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REVIEW

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,

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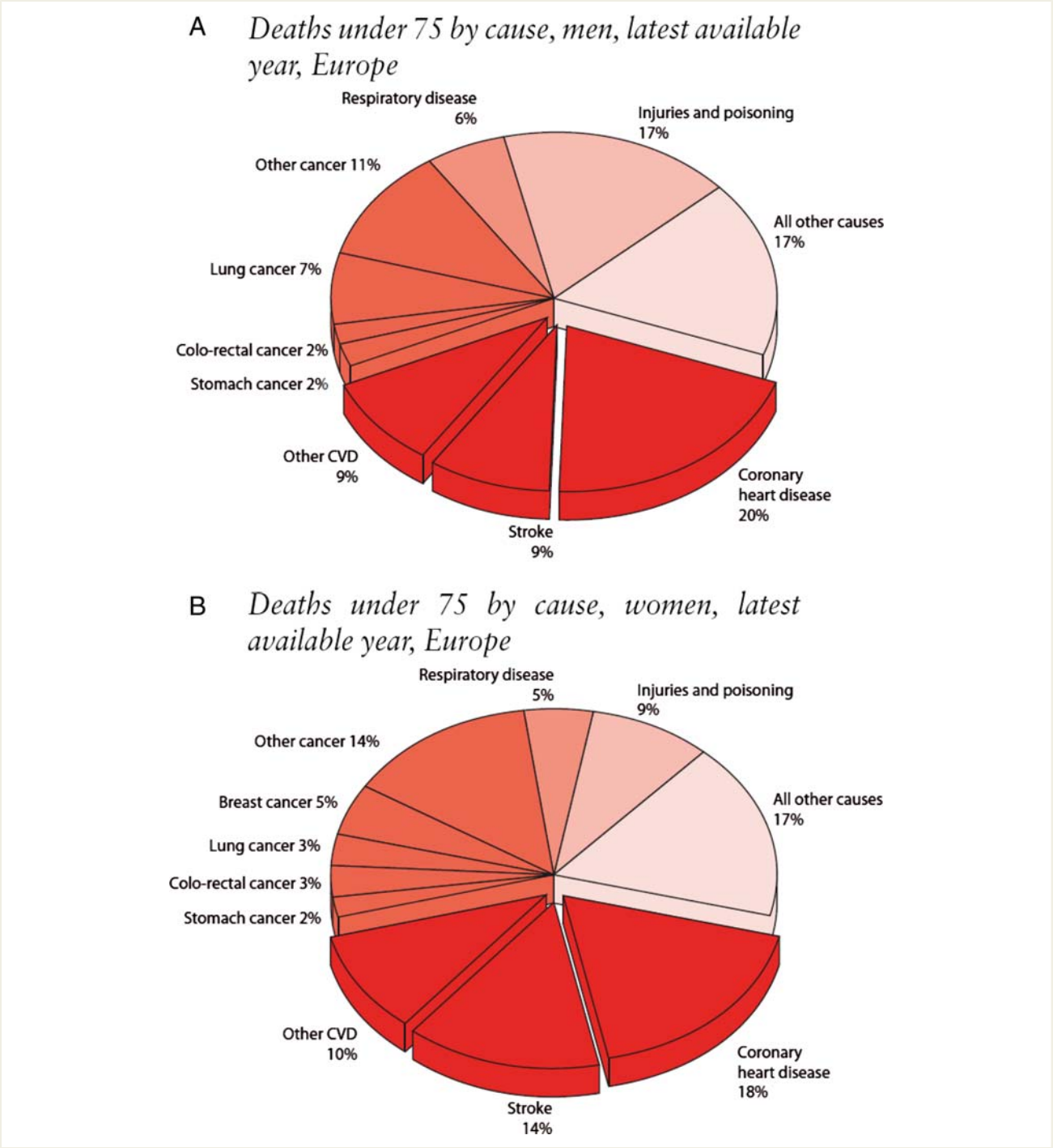

Figure 1 Death rates in Europe, men and women <75 years of age; www.ehnheart.org/cdv-statistics.html, reprinted with permission from the World Health Organization.

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.[5]

In the report from the European Heart Health Strategy (EuroHeart), it has been concluded that women are currently still underrepresented in research in many important areas of cardiology.[6] 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.[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

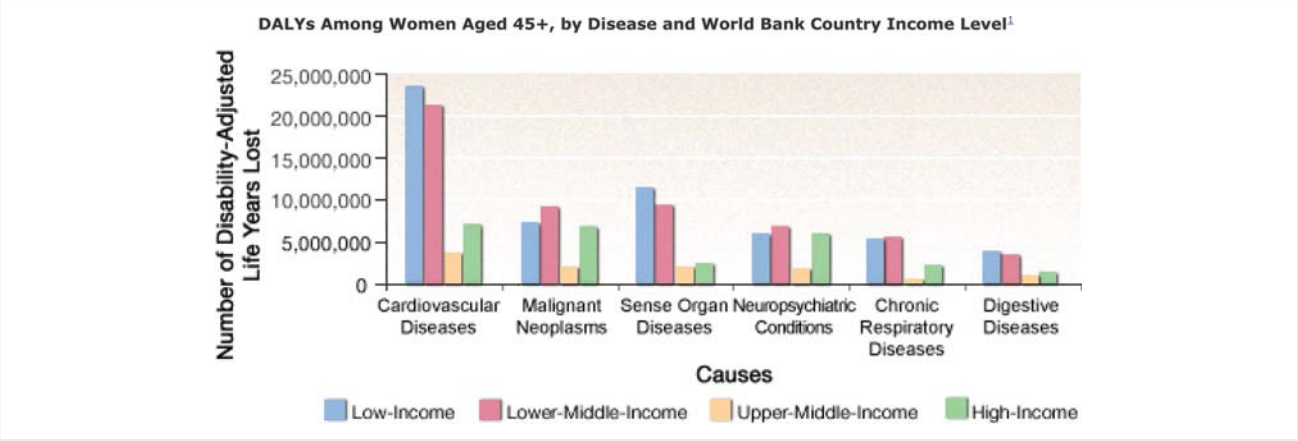

Figure 2 World-wide disability-adjusted life years among women aged 45+ by disease and income level; http://www.globalhealth.org/womens_health/global_view/, reprinted with permission from the World Health Organization.

occurrence of CVD throughout a women'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 Euro-Heart 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.[19] 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.[34,35] 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.[50,51] 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.[7,62] 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.[17,74] 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.[75] At all ages women present less often with chest pain when having an ACS with more concomitant vaso-vegetative symptoms relative to men.[76,77] 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.[78] This may be (partially) caused by the limitations of current non-invasive and invasive imaging modalities when applied to women.[79–81] 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.[82] 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.[83] Further, with the use of intravascular ultrasound (IVUS) an increased thrombotic activity has been found in women presenting with stable and unstable coronary syndromes.[84] 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.[85,86]

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.[87,88] 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.[89,90] 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.[91] Women with ACS are generally older with more clustering of risk factors that may contribute to their higher risk in mortality.[92] 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.[93,94] 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.[94] Further, women have less collateral flow and CFR and more signs of microvascular dysfunction that may interfere with a worse prognosis.[17] After coronary interventions, especially when glycoprotein IIb/IIIa inhibitors are used, women have more bleeding complications relative to men.[82,95]

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 recurrent hospitalizations and repeated use of coronary angiograms.[17,96,97] 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.[21,93,97,98] 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.[93] 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.[99] Many women without obstructive CAD but objective signs of ischaemia have endothelial dysfunction of their microvascular coronary system.[17,19] 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.[100] The interaction of these components may be different among men and women within different age-groups and within various vascular beds.[101] 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.[102,103] 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.[104] 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.[105,106] In a meta-analysis of six randomized primary prevention trials, the risk of CVD events was significantly reduced independent from sex.[107] 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.[108] 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.[109] This has resulted yet in an adaptation to the most recent European guidelines on atrial fibrillation.[110] 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.[108] 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%.[111,112] 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.[113–115] 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.[112] 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.[116,117] 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.[118] More gender-specific patterns in gene expression during progression of HF have been identified.[119]

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.[120–122] Women more frequently have dysfunction of the thyroid than men, but its role in inducing (subclinical) cardiomyopathies is still controversial.[123,124]

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.[125] In the second European Heart Survey, however, an important improvement in the use of diagnostic procedures and medical treatment was established.[126] 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.[127] In most studies on HF a better survival was demonstrated in women relative to men.[128,129] 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.[130,131] 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.[121] 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

Table 2 Gender differences in cardiovascular disease

Subject	Important aspects in women (relative to men)
Epidemiology	7–10 years later onset cardiovascular disease More DALYs lost to cardiovascular disease at older age
Atherosclerosis	Inflammation and oxidative stress Lower atheroma burden at younger ages (<65 years) Oestrogens involved in plaque composition/vascular function Vascular dysfunction and small vessel disease ACS with 'normal' or non-obstructive CAD More plaque erosions than plaque ruptures at ACS
Heart failure	Hypertension and diabetes main causes of heart failure Predominant heart failure with preserved LVEF Ageing women more LVH (men more fibrosis)
Thrombosis	Changes platelet activity, coagulation factors, fibrinolytic activity related to hormonestatus pre-/post-menopause, pregnancy, etc. Bleeding complications after interventions Increased risk thrombosis with AF
Risk factors	Hypertension Higher prevalence at older age Higher association with strokes, LVH, and diastolic heart failure Diabetes >50% higher CVD mortality Diffuse atherosclerosis, higher co-morbidity Independent risk factor for heart failure Lipids Low HDL and elevated TG more related to CVD Increase total cholesterol and LDL-C after menopause
Sex-related risk factors	Pregnancy-related hypertension and gestational diabetes Hormonal dysfunction pre-menopause/PCOS/POF Menopause
Life-style and psychosocial factors	Smoking <55 years higher risk ACS Obesity/physical inactivity Anxiety/stress Lower socio-economic status
Diagnosis	Differences in symptom presentation/communication More angina with less obstructive CAD Lower sensitivity and specificity non-invasive testing
Therapy	Gender differences effectivity/interaction/side effects

healthcare.[10] 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.[132,133] 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.[134] 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.[72] 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*).

Conflict of interest: none declared.

References

1. Atella V, Brady A, Catapano AL, Critchley J, Graham IM, Hobbs FD, Leal J, Lindgren P, Vanuzzo D, Volpe M, Wood D, Paoletti R. Bridging science and health policy in cardiovascular disease: focus on lipid management. *Atherosclerosis* 2009;**10**(suppl):3–21.
2. Healy B. The Yentl syndrome. *N Engl J Med* 1991;**325**:274–276.
3. www.GBD_report_2004update_full.pdf.
4. Towfighi A, Zheng L, Ovbiagele B. Sex-specific trends in midlife coronary heart disease risk and prevalence. *Arch Intern Med* 2009;**169**:1762–1766.
5. Kotseva K, Wood D, De Backer G, De Bacquer D, Pyörälä K, Keil U, for the EUROASPIRE Study Group. Cardiovascular prevention guidelines in daily practice: a comparison of EUROASPIRE I,II, and III surveys in eight European countries. *Lancet* 2009;**373**:929–940.
6. Stramba-Badiale M. Women and research on cardiovascular diseases in Europe: a report from the European Heart Health Strategy (EuroHeart) project. *Eur Heart J* 2010;**31**:1677–1681.
7. Mosca L, Banka CL, Benjamin EJ, Berra K, Bushnell C, Dolor RJ, Ganiats TG, Gomes AS, Gornik HL, Gracia C, Gulati M, Haan CK, Judelson DR, Keenan N, Kelepouris E, Michos ED, Newby LK, Oparil S, Ouyang P, Oz MC, Petitti D, Pinn VW, Redberg RF, Scott R, Sherif K, Smith SC Jr, Sopko G, Steinhorn RH, Stone NJ, Taubert KA, Todd BA, Urbina E, Wenger NK; Expert Panel/Writing Group; American Heart Association; American Academy of Family Physicians; American College of Obstetricians and Gynecologists; American College of Cardiology Foundation; Society of Thoracic Surgeons; American Medical Women's Association; Centers for Disease Control and Prevention; Office of Research on Women's Health; Association of Black Cardiologists; American College of Physicians; World Heart Federation; National Heart, Lung, and Blood Institute; American College of Nurse Practitioners. Evidence-based guidelines for cardiovascular disease prevention in women: 2007 update. *Circulation* 2007;**115**:1481–1501.
8. Melloni C, Berger JS, Wang TY, Gunes F, Stebbins A, Pieper KS, Dolor RJ, Douglas PS, Mark DB, Newby LK. Representation of women in randomized clinical trials of cardiovascular disease prevention. *Circ Cardiovasc Qual Outcomes* 2010;**3**:135–142.
9. Regitz-Zagrosek V. Therapeutic implications of the gender-specific aspects of cardiovascular disease. *Nat Rev Drug Discov* 2006;**5**:425–439.
10. Kim AM, Tingen CM, Woodruff TK. Sex bias in trials and treatment must end. *Nature* 2010;**465**:688–689.
11. Kleijn de MJ, Schouw van der YT, Verbeek AL, Peeters PH, Banga JD, Graaf van der Y. Endogenous estrogen exposure and cardiovascular mortality risk in postmenopausal women. *Am J Epidemiol* 2002;**155**:339–345.
12. Hu FB, Grodstein F, Hennekens CH, Colditz GA, Johnson M, Manson JE, Rosner B, Stampfer MJ. Age at natural menopause and risk of cardiovascular disease. *Arch Intern Med* 1999;**159**:1061–1066.
13. Ossewaarde ME, Bots ML, Verbeek AL, Peeters PH, van der Graaf Y, Grobbee DE, van der Schouw YT. Age at menopause, cause-specific mortality and total life expectancy. *Epidemiology* 2005;**16**:556–562.
14. Avalos I, Rho YH, Chung CP, Stein CM. Atherosclerosis in rheumatoid arthritis and systemic lupus erythematosus. *Clin Exp Rheumatol* 2008;**26**(5 Suppl 51): S5–S13.
15. Burke AP, Farb A, Malcolm G, Virmani R. Effect of menopause on plaque morphologic characteristics in coronary atherosclerosis. *Am Heart J* 2001;**141**: S58–S62.
16. Frink RJ. Gender gap, inflammation and acute coronary disease: are women resistant to atheroma growth? Observations at autopsy. *J Invasive Cardiol* 2009; **21**:270–277.
17. Shaw LJ, Bugiardini R, Bairey Merz CN. Women and ischemic heart disease. Evolving knowledge. *J Am Coll Cardiol* 2009;**54**:1561–1575.
18. Burke AP, Farb A, Malcolm GT, Liang Y, Smialek J, Virmani R. Effect of risk factors on the mechanism of acute thrombosis an sudden coronary death in women. *Circulation* 1998;**97**:2110–2126.
19. Bugiardini R, Bairey Merz CN. Angina with 'normal' coronary arteries: a changing philosophy. *JAMA* 2005;**293**:477–484.
20. Buchthal SD, den Hollander JA, Merz CN, Rogers WJ, Pepine CJ, Reichek N, Sharaf BL, Reis S, Kelsey SF, Pohost GM. Abnormal myocardial phosphorus-31 nuclear magnetic resonance spectroscopy in women with chest pain but normal coronary angiograms. *N Engl J Med* 2000;**342**:829–835.
21. Johnson BD, Shaw LJ, Buchthal SD, Bairey Merz CN, Kim HW, Scott KN, Doyle M, Olson MB, Pepine CJ, den Hollander J, Sharaf B, Rogers WJ, Mankad S, Forder JR, Kelsey SF, Pohost GM; National Institutes of Health-National Heart, Lung, and Blood Institute. Prognosis in women with myocardial ischemia in the absence of obstructive coronary disease: results from the National Institutes of Health- national Heart, Lung and Blood Institute-sponsored Women's Ischemia Syndrome Evaluation WISE). *Circulation* 2004; **109**:2993–2999.
22. Camici PG, Crea F. Coronary microvascular dysfunction. *N Engl J Med* 2007;**356**: 830–840.
23. Hellings WE, Pasterkamp G, Verhoeven BAN, de Kleijn DPV, de Vries JPPM, Seldenrijk KA, van den Broek T, Moll FL. Gender-associated differences in plaque phenotype of patients undergoing carotid endarteriectomy. *J Vasc Surg* 2007;**45**:289–297.
24. Hellings WE, Peeters W, Moll FL, Piers RD, van Setten J, Van der Spek PJ, de Vries JPPM, Seldenrijk KA, de Bruin PC, Vink A, Velema E, de Kleijn DP, Pasterkamp G. Composition of carotid atherosclerotic plaque is associated with cardiovascular outcome. A prognostic study. *Circulation* 2010;**121**: 1941–1950.
25. Anand SS, Islam S, Rosengren A, Franzosi MG, Steyn K, Yusufali AH, Keltai M, Diaz R, Rangarajan S, Yusuf S; INTERHEART Investigators. Risk factors for myocardial infarction in women and men: insights from the INTERHEART study. *Eur Heart J* 2008;**29**:932–940.
26. Tan YY, Gast GCM, van der Schouw YT. Gender differences in risk factors for coronary heart disease. *Maturitas* 2010;**65**:149–160.
27. Cooney MT, Dudina AL, Graham IA. Value and limitations of existing scores for the assessment of cardiovascular risk. *J Am Coll Cardiol* 2009;**54**:1209–1227.
28. Prescott E, Hippe M, Schnohr P, Hein HO, Vestbo J. Smoking and risk of myocardial infarction in women and men: longitudinal population study. *BMJ* 1998; **316**:1043–1047.
29. Burt VL, Whelton P, Roccella EJ, Brown C, Cutler JA, Higgins M, Horan MJ, Labarthe D. Prevalence of hypertension in the US adult population. Results from the Third National Health and Nutrition Examination Survey, 1988–1991. *Hypertension* 1995;**25**:305–313.
30. Staessen JA, van der Heijden-Spek JJ, Safar ME, Den Hond E, Gasowski J, Fagard RH, Wang JG, Struijker Boudier HA, van Bortel LM. Menopause and the characteristics of the large arteries in a population study. *J Hum Hypertens* 2001;**15**:511–518.
31. Coylewright M, Reckelhoff JF, Ouyang P. Menopause and hypertension. An age-old debate. *Hypertension* 2008;**51**:952–959.
32. Vasan RS, Larson MG, Leip EP, Evans JC, O'Donnell CJ, Kannel WB, Levy D. Impact of high-normal blood pressure on the risk of cardiovascular disease. *N Engl J Med* 2001;**345**:1291–1297.
33. Huxley R, Barzi F, Woodward M. Excess risk of fatal coronary heart disease associated with diabetes in men and women: meta-analysis of 37 prospective cohort studies. *BMJ* 2006;**332**:73–78.
34. Preis SR, Hwang SJ, Coady S, Pencina MJ, D'Agostino RB, Savage PJ, Levy D, Fox CS. Trends in all-cause and cardiovascular disease mortality among women and men with and without diabetes mellitus in the Framingham Heart Study, 1950–2005. *Circulation* 2009;**119**:1728–1735.
35. Aboyans V, Lacroix P, Criqui MH. Large and small vessels atherosclerosis: similarities and differences. *Prog Cardiovasc Dis* 2007;**50**:112–125.
36. De Simone G, Devereux RB, Chinali M, Lee ET, Galloway JM, Barac A, Panza JA, Howard BV. Diabetes and incident heart failure in hypertensive and normotensive participants of the Strong Heart Study. *J Hypertens* 2010;**28**:353–360.
37. Horwich TB, Fonarow GC. Glucose, obesity, metabolic syndrome and diabetes. Relevance to incidence of heart failure. *J Am Coll Cardiol* 2010;**55**:283–293.
38. Abbey M, Owen A, Suzakawa M, Roach P, Nestel PJ. Effects of menopause and hormone replacement therapy on plasma lipids, lipoproteins and LDL-receptor activity. *Maturitas* 1999;**33**:259–269.
39. Kannel WB, Castelli WP, Gordon T, McNamar PM. Serum cholesterol, lipoproteins, and the risk of coronary heart disease. The Framingham Study. *Ann Intern Med* 1971;**74**:1–12.
40. Regitz-Zagrosek V, Lehmkuhl E, Mahmoodzadeh S. Gender aspects of the role of the metabolic syndrome as a risk factor for cardiovascular disease. *Gend Med* 2007;**4**(suppl):S162–S177.
41. Wong ND, Pio J, Valencia R, Thakal G. Distribution of C-reactive protein and its relation to risk factors and coronary heart disease risk estimation in the National Health and Nutrition Examination Survey (NHANES) III. *Prev Cardiol* 2001;**4**: 109–114.
42. Johnson BD, Dwyer KM, Stanczyk FZ, Bitner V, Berga SL, Braunstein GD, Azziz R, Yang Y, Hale GE, Bairey Merz CN. The relationship of menopausal status and rapid menopausal transition with carotid intima-media thickness progression in women: a report from the Los Angeles atherosclerosis study. *J Clin Endocrinol Metab* 2010;**95**:4432–4440.
43. Mendelsohn ME, Karas RH. The protective effects of estrogen on the cardiovascular system. *N Engl J Med* 1999;**340**:1801–1811.
44. Stampfer MJ, Colditz GA. Estrogen replacement therapy and coronary heart disease: a quantitative assessment of the epidemiologic evidence. *Prev Med* 1991;**20**:47–63.
45. Hulley S, Grady D, Bush T, Furberg C, Herrington DM, Riggs B, Vittinghoff E. The Heart and Estrogen/progestin Replacement Study (HERS) research group.

Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. *JAMA* 1998;**280**:605–613.
46. Writing group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women. Principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002; **288**:321–333.
47. Manson JE, Hsia J, Johnson KC, Rossouw JE, Assaf AR, Lasser NL, Trevisan M, Black HR, Heckbert SR, Detrano R, Strickland OL, Wong ND, Crouse JR, Stein E, Cushman M. Women's Health Initiative investigators. Estrogen plus progestin and the risk of coronary heart disease. *N Engl J Med* 2003;**349**:523–534.
48. Mikkola TS, Clarkson TB. Estrogen replacement therapy, atherosclerosis and vascular function. *Cardiovasc Res* 2002;**53**:605–619.
49. Herrington DM, Espeland MA, Crouse JR III, Robertson J, Riley WA, McBurnie MA, Burke GL. Estrogen replacement and brachial artery flow-mediated vasodilatation in older women. *Arterioscler Thromb Vasc Biol* 2001;**21**: 1955–1961.
50. Kok HS, van Asselt KM, van der Schouw YT, van der Tweel I, Peeters PH, Wilson PW, Pearson PL, Grobbee DE. Heart disease risk determines menopausal age rather than the reverse. *J Am Coll Cardiol* 2006;**47**:1976–1984.
51. Matthews KA, Crawford SL, Chae CU, Everson-Rose SA, Sowers MF, Sternfeld B, Sutton-Tyrrell K. Are changes in cardiovascular disease risk factors in midlife women due to chronological aging or due to the menopausal transition? *J Am Coll Cardiol* 2009;**54**:2366–2373.
52. Van der Schouw YT, Grobbee DE. Menopausal complaints, oestrogens, and heart disease risk: an explanation for discrepant findings on the benefits of postmenopausal hormone therapy. *Eur Heart J* 2005;**26**:1358–1361.
53. Gast G-CM, Grobbee DE, Pop VJM, Keyzer JJ, Wijnands-van Gent CJM, Samsioe GN, Nilsson PM, van der Schouw YT. Menopausal complaints are associated with cardiovascular risk factors. *Hypertension* 2008;**51**:1492–1498.
54. Gast G-CM, Pop VJ, Samsioe GN, Grobbee DE, Nilsson PM, Keyzer JJ, Wijnands-van Gent CJ, van der Schouw YT. Vasomotor menopausal symptoms are associated with increased risk of coronary heart disease. *Menopause* 2011; **18**:146–151.
55. Bairey Merz CN, Johnson BD, Sharaf BL, Bittner V, Berga SL, Braunstein GD, Hodgson TK, Matthews KA, Pepine CJ, Reis SE, Reichek N, Rogers WJ, Pohost GM, Kelsey SF, Sopko G; WISE Study Group. Hypoestrogenemia of hypothalamic origin and coronary artery disease in premenopausal women: a report from the NHLBI-sponsored WISE study. *J Am Coll Cardiol* 2003;**41**: 413–419.
56. Shaw LJ, Bairey Merz CN, Azziz R, Stanczyk FZ, Sopko G, Braunstein GD, Kelsey SF, Kip KE, Cooper-Dehoff RM, Johnson BD, Vaccarino V, Reis SE, Bittner V, Hodgson TK, Rogers W, Pepine CJ. Postmenopausal women with a history of irregular menses and elevated androgen measurements at high risk for worsening cardiovascular event-free survival: results from the National Institutes of Health-NHLBI sponsored Women's Ischemia Syndrome Evaluation. *J Clin Endocrinol Metab* 2008;**93**:1276–1284.
57. Bellamy L, Casas JP, Hingorani AD, Williams DJ. Preeclampsia and risk of cardiovascular disease and cancer later in life: systematic review and meta-analysis. *BMJ* 2007;**335**:974–983.
58. Magnussen EB, Vatten LJ, Smith GD, Romundstad PR. Hypertensive disorders in pregnancy and subsequently measured cardiovascular risk factors. *Obstet Gynaecol* 2009;**114**:961–970.
59. McDonald SD, Malinowski A, Zhou Q, Yusuf S, Devereaux PJ. Cardiovascular sequelae of preeclampsia/eclampsia: a systematic review and meta-analysis. *Am Heart J* 2008;**156**:918–930.
60. Retnakaran R, Ying Q, Zinman B, Sermer M, Hanley A, Conelly P. Glucose intolerance in pregnancy and postpartum risk of metabolic syndrome in young women. *J Clin Endocrinol Metab* 2010;**95**:670–677.
61. Bellamy L, Casas JP, Hingorani AD, Williams DJ. Type 2 diabetes mellitus after gestational diabetes: a systematic review and meta-analysis. *Lancet* 2009;**373**: 1773–1779.
62. Drost JT, Maas AH, van Eyck J, van der Schouw YT. Preeclampsia as a female-specific risk factor for chronic hypertension. *Maturitas* 2010;**67**:321–326.
63. Rozanski A, Blumenthal JA, Davidson KW, Saab PG, Kubzansky L. The epidemiology, pathophysiology and management of psychosocial risk factors in cardiac practice. *J Am Coll Cardiol* 2005;**45**:637–651.
64. Low CA, Thurston RC, Matthews KA. Psychosocial factors in the development of heart disease in women: current research and future directions. *Psychosom Med* 2010;**72**:842–854.
65. Von Känel R, Orth-Gomér K. Autonomic function and prothrombotic activity in women after an acute coronary event. *J Womens Health* 2008;**17**:1331–1337.
66. Orth-Gomer K, Leineweber C. Multiple stressors and coronary disease in women. The Stockholm female coronary risk study. *Biol Psychol* 2005;**69**:57–66.
67. Prasad A, Lerman A, Rihal CS. Apical ballooning syndrome (Tako-Tsubo or stress cardiomyopathy): a mimic of acute myocardial infarction. *Am Heart J* 2008;**155**:408–417.
68. Vidi V, Rajesh V, Singh PP, Mukherjee JT, Lago RM, Venesy DM, Waxman S, Pyne CT, Piemonte TC, Gossman DE, Nesto RW. Clinical characteristics of Tako-Tsubo cardiomyopathy. *Am J Cardiol* 2009;**104**:578–582.
69. Summers MR, Lennon RJ, Prasad A. Pre-morbid psychiatric and cardiovascular diseases in apical ballooning syndrome (Tako-Tsubo/stress-induced cardiomyopathy). *J Am Coll Cardiol* 2010;**55**:700–701.
70. Leifheit-Limson EC, Reid KJ, Kasl SV, Lin H, Jones PG, Buchanan DM, Parashar S, Peterson PN, Spertus JA, Lichtman JH. The role for social support in health status and depressive symptoms after acute myocardial infarction: evidence for a stronger relationship among women. *Circ Cardiovasc Qual Outcomes* 2010; **3**:143–150.
71. Orth-Gomér K, Schneiderman N, Wang HX, Walldin C, Blom M, Jernberg T. Stress reduction prolongs life in women with coronary disease. The Stockholm women's intervention trial for coronary heart disease (SWITCHD). *Circ Cardiovasc Qual Outcomes* 2009;**2**:25–32.
72. Graham I, Atar D, Borch-Johnsen K, Boysen G, Burell G, Cifkova R, Dallongeville J, De Backer G, Ebrahim S, Gjelsvik B, Herrmann-Lingen C, Hoes A, Humphries S, Knapton M, Perk J, Priori SG, Pyorala K, Reiner Z, Ruilope L, Sans-Menendez S, Op Reimer WS, Weissberg P, Wood D, Yarnell J, Zamorano JL, Walma E, Fitzgerald T, Cooney MT, Dudina A, Vahanian A, Camm J, De Caterina R, Dean V, Dickstein K, Funck-Brentano C, Filippatos G, Hellemans I, Kristensen SD, McGregor K, Sechtem U, Silber S, Tendera M, Widimsky P, Zamorano JL, Altiner A, Bonora E, Durrington PN, Fagard R, Giampaoli S, Hemingway H, Hakansson J, Kjeldsen SE, Larsen L, Mancia G, Manolis AJ, Orth-Gomer K, Pedersen T, Rayner M, Ryden L, Sammut M, Schneiderman N, Stalenhoef AF, Tokgözoglu L, Wiklund O, Zampelas A; European Society of Cardiology (ESC); European Association for Cardiovascular Prevention and Rehabilitation (EACPR); Council on Cardiovascular Nursing; European Association for Study of Diabetes (EASD); International Diabetes Federation Europe (IDF-Europe); European Stroke Initiative (EUSI); Society of Behavioural Medicine (ISBM); European Society of Hypertension (ESH); WONCA Europe (European Society of General Practice/Family Medicine); European Heart Network (EHN); European Atherosclerosis Society (EAS). European guidelines for cardiovascular disease prevention in clinical practice. *Eur J Cardiovasc Prev Rehabil* 2007;**14**(suppl.2):S1–S113.
73. Mosca L, Linfante AH, Benjamin EJ, Berra K, Hayes SN, Walsh BW, Fabunmi RP, Kwan J, Mills T, Simpson SL. National study of physician awareness and adherence to cardiovascular disease prevention guidelines. *Circulation* 2005;**111**: 499–510.
74. Bairey Merz CN, Mark S, Boyan BD, Jacobs AK, Shah PK, Shaw LJ, Taylor D, Marbán E. Proceedings from the Scientific Symposium: sex differences in cardiovascular disease and implications for therapies. *J Womens Health* 2010;**19**: 1059–1072.
75. Pope JH, Aufderheide JP, Ruthazer R, Woolard RH, Feldman JA, Beshansky JR, Griffith JL, Selker HP. Missed diagnoses of acute cardiac ischemia in the emergency department. *N Engl J Med* 2000;**342**:1163–1170.
76. Canto JG, Goldberg RJ, Han MM, Bonow RO, Sopko G, Pepine CJ, Long T. Symptom presentation of women with acute coronary syndromes. Myth vs reality. *Arch Intern Med* 2007;**167**:2405–2413.
77. Dey S, Flather MD, Devlin G, Brieger D, Gurfunkel EP, Steg PG, Fitzgerald G, Jackson EA, Eagle KA; Global Registry of Acute Coronary Events investigators. Sex-related differences in the presentation, treatment and outcomes among patients with acute coronary syndromes: the Global Registry of Acute Coronary Events. *Heart* 2009;**95**:20–26.
78. Daly CA, Clemens F, Sendon JLL, Tavazzi L, Boersma E, Danchin N, Delahaye F, Gitt A, Julian D, Mulcahy D, Ruzyllo W, Thygesen K, Verheugt F, Fox KM; Euro Heart Survey Investigators. Gender differences in the management and clinical outcome in stable angina. *Circulation* 2006;**113**:490–498.
79. Mieres JH, Shaw LJ, Arai A, Budoff MJ, Flamm SD, Hundley WG, Marwick TH, Mosca L, Patel AR, Quinones MA, Redberg RF, Taubert KA, Taylor AJ, Thomas GS, Wenger NK; Cardiac Imaging Committee, Council on Clinical Cardiology, and the Cardiovascular Imaging and Intervention Committee, Council on Cardiovascular Radiology and Intervention, American Heart Association. Role of noninvasive testing in the clinical evaluation of women with suspected coronary artery disease. *Circulation* 2005;**111**:682–696.
80. Stangl V, Witzel V, Baumann G, Stangl K. Current diagnostic concepts to detect coronary artery disease in women. *Eur Heart J* 2008;**29**:707–717.
81. Wenger NK, Shaw LJ, Vaccarino V. Coronary heart disease in women: update 2008. *Clin Pharmacol Ther* 2008;**83**:37–51.
82. Jacobs AK. Coronary intervention in 2009. Are women no different than men? *Circ Cardiovasc Intervent* 2009;**2**:69–78.

83. Pepine CJ, Anderson RD, Sharaf BL, Reis SE, Smith KM, Handberg EM, Johnson BD, Sopko G, Bairey Merz CN. Coronary microvascular reactivity to adenosine predicts adverse outcome in women evaluated for suspected ischemia. Results from the National Heart, Lung and Blood Institute WISE (Women's Ischemia Syndrome Evaluation) Study. *J Am Coll Cardiol* 2010;**55**: 2825–2832.
84. Kruk M, Pregowski J, Mintz GS, Maehara A, Tyczynski P, Witkowski A, Kalinczuk L, Hong YJ, Pichard AD, Satler LF, Kent KM, Suddath WO, Waksman R, Weissman NJ. Intravascular ultrasonic study of gender differences in ruptured coronary plaque morphology and its associated clinical presentation. *Am J Cardiol* 2007;**100**:185–189.
85. Doyle M, Weinberg N, Pohost GM, Bairey Merz CN, Shaw LJ, Sopko G, Fuisz A, Rogers WJ, Walsh EG, Johnson BD, Sharaf BL, Pepine CJ, Mankad S, Reis SE, Vido DA, Rayaro G, Bittner V, Tauxe L, Olson MB, Kelsey SF, Biederman RWW. Prognostic value of global MR myocardial perfusion imaging in women with suspected myocardial ischemia and no obstructive coronary disease. Results from the NHLBI-sponsored WISE (Women's Ischemic Syndrome Evaluation) Study. *J Am Coll Cardiol Img* 2010;**3**:1030–1036.
86. Shaw LJ, Min JK, Narula J, Lin F, Bairey Merz CN, Callister TQ, Berman DS. Sex differences in mortality associated with computed tomographic angiographic measurements of obstructive and nonobstructive coronary artery disease. An exploratory analysis. *Circ Cardiovasc Imaging* 2010;**3**:473–481.
87. Clayton TC, Pocock SJ, Henderson RA, Poole-Wilson PA, Shaw TR, Knight R, Fox KA. Do men benefit more than women from an interventional strategy in patients with unstable angina or non-ST-elevation myocardial infarction? The impact of gender in the RITA3 trial. *Eur Heart J* 2004;**25**:1641–1650.
88. O'Donoghue M, Boden WE, Braunwald E, Cannon CP, Clayton TC, de Winter RJ, Fox KA, Lagerqvist B, McCullough PA, Murphy SA, Spacek R, Swahn E, Wallentin L, Windhausen F, Sabatine MS. Early invasive versus conservative treatment strategies in women and men with unstable angina and non-ST-elevation myocardial infarction: a meta-analysis. *JAMA* 2008;**300**:71–80.
89. Vaccarino V, Parsons L, Every NR, Barron HV, Krumholz HM. Sex-based differences in early mortality after myocardial infarction. National Registry of Myocardial Infarction 2 Participants. *N Engl J Med* 1999;**341**:217–225.
90. Lawesson SS, Stenestrand U, Lagerqvist B, Wallentin L, Swahn E. Gender perspective on risk factors, coronary lesions and long-term outcome in young patients with ST- elevation myocardial infarction. *Heart* 2010;**96**:453–459.
91. Berger JS, Elliott L, Gallup D, Roe M, Granger CB, Armstrong PW, Simes RJ, White HD, Van de Werf F, Topol EJ, Hochman JS, Newby LK, Harrington RA, Califf RM, Becker RC, Douglas PS. Sex differences in mortality following acute coronary syndromes. *JAMA* 2009;**302**:874–882.
92. Hochman JS, Tamis JE, Thompson TD, Weaver WD, White HD, Van de Werf F, Aylward P, Topol EJ, Califf RM. Sex, clinical presentation, and outcome in patients with acute coronary syndromes. *N Engl J Med* 1999;**341**:226–232.
93. Gulati M, Cooper-DeHoff RM, McClure C, Johnson D, Shaw LJ, Handberg EM, Zineh I, Kelsey SF, Arnsdorf MF, Black HR, Pepine CJ, Merz CN. Adverse cardiovascular outcomes in women with nonobstructive coronary artery disease. A report from the Women's Ischemia Syndrome Evaluation Study and the St James Women take Heart Project. *Arch Intern Med* 2009;**169**:843–850.
94. Arant CB, Wessel TR, Ridker PM, Olson MB, Reis SE, Johnson DB, Sharaf BL, Pauly DF, Handberg E, Zineh I, Sopko G, Kelsey SF, Noel Bairey Merz C, Pepine CJ. Multimarker approach predicts adverse cardiovascular events in women evaluated for suspected ischemia: a report from the NHLBI-sponsored WISE-study. *Clin Cardiol* 2009;**32**:244–250.
95. Alexander KP, Chen AY, Newby LK, Schwartz JB, Redberg RF, Hochman JS, Roe MT, Gibler WB, Ohman EM, Peterson ED; CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines) Investigators. Sex differences in major bleeding with glycoprotein IIb/IIIa inhibitors: results from the CRUSADE initiative. *Circulation* 2006;**114**:1380–1387.
96. Hemingway H, Langenberg C, Damant J, Frost C, Pyörälä K, Barrett-Connor E. Prevalence of angina in women versus men. A systematic review and meta-analysis of international variations across 31 countries. *Circulation* 2008; **117**:1526–1536.
97. Robinson JG, Wallace R, Limacher M, Ren H, Cochrane B, Wassertheil-Smoller S, Ockene JK, Blanchette PL, Ko MG. Cardiovascular risk in women with non-specific chest pain (from the Women's Health Initiative hormone trials). *Am J Cardiol* 2008;**102**:693–699.
98. Bugiardini R, Manfrini O, Pizzi C, Fontana F, Morgagni G. Endothelial function predicts future development of coronary artery disease: a study of women with chest pain and normal coronary angiograms. *Circulation* 2004;**109**:2993–2999.
99. Xhyheri B, Bugiardini R. Diagnosis and treatment of heart disease: are women different from men? *Prog Cardiovasc Dis* 2010;**53**:227–236.
100. Borissoff JI, Heeneman S, Kilinç E, KaššáK P, van Oerle R, Winckers K, Govers-Riemslag JW, Hamulyák K, Hackeng TM, Daemen MJ, ten Cate H, Spronk HM. Early atherosclerosis exhibits an enhanced procoagulant state. *Circulation* 2010;**122**:821–830.
101. Mackman N. Triggers, targets and treatments for thrombosis. *Nature* 2008;**451**: 914–918.
102. Roshan TM, Normah J, Rehman A, Naing L. Effect of menopause on platelet activation markers determined by flow cytometry. *Am J Hematol* 2005;**80**:257–261.
103. Sowers MR, Matthews KA, Jannausch M, Randolph JF, McConnell D, Sutton-Tyrrell K, Little R, Lasley B, Pasternak R. Hemostatic factors and estrogen during the menopausal transition. *J Clin Endocrinol Metab* 2005;**90**:5942–5948.
104. Herrington DM, Potvin Klein K. Genome and hormones: gender differences in physiology. Invited review: pharmacogenetics of estrogen replacement therapy. *J Appl Physiol* 2001;**91**:2776–2784.
105. Ridker PM, Cook NR, Lee IM, Gordon D, Gaziano JM, Manson JE, Hennekens CH, Buring JE. A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. *N Engl J Med* 2005; **352**:1293–1304.
106. Steering Committee of the Physicians' Health Study Research Group. Final report on the aspirin component of the ongoing Physicians' Health Study. *N Engl J Med* 1989;**321**:129–135.
107. Berger JS, Roncaglioni MC, Avanzini F, Pangrazzi I, Tognoni G, Brown DL. Aspirin for the primary prevention of cardiovascular events in women and men. A sex-specific meta-analysis of randomized controlled trials. *JAMA* 2006;**95**:306–313.
108. Capodanno D, Angiolillo DJ. Impact of race and gender on antithrombotic therapy. *Thromb Haemost* 2010;**104**:471–484.
109. Fang MC, Singer DE, Chang Y, Hylek EM, Henault LE, Jensvold NG, Go AS. Gender differences in the risk of ischemic stroke and peripheral embolism in atrial fibrillation: the AnTicoagulation and Risk factors In Atrial fibrillation (ATRIA) study. *Circulation* 2005;**112**:1687–1691.
110. European Heart Rhythm Association; European Association for Cardio-Thoracic Surgery, Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S, Van Gelder IC, Al-Attar N, Hindricks G, Prendergast B, Heidbuchel H, Alfieri O, Angelini A, Atar D, Colonna P, De Caterina R, De Sutter J, Goette A, Gorenek B, Heldal M, Hohloser SH, Kolh P, Le Heuzey JY, Ponikowski P, Rutten FH. Guidelines for the management of atrial fibrillation. *Eur Heart J* 2010;**31**:2369–2429.
111. Mosterd A, Hoes AW. Clinical epidemiology of heart failure. *Heart* 2007;**93**: 1137–1146.
112. Task Force for Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of European Society of Cardiology, Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, Strömberg A, van Veldhuisen DJ, Atar D, Hoes AW, Keren A, Mebazaa A, Nieminen M, Priori SG, Swedberg K; ESC Committee for Practice Guidelines, Vahanian A, Camm J, De Caterina R, Dean V, Dickstein K, Filippatos G, Funck-Brentano C, Hellemans I, Kristensen SD, McGregor K, Sechtem U, Silber S, Tendera M, Widimsky P, Zamorano JL. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008. *Eur Heart J* 2008;**29**:2388–2442.
113. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. *N Engl J Med* 2006;**355**:251–259.
114. Nieminen MS, Harjola VP, Hochadel M, Drexler H, Komadja M, Brutsaert D, Dickstein K, Ponikowski P, Tavazzi L, Follath F, Lopez-Sendon JL. Gender-related differences in patients presenting with acute heart failure. *Results from Euro Heart Failure Survey II. Eur J Heart Fail* 2008;**10**:140–148.
115. Regitz-Zagrosek V, Brokat S, Tschope C. Role of gender in heart failure with normal left ventricular ejection fraction. *Prog Cardiovasc Dis* 2007;**49**:241–251.
116. Petrov G, Regitz-Zagrosek V, Lehmkuhl E, Krabatsch T, Dunkel A, Dandel M, Dworatzek E, Mahmoodzadeh S, Schubert C, Becher E, Hampl H, Hetzer R. Regression of myocardial hypertrophy after aortic valve replacement. Faster in women? *Circulation* 2010;**122**(Suppl. 11):S23–S28.
117. Fliegner D, Schubert C, Penkalla A, Witt H, Kararigas G, Dworatzek E, Staub E, Martus P, Ruiz Noppinger P, Kintscher U, Gustafsson JA, Regitz-Zagrosek V. Female sex and estrogen receptor-beta attenuate cardiac remodeling and apoptosis in pressure overload. *Am J Physiol Regul Integr Comp Physiol* 2010;**298**: R1597–R1606.
118. Regitz-Zagrosek V, Oertelt-Prigione S, Seeland U, Hetzer R. Sex and gender differences in myocardial hypertrophy and heart failure. *Circ J* 2010;**74**: 1265–7123.
119. Heidecker B, Lamirault G, Kasper EK, Wittstein IS, Champion HC, Breton E, Russell SD, Hall J, Kittleson MM, Baughman KL, Hare JM. The gene expression profile of patients with new-onset heart failure reveals important gender-specific differences. *Eur Heart J* 2010;**31**:1188–1196.
120. Ntusi NB, Mayosi BM. Aetiology and risk factors of peripartum cardiomyopathy: a systematic review. *Int J Cardiol* 2009;**131**:168–179.
121. Yamac H, Bultman I, Sliwa K, Hilfiker-Kleiner D. Prolactin: a new therapeutic target in peripartum cardiomyopathy. *Heart* 2010;**96**:1352–1357.

122. Jones LW, Haykowsky MJ, Swartz JJ, Douglas PS, Mackey JR. Early breast cancer therapy and cardiovascular injury. *J Am Coll Cardiol* 2007;**50**:1435–1441.
123. Gerdes AM, Iervasi G. Thyroid replacement therapy and heart failure. *Circulation* 2010;**122**:385–393.
124. Dörr M, Ittermann T, Aumann N, Obst A, Reffelmann T, Nauck M, Wallaschofski H, Felix SB, Völzke H. Subclinical hyperthyroidism is not associated with progression of cardiac mass and development of left ventricular hypertrophy in middle-aged and older subjects. Results from a five-year follow-up. *Clin Endocrinol* 2010;**73**:821–826.
125. Cleland JGF, Swedberg K, Follath F, Komadja M, Cohen-Solal A, Aguilar AC, Dietz R, Gavazzi A, Hobbs R, Korewicki J, Madeira HC, Moiseyev VS, Preda I, van Gilst WH, Widimsky J, Freemantle N, Eastaugh J, Mason J; Study Group on Diagnosis of the Working Group on Heart Failure of the European Society of Cardiology. The EuroHeart Failure survey programme—a survey on the quality of care among patients with heart failure in Europe. *Eur Heart J* 2003;**24**:442–463.
126. Nieminen MS, Brutsaert D, Dickstein K, Drexler H, Follath F, Harjola VP, Hochadel M, Komadja M, Lassus J, Lopez-Sendon JL, Ponikowski P, Tavazzi L, on behalf of the EuroHeart Survey investigators. EuroHeart Failure Survey II (EHFS II): a survey on hospitalized acute heart failure patients: description of population. *Eur Heart J* 2006;**27**:2725–2736.
127. Rathore SS, Wang Y, Krumholz HM. Sex-based differences in the effect of digoxin for the treatment of heart failure. *N Engl J Med* 2002;**347**:1403–1411.
128. Simon T, Mary-Krause M, Funck-Brentano C, Jaillon P. Sex differences in the prognosis of congestive heart failure: results from the Cardiac Insufficiency bisoprolol Study (CIBIS II). *Circulation* 2001;**103**:375–380.
129. Parashar S, Katz R, Smith NL, Arnold AM, Vaccarino V, Wenger NK, Gottdiener JS. Race, gender and mortality in adults ≥65 years of age with incident heart failure (from the Cardiovascular Health Study). *Am J Cardiol* 2009; **103**:1120–1127.
130. Moss AJ, Hall WJ, Cannom DS, Klein H, Brown MW, Daubert JP, Estes NA III, Foster E, Greenberg H, Higgins SL, Pfeffer MA, Solomon SD, Wilber D, Zareba W; MADIT-CRT Trial Investigators. Cardiac-resynchronization therapy for the prevention of heart-failure events. *N Engl J Med* 2009;**361**:1329–1338.
131. Peterson PN, Daugherty SL, Wang Y, Vidaillet HJ, Heidenreich PA, Curtis JP, Masoudi FA. Gender differences in procedure-related adverse events in patients receiving implantable cardioverter-defibrillator therapy. *Circulation* 2009;**119**: 1078–1084.
132. Stramba-Badiale M, Fox KM, Priori SG, Collins P, Daly C, Graham I, Jonsson B, Schenck-Gustafsson K, Tendera M. Cardiovascular diseases in women: a statement from the policy conference of the European Society of Cardiology. *Eur Heart J* 2006;**27**:994–1005.
133. Collins P, Rosano G, Casey C, Daly C, Gambacciani M, Hadji P, Kaaja R, Mikkola T, Palacios S, Preston R, Simon T, Stevenson J, Stramba-Badiale M. Management of cardiovascular risk in the perimenopausal woman: a consensus statement of European cardiologist and gynaecologists. *Eur Heart J* 2007;**28**: 2028–2040.
134. Dallongevillle J, De Bacquer D, Heidrich J, De Backer G, Prugger C, Kotseva K, Montaye M, Amouyel P; EUROASPIRE Study Group. Gender differences in the implementation of cardiovascular prevention measures after an acute coronary event. *Heart* 2010;**96**:1744–1749.