Ischemic heart disease in women: are there sex differences in pathophysiology and risk factors?: position paper from the Working Group on Coronary Pathophysiology Microcirculation of the European Society of Cardiology

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Abstract: Cardiovascular disease is the leading cause of death in women, and knowledge of the clinical consequences of atherosclerosis and cardiovascular disease in women has grown tremendously over the past 20 years. Research efforts have increased and many reports on various aspects of ischemic heart disease (IHD) in women have been published highlighting sex differences in pathophysiology, presentation and treatment of IHD. Data, however, remain limited. A description of the state of the science, with recognition of the shortcomings of current data, is necessary to guide future research and move the field forward. In this report, we identify gaps in existing literature and make recommendations for future research. Women largely share similar cardiovascular risk factors for IHD with men; however, women with suspected or confirmed IHD have less coronary atherosclerosis than men, even though they are older and have more cardiovascular risk factors than men. Coronary endothelial dysfunction and microvascular disease have been proposed as important determinants in the etiology and prognosis of IHD in women, but research is limited on whether sex differences in these mechanisms truly exist. Differences in the epidemiology of IHD between women and men remain largely unexplained, as we are still unable to explain why women are protected towards IHD until older age compared with men. Eventually, a better understanding of these processes and mechanisms may improve the prevention and the clinical management of IHD in women.

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ESC Position Paper

Working Group on Coronary Pathophysiology & Microcirculation

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Ischemic Heart Disease in Women: Are There Sex Differences in Pathophysiology, Presentation, Treatment and Outcomes?

Abstract

Knowledge of the clinical consequences of atherosclerosis and cardiovascular disease in women has grown tremendously over the years. Research efforts have increased and published reports on various aspects of heart disease in women have proliferated. These reports have highlighted important sex differences in the pathophysiology, presentation and treatment of ischemic heart disease, and have denounced pervasive sex-related disparities in referral and treatment for heart disease as a major reason for outcome differences between the sexes. However, data still remain limited.

This report reviews current knowledge supporting sex differences in the pathophysiology, presentation and treatment of ischemic heart disease. A clear definition of the state of the science, with recognition of the shortcomings of current data, is necessary to guide future research and move the field forward. We will identify gaps in existing literature and make recommendations for future research.

Epidemiology

Cardiovascular disease (CVD) is the leading cause of death in both women and men worldwide, and a major cause of morbidity. According to the Global Burden of Disease, in 2004 CVD caused almost 32% of deaths in women worldwide, versus 27% in men (1). In Europe, 54% of all females' death are from CVD, versus 43% in men (2). Ischemic heart disease (IHD), the most common form of CVD, is also the single most frequent cause of death in Europe. Over one in five women (22%) and over one in five men (21%) die from IHD (2). With the aging of the population, and because of women's longer life expectancy than men, the proportion of persons, particularly women, with CVD is expected to rise even further in the upcoming decades.

Clinical Presentation

There are important differences in clinical presentation between women and men. Women are more likely to develop angina as their first manifestation of IHD, while men are more likely to present with an AMI; this fact has been known since the early Framingham Heart Study results (3). This presentation pattern has been confirmed in more recent studies showing that women have on average 20% higher rate of angina pectoris than men across many countries in the world, irrespective of their rate of coronary death (4). The female excess for angina contrasts with an almost universal excess of AMI among men.

In the settings of acute coronary syndromes, women and men have different clinical profiles and presentation, with fewer women than men presenting with ST-elevation AMI, but more presenting with unstable angina (5, 6). Women with acute coronary syndromes also are older, have more comorbidities and worse baseline clinical characteristics than men. Recent studies have shown that these sex differences in presentation are more pronounced among younger patients. In the Euro Heart Survey of

acute coronary syndromes involving more than 10,000 patients, women under 65 years of age were more likely than men to present with unstable angina, and less likely to have ST-elevation myocardial infarction, whereas women and men over 65 years had similar presentation (7). In the National Registry of Myocardial Infarction, women younger than 55 years were more likely than men to have a history of diabetes, heart failure or stroke, and a higher Killip class (an index of systolic dysfunction); again, these sex differences in presentation were less pronounced or absent among older patients (8).

Chest Pain and IHD in Women. Women with IHD are less likely than men to have classical angina symptoms, while they have more nonspecific symptoms and more physical limitations than men (9, 10). Women are more disabled by IHD than men despite the fact that they have less obstructive coronary artery disease (6, 7, 11). In fact, decline in functional status and chest pain, particularly when not following a "classical" pattern, correlate little with presence of ischaemia and severity of coronary atherosclerosis among women (12). Thus, chest pain is a less accurate predictor of IHD in women than in men, which may pose diagnostic challenges. However, it is important to remember that classic angina is still the most common symptom of IHD in women and an important prognostic indicator. For example, in the Worcester Heart Attack Study chest pain was the most common chief complaint in both women and men, although it was present in only 54% of women versus 69% of men (13). Typical symptoms of angina pectoris are also the strongest predictors of acute coronary syndromes in women (14). It is therefore important for physicians to work up women who present with symptoms suggestive of cardiac ischaemia, and not dismiss them as non-cardiac in origin. The fact that women with a nonspecific chest pain presentation may include many cases of true ischaemia is suggested by recent data, from the Women's Health Initiative, showing that a hospitalization for non-specific chest pain doubled the risk for a subsequent ischemic event in postmenopausal women over the next 5 to 7 years (15).

Coronary Syndrome X. Not only women with IHD tend to experience nonspecific symptoms that may confuse their presentation and detract from a cardiac cause; they may also, more frequently than

men, experience chest pain with no evidence of obstructive coronary artery disease. This syndrome, also known as “syndrome X”, is much more common in women than in men (16). These women continue to have recurrent chest pain despite maximal anti-ischemic treatment; they are substantially limited in everyday life and consume a great deal of healthcare resources (17). As addressed in later sections, this syndrome may label a heterogeneous group of patients.

Symptom Recognition

Many women fail to attribute symptoms of myocardial ischaemia to a cardiac problem. This problem may not be unique to women, however. In a recent study, less than 40% of both women and men hospitalized for AMI interpreted their symptoms as cardiac in origin (18). However, while in men severity of chest pain was a significant predictor of symptom interpretation as cardiac in origin, this was not true for women, suggesting that under-recognition of ischemic symptoms may be a larger problem in women. In another series of AMI patients that only included women, women reported a variety of prodromal symptoms before the AMI, including fatigue, sleep disturbances and shortness of breath, while less than 30% reported chest discomfort (19).

Historically, awareness of heart disease as the leading cause of death has been low among women. A survey of United States women has shown that although levels of heart disease awareness have improved since 1997, almost half of women remain unaware that ischemic heart disease is the leading cause of death among women (20). Additionally, only about half of women would call 9-1-1 (emergency services) if they thought they were having symptoms of a heart attack. Thus, the lack of appropriate identification of IHD in women continues to be a significant public health concern. This problem, in conjunction with more subtle symptoms, and more adverse outcomes in women with AMI as compared with men, represents substantial challenge for the prevention and clinical care of IHD in women.

These issues concerning presentation and recognition of ischaemic symptoms in women continue to raise questions regarding specificity/ sensitivity of clinical symptoms in this population. Many other questions remain unanswered. Is age and menopausal status important in relation to the clinical presentation? What is the true extent of sex differences in symptom recognition and awareness of IHD risk, since few studies have compared women to men? Are sex differences in presentation a reflection of differences in the pathophysiology of AMI, or rather differences in recognition of cardiac symptoms between men and women? Are there any geographical/ethnical/racial differences in clinical presentation? Many large published studies and surveys were done in the United States or Western Europe and there is a relative lack of data coming from other areas.

Trends Over Time

In many Western countries cardiovascular mortality has declined among women since the mid-1960's, similar to men (21). However, until the year 2000, in the U.S. the total number of deaths due to cardiovascular disease has slightly increased in women, while it has decreased among men (22). This increase probably reflects changing population demographics towards a larger proportion of older people, the majority of whom are women. In fact, age-standardized rates show a similar decline in women and men in the United States and many other Western countries (21, 23, 24). After the year 2000, even the number of cardiovascular deaths has shown a similar, if not steeper, downward trend in American women compared with men (22). However, when looking at different age groups, the decrease in mortality rates appears to have slowed down since 2000 in middle-aged women and men (age 35 to 54 years), while it has continued steadily among older people (25). In addition to an overall decline in cardiovascular mortality from population statistics, there has been a decline in hospital mortality rates for AMI among American women and men of all ages, which has been more substantial in women than in men (8).

It should be noted that these favorable trends are not universal. For example they do not apply to Eastern Europe, where mortality from both IHD and CVD rose up to the most recent calendar period for both women and men, with the exception of Hungary, whose rates leveled off (at very high rates) in the mid 1990s, and Poland and the Czech Republic, whose rates have tended to decline since the mid 1990s (21). In the Russian Federation mortality rates from IHD and CVD for both women and men during 1995–1998 were among the highest in the world.

In terms of CVD risk factors, there have been mixed trends for both women and men over the 1990s. On the positive side, both sexes experienced a reduction in the prevalence of high-risk levels of cholesterol (between 1988 and 2002); on the other hand, an increase in obesity and high C-reactive protein (CRP) was noted, particularly among women (26). Furthermore, the percentage of women with high blood pressure increased, whereas it decreased among men. A recent update from the same ongoing U.S. survey, up to 2004, provided additional evidence of a somewhat worsening risk factor profile among women (27).

Risk factors

Risk estimates associated with traditional cardiovascular risk factors are overall similar in women and men and across various regions of the world (28). However, the increased risk associated with hypertension and diabetes, and the protective effect of exercise and alcohol, seem to be greater in women than in men. Collectively, nine potentially modifiable risk factors (smoking, hypertension, diabetes, waist/hip ratio, dietary patterns, physical activity, consumption of alcohol, plasma apolipoproteins, and psychosocial factors) account for 94% of the population attributable risk of AMI in women and 90% in men (28). For women with favorable levels for all 5 major risk factors (blood pressure, serum cholesterol, body mass index, diabetes, and smoking) at younger ages, IHD and CVD are

rare events (29). Unfortunately, only about 20% of women younger than 40 years of age meet these low risk criteria (29), and 48% of women have a clustering of three or more metabolic risk factors for IHD (30).

Smoking. Smoking is the single most important preventable cause of IHD in women, and the leading cause of IHD in women younger than 50 years old (31). There is a dose-dependent relationship between total cigarettes consumption per day and risk of AMI; as few as one to five cigarettes per day increases a patient's risk (28, 32). There is also a well-established increased risk for women who smoke and also use oral contraceptives for venous thrombosis and IHD (33). After cessation of smoking, the risk of IHD in both women and men declines rapidly (within months), and falls to the level of the risk among nonsmokers within 5 to 10 years after cessation (32, 34). Exposure to passive smoking is also a risk factor for IHD in women, increasing their risk of 24% (22% in men) (35). Although the prevalence of smoking is still slightly higher in men than in women, the decline in tobacco use in recent decades has been less pronounced in women than in men.

Hypertension. For women, as for men, hypertension is a major cause of IHD, as well as of congestive heart failure and stroke (36). Hypertension is a highly prevalent risk factor that becomes more common in women than in men over the age of 55 years, and is particularly prevalent among black women (37). In the INTERHEART study, a large international case-control study of AMI, the population attributable risk for hypertension was 36% in women, indicating that the risk of AMI could be reduced by 36% were hypertension eliminated as a risk factor. The corresponding figure in men was 19%. Hypertension is 2 to 3 times more common in women taking oral contraceptives, especially among obese and older women, than in women not taking them. In older women, isolated systolic hypertension is the most common form of hypertension. A 3-fold increase in IHD and stroke is found in women with a systolic blood pressure >185mmHg as compared with women with a level of <135mmHg (38). Control of any form of hypertension has been demonstrated to reduce the risk of coronary artery

disease and stroke in both sexes, as shown by the large clinical trials with a fair representation of women (39). Unfortunately, various iterations of the ongoing National Health and Nutrition Examination Study (NHANES) survey have continued to show low rates of hypertension awareness, treatment and control among American women, as in men, although these rates have increased over time (40, 41).

Dyslipidemia. Almost half (48%) of American women 20 years of age or older have a total cholesterol level ≥ 200 mg/dL, and almost one third (32%) have a low-density lipoprotein (LDL)-cholesterol ≥ 130 mg/dL (22). Although women tend to have more favorable lipid profiles than men from age 20 to 50, after the onset of menopause cholesterol levels increase in women, while they remain steady in men. Total and LDL-cholesterol levels predict fatal IHD in both middle-aged (< 65 years) and older (≥65 years) women as well as men, but the strength and consistency of these relationships in older women is diminished (42). Reduced high-density-lipoprotein (HDL) cholesterol and high triglyceride levels appear to be more important risk factors in women than in men. HDL-cholesterol levels inversely predict IHD in both middle-aged and older women, but not in older men (42). Among 32,826 post-menopausal women from the Nurses' Health Study, HDL-cholesterol was the lipid parameter that best discriminated risk of IHD (43). Hypertriglyceridemia, on the other hand, is associated with 37% increased CVD risk in women, independent of other risk factors including HDL-cholesterol; the corresponding estimate for men is 14% (44).

In women with known CVD, treatment of hyperlipidemia is effective in reducing IHD events and IHD mortality, but it does not affect total mortality. For women without CVD (primary prevention), lipid lowering does not affect total or IHD mortality; lipid lowering may reduce non-fatal IHD events, but evidence is insufficient to determine this conclusively (45). The recent Intervention Trial Evaluating Rosuvastatin (JUPITER) evaluated the benefits of statin therapy in apparently healthy individuals with elevated high sensitivity C-reactive protein (hsCRP) but without an elevation in LDL-cholesterol. Among women, statin therapy significantly reduced the primary combined end point of AMI, stroke,

hospitalization for unstable angina, arterial revascularization, or cardiovascular death (46). However, because of the small number of events, the absolute risk reduction was small (about half of a percentage point) and the effects on "hard" endpoints such as fatal or non-fatal AMI, stroke or cardiovascular mortality or total mortality were not statistically significant. Therefore, it is still debatable whether statins, or other lipid-lowering medications, are useful for the primary prevention of CVD in women.

Type 2 Diabetes and Obesity. Diabetes mellitus is a major risk factor for IHD for both men and women, and among women, it nullifies the female advantage over men towards developing IHD (47). Although in many studies diabetes is associated with higher IHD risk in women than in men, this is in part due to a higher rate of coexisting risk factors in women with diabetes (48) and to the better survival (relative to men) of women without diabetes (47). The mortality rates of women with diabetes is similar, or less, that of men with diabetes (47, 48). These statistics, however, may be worsening for women. CVD mortality reductions in the past 30 years have been achieved for diabetic men but not for diabetic women; a better survival for women with diabetes than men in the 1970's and early 1980's was essentially eliminated in 1988 to 2000 (49).

Obesity is an important risk factor for diabetes and CVD. It is found in 33% of women (and 31% of men), including 7% women (versus 3% men) being extremely obese (body mass index ≥ 40) (50). Obesity is particularly a problem among black women (54%, versus 30% in white women), with a prevalence of extreme obesity of 15% in this group (50). There is a gradient of coronary risk with increasing overweight, with the heaviest category of women having a 4-fold increased risk for CVD compared with lean women (51). Polycystic ovary syndrome is found in 10% to 13% of women but is often unrecognized; it is linked with a clustering of risk factors, including obesity and type 2 diabetes mellitus, and increased IHD risk after menopause (52).

Risk Scores for IHD

An increasing number of CVD risk factors has a cumulative effect on IHD risk both in women and in men. For example, among persons aged 18 to 39 years without prior IHD in the Chicago Heart Association Detection Project in Industry, the 31-year age-adjusted IHD death rate per 10,000 person-years was lowest for low-risk women (0.7) and increased with the number of risk factors to 2.4 and 5.4 in women with 1, or two or more risk elevated risk factors (29). The INTERHEART study also clearly demonstrated such a cumulative effect of modifiable risk factors, including current or former smoking, diabetes, hypertension, abdominal obesity, psychosocial stressors, irregular consumption of fruits and vegetables, no alcohol intake, avoidance of regular exercise, and plasma lipids (28).

Probably the best-known risk algorithm for IHD for asymptomatic persons is the Framingham Risk Score, which includes age, hypertension, smoking, diabetes, and hyperlipidemia (53). A problem with this score is that much of the middle-aged population is classified as low to intermediate risk. This is particularly true for women: even up to age 80 years, more than three quarters of women have a 10-year Framingham risk that is <10% (54). Many other risk scores have been proposed that have mostly included the same traditional risk factors, but have occasionally added other factors such as family history, measures of social deprivation or new biomarkers such as C-reactive protein (CRP). Some of the scoring systems developed in European countries include the SCORE (Systematic Coronary Risk Evaluation), the ASSIGN (Assessing Cardiovascular Risk to Scottish Intercollegiate Guidelines Network/SIGN to Assign Preventative Treatment), and the QRISK (QRESEARCH cardiovascular risk algorithm) (55). Whether these risk scores perform better than the Framingham Risk Score for risk prediction in women remains to be demonstrated. A risk score that has been developed for women is the Reynolds Risk Score (56), whose main difference from the FRS is the incorporation of parental history of IHD and CRP. This score reclassified 15% of intermediate-risk women to high risk in the

Women's Health Study, therefore it has some promise. However, it needs validation in other populations.

Novel Biomarkers

In an effort to improve prediction and guide prevention, particularly for the large segment of the population who is currently classified as being at intermediate risk based on existing risk algorithms, more than 100 new risk markers have been proposed in recent years. However, consensus conferences have consistently recommended against the use of these markers for lack of evidence that they help improve risk prediction (57, 58). A recent summary of systematic reviews conducted for the United States Preventive Services Task Force has reviewed the evidence concerning 9 novel risk factors: CRP, coronary artery calcium score as measured by electron-beam computed tomography, lipoprotein(a) level, homocysteine level, leukocyte count, fasting blood glucose, periodontal disease, ankle-brachial index, and carotid intima-media thickness (59). Each factor's potential clinical value was evaluated by using a set of criteria that emphasized the importance of the effect on the reclassification of intermediate-risk persons. This review concluded that current evidence does not support the routine use of any of the 9 risk factors for screening and risk stratification of intermediate-risk persons. Of the risk markers evaluated, CRP was the best candidate for screening, however evidence is still lacking to recommend routine use. In women, in particular, a CRP level >3.0 mg/L reclassified only 5% of intermediate-risk women in the Women's Health Study (60), and none in the Cardiovascular Health Study (61), suggesting a small and inconsistent effect (59). However, when incorporated into the Reynolds risk score, CRP assessment may be of utility in women, as reported above, although validation of this risk algorithm is needed in populations other than the Women's Health Study.

Psychosocial Risk Factors

There is growing evidence that psychological stress can influence the onset and clinical course of IHD (62). In the INTERHEART Study, the combined exposure to psychosocial risk factors including depression, perceived stress at home or work, low locus of control, and major life events, was significantly associated with AMI with an adjusted odds ratio (OR) of 2.6 in men and 3.5 in women (28). Individually, each of these factors predicted AMI in a fairly similar fashion in both men and women (63).

Depression is about twofold more prevalent in women than in men; it is uniquely common, up to 40%, in younger women with AMI (64). Depression is an important risk factor for adverse cardiac events in women, increasing a woman's risk of at least 50% (65-67). In addition to cardiac outcomes, depression is related to worse quality of life in cardiac patients (68), and worse health status benefits after bypass surgery, particularly in women (69). Furthermore, depression is one of the strongest predictors of nonadherence to medical treatment (70, 71) and an important correlate of lifestyle behaviors such as smoking (72) and sedentary lifestyle (73).

Chronic emotional distress of various types, such as anxiety, marital stress, and exposure to early life adversities, has been linked to cardiovascular risk in women. Based on a recent meta-analysis, anxiety is a moderate but independent risk factor for incident IHD and cardiac death in both men and women, although individual study results are heterogeneous (74). A series of studies of Scandinavian women with acute coronary syndromes have demonstrated robust associations of marital stress with subsequent cardiac events (75), as well as with progression of coronary artery disease measured with quantitative coronary angiography (76). A study of United States women without a history of IHD linked marital satisfaction to less atherosclerosis in the carotid arteries and aorta measured by ultrasound, and to less rapid progression of carotid atherosclerosis (77). Psychological trauma, particularly if occurring

early in life, such as childhood maltreatment, is an emerging risk factor for IHD which is particularly common among women (78).

In addition to chronic stressors, acute psychological factors such as stressful episodes, acute anger, sudden mood disturbances and extreme excitement can trigger AMI and sudden cardiac death in susceptible individuals (79). Although it is unknown whether there are sex differences in these effects, a stress-induced condition known as "takotsubo cardiomyopathy", is almost exclusively seen among women (80). It manifests as severe, reversible left ventricular dysfunction, with markedly elevated levels of plasma catecholamines.

Unfortunately, psychological interventions aimed at reducing stress or treating depression or other psychosocial risk factors have shown little to no effect on IHD incidence and total or cardiac mortality, although they do achieve small reductions in anxiety and depression in patients with IHD (81). When results are reported separately by sex, men show a borderline statistically significant benefit (odds ratio [OR] 0.73, 95% confidence interval [CI] 0.51-1.05), while in women the estimate is null (OR 1.01, 95% CI 0.46-2.23) (82). It may be that traditional psychosocial interventions do not work well for women, and that strategies that address more specifically women's needs and stressors should be developed. This is suggested by a recent study by Orth-Gomer and colleagues (83), documenting a remarkable decrease in mortality (about 70% lower) in women with IHD randomized to a stress-reduction intervention specifically tailored to women, compared to usual care.

Pathophysiology

Atherosclerosis

Women have less obstructive coronary artery disease along the entire spectrum of acute coronary syndromes (6, 7, 11) and across all age groups (7). This advantage appears more marked in the coronary tree than other vascular beds. The population-based Rotterdam Study examined sex

differences in atherosclerosis at different sites in the vascular tree among participants of age ≥55 years (84). A higher calcium score (>1000) was found in men than in women in all age categories; interestingly, sex differences were more evident in the coronary arteries than in other vascular territories. Nicholls et al. (85) reported that atheroma volume in women with angiographic coronary artery disease is less than in men, including both intraluminal plaque and atheroma within the media, despite the presence of more cardiovascular risk factors in women. Recently, Han et al. (86), by measuring atheroma burden using intravascular ultrasonography (IVUS), have extended this observation to patients without obstructive coronary artery disease, and demonstrated that even at this early stage women have a lower atheroma burden, and different atheroma morphology, compared with men.

Vascular Function

Community samples have demonstrated that women have better peripheral endothelial function than men (measured as percent of flow-mediated vasodilation from baseline) until about age 70 and at all levels of risk factors (87-89). Better vascular function has also been noted in women referred for coronary angiography but without obstructive coronary artery disease, compared with men. In the study by Han et al. (86), in addition to less plaque burden women had less diffuse epicardial endothelial dysfunction than men. Whether better vascular function in women than men is also found among patients with AMI or other acute coronary syndromes, is not known. However, abnormal endothelial function appears to be a prognostic factor in women, as suggested by a small follow-up study part of the Women's Ischaemia Syndrome Evaluation (WISE) study (90). More data are needed, however, to confirm these findings.

Vascular Tissue Repair

Ultimately the balance between injury and repair is thought to be the major determinant of cardiovascular disease progression, with endothelial progenitor cells (EPCs) playing an important role in

vascular repair. Endogenous mobilization of endothelial progenitor cells is associated with an enhanced reendothelialization, an improvement of endothelial function, and reduced atherosclerotic burden. Thus, EPCs may provide a circulating pool of cells that could constitute a cellular "repair" mechanism at the sites of vascular injury. A recent study based on 210 healthy subjects (104 males and 106 females), demonstrated higher steady-state levels of EPC (CD34+KDR+) in fertile women than in men, while they were not different between postmenopausal women and age-matched men (91). These sex gradients mirrored differences in cardiovascular profile, vascular function (brachial artery flow-mediated dilation), and carotid intima-media thickness. EPCs are mobilized cyclically in fertile women according to the menstrual cycle (91, 92), in synchrony with the level of circulating 17beta-estradiol (92), and they could represent an important mechanism of protection for premenopausal women. Therefore, estrogen may play a role in stimulating vascular repair; data from animal studies support this notion (93).

Microvascular disease

Coronary microvascular dysfunction is a term used to designate abnormalities in the vasomotor or metabolic regulation of the small coronary arterioles (<500 μm in diameter), which are not visualized by coronary angiography and are the main determinants of coronary vascular resistance (94). It is a complex phenomenon that includes both endothelium-dependent and endothelium-independent pathways but can also be caused by structural changes in the vessel wall, such as vascular remodeling. Coronary microvascular disease may precede the development of frank IHD and bears independent prognostic value (95). Coronary microcirculatory function can be assessed invasively by measuring coronary flow reserve in response to adenosine with an intracoronary Doppler wire. Non-invasive methods for the measurement of coronary flow reserve include positron emission tomography, magnetic resonance imaging, and transthoracic echocardiography with contrast material (94).

Experimental studies suggest that sex plays a relevant role in a number of microvascular mechanisms which may affect microvascular function and disease. Sex-specific differences in microvascular blood flow and vasodilatory capacity are observed very early in development. In a study on skin microcirculation in newborn preterm (24-28 wk) infants, Stark and coworkers (96) observed that male infants had higher baseline flow than females. In animal experiments, differences in superoxide concentration and vascular permeability of venules were also described (97). Some of the reported sex differences are related to gonadal hormones and their receptors. However, genetic differences may also exert effects independent from gonadal function (98).

Based on experimental data and clinical observation, coronary microvascular dysfunction is put forth as a major etiological factor for IHD in women, and a frequent determinant of chest pain in the absence of significant coronary obstruction—known as “microvascular angina”(99, 100). To date, however, microvascular angina remains a controversial entity (101), and few clinical studies have addressed the role of microvascular dysfunction as a determinant of IHD in women other than within the context of cardiac syndrome X. In a recent follow-up study of 189 WISE women with suspected coronary ischaemia, coronary flow reserve after intracoronary adenosine was significantly related to increased risk of major adverse outcomes (death or hospitalization for nonfatal AMI, congestive heart failure or stroke), with an adjusted hazards ratio of 1.14 per unit decrease of log-transformed coronary flow reserve (102). Data are needed in less selected samples of women, and using noninvasive methods of coronary flow reserve, to confirm these findings. Also, data are needed to support the concept that this phenomenon is more prevalent among women than men. Currently, the only proof is the observation that coronary syndrome X is more frequent in women, but this syndrome only accounts for a small proportion of IHD in women. The few studies that have compared coronary flow reserve in response to adenosine between women and men referred for coronary angiography have found similar

values (86, 103); in one study coronary flow reserve was lower in women, but this difference was largely explained by women's older age and smaller body size (86).

Autonomic Function

There are important sex differences in the autonomic nervous control of the cardiovascular system. Men tend to have higher sympathetic activity whereas a higher parasympathetic cardiac autonomic activity is more prevalent in women (104). These differences may be the result of developmental differences (e.g. body fat distribution) or hormonal differences between women and men (104, 105). Other factors that modulate or alter autonomic cardiac activity, and may potentially influence sex differences, include age (106), obesity (105), changes in hormone levels (104), inflammation (107) and psychological disorders (e.g. depression) (108).

Airaksinen et al. showed that vagal activation was more common in women than men during acute coronary occlusion, suggesting that this might have beneficial antiarrhythmic effects (109). However, in patients with cardiac syndrome X, who are mostly postmenopausal women, an imbalance of autonomic nervous activity has been reported. Lanza et al. (110) showed I-metaiodobenzylguanidine (MIBG) myocardial scintigraphy defects, a measure of autonomic nervous system activity, in 75% of cardiac syndrome X patients (64% women). In addition, in patients with cardiac syndrome X, a relationship between vagal impairment, measured by means of heart rate variability, and non-invasive coronary flow reserve measurements has been described (111). Furthermore, Ponikowski et al. (112) showed that marked vagal withdrawal, detected by heart rate variability analysis, preceded ST-segment depression on 24-hour Holter monitoring in a predominantly female sample (19 women out of 23 patients). Although women are more often affected by cardiac syndrome X than men, no study so far has been conducted to examine sex differences in cardiac autonomic activity in IHD patients.

Another condition in which autonomic dysfunction is likely to play a pathogenic role is takotsubo cardiomyopathy. A recent study showed significant impairment in heart rate variability at the index event compared to after 3 months (113), suggesting that acute autonomic dysfunction may induce neurogenic stunning of the myocardium leading to the clinical picture of stress-induced cardiomyopathy. Therefore, although women have normally a more favourable autonomic function profile than men, specific syndromes that are more common among women (cardiac syndrome X, takotsubo cardiomyopathy) are paradoxically linked to adverse autonomic function.

Role of Sex Hormones

The lower incidence of CVD in premenopausal women compared with men of similar age and the menopause-associated increase in cardiovascular disease, have long suggested that ovarian hormones underlie a protective effect on the vascular system for women. Indeed, sex steroid hormones exert multiple direct and indirect effects on cardiovascular physiology (114). Up to now, research has focused on the effects of estrogen and estrogen receptors (ERs), whereas other hormones, such as progesterone and testosterone and their receptors (PR and AR), have received much less consideration.

***Sex Hormones and Vascular Function*.** Estrogens improve the arterial wall response to injury and inhibit the development of atherosclerosis by promoting reendothelialization, inhibiting smooth-muscle cell proliferation, and matrix deposition following vascular injury (115). Estrogens also decrease systemic vascular resistance, improve coronary and peripheral endothelial function and prevent coronary artery spasm in women with and without coronary atherosclerosis (116, 117). Interestingly, intracoronary infusion of estradiol improves endothelial function and coronary blood flow in female patients, but not in male patients with coronary artery disease (117).

Estrogens cause vasodilation through both rapid increases in the production of nitric oxide (NO) and the induction of NO genes (115). Estrogens also modulate relaxation through the endothelium-

derived hyperpolarizing factor (EDHF) (118), by inducing vasodilator prostanoids (PGE_2, PGI_2) (119), and by inhibiting the production of endothelin-1 (120). Additionally, estrogens modulate myogenic vascular responses by reducing the basal tone of microvessels (119). The majority of these effects have been attributed to estrogens acting on two distinct receptors, ERα and ERβ, which are expressed both in vascular endothelial and smooth muscle cells (115). ERα appears to mediate most of the protective effects of estrogen against vascular injury and atherosclerosis (121). ERβ expression is enhanced in the vascular wall of women with IHD, whereas ERα predominates in unaffected women (122). **(Fig 1)**

In addition to estrogen, progesterone may also contribute to sex-specific differences in the regulation of vascular function; its effects however, remain controversial (123). Testosterone, on the other hand, was shown to have negative effects on blood pressure and cardiovascular morbidity and mortality (124).

Post-Menopausal Hormone Therapy. Initial observational studies showed reduced incidence of CVD in postmenopausal women receiving hormone replacement therapy (HRT) (125, 126). However, it has recently become clear that hormone therapy (HT) has complex biological effects; for example, HT has both anti-inflammtory and proinflammatory effects and it both activates coagulation and improves fibrinolysis (127). These effects depend on the route of administration, doses of estrogens, age of women, and other factors. Given orally, HT clearly increases CRP (128). The Heart and Estrogen/Progestin Replacement Study (HERS), and the Women's Health Initiative (WHI) clinical trials did not support beneficial effects of hormone replacement therapy (HRT) in postmenopausal women neither in secondary nor in primary cardiovascular prevention (129-131). Indeed, the WHI study was terminated early due to a small but significant increase in cardiovascular events and other adverse outcomes in the HRT group. It has been argued that the timing of initiation of HRT after the onset of menopause may influence the response to treatment for CVD prevention. A post-hoc analysis of the WHI trial suggested that the CVD risk may be decreased when HRT is started earlier (within 10 years of

menopause) (132). The fact remains, however, that no trial of HRT has conclusively demonstrated a beneficial effect towards CVD in either primary or secondary prevention; if anything, risk is slightly increased. Therefore, HRT should not be used for the prevention of CVD in women.

Clinical Outcomes

Acute Coronary Syndromes

Because IHD on average occur later in life women than in men, women are older and have more comorbidities, such as history of hypertension, diabetes, heart failure and stroke, at the time of the acute coronary syndrome (133). Starting in the mid-1980's-early 1990's (134), studies have consistently documented higher unadjusted mortality and complication rates in women after acute coronary syndromes compared with men. Once differences in age and comorbidity are accounted for in the analysis, however, literature appears inconsistent regarding whether sex differences in prognosis persist. The reasons for these discrepancies is likely due to the fact that sex differences in mortality after acute coronary syndromes do not occur across the board, but only in specific patient subgroups.

The first group in which women with IHD fare worse than men is the AMI patients with ST-segment elevation (STEMI) (6, 135, 136). In contrast, no sex differences are usually found among the AMI patients without ST segment elevation (NSTEMI) after adjustment for age and risk factors. Among unstable angina patients, women actually have a significantly better prognosis than men after adjusting for age and risk factors (6, 137). The reasons underlying these sex differences in outcome according to type of acute coronary syndrome are unclear, but they are likely related to pathophysiology. For example, a transmural infarction (or a STEMI) is thought to be caused by acute occlusion due to a thrombus on a ruptured or eroded atherosclerotic plaque, a phenomenon less common in other acute coronary syndromes (138). It is possible, then, that women's smaller coronary vessels pose them at higher risk (relative to men) after STEMI but not after other types of ischemic events.

The second group in which a poorer prognosis of women is found relative to men is the young and middle-aged AMI patients, i.e., patients less than 60 or 65 years old (but the younger the age, the larger the excess mortality in women). In contrast, among older patients, there are no differences in outcome or even a tendency for women to do better. Originally reported by Vaccarino et al. (139, 140), this finding has now been confirmed many population-based and registry studies (141-146) and is seen in both STEMI and NSTEMI patients (135). This interaction with age is less apparent in datasets from randomized clinical trials (6, 147), probably because of selection characteristics and possible differential enrollment by sex in these trials. A similar pattern of adverse outcome for younger women (but not older women) compared with men is observed for mortality (148) and recovery (10, 149) after coronary bypass (CABG) surgery, and for complications (150) and death (151) after percutaneous interventions.

It is unclear why sex differences in the outcome of AMI or revascularization procedures are seen in young and middle-aged patients but not older patients. One would expect that women less than 50 years of age, the majority of whom are likely premenopausal, should be protected, rather than at higher risk, compared with age-matched men in terms of survival and cardiovascular risk. However, in order for IHD to occur at younger age in women, it is likely an aggressive disease, or perhaps it is driven by multiple, severe risk factors, or by a high-risk genetic background. Indeed, younger women with MI compared with men have a higher rate of risk factors and comorbidities such as diabetes, history of heart failure, and stroke, although these factors do not entirely explain sex differences in outcome (8, 140). It is possible that unaccounted comorbidities and risk factors are responsible for the residual outcome differences seen in comparison with men. Alternatively, non-traditional, or unknown, risk factors may be involved. Although we do not have a full explanation for the excess mortality risk in young women compared with similarly-aged men, this excess risk is narrowing (8), reflecting a sharper mortality decline among younger women than men in recent years. This change over time suggests that

environmental or behavioral causes of sex differences in outcomes may be more important than biological ones.

Stable Angina

Stable angina as the first presentation of coronary disease is more common in women (47% of all IHD cases) than men (32%) (152). A large community study found that women and men of every age presenting with stable angina have an similar increased coronary mortality relative to the general population (153). Women with angina who were younger than 75 years, however, had higher coronary-standardized mortality ratios than men; among those aged 55 to 64 years, for example, it was 4.7 in women and 2.4 in men (153). A major conclusion of this large study is that the contemporary prognosis of patients with stable angina is not good as traditionally assumed. The incidence of angina in both men and women is similar, with age-standardized annual incidence of 2.03 and 1.89, respectively, per 100 population. This lack of male excess contrasts with the high rate of "nonobstructive" coronary angiography in women and it also contrasts with the male predominance in AMI. These gender differences are important as they may reflect pathophysiological differences between men and women in the development of CAD.

Chest Pain with Normal Coronary Angiograms

Chest pain with normal coronary angiograms, also known as "syndrome X", is more common in women than men and in many of these patients microvascular abnormalities have been demonstrated (100). The mode of presentation of this syndrome ranges from uncomplicated chest pain to severe ischemia and AMI in patients with angiographically normal smooth coronary arteries. Authors have labeled this syndrome in a number of different ways, such as cardiac syndrome X, vasotonic angina, and "the sensitive heart" (154-156). Yet, these terms are often used to describe different clinical presentations. Asbury & Creed define cardiac syndrome X as "chest pain, positive exercise test for myocardial ischemia and angiographically smooth coronary arteries"(157). Crea & Lanza defined it as a

form of stable effort angina, which can reasonably be attributed to abnormalities in the coronary microvascular circulation even in the presence of near normal coronary arteries at angiography (158).

Kaski et al. (159) followed 99 patients with cardiac syndrome X (78 women) and found that long-term survival was not adversely affected. These findings were recently confirmed by Lamendola et al. in 155 cardiac syndrome X patients who were followed for over 10 years (160). None of the patients in these studies died from a cardiovascular cause or had major cardiovascular events. Two recent studies, one in Germany (161) and the other in The Netherlands (162) further confirmed that cardiac syndrome X patients presenting with stable, effort-induced angina have good long term prognosis, comparable to that of the general population. Cardiac syndrome X patients presenting with unstable angina also have a benign prognosis. Studies have consistently shown an annual event rate of approximately 2% (163, 164), which is similar to the rate of asymptomatic women in the community (165).

However, some studies have suggested an impaired outcome in subsets of patients with angina and normal coronary angiograms. Gulati et al. reported a high number (7.9%) of cardiovascular events (AMI, hospitalization for heart failure, stroke, cardiac mortality, and all-cause mortality) among 540 women from the WISE study, with symptoms suggestive of ischaemia and normal coronary angiograms compared to 1000 healthy women (165). Furthermore, in a subset of the WISE study, Johnson et al. showed that evidence of myocardial ischaemia, which was found in 14 (20%) of the patients, predicted cardiovascular outcome after three years (166). However, the higher event rate was due to hospitalizations for angina and repeat angiography: no deaths or AMI events were documented in this small group. In 42 women with *de novo* angina, reversible myocardial ischaemia on single-photon emission tomography (SPECT) and normal coronary angiograms, Bugiardini et al. (167) reported that endothelial dysfunction, assessed by intracoronary acetylcholine provocation, was predictive of the development of coronary atherosclerosis at 10 years of follow-up. Furthermore, impaired coronary endothelial function in response to acetylcholine was independently linked to adverse cardiovascular

outcomes in 163 WISE women with a clinical indication for coronary angiography, most of whom had no or only mild epicardial coronary artery disease (90).

In the WISE study, coronary flow reserve after intracoronary adenosine, a marker of endothelium-independent vascular function, was also significantly related to increased risk of major adverse outcomes among women with chest pain without obstructive coronary artery disease (102). Others have reported similar findings (168). Other mechanisms of myocardial ischemia have been studied in these patients. Fragasso et al. (169), for example, showed that patients with cardiac syndrome X in whom slow coronary flow caused transient myocardial hypoperfusion were at a higher risk for future events compared to those without myocardial perfusion defects. Furthermore, Leu et al. (170) reported that biomarkers for oxidative stress were independent predictors of future cardiovascular events in cardiac syndrome X.

Because most studies have either included only women, or had a small sample size of men, it is currently unclear whether there are sex differences in the outcome of cardiac syndrome X. Dey et al. (171) did not find a significant sex difference in outcome between 857 men and 703 women with acute coronary syndromes and normal or mildly diseased coronary arteries after 6 months of follow-up. In contrast, in a large Canadian cohort presenting for cardiac catheterization for suspected ischemia, women with normal coronary arteries were 4 times more likely to be re-admitted for unstable angina and repeat revascularization at 3 years, compared to men; there were no differences in other major CVD events and in total mortality, however (172).

Based on existing evidence, it appears that cardiac syndrome X encompasses heterogeneous patient groups; differences in patient populations may explain differences in prognosis found in different studies. Therefore, the overall benign prognosis described in many studies could be driven by the majority of women in this group who do not have myocardial ischaemia. However, the relatively

small subgroup that does have ischaemia appears to be at increased risk for subsequent events and mortality. Thus, future outcome studies should include well-characterized cohorts where the mechanisms for microvascular angina have been thoroughly studied. In addition, although cardiac syndrome X more often affects women than men, there have been no long-term follow-up studies comparing equally sized groups of women and men suffering from the condition. Finally, future studies should apply the recently published recommendations for inclusion criteria for cardiac syndrome X (100) and also distinguish between stable and acute clinical presentations.

Revascularization Procedures

Coronary Artery Bypass. Sex differences have long been reported in the outcome of patients undergoing coronary revascularization, with a higher rate of mortality and complications among women. Women undergoing Coronary Artery Bypass (CABG) surgery suffer a greater operative mortality compared to men, with the relative risk for women ranging from 1.4 to 4.4 (173-176). This difference has been attributed to anatomical reasons, specifically women's smaller body size and smaller coronary vessels, as well as to a higher surgical risk due to older age and presence of co-morbidities, such as diabetes and hypertension. In addition, in women surgery is more often performed on an emergency basis, which adds to the risk of these patients.

In a large cohort of patients undergoing CABG (148), women had less severe coronary artery disease and higher left ventricular ejection when compared to men in every age group. Nevertheless, in the youngest age category (<50 years old), the in-hospital mortality rate was three-fold higher for women compared to men (3.4% vs. 1.1%) and, among the patients aged 50-69 years, it was 2.4-fold higher (2.6% vs. 1.1%); the mortality difference in older patients was less marked. These findings parallel those for AMI described above, whereby an excess mortality risk for women compared with men is more marked in younger than older patients.

Percutaneous Coronary Interventions. Percutaneous coronary interventions (PCI) in women are also reported to be less successful when compared to men, with women showing a higher complication rate, a lower rate of procedure success, more angina and larger use of antianginal medications after PCI (177-179).

In the National Heart Lung and Blood Institute's Coronary Angioplasty Registry 546 women (out of 2,136 patients) who underwent PCI were an average of 4.5 years older than the male patients and had more cardiovascular risk factors and more severe angina; however, their coronary artery disease as assessed by angiography was similar. Despite similar rates of angiographic success and clinical success, women had more initial complications and a considerably higher procedural mortality rate (2.6% versus 0.3%). For patients who survived the initial procedure, however, 4-year survival was similar for men and women (177). More recent reports, however, have found fewer or no outcome differences between women and men after PCI. The Bypass Angioplasty Revascularization Investigation (BARI) (180) analyzed 489 women and 1340 men and showed no gender differences in either early or late mortality after PCI and CABG. Other recent studies (181-183) focusing on newer treatment strategies such as the use of drug eluting stents, have reported improved outcomes in women with result similar to men.

Coronary artery size has been attributed an important role in worsening outcomes of women undergoing coronary revascularization. In this regard, gender is a strong, independent predictor of coronary artery size, even when taking into account differences in body size (184). However, despite having smaller vessel size and worse outcomes, women present with a lower risk of restenosis after coronary stenting (185). Differences in coronary artery dimensions may, therefore, explain some, but not all the excess gender-related risk with coronary artery revascularization, underscoring the importance of other factors (186).

Clinical Management

Diagnostic Strategies

Physicians tend to underestimate cardiovascular risk in women, and this may lead to missed or delayed diagnoses of IHD in women (187). Based on recent data from the United States' Center of Disease Control (CDC), women are more likely to die of a cardiac arrest before hospital arrival (52%) as compared with men (43%) (188); this difference could be due to failure of detection or prevention of IHD in women relative to men. The diagnosis of ischemic heart disease in women is hampered by several difficulties, which can be partly explained by gender-related differences in the prevalence of IHD and its risk factors and in clinical manifestation. For a sizeable proportion of women presenting for chest pain evaluation, our traditional diagnostic strategies that focus on detection of severe coronary stenosis may be inadequate. Unique challenges in the evaluation of IHD in women include greater symptom burden, higher rate of functional disability, and lower prevalence of obstructive coronary artery disease as compared with men.

Exercise Electrocardiogram. The exercise ECG is the most frequently performed diagnostic test to assess IHD and often represents the first investigational step for women presenting with chest pain. Using the threshold of 1.0 mm ST-segment depression to define abnormality, the diagnostic accuracy is lower in women (sensitivity and specificity ranging from 60 to 70%) compared to men (reaching about 80%). This lower accuracy in women is in part related to functional impairment, precluding women to perform adequate exercise stress. In fact women are often incapable to perform > 5 metabolic equivalents (METs) of treadmill exercise testing, leading to inadequate heart rate responses (189). In sedentary women an early hyper-exaggerated heart response associated with excessive dyspnea and premature fatigue can be seen already after a few minutes of exercise, in particular with the Bruce protocol. Additional reasons leading to diminished accuracy of stress ECG testing in women include ST-segment abnormalities due to menstrual cycle or other hormonal changes such as peri-menopause (190-

192) and lower QRS voltage. The diagnostic accuracy can be improved by using imaging-based testing such as single-photon emission tomography (SPECT) myocardial perfusion imaging, stress echocardiography or magnetic resonance imaging (MRI).

Myocardial Perfusion Single-Photon Emission Computed Tomography (SPECT). The assessment of stress-induced myocardial perfusion abnormality using SPECT is the most commonly used nuclear-based technique for the investigation of women presenting with chest pain symptoms (193). The diagnostic accuracy is higher than for exercise ECG testing and reaches a sensitivity of 85% and specificity of 70% (189, 194). The accuracy is, however, lower in women with limited exercise capability. For this reason, pharmacologic stress using adenosine or dipyridamole is often recommended. In addition, in order to reduce soft tissue attenuation artifacts (due to voluminous breast tissue or obesity) the higher energy technetium (Tc-99m) radioisotope is preferred in women (195). Additionally, the analysis of global and regional left ventricular wall motion and function, as well as wall thickness, can increase diagnostic specificity and, therefore, reduce false positive tests. Computer algorithms for attenuation correction of SPECT imaging have also resulted in dramatic improvement in diagnostic accuracy for women with chest pain.

Another challenge with the use of SPECT imaging in women is due to their smaller heart size and, consequently, potentially smaller myocardial areas with reduced perfusion that may be missed by currently available SPECT cameras with limited spatial resolution. Since SPECT perfusion defects are identified based upon differences in regional blood flow distribution normalized across the entire myocardium, it is possible that in the setting of global coronary vascular dysfunction SPECT may miss regional defects despite severe ischemia. This could be the case for three-vessel disease or left main coronary disease in conjunction with a left dominant coronary artery, where global ischemia could be

present. In these cases, the use of both stress echocardiography and MRI may provide unique advantages over SPECT.

Stress Echocardiography. Stress echocardiography is used to assess stress-induced wall motion abnormalities, which appear in ischemic areas. The indisputable advantages of stress echocardiography over nuclear imaging are the lower cost, the absence of radiation exposure and the ability to image both cardiac structure and function. Despite these advantages, echocardiographic techniques can be suboptimal in women due to decreased exercise tolerance, obesity and lung disease limiting acoustic windows. For reasons similar to those discussed before under nuclear stress techniques, pharmacologic stress testing (using dobutamine or dipyridamole) may be preferred in women with reduced exercise capacity (196). In addition, the accuracy of stress echocardiography depends on the experience of the operator. For optimal interpretation, a rapid assessment of multiple echocardiographic views at peak heart rate is essential. Despite these limitations, exercise echocardiography is a highly accurate technique for the detection of IHD in women with a sensitivity of 85% and a specificity of 75% (189, 194).

Cardiac Magnetic Resonance Imaging. Cardiac magnetic resonance imaging has recently emerged as a novel operator-independent diagnostic tool allowing the diagnosis of structural heart disease and ischemia. As for the other imaging techniques, cardiac MRI allows detection of ischemia by using pharmacologic measures to induce myocardial hyperemia, in combination with kinetic analysis of contrast agents. The study of first-pass perfusion is typically performed after 3 minutes of adenosine-induced hyperemia by acquiring 3 to 5 short axis slices (8-10mm thickness) every second heart beat over 40-60 beats. Alternatively, wall motion can be analysed after dobutamine (in analogy to stress echocardiography protocols) to evaluate myocardial viability and ischemia. In a recent meta-analysis, stress-induced wall motion abnormality imaging with MRI demonstrated a sensitivity of 83% and a

specificity 86% compared with coronary angiography; MRI perfusion imaging had a sensitivity of 0.91 and specificity of 0.81 (197). Unfortunately, data specific for women are not available.

MRI imaging with late gadolinium enhancement (in which imaging is performed 10-20 minutes after contrast medium injection) provides additional information in that it enables detection and quantification of myocardial scar tissue. In addition, information of cardiac volumes and function as well as regional motion and wall thickening can be assessed (198-200).

Cardiac MRI may also provide a unique clinical utility for the evaluation of subendocardial ischemia. This technique has been shown to be reproducible, and accurate in comparison with quantitative coronary angiography (201). Accuracy in ischemia detection is superior to SPECT imaging (202) and viability detection is similar to PET imaging (203). Indeed, cardiac MRI was recently used to demonstrate subendocardial hypoperfusion during the intravenous administration of adenosine in women with chest pain without obstructive coronary artery disease (204). Cardiac MRI has therefore the potential to identify certain subgroups of patients with syndrome X who have subendocardial ischemia (205).

In summary, for women with chest pain performing at sub-maximal exercise levels during exercise testing, pharmacologic testing is indicated. In general, given the lower prevalence of obstructive coronary artery disease, the diagnosis of IHD is more complex in women and in general it requires the use of imaging testing such as SPECT, stress echocardiography or magnetic resonance imaging.

Treatment of ACS

Thrombolytic therapy has been shown to reduce mortality similarly in men and women (211). In addition, primary percutaneous coronary intervention for acute coronary syndromes is as effective in women as in men (212). Nevertheless, for many decades authors have denounced that women with ACS are treated less aggressively than men. In recent studies, however, reported differences in treatment by

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sex were small; therefore nowadays one needs to be careful about whether sex differences in treatment are clinically meaningful and whether they indicate true disparities. As the size of cardiovascular databases continues to grow, even tiny differences can become statistically significant. In the Get With the Guidelines–Coronary Artery Disease (GWTG-CAD) database, sex differences in receipt of aspirin and beta-blockers were only 2 percentage points (136). In other large contemporary databases, such as CRUSADE (206), GRACE (171), NRMI (207), CURE (208) and Medicare(209), differences were similarly small. Some studies, however, have reported larger differences by sex in reperfusion therapy among STEMI patients, although results vary (136, 207, 209). In part, these gaps in treatment by sex may derive from bleeding concerns among women. Although larger treatment differences are usually seen for less evidence-based procedures, such as coronary catheterization and revascularization procedures (206-209), even for these interventions it is unclear whether differences reflect true disparities, since women's lower prevalence of obstructive coronary disease at catheterization explained the lower use of revascularization in a number of studies (206, 208).

Perhaps the appropriate question is not if treatments for IHD are the same in women and in men, but whether they *should be* the same. Medical treatment may carry different benefits in men and women. For example, registry data on statin effects suggest that benefits in women with MI are less than in men (215). In contrast, beta blockers substantially improve survival in women, with possibly a greater benefit than in men (216). Men, however, may experience a larger benefit than women from angiotensin-converting enzyme (ACE) inhibitors (217). According to the Committee on Understanding the Biology of Sex and Gender Differences convened by the Institute of Medicine in 2001 (218), acknowledging these differences means we can no longer assume that a given therapy works the same in men and women.

Treatment of Stable Angina

As with men, the main goals of treatment in women with stable angina are, first, to reduce pain and discomfort; second, to reduce subsequent cardiovascular events and death; third, to maximise independence and quality of life; fourth, to avoid the need for hospitalization while at the same time recognizing when emergency care is urgently required; and lastly, to enhance knowledge and understanding or the condition and its treatment. Management strategies are similar in men and women despite uncertainties about sex differences in response to treatment (219-221). The majority of patients recruited to clinical trials have been male making it difficult to derive independent conclusions regarding benefit in females. Furthermore, there are limited data overall regarding the treatment of stable angina and the prevention of major acute cardiovascular events in patients with angina (222).

Lifestyle Changes. Healthy life-style advice is the first-line treatment which should be offered to all women. Reduction of overall risk profile can be achieved through consumption of a healthy diet, maintenance of a healthy weight, stopping smoking, and practicing regular exercise. As women with stable angina are older than men, the presence of concomitant diseases may limit ability to exercise, while their frequent role in food purchase and preparation creates an opportunity for improvements in diet.

Avoidance of Angina. This can be achieved by (1) slowing down exercise or by taking rest breaks (if physical exertion triggers angina) (2) avoiding large meals and rich foods (if heavy meals trigger angina) (3) avoid stressful or upsetting situations (if emotional stress triggers angina) or learn better ways to handle stress. Notably, stress related symptoms, as opposed to exercise-related symptoms, are common in women.

Pharmacological Intervention for Chest Pain. Women may have more to gain than men when it comes to symptom relief by drug therapy, as they have less obstructive disease and more commonly have vasospastic disease and cardiac Syndrome X angina (222). Clinical trials of drug therapies included

mainly men who are known to have a greater degree of obstructive coronary artery disease. However, women with stable angina should not be deprived of treatment strategies which are deemed efficacious in reducing symptoms and improving quality of life.

Secondary Prevention Treatments. *Acetylsalicylic acid (ASA)*: Elderly female patients have been shown to be less tolerant of low dose ASA, than are their male counterparts. However, this remains a recommended secondary prevention strategy in women (ref?). *Statins*: While there has been recent controversy regarding the use of statins in primary prevention for elderly and female patients, there is no disagreement about their value in the presence of established IHD. As with other drugs, however, there may be sex differences in the pharmacokinetics (absorption, metabolism, and excretion), and hence in the efficacy and risk profile of some statins. *ACE inhibitors:* Three studies of ACE-inhibitor treatment for stable coronary disease (including angina) collectively demonstrated a benefit in women?? (refs??), as has a large meta-analysis of the benefits of these drugs (ref??). *Heart Rate Lowering Drugs*: The strategy of heart rate lowering is designed to reduce myocardial oxygen demand while at the same time increasing the time available for diastolic coronary blood flow. The relative lack of obstructive disease in some women with angina may make this strategy less effective as a method for symptom relief than in men. *Beta-Blockers:* Having a role in prevention of sudden death and myocardial infarction, rate lowering with beta-blockers remains the first-line option for rate control in both men and women. *Diltiazem and verapamil:* Rate lowering calcium channel blockers are much less effective than are beta-blockers or the new selective inhibitors of the cardiac pacemaker current (If channel inhibition). *Ivabradine:* Is effective at treating angina symptoms and extending exercise time. As women have a lower body mass, the relative efficacy of this and other drugs may actually be slightly higher due to higher blood concentrations. For the same reason elderly females with a low body mass index are more likely to develop dose-related intolerance / side effects. *Vasodilating Drugs*: *Nitrates*: are the class of drugs most commonly used to prevent and treat angina, having the main side-effect of headache.

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Kommentar [VV3]: Refs?? Data specifically for women?

This is reported to be more common in patients without obstructive coronary disease – as is more often the case in women. The presence of headache has been suggested as a test to exclude obstructive disease (225). *Calcium channel blockers*: have been shown to be effective in the prevention of hypertension related pathologies such as stroke. This is true for women as much as men. The more frequent presence of vasospasm in women makes this type of drug possibly appropriate for symptom relief. *Nicorandil*: has an evidence base in support of a preventative as well as palliative role in both men and women.

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***Cardiac Rehabilitation*.** Women are less likely to be referred for cardiac rehabilitation after myocardial infarction and heart surgery (refs?), however cardiac rehabilitation remains a major secondary prevention strategy in women as in men. Exercise training within rehabilitation programs encourages women to learn how to exercise safely, strengthen their muscles, and improve stamina. Exercise plans need to be based on individual abilities, needs, and interests. Understanding the nature and causes of stable angina is particularly important in women who have a diagnosis of cardiac Syndrome X. Learning how to cope with the stress of adjusting to a new lifestyle and dealing with fears about the future are particularly important and thus education, counseling, and training is of pivotal importance.

Conclusions and Recommendations for Future Research

Women largely share the same cardiovascular risk factors for IHD as men, however, there are important sex differences in clinical presentation of IHD, prevalence of coronary atherosclerosis, coronary vascular physiology and outcomes of IHD. Experimental data suggest complex differences in the regulation of vasomotor function of microvessels of female and males. These experimental findings contribute to the understanding of sex differences in IHD. On the clinical side, a larger role has been proposed for coronary endothelial dysfunction and microvascular disease in the etiology and prognosis

of IHD in women than in men, but research is limited. Key questions remain about the prevalence of these vascular abnormalities in women with and without symptomatic IHD, and whether they affect women more than men. Finally, more data are needed to explain why women are protected towards IHD until older age, while they have more adverse outcomes after MI despite having less obstructive coronary artery disease. These differences in epidemiology and clinical outcomes between women and men may reflect important aspects of cardiovascular pathophysiology and pathogenesis that differ between the sexes. Eventually, better understanding of these processes may improve the clinical management of IHD in women, because it may help to devise new strategies for prevention, detection, and treatment of IHD that are better tailored to women.

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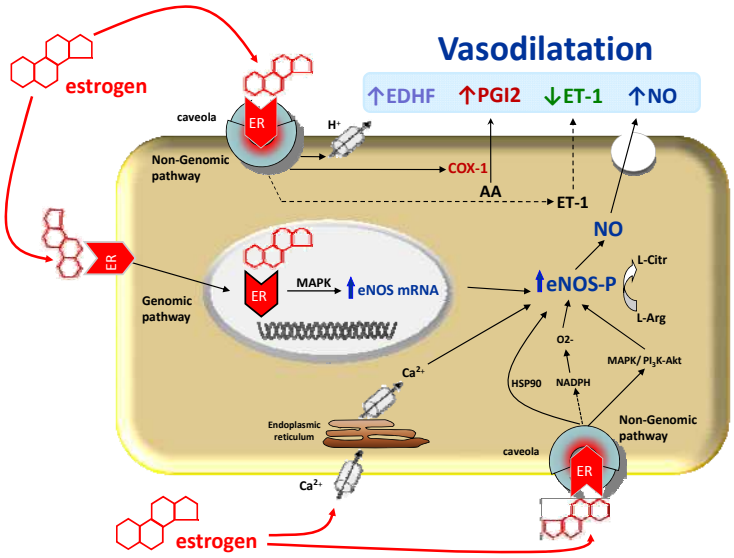

Fig.1

Proposed mechanisms by which estrogen modulates the regulation of vasomotor function.