



Commentary

Issues in cardiovascular disease in women

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ABSTRACT

Cardiovascular disease (CVD) due to atherosclerosis is the most common cause of death of both men and women in developed countries. Despite a lower age-related risk, ultimately more women die of CVD compared to men. Women are also disadvantaged at all stages of diagnosis and management of CVD. Mortality from acute coronary events is higher in women. Even though the lifetime risk in women (1 of 2) is very high, majority of deaths from CVD is preventable in women. Since women develop CVD 10 year later, increased prevalence of associated diabetes, hypertension, and dyslipidemias and other components of metabolic syndrome need special consideration in women with CVD. Therefore, gender-specific approach and awareness of women at risk is crucial. In this review, current evidence and guidelines were discussed according to pathogenesis, risk factors, diagnosis, and treatment of CVD in women.

Key words: *Atherosclerosis, coronary artery disease, endothelium, estrogens, vascular disease, women.*

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Introduction

Cardiovascular disease (CVD) due to atherosclerosis is the most common cause of death in developed countries. The process of atherosclerosis leads to formation of atherosclerotic plaques that ultimately causes development of thrombus and obstruction of lumen. This leads to specific syndromes like acute coronary syndrome or stroke according to involving site [1]. Although it is also the most common cause of death among women, atherosclerosis is typically seen as a disease specific to men. Moreover, compared with men, there is generally a delay in diagnosis and treatment in women [2, 3].

The aim of this review is to discuss the recent advances in cardiovascular care of women and gender-specific approach to the diagnosis and the management of CVD.

Atherogenesis

Atherosclerosis is a multifocal immune inflammatory disease of medium-sized and large arteries fueled by lipids. Lipid retention, oxidation with ensuing chronic inflammation at specific sites, is the underlying disease mechanism [4]. The process of atherosclerosis is thought to begin with fatty streaks and ultimately leads to formation of atherosclerotic plaques. Endothelial cells, leukocytes, and intimal smooth muscle cells are the major players involved in the development of these plaques.

Typically the most important ‘major’ risk factors of atherosclerosis are hypertension, smoking, diabetes mellitus, and hyperlipidemia. Other risk factors are male gender, obesity, family history, certain ethnic origins, and inflammatory markers (e.g. C-reactive protein, cytokines) (**Table 1**). Disease process is thought to be accelerated by atherogenic lipoproteins, the first of which being low-density lipoprotein (LDL) [4].

The knowledge about individual susceptibility and arterial susceptibility to atherogenic stimuli is limited. Atherosclerosis is a complex multifocal arterial disease involving interactions of genetic and environmental factors. Mechanism of formation of plaques is thought to be the same regardless of sex, ethnic group, or other risk factors [4]. However, recent observations from Women’s Ischemia Syndrome Evaluation (WISE) study have raised the debate about gender-based differences in vascular wall, atherosclerotic plaque deposition, pathophysiology and cardiovascular imaging techniques [5]. Genetic polymorphisms also significantly influence the development of atherosclerosis in both men and women [6].

Protective factors against atherothrombosis

Alcohol, exercise, increased high-density lipoprotein cholesterol (HDL-C) and its major apolipoprotein, Apo-A-I, are protective for atherothrombosis. Increased levels of HDL-C and Apo-A-I are associated with slow plaque pro-



gression [7]. Additionally increased low-density lipoprotein cholesterol (LDL-C) level is associated with high risk of atherosclerosis that decreasing LDL-C can lower the incidence of CVD by up to one third [7]. High apolipoprotein B (Apo B) levels are also associated with more atherogenic risk profile [8].

Oxidative stress

Oxidative stress has been proposed as a mechanism for atherosclerosis. Virtually all of the known risk factors for atherosclerosis result in generation of reactive oxygen species in the vascular wall, thus causing endothelial dysfunction. Endothelial dysfunction induces vascular inflammation that may start a vicious cycle of oxidative stress and vascular inflammation ultimately leading to atherosclerosis [10] (Figure 1). Oxidative stress is also thought to play a major role in the development of metabolic syndrome and its major manifestations, namely coronary artery disease, hypertension, and diabetes [11]. Oxidative stress also causes atherogenic dyslipidemia which mainly involves the formation of oxidized LDL [12].

Endothelial cells control vascular hemostasis by mechanisms requiring endothelial-derived nitric oxide (NO) [13]. Increased reactive oxygen species reduce bioactive NO which cause endothelial dysfunction, initial step in the pathogenesis of atherosclerosis [13, 14].

Lifestyle changes and risk modification (Table 1) ameliorates oxidative stress [11]. Pathways involving oxidative stress are also important targets for the development of novel therapeutic agents. Fasudil, a Rho kinase inhibitor, improve endothelial function in smokers [14] and decrease atherosclerotic lesion size in mice [15]. Rho kinases mediate various cell functions including proliferation, migration, adhesion, apoptosis and contraction. NO inhibits RhoA and thought to be involved in the pathogenesis of atherosclerosis.

Risk factors and vascular disease

Evidence indicates that conventional risk factors for atherosclerosis account for the vast majority of incidence for CVD observed in both men and women [16] (Table 1). The prevalence of obstructive CVD in women is relatively low before menopause (average age ~51 years), only approaching equal prevalence rates for men and women in their seventh decade of life [17-19]. Despite the lower age-specific risk in women, total number actual deaths increases with age [20] and ultimately more women will die of CVD [2, 21].

There is gender related variability in the prevalence and outcome associated with the traditional risk factors (Table 1). Overall rates of hypertension and smoking are higher in men, however, for women smokers, mortality risk from cigarettes is equivalent to risk associated with weighting ~42 kg more than her non-smoker counterpart [22].

The total cholesterol values have been reported to be higher in men until fifth decade of life. However, beyond this age, women have higher values [23]. Also, gender differences in HDL levels diminish with advancing age and women have 2-fold higher concentration of large HDL particles when compared to men (8 vs. 4 mmol/l).

Table 1. Risk factors for cardiovascular disease in women [9].

Modifiable risks – risk or prevalence is higher in women than men

- Tobacco use*
- High triglyceride levels*
- Diabetes[†]
- Obesity[†]
- Depression[†]

Modifiable risks – risk is similar in men and women

- High blood pressure
- High total cholesterol
- Low HDL-cholesterol
- Combined hyperlipidemia
- Unhealthy diet
- Physical inactivity
- Stress

Risks for women only

- Oral contraceptive use
- Hormone replacement therapy
- Polycystic ovary syndrome
- Risk of heart attack highest early in each menstrual cycle

Non-modifiable risks for men and women

- Advancing age
- Gender
- Heredity
- Ethnicity/race

* Higher risk among women

† Higher prevalence in women

Women have less atherogenic lipoprotein subclass profiles than men [24]. Hypertriglyceridemia has been reported as more potent independent risk factor for ischemic heart disease (IHD) in men compared to women [18].

Although young diabetic women have a low prevalence of atherosclerosis [25], a significantly higher cardiovascular mortality in diabetic women, as compared with diabetic men, has been reported [26]. This indicates that the di-

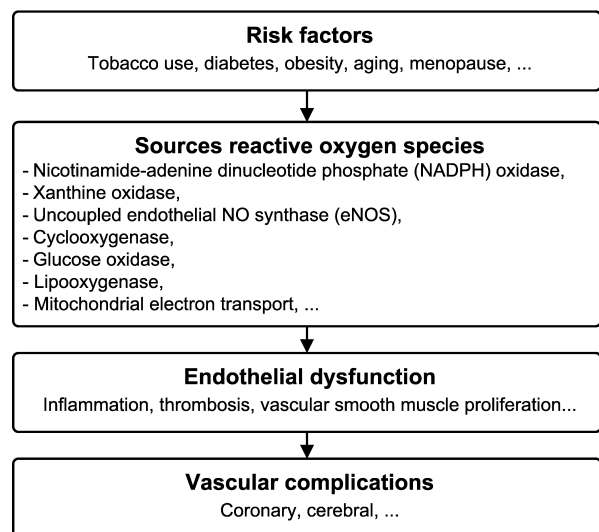


Figure 1. Oxidative stress and development of atherosclerotic vascular disease.

Table 2. Highlights from current guidelines/statements about cardiovascular disease (CVD) in women.

Guideline/Statement	Year*	Highlights with reference to women
American Heart Association (AHA) [33]	2007	<ul style="list-style-type: none"> - Provides the current clinical recommendations for the prevention of CVD in women over 20 years or age. - Considered very high lifetime risk (1 in 2 women), nearly all women are at risk for CVD. - Women with established CVD or multiple risk factors are candidates for more aggressive therapy. - Aspirin therapy should be considered for all women for stroke prevention (but not myocardial infarction) - Hormone replacement therapy, selective estrogen receptor modulators, antioxidant supplements (e.g., Vitamins E, C), folic acid should NOT be used for primary or secondary prevention of CVD in women. - Guidelines for prevention of CVD in women are presented in three headings; Lifestyle changes, major risk interventions, preventive drug interventions.
European Society of Cardiology (ESC) [2, 21]	2007	<ul style="list-style-type: none"> - Since women develop CVD 10 year later, despite lower risk scores, more women ultimately die of CVD compared with men (55% vs. 45%). - Mortality from acute coronary syndromes is higher in women. - Compared with men, women are disadvantaged at all stages of risk assessment, diagnosis and treatment of CVD. - The principles of risk estimation and further management are similar in women. - Diabetes carries a higher risk for fatal CVD in women. - Hormone replacement therapy has not been associated with a reduction in CVD risk.
Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VII) [34]	2003	<ul style="list-style-type: none"> - Gender differences were emphasized in evaluation and treatment. - Unlike hormone replacement therapy, oral contraceptives might be associated with increased risk of hypertension. Development of hypertension is a reason to change contraceptive method. - Separate guidelines for the treatment of chronic hypertension in pregnant women with emphasis to close follow-up, avoidance angiotensin converting enzyme inhibitors and preference of methyldopa, β-blockers, and vasodilators.

* Publication date of guideline/statement.

abetes eliminates the 'female advantage'. Decreased physical activity after menopause (resulting in weight gain, insulin resistance and hypertension) along with the loss of ovarian estrogen (causing male type deposition of abdominal fat) cause significantly increased CVD risk in women [27]. Metabolic alterations associated with obesity are important factors in placing women at risk for CVD and cardiac events. The WISE study has reported that overweight women are more likely to have CVD than normal weight women [28].

Metabolic syndrome represents a clustering of risk conditions namely, insulin resistance, dyslipidemia (high TG, high LDL, and low HDL), hypertension, and abdominal obesity. Women with metabolic syndrome have an increased prevalence of subclinical disease and are at immediate cardiovascular mortality risk [29]. Also, women having a history of polycystic ovary syndrome (PCOS) have an increased frequency of multiple risk factors like central obesity, insulin resistance, diabetes, and other manifestations of metabolic syndrome and hence increased risk of CVD [30, 31]. However, not all women with PCOS share the same cardiovascular risk profiles [32].

Estradiol, the predominant estrogen in premenopausal years, has been hypothesized to provide relative protection from CVD in premenopausal period. The postmenopausal women have estrone produced by peripheral conversion of androgens in adipose tissue. Animal studies have demonstrated antiatherogenic effects, reduction of cellular hypertrophy, anti-oxidative and anti-inflammatory properties of

estrogen [35]. Studies have suggested that premenopausal estrogen deficiency due to central ovarian failure may be a potent risk factor for IHD [36]. These gender-based differences in CVD prevalence might be due to the fact that androgens have been shown to express atherosclerotic genes in men but not in women [37].

Evidences indicate that traditional risk factors of CVD underestimate the risk in women [38]. In addition, novel risk markers namely, inflammatory markers (high sensitivity C-reactive protein (hsCRP), fibrinogen, IL-6), retinal artery narrowing, coronary calcification may provide improved accuracy for the detection of CVD in women [38, 39]. hsCRP measurement provides both diagnostic and prognostic value in estimating cardiovascular events in large epidemiologic cohorts of women [39]. Also, hsCRP has been related to other cardiovascular risk markers like metabolic syndrome, type 2 diabetes, and congestive heart failure [40].

Vascular disease risk conditions

Considerable experimental and clinical data indicate that sex has an important influence on cardiovascular physiology and women with IHD have more severe form of vascular disease compared with men [41]. In some cases vascular disease risk factors might be unique for women. These factors include peripartum conditions (hypertensive disorders of pregnancy, gestational diabetes, coronary or aortic root dissection and delivery of small for gestational age baby), polycystic ovary syndrome, hypoenestrogenemia (hypothalamic in origin).

Table 3. Important studies and their significant findings with special interest to women.

Study	Year	Type of study and enrollment	Findings
Nurses' Health Study ¹ [42]	1976	- Observational study (over 238 000 nurse participants)	- Determine the relationships of hormonal factors, a variety of nutrients, diabetes, exercise, and brand of cigarettes smoked with the subsequent risk of coronary heart disease, pulmonary embolism, and stroke in a cohort of registered female nurses. - Smoking four to five cigarettes a day almost doubles the CVD risk.
Women's Health Study ² [43, 44]	1991	- Randomized, double-blind, placebo-controlled trial using a 2x2 factorial design (39 876 women)	- Effect of vitamin E and aspirin compared with placebo on all important vascular events in women over 45 years of age. - Aspirin lowered the risk of stroke without affecting the risk of myocardial infarction or death from cardiovascular causes.
Women's Ischemia Syndrome Evaluation (WISE) ³ [28, 45-47]	2001	- Interventional diagnostic study (women over 18 years who have suspected ischemic heart disease)	- Aimed to evaluate innovative diagnostic methods that will improve the diagnostic reliability of cardiovascular testing in evaluation of ischemic heart disease in women. - Ischemia due to vascular dysfunction plays an important role in women that obstructive lesion strategy <i>per se</i> is incomplete for management of women. - Stress echocardiography and SPECT imaging techniques have a high degree of accuracy two- to five-year event-free survival in women with chest pain symptoms.
INTERHEART study [16]	2004	- Case-control study (15 152 cases and 14 820 controls were enrolled from 52 countries)	- Investigated the effects of modifiable risk factors on myocardial infarction (MI). - Nine factors were investigated; smoking, history of hypertension or diabetes, waist/hip ratio, dietary patterns, physical activity, consumption of alcohol, blood apolipoproteins, and psychosocial factors. - These factors are important in the etiology of MI irrespective of geographic location and gender.
European Heart Surveys in Angina ⁴ [3, 48]	2003	- Prospective study including 3779 ambulatory patients with new-onset stable angina presenting to a cardiologist as an outpatient.	- Noninvasive and invasive diagnostic procedures including coronary revascularization are less likely to be performed in women (especially over 70 years of age).
MRC/BHF Heart Protection Trial (HPS) ⁵ [49-51]	1994	- Randomized placebo controlled trial (20 536 high-risk individuals, 5082 women)	- Use of statin and vitamin supplementation in high risk population for cardiovascular disease. - Significant reduction in all-cause mortality and a 24% reduction in vascular events. - Women had the same benefits as men.
Lyon Heart Study ⁶ [52]	1994	- Randomized single-blinded secondary prevention trial (605 men and women)	- Determine the significance of Mediterranean diet in secondary prevention of coronary heart disease. - Alpha-linolenic acid-rich Mediterranean diet seems to be more efficient than presently used diets in the secondary prevention of coronary events and death.

¹ Nurses' Health Study started in 1976 and extended in 1989.

<http://www.channing.harvard.edu/nhs/>

² Women's Health Study started in 1991 and completed in 2009.

<http://clinicaltrials.gov/ct/show/NCT00000479>

³ Started in 2001 and completed in 2007.

<http://clinicaltrials.gov/ct2/show/NCT00000554>

⁴ Euro Heart Survey (EHS) is an international clinical research program implemented by European Society of Cardiology (since 1999). Euro Heart Survey on Angina is the survey of EHS on angina pectoris, completed in 2003.

<http://www.escardio.org/GUIDELINES-SURVEYS/EHS/ANGINA-PECTORIS/Pages/ehs-on-angina.aspx>

⁵ Study was held between 1994 and 1997. Main results were posted in 2002, stroke results were posted in 2004.

<http://www.ctsu.ox.ac.uk/~hps/>

⁶ <http://www.americanheart.org/presenter.jhtml?identifier=4655>

Hypertensive disorders of pregnancy are associated with significant increase in IHD later in mother's life [53, 54]. Gestational diabetes occurs in 2% to 9% of pregnancies results in sustained glucose intolerance or diabetes in most

cases and eventually vascular disease and IHD [55]. Women delivering small for gestational age babies and very thin babies are also at increased risk for IHD since they have impaired vascular function that interferes with placental

function. These peripartum conditions play a role in life-long risk for IHD in women and have been linked to oxidative stress, endothelial dysfunction, insulin resistance, defective angiogenesis, and dyslipidemia [16, 56-59].

A number of epidemiologic studies have shown that women who had a history of preeclampsia are at increased risk for CVD later in life [54, 60]. Because preeclampsia is now considered a vascular endothelial disease, preeclampsia and CVD share many risk factors. Several risk factors predispose the development of atherosclerosis as well as preeclampsia: obesity, diabetes, thrombophilia, hypercholesterolemia, advanced age, dyslipidemia, hyperhomocysteinemia and pre-existing hypertension. Preeclampsia is an independent risk factor for CVD even after adjusting for other risk factors [61]. In addition, a strong family history of aggregate cardiovascular risk increases the likelihood for developing preeclampsia and transient hypertension of pregnancy [62]. Parallel pathophysiologic consequences of preeclampsia and atherosclerotic disease has been suggested by others [61]. Atherosclerosis, like preeclampsia, is associated with endothelial dysfunction, which may be caused by oxidative stress and subsequent lipid peroxidation, hyperlipidemia or hyperhomocysteinemia [61]. Women with a history of preeclampsia should be informed that they might have an increased risk for cardiovascular disease.

Gender-specific differences with regard to cardiovascular risk

Lerman and Sopko [28] have concluded that about one half of the women referred to a cardiology setup for suspected ischemia do not have obstructive coronary disease, yet their prognosis is not benign in terms of future events and persistent symptoms. There is no "typical" clinical presentation for women with IHD. Women with coronary artery disease (CAD) are more likely to suffer death or myocardial infarction and less likely to have completely successful treatment of angina [3]. Increased awareness of women at risk of IHD and a gender-based approach is necessary for diagnosis before progression of disease (**Table 2**).

There are gender-specific differences in process of risk factors and atherosclerotic responses. Etiology and symptomatology of the chest pain in women is not well understood. Probably decades of relatively higher levels of inflammation, coupled with risk factors occurring after a loss of estrogen during menopause may cause more frequent endothelial dysfunction resulting in atherogenesis. High estrogen levels before menopause and decreasing estrogen and progesterone levels after menopause are believed to influence IHD in women. Possibly variation in plasma sex hormones and receptor genes influence vascular endothelium and vascular smooth muscle factors resulting in gender-differences in vascular structure and function contributing to genesis of IHD.

Vascular structure

Intravascular ultrasound assessment of coronary artery size has revealed the gender-related differences in size. Independent of the body size, coronary arteries of women are smaller than men [63]. Also, unique remodeling of female vessels occurs during and after pregnancy. This is consi-

dered as physiologic remodeling of vessels, but in the presence of peripartum conditions linked with IHD, this difference might become pathologic. Gender-related difference in remodeling has been described in cardiac transplant recipients and transgender patients. In a longitudinal study in transplanted female hearts, in women little change was observed in coronary arterial size, but, when transplanted to men showed progressive coronary enlargement and left ventricular hypertrophy independent of the body size [64]. Estrogen intake in genetic men cause smaller brachial artery size and androgen intake in genetic women cause larger brachial arterial size as compared to controls [65, 66]. These findings indicate that androgens cause enlargement of arteries i.e. positive remodeling which may be a marker of vascular injury and explains the phenomenon of high event rate in females with non-obstructive coronary angiographic findings [65]. Evidence from intravascular ultrasound and autopsy data support the role of sex-hormone-mediated positive remodeling in women whereby greater atherosclerotic storage may be promoted minimizing luminal intrusion of plaque [67] and a similar phenomenon has been reported after cardiac transplantation [68]. Structurally, women's coronary vessels are smaller in size and appear to contain more diffuse microvasculature. These micro vessels appear to be more dysfunctional compared with men [69]. Vessels in women might show impaired vasodilator responses [70].

Vascular function

Since women's vessels spend considerable time under widely varying hormonal influences (e.g. puberty, pregnancy, peripartum, and menopause), vascular responses might be more profound compared with men. Evidence indicates that combination of smaller arterial size, potentially more prominent positive remodeling, and a greater role of microvasculature, namely, retinal artery narrowing or coronary calcification, carry an increased risk [71]. Also, smaller arterial size contributes to the lower rates of success with revascularization strategies and more frequent angina [72].

Endothelial function

Cardiovascular risk factors activate a number of pro-oxidative processes that reduce the bioavailability of nitric oxide as part of the transition from normal endothelial function to endothelial dysfunction [73]. In the WISE study, coronary endothelial function studied using acetylcholine demonstrated almost 75% had mild or no angiographic CAD, and during a 4-year follow up cardiovascular events were independently predicted by coronary vascular endothelial function [70]. Vascular injury resulting in endothelial dysfunction has been linked to positive remodeling of large coronary arteries without flow-limiting lesions [74].

Normal vascular endothelial repair may be adequate for the injury, but over time, repair processes may become inadequate due to many reasons namely, loss of estrogen, overwhelming oxidative stress, metabolic syndrome, hypertension, obesity, aging etc. Endothelial progenitor cells (EPCs) derived from bone marrow has been demonstrated to be important in vascular repair and become depleted in individuals with multiple risk conditions [75]. The

balance between injury and repair is thought to be the major determinant of cardiovascular disease progression, with EPCs playing an important role in vascular repair. Also, EPC activity can be stimulated with statin therapy raises the possibility that risk improvement may be partly mediated by restoration of EPC function [76, 77].

Unique conditions associated with endothelial dysfunction in women namely pregnancy-associated hypertension or metabolic disorders make such women more vulnerable to develop IHD [78-83]. Thus, women are more vulnerable to continuing injury leading to more atherosclerosis than those with other high risk conditions. The accelerated apoptosis of injured endothelium and defective repair by an exhausted or senescent progenitor pool affect the prevalence and progression of atherosclerotic disease progress. EPC release is stimulated by menstrual cycle in premenopausal women and it can be speculated that the lower susceptibility to atherosclerotic disease in this subset is at least partially explained by the increased availability of repair mechanisms. Also, in the WISE study, it was observed that anemia is an important risk factor for atherosclerosis [39, 75]. However, it is not clear whether anemia is a manifestation of a defect in bone marrow hematopoietic progenitor cell pool or not.

Factors affecting diagnostic testing in women

The currently available diagnostic test in symptomatic women include exercise ECG evaluation, stress echocardiography, single photon emission computed tomography (SPECT) imaging, magnetic resonance subendocardial perfusion, spectroscopic imaging and various blood biomarkers. Gender-specific differences are reported in terms of pathophysiology and symptomatology of IHD in women [76, 78, 79, 82]. While interpreting the accuracy of diagnostic testing, menopausal status/menstrual status, current use of hormone replacement therapy should be considered, due to greater prevalence of ischemia in menopausal and luteal phase of menstrual cycle [84, 85].

The WISE study showed that vascular dysfunction plays an important role in women and stress echocardiography and SPECT imaging techniques have a high degree accuracy for near term prognosis [28, 45-47]. European Heart Surveys in Angina study revealed that noninvasive and invasive diagnostic procedures including coronary revascularization are less likely to be performed in women [3, 48] (Table 3).

Conclusion

To conclude, a large body of evidences show gender-related differences in cardiovascular epidemiology with notable difference in disease prevalence and associated clinical outcome for the women. A unique risk profile in women in terms of hyperestrogenemia coupled with adverse effects of a protracted dysmetabolic state, vascular disease-related conditions like hypertensive disorders of pregnancy, gestational diabetes, peripartum dissection, polycystic ovarian syndrome, and postmenopausal state lending support to the notion that women develop a more severe or somewhat different form of vascular disease than men. A better understanding of these findings would pave

the way for new directions for improving management of the vasculopathy underlying CVD in women.

CVD is the most common cause of death in women as in men. Most of the CVD related deaths in women are preventable, therefore gender specific differences should be considered in the management.

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