy have been shown to be predictors for hypertension and CVD events.57,58 Women with a placental syndrome in combination with poor foetal growth or intrauterine death are considered to be at the greatest risk.59 Further, an impaired glucose tolerance during pregnancy and gestational diabetes are female-specific risk factors for the development of diabetes and the MetS in relatively young women.60,61 The obstetric history is not yet included in the guidelines for CVD prevention in women, but a healthy lifestyle after index-pregnancy is recommended.62 Thus far, most female-specific risk factors are not included in the guidelines for CVD prevention in women, as their causative impact on women’s risk and their added predictive value to the current components of the guidelines are still not elucidated.

Gender differences in psychosocial factors

Observational studies indicate that psychological factors strongly influence the course of IHD.63,64 Coping with stress and emotions as well as depression and anxiety disorders are more associated with elevated CVD risk among women than men. Alterations in autonomic function, as measured by heart rate variability, have been associated with prothrombotic changes in women with IHD.65 Women more often have a lower socio-economic status than men that negatively affects a healthy lifestyle behaviour and the occurrence of obesity and other cardiovascular risk factors. The combination of work and marital stress has also been associated with an increased risk in CVD events in females.66 The acute stress-induced cardiomyopathy (Tako-Tsubo) is more than nine times prevalent in older women than in men and may occur more frequently than it is currently diagnosed.67,68 The aetiology of this syndrome is still unknown, but depression and anxiety disorders may play an important role.69 A lower social support after CVD events affects prognosis and health status particularly in women.70 On the other hand, group-based psychosocial intervention programmes may improve survival in women with IHD.71 The importance of behavioural factors has been adopted in the latest ESC guidelines for CVD prevention, but a more gender-specific approach to cardiology patients will be needed in education and training of healthcare providers.72

Ischaemic heart disease detection in women

Sex differences in symptom presentation of stable IHD are common in daily practice, but the awareness of CVD health risk in women among healthcare givers is relative low and women are often misunderstood for their symptoms.73 Differences in atherosclerotic disease progression between middle-aged men and women may translate into a more ‘atypical’ symptom presentation in women when compared with the classical pattern in
males. As the chance of having obstructive coronary lesions increases in ageing women, symptoms of angina pectoris become more comparable with their male counterparts. Women <55 years of age are an important subset of patients with missed diagnoses of ACS at the emergency departments. At all ages women present less often with chest pain when having an ACS with more concomitant vaso-vegetative symptoms relative to men. In the European Heart Survey on stable angina pectoris an important gender bias in the use of investigations and evidence-based medical therapy was found. This may be (partially) caused by the limitations of current non-invasive and invasive imaging modalities when applied to women. Coronary angiography is the golden standard to detect obstructive CAD, but may be less suited in women at middle age because an abnormal vascular reactivity may contribute relatively more to symptoms than the presence of stenoses. As was shown in the Women’s Ischemia Syndrome Evaluation Study (WISE), additional coronary flow reserve measurements (CFR) may reveal abnormal coronary vasoreactivity in women with anginal symptoms and non-obstructive CAD. Further, with the use of intravascular ultrasound (IVUS) an increased thrombotic activity has been found in women presenting with stable and unstable coronary syndromes. A more frequent application of CFR measurements and IVUS in females to routine coronary angiography may add to a better understanding of their clinical presentation with anginal symptoms. However, the use of these more advanced intracoronary imaging techniques is merely limited to experienced interventional centres. To improve a more widespread clinical assessment of IHD in women, advanced non-invasive imaging modalities, such as MR perfusion imaging, radionuclide imaging and computed tomographic angiography (CCTA), should be more promoted for focusing on IHD detection in females.

Gender differences in treatment and outcomes of acute coronary syndromes

While in STEMI both genders have equal benefit of early percutaneous coronary interventions, therapeutic strategies in low-risk non-STEMI patients show differences between men and women. In the FRISC II and RITA 3 trials, early invasive strategy of patients with biomarker negative unstable angina or low-risk non-STEMI ACS was proved to reduce mortality in men, but not in women. Analyses of sex-based differences in outcomes after ACS have revealed conflicting results. In-hospital mortality rates in young women with ACS are significantly higher compared with similarly aged men. In a recent large meta-analysis of 11 randomized ACS trials, it was shown that sex-based differences in 30-day mortality among patients with various manifestations of ACS are largely explained by clinical differences at presentation and the severity of angiographically documented disease. Women with ACS are generally older with more clustering of risk factors that may contribute to their higher risk in mortality. Gender bias in treatment and sex-related disparities in vascular flow and structure may further add to this increased mortality. While women with ACS have less extensive obstructive and more diffuse coronary artery disease compared with men, the mortality and event rates in non-obstructive coronary artery disease are higher in women. This so-called ‘gender-paradox’ is still incompletely understood. In the WISE study, a combination of elevated inflammatory biomarkers was found to be related to IHD outcomes in women, independent of traditional cardiovascular risk factors. Further, women have less collateral flow and CFR and more signs of microvascular dysfunction that may interfere with a worse prognosis. After coronary interventions, especially when glycoprotein IIb/IIIa inhibitors are used, women have more bleeding complications relative to men.

Treatment and outcomes of stable coronary syndromes in women

Symptoms of chest pain are more prevalent in women than in men and often lead to frequent hospitalizations and repeated use of coronary angiograms. However, the prognosis of women with recurrent chest pain without obstructive CAD is less benign than previously considered and strongly depends on the number of cardiovascular risk factors that are present. The 5-years IHD event risk of symptomatic women with non-obstructive CAD is almost 50% higher compared with symptomatic women with normal coronary arteries. It is therefore important that women with recurrent anginal symptoms are screened for their risk factors and that they are treated according to the latest guidelines for secondary prevention. Concomitant prescription of medications for symptom relief of angina pectoris is equally important, including antiplatelet therapy with aspirin. Many women without obstructive CAD but objective signs of ischaemia have endothelial dysfunction of their microvascular coronary system. The relationship between microvascular dysfunction and epicardial atherosclerosis is yet not fully understood and will need more exploration in the future.

Gender differences in thrombosis

Gender differences in coronary thrombosis are still rather unexplored and involve platelet activity, the coagulation cascade and the fibrinolytic system. At the initial stages of atherosclerotic plaque formation increased functional activity of many coagulation proteins is detectable. The interaction of these components may be different among men and women within different age-groups and within various vascular beds. In pre-menopausal women platelet activity is less thrombotic compared with post-menopausal women, presumably related to the presence of oestrogen β-receptors on the platelet surface area, and levels of coagulation factors change throughout menopause transition. Women experience many fluctuations in thrombotic activity in their life-times during menstrual cycle, with the use of oral contraceptives, in pregnancies and after menopause. Genetic polymorphisms in women may interact with circulating oestrogen levels and increase the risk of thrombosis. In the Womens’ Health Study, it was found that primary prevention of ACS with aspirin in women is not useful <65 years of age, while its preventive effect has been demonstrated in men. In a meta-analysis of six randomized primary prevention trials, the risk of CVD events was significantly reduced independent from sex. However, the benefit was different for men and women showing significant reductions for ACS in men and for ischaemic stroke in women, suggesting differences dependent on various vascular beds. For ADP receptor blockers, including clopidogrel and prasugrel, a
meta-analysis showed a less profound reduction in any CVD events in women vs. men, for the combination of aspirin and clopidogrel in comparison with aspirin alone. Whether this effect is the result of chance or variation in sex-related biological effects remains uncertain. During atrial fibrillation women who are not using anticoagulants have an almost two times higher intrinsic risk of stroke and thrombo-embolism relative to men. This has resulted yet in an adaptation to the most recent European guidelines on atrial fibrillation. There are no apparent major differences in recurrent thrombosis or bleeding risk between men and women being treated with vitamin K antagonists. This may for a large part be explained by the dose adjustment based on international normalized ratio. The available data for novel oral anticoagulants including dabigatran and rivaroxaban do not suggest sex-dependent differences in recurrent thrombotic events or bleeding. However, these data are still confined to relative short-term follow-up observation. Our understanding of gender differences with regard to antithrombotic strategies in heart disease is currently still limited and will need more exploration to be able to provide more optimized therapy in women.

Heart failure
Gender differences in epidemiology and aetiology
The prevalence of HF in the European population is between 2 and 3% and rises sharply at 75 years of age. In 70- to 80-year-old people its occurrence is estimated at 10–20%. More than half of all patients with HF are females and given their longer life expectancy the proportion of elderly women with HF will further increase. Women more often have HF with a preserved ejection fraction due to hypertension and diabetes while men more frequently present with systolic HF due to ischaemia and/or previous myocardial infarctions. These major causal gender differences in HF are still insufficiently recognized in clinical practice. Gender-related issues on HF were even barely addressed in the latest 2008 ESC guidelines. Left ventricular remodelling shows differences between men and women: while pressure overload leads to more fibrosis and dilatation in men, women tend to have smaller hearts with more hypertrophy. Animal studies, as well as measurements in human hearts suggest that the interaction of female sex and oestrogen may prevent the up-regulation of collagen in female pressure-overloaded human hearts. More gender-specific patterns in gene expression during progression of HF have been identified.

Other potential causes for (subclinical) HF in women, such as peripartum cardiomyopathy and LV dysfunction due to adjuvant chemotherapy for breast cancer, remain often unrecognized and will need better surveillance in clinical practice and attention in the guidelines. Women more frequently have dysfunction of the thyroid than men, but its role in inducing (subclinical) cardiomyopathies is still controversial.

Gender differences in diagnosis, treatment, and outcomes of heart failure
Signs and symptoms of HF may be difficult to interpret in women, especially in obese subjects and elderly females. Tiredness and fatigue are often reported symptoms that may easily be attributed to psychosocial-related factors. In the first European Heart Survey on HF there was a significant under-use of echocardiography, especially in women with a lower adherence to evidence-based medication. In the second European Heart Survey, however, an important improvement in the use of diagnostic procedures and medical treatment was established. Gender differences in response to HF therapy have been reported: in a post hoc analysis of the DIG-trial in patients with systolic HF, it was shown that digoxin treatment increases mortality in women compared with placebo, whereas not in men. In most studies on HF a better survival was demonstrated in women relative to men. Although women seem to benefit more from biventricular/ICD therapy, they receive less often devices and have more procedure-related adverse events and bleeding complications. No data are available yet on biventricular/ICD therapy in patients with preserved ejection fractions. In women with peripartum cardiomyopathy, successful new developments with prolactine treatment have been reported. The broad spectrum of underlying aetiologies of HF and their different clinical presentation within both genders is a challenge for future research.

Strategies to improve perspectives of cardiovascular disease in women
As CVDs are the most important causes of death in women in the Western world and its prevalence is increasing rapidly in many developing countries, important steps forward have to be established in the coming years to improve cardiovascular health in females. This implicates in the first place that governmental support is needed to put research efforts that are especially targeted for women on the agenda. Additional public health efforts are needed to increase awareness among women and healthcare givers about their CVD risk. More educational programmes on gender-specific aspects of cardiovascular care are needed on the level of cardiologists, gynaecologists, general practitioners, medical students, nurses, and other relevant workers in

Table 1 Strategies to improve perspectives of cardiovascular disease in women

| Governmental support to encourage more cardiovascular research in women |
| Public health efforts to increase awareness cardiovascular disease risk in women |
| Development educational programmes on gender differences cardiovascular diseases |
| Standardized registration of gender differences in cardiovascular care |
| More interaction among various medical disciplines involved in women’s health |
| More gender-specific analysis and higher enrolment of women in clinical trials |
| Use of appropriate study designs and statistical tools to detect gender effects |
| Improve sensitivity and specificity for symptom evaluation of cardiovascular disease in women |
| Provide gender-specific data in all guidelines on cardiovascular disease |
| Implementation of gender-specific strategies in clinical practice |
Female-specific research and clinical programmes should aim at a more multidisciplinary approach to cardiovascular health in women, such as interaction with gynaecologists, obstetricians, endocrinologists, psychologists, etc. First multidisciplinary initiatives have been undertaken for multidisciplinary risk management in perimenopausal women. Programmatic efforts may be developed to improve detection or tracking of gender differences in cardiovascular care (e.g. electronic health records tracking gender-specific mortality rates by region or country across diagnostic codes). In clinical studies, measures should become standard to include more women with appropriate steps in study design and analysis. If applicable, inclusion of specific markers of disease in women may be considered with sufficient power for the analysis. The longer life expectancy of women has to be considered when the natural course of diseases is discussed. Recommendations on proposed strategies to improve cardiovascular health in women are summarized in Table 1.

Priorities to ameliorations in cardiovascular care for women should be discussed within multidisciplinary teams, with a focus on the greatest threats to cardiovascular health in women that are to be expected in the upcoming years. The growing burden of obesity for instance, will have an enormous impact on the occurrence of diabetes, hypertension, IHD, and HF in women. More efforts should be undertaken to implement existing secondary prevention guidelines in females after coronary events. The current SCORE guidelines have comparable limitations to the Framingham guidelines for primary prevention in women and tend to underestimate CVD risk in especially the younger age-groups. Improvements in symptom evaluation of IHD and diagnostic strategies in women are needed on the short term as symptomatic females are often misdiagnosed in daily clinical practice. Gender-related differences are also important in other fields of Cardiology, such as cardiac arrhythmias, that we have not discussed further in this paper. With this ‘red alert’ for woman’s heart we aimed to emphasize the need for more specific attention and research on female aspects of cardiovascular care (summary in Table 2).

**Table 2 Gender differences in cardiovascular disease**

<table>
<thead>
<tr>
<th>Subject</th>
<th>Important aspects in women (relative to men)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Epidemiology</strong></td>
<td>7–10 years later onset cardiovascular disease\nMore DALYs lost to cardiovascular disease at older age</td>
</tr>
<tr>
<td><strong>Atherosclerosis</strong></td>
<td>Inflammation and oxidative stress\nLower atheroma burden at younger ages (&lt; 65 years)\nOestrogens involved in plaque composition/vascular function\nVascular dysfunction and small vessel disease\nACS with ‘normal’ or non-obstructive CAD\nMore plaque erosions than plaque ruptures at ACS</td>
</tr>
<tr>
<td><strong>Heart failure</strong></td>
<td>Hypertension and diabetes main causes of heart failure\nPredominant heart failure with preserved LVEF\Ageing women more LVH (men more fibrosis)</td>
</tr>
<tr>
<td><strong>Thrombosis</strong></td>
<td>Changes platelet activity, coagulation factors, fibrinolytic activity related to hormone status pre-/post-menopause, pregnancy, etc.\nIncreased risk thrombosis with AF</td>
</tr>
<tr>
<td><strong>Risk factors</strong></td>
<td>Hypertension\nHigher prevalence at older age\nHigher association with strokes, LVH, and diastolic heart failure\nDiabetes\n&gt;50% higher CVD mortality\nDiffuse atherosclerosis, higher co-morbidity\nIndependent risk factor for heart failure</td>
</tr>
<tr>
<td><strong>Lips</strong></td>
<td>Low HDL and elevated TG more related to CVD\nIncrease total cholesterol and LDL-C after menopause</td>
</tr>
<tr>
<td><strong>Sex-related risk factors</strong></td>
<td>Pregnancy-related hypertension and gestational diabetes\Hormonal dysfunction pre-menopause/PCOS/POF\Menopause</td>
</tr>
<tr>
<td><strong>Life-style and psychosocial factors</strong></td>
<td>Smoking &lt;55 years higher risk ACS\Obesity/physical inactivity\Anxiety/stress\Lower socio-economic status</td>
</tr>
<tr>
<td><strong>Diagnosis</strong></td>
<td>Differences in symptom presentation/communication\More angina with less obstructive CAD\Lower sensitivity and specificity non-invasive testing</td>
</tr>
<tr>
<td><strong>Therapy</strong></td>
<td>Gender differences effectivity/interaction/side effects</td>
</tr>
</tbody>
</table>

**Conflict of interest:** none declared.
References


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