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Ischemic Heart Disease in Women: A Focus on Risk Factors

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Abstract

Heart disease remains a major contributor to morbidity and mortality in women in the United States and worldwide. This review highlights known and emerging risk factors for ischemic heart disease (IHD) in women. Traditional Framingham risk factors such as hypertension, hyperlipidemia, diabetes, smoking, as well as lifestyle habits such as unhealthy diet and sedentary lifestyle are all modifiable. Health care providers should be aware of emerging cardiac risk factors in women such as adverse pregnancy outcomes, systemic autoimmune disorders, obstructive sleep apnea, and radiation-induced heart disease; psychosocial factors such as mental stress, depression, anxiety, low socioeconomic status, and work and marital stress play an important role in IHD in women. Appropriate recognition and management of an array of risk factors is imperative given the growing burden of IHD and need to deliver cost-effective, quality care for women.

Keywords

women; ischemic heart disease; cardiac risk factors

Background

Despite the decline in (IHD) mortality in both women and men, women remain the majority who die from cardiovascular disease (CVD), with an estimated 515,000 women each year diagnosed with coronary heart disease (CHD) ¹. Furthermore, data indicate that CVD mortality among young women between the ages of 35–54 is increasing ¹. Traditional and non-traditional risk factors contribute to development of IHD in both women and men, but some risk factors are unique to women (e.g. pregnancy-related complications) or selectively disadvantage women (e.g. depression). This review highlights known and emerging risk factors for IHD in women (Figure). Many risk factors are implicated in IHD in women;

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while some risk factors are causal (i.e. hypertension, smoking, dyslipidemia), many risk factors are associative (i.e. depression) and it is often difficult to determine the exact contribution of non-traditional risk factors in isolation. The impact of non-traditional risk factors on IHD in women may be higher than in men due to the increased prevalence of certain risk factors in women; however, the pathophysiologic relationship between IHD and non-traditional risk factors such as mental stress-induced ischemia, depression, and anxiety in women is not clearly understood but is an active area of investigation ^{2, 3}.

Risk Factors

Framingham Risk Factors and Risk Equivalents

While clinicians have relied on the Framingham Risk Score (FRS) to assess CVD risk, data show that FRS underestimates risk in women and classifies 90% of women as low risk ⁴. The 2013 ACC/AHA guidelines on the assessment of CVD risk recommend estimating a 10-year or lifetime atherosclerotic CVD risk derived from pooled cohort equations that take into account diverse ethnic populations and stroke risk in women ⁵.

Hypertension

Hypertension underdiagnosed and undertreated remains a major risk factor for IHD in women ¹. The prevalence of hypertension in women and men continues to increase, and it is estimated that lifetime risk of developing hypertension is at least 90% ⁶. Hypertension significantly increases the risk of myocardial infarction, heart failure, atrial fibrillation, stroke, and renal failure. Identification and treatment of hypertension is imperative and despite the many anti-hypertensive medications available, only one of two hypertensive Americans are adequately treated ⁷. Pre-menopausal women are at a higher risk of hypertensive end-organ damage than age-matched men, including microalbuminuria and left ventricular hypertrophy ⁸. Blood pressure (BP) increases during the menopausal transition may be related to the decline in estrogen levels, which leads to upregulation of the renin-angiotensin system, production of vasoconstrictive factors such as endothelin, and increased salt sensitivity ⁹. Over age 65, hypertension prevalence is higher in women than men, but less than half receive adequate treatment ^{10, 11}. The prevalence of hypertension is 25.3% among Hispanic women, and only 37.5% have controlled BP ¹². Untreated white-coat hypertension is also associated with increased CVD risk and ambulatory BP monitoring has demonstrated that more women have “white coat” hypertension than men ^{13, 14}. The 2014 hypertension guidelines are controversial and may selectively disadvantage women 60 years and older by raising the SBP threshold for initiation of treatment, given that recent NHANES data document that 62% of hypertensive Americans are women and over 40% of these are African American. Older women and African Americans are known to be at high risk for stroke, CKD, and heart failure complications due to hypertension ¹⁵.

Hyperlipidemia

Elevated serum lipid levels are the greatest contributor to development of IHD worldwide, and clinical trials have shown that low density lipoprotein cholesterol (LDL-C) reduction with statins leads to improved CVD outcomes ^{16, 17}. The 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol advocates comparable initiation of statins in women and

men with LDL-C > 190 mg/dL or an estimated 10-year ASCVD risk of 7.5%¹⁷. Statin therapy has similar proportional benefits for women and men in CVD event reduction¹⁸. Among the elderly, women are 20% less likely than men to use statins¹⁹. This may reflect a potential higher vulnerability of elderly women to statin-induced myalgia or underprescription to this population, although data are lacking²⁰. High non-HDL-C and triglyceride levels are more important CVD risk factors in women than men, especially women with diabetes^{21, 22}.

Smoking

Tobacco use increases IHD risk, including progression of atherosclerosis, myocardial infarction (MI), and sudden cardiac death. Tobacco use is increasing among teenagers and young adults; and in particular, women use smoking as a weight management strategy. Smoking is a stronger risk factor for MI in middle-aged women compared to men, with a 6 fold increased risk vs. 3 fold increased risk in men²³. Smoking as few as 2–3 cigarettes daily increases risk of CVD; with cessation risk decreases substantially within 3 years²⁴. Tobacco is the most common preventable cause of heart disease; smoking status should be addressed at each visit and avoidance of environmental tobacco exposure recommended^{25, 26}.

Diabetes

A diabetic woman is at 4–6 times increased risk of developing IHD compared to 2–3 times increased risk in a diabetic man^{27–29}. The greater impact of diabetes on women may be partially due to a greater increase in adiposity and insulin resistance in diabetic women³⁰. Multiple studies indicate that diabetes is a stronger prognostic predictor of mortality in women than in men³¹. Early diagnosis of diabetes is essential, particularly in ethnic groups at high risk for diabetes such as African Americans, Hispanics, American Indians, and Pacific Islander Americans. While glucose-lowering therapy reduces microvascular complications, data are inconclusive whether treatment of hyperglycemia reduces macrovascular complications³².

Peripheral Arterial Disease (PAD)

PAD is a risk equivalent for IHD, and both share risk factors such as hypertension, diabetes and smoking. Ankle-brachial-index to screen for PAD is an inexpensive test for risk stratification in women and men, but unfortunately is not reimbursed for use for cardiac risk stratification by most payers. In women and men with stable IHD and PAD, depression was independently associated with PAD in women, and smoking and elevated fibrinogen levels with PAD in men³³. Women with PAD who undergo vascular intervention are more likely to be older, have more severe and complex disease, and are at risk of adverse outcomes with higher rates of transfusion and embolism, although they have similar procedural success as men³⁴. In the Jackson Heart Study of women and men (mean age of 55), lower ankle-brachial index was associated with coronary artery calcification³⁵.

Chronic Kidney Disease (CKD)

CKD is an IHD risk equivalent in both women and men³⁶. Risk factors such as hypertension, hyperlipidemia, and diabetes are higher in those with a reduced glomerular filtration rate, and CKD is associated with coronary artery calcification independent of traditional risk factors³⁷. In the Women's Ischemia Syndrome Evaluation (WISE) Study, women with serum creatinine of 1.2 to 1.9 mg/dL were more likely to have significant angiographic stenosis (50% stenosis in 1 coronary artery) compared to women with a normal serum creatinine (61% vs. 37%; $p<0.001$)³⁸. Mortality from end stage renal disease is high, and approximately 50% of CKD deaths are related to CVD. In a large community based population, as estimated GFR decreased, rates of hospitalization, CVD events, and death increased³⁹.

Non-Framingham Risk Factors

Overweight and Obesity

While elevated BMI is associated with increased fatal and nonfatal IHD in both women and men, sex differences in fat distribution have been implicated in IHD. Females predominantly accumulate subcutaneous fat, whereas men accumulate significantly more visceral fat. Postmenopausal women have increased visceral fat accrual, which has implications for development of insulin resistance, inflammatory responses, and lipolysis⁴⁰. Excess visceral fat and pericardial fat are prominent risk factors for CVD morbidities independent of traditional measures of obesity⁴¹. Several CVD risk factors are significantly associated with overweight and obesity. In particular, hypertension has a strong association with being overweight (OR=2.1) and obese (OR=5.2) in women, and diabetes has a strong association with abdominal obesity (OR=3.9) in women⁴². Weight loss improves cholesterol profiles, lowers blood pressure, and reduces the risk of developing diabetes⁴³.

Current ACC/AHA/The Obesity Society (TOS) guidelines recommend that health care providers should measure waist circumference and calculate BMI at least annually, and overweight and obese individuals and women with waist circumference of >35 inches (88 cm) should be counseled regarding their elevated CVD risk⁴⁴. The guidelines recommend for weight loss in women, prescribing a 1,200–1,500 kcal/day diet with a 500–750 kcal/day energy deficit, and referral for nutrition counseling. Providers should strongly recommend a long-term weight loss maintenance program that involves regular contact with a weight loss/nutrition professional. Bariatric surgery can be considered in women with a BMI ≥40 or in those with BMI ≥35 with comorbid condition related to obesity⁴⁴.

Family History

A family history of IHD is present in the majority of patients with premature IHD, but family history is not incorporated in the recent ACC/AHA Atherosclerotic CVD Risk Estimator^{5, 45}. Family history of MI is an independent prognostic indicator of increased IHD risk in both women and men⁴⁶. Gender differences in the impact of family history on IHD risk have been controversial. In a multivariate analysis of traditional Framingham risk factors, family history was predictive of major adverse CVD events in women but there was no significant increased risk in men⁴⁷. A larger study showed gender differences as well.

Examination of the Physician's Health Study and Women's Health Study revealed that a history of maternal MI up to 79 years was associated with increased CVD risk for both sons and daughters, while paternal MI conferred increased CVD risk for sons, but only premature paternal MI (<50 years) conferred increased risk for daughters ⁴⁸.

Metabolic Syndrome

The metabolic syndrome is a clustering of risk factors that increases risk of IHD ⁴⁹. Recent research has focused on the individual risk factors of the metabolic syndrome, and the risk of diabetes increases as the number of components of the syndrome increase^{50,51}.

Dysregulation of metabolic factors such as tumor necrosis factor-3, leptin, and adiponectin contributes to the development of CVD, and serum adiponectin levels predict CVD risk and mortality in men and women ^{52, 53}. Adiponectin may be a novel therapeutic target for metabolic syndrome and CVD ⁵³.

Polycystic Ovary Syndrome (PCOS)

Cardiac risk factors such as diabetes, obesity, hypertension, and metabolic syndrome are prevalent in women with PCOS, and education of such women regarding weight management and exercise can improve their cumulative cardiac risk. Although no long-term outcome studies evaluate increased CVD risk in PCOS, women with PCOS have elevated coronary artery calcium compared to healthy matched controls with normal ovulation ⁵⁴.

Adverse Pregnancy Outcomes

Pregnancy is a metabolic stress test, and serves to predict future CV health. The 2011 guidelines for CVD prevention in women incorporated adverse pregnancy outcomes (APOs) as cardiac risk factors ¹. These include gestational diabetes, pre-eclampsia, eclampsia, and pre-term delivery, all associated with increased future heart disease risk ^{55, 56}. A diagnosis of pre-eclampsia doubles the risk of future diabetes and stroke⁵⁷, and quadruples the risk of hypertension later in life. If woman has a history of preeclampsia, she should be screened within 6 months to 1 year post-partum for hypertension and then screened annually ^{58, 59}. Women with gestational diabetes should be screened within 6 weeks post-partum for diabetes; if they have impaired fasting glucose at 6 weeks post-partum, they should be screened annually ^{60–62}. When assessing a woman's cardiac risk, it is important to obtain a thorough pregnancy history. No outcome data reflect the impact of early treatment of women with APOs, but risk factors should be assessed and current ASCVD prevention guidelines followed.

Systemic Autoimmune Disorders

Systemic autoimmune disorders, such as systemic lupus erythematosus (SLE) and rheumatoid arthritis are highly prevalent in women, and have substantial evidence linking them with increased CVD risk ¹. IHD is a leading cause of morbidity and mortality in SLE patients, and rheumatoid arthritis is associated with a two-to-threefold higher risk of MI and increased CVD mortality ⁶³. Traditional CVD risk factors do not fully explain the substantially increased rate of IHD in patients with SLE, suggesting that underlying chronic inflammation may contribute to increased IHD risk. An increased risk is attributed to

systemic inflammation and rupture of vulnerable plaque⁶⁴. To complicate the matters, treatment for autoimmune disorders involves corticosteroids, which are associated with metabolic syndrome and premature atherosclerosis⁶⁵. Coronary artery calcium may be more predictive of CVD risk than Framingham risk scores in women with SLE and rheumatoid arthritis⁶⁶. Coronary microvascular dysfunction (CMD) has also been suggested to contribute to ischemia and angina in SLE patients without obstructive CAD⁶⁷. The CVD risk of SLE and other autoimmune disorders in men is not well described due to the low prevalence of these conditions in men compared to women.

Radiation Therapy

Chest wall or mediastinal radiation for treatment of malignancies such as Hodgkin's lymphoma and breast cancer is associated with coronary atherosclerosis and IHD, as well as pericardial and valvular disease. The risk of radiation-induced IHD increases in the presence of risk factors, mandating increased risk factor control in such women. Heart disease risk starts within the first 5 years after radiation exposure, and continues to at least 20 years, and rate of events increases by 7.4% per gray of radiation⁶⁸. Left-breast radiation doses to the heart are higher than right-sided breast radiation; left breast and chest wall radiation is associated with mid-left anterior descending, distal diagonal, and proximal right coronary artery atherosclerosis⁶⁹. In women and men, complications of radiation therapy for head and neck cancer include subclavian/carotid artery atherosclerosis and thrombosis; a review demonstrated a dose response relationship between frequency of carotid stenosis and radiation dose exposure⁷⁰. It is critically important to recommend continued screening for secondary and tertiary cancers in these women, while addressing CVD prevention.

Obstructive Sleep Apnea (OSA)

OSA contributes to CVD risk by increased sympathetic drive, oxidative stress, and inflammation⁷¹. Apneic episodes and sleep disordered breathing contribute to systemic and pulmonary hypertension, as well as significant electrical disturbances and a reduction in heart rate variability⁷¹. There are gender differences in presentation of OSA, with women more likely to present with insomnia, have a history of depression and thyroid dysfunction⁷². OSA is more frequently reported in men and may be underdiagnosed in women⁷³. Clinicians should be astute in suspecting and screening for OSA in women as they may present atypical complaints of morning headaches, insomnia, and depression.

Osteopenia/Osteoporosis

Severity of osteoporosis is associated with cardiac events⁷⁴. Women have lower vitamin D levels compared to men, and a low vitamin D level is associated with hypertension, diabetes, and IHD. In Framingham Offspring Study participants, those with low vitamin D levels had a 1.62 times increased events compared to those with higher levels⁷⁵. However, data from NHANES III showed that a low vitamin D level was not associated with increased mortality⁷⁶. No randomized controlled trials have shown any benefit of Vitamin D or calcium supplementation on CVD risk, and at present the use of Vitamin D and calcium is only recommended for bone health and not for primary prevention of CVD⁷⁷⁻⁷⁹.

Anemia

In the Atherosclerosis Risk in Communities (ARIC) study, 13 % of women were anemic (vs. 4.8% men); during a follow-up of 6.1 years, a low hemoglobin level was an independent risk factor for CVD events⁸⁰. In the WISE study, 21% of women were anemic (Hb < 12 g/dL); anemia was not associated with severity of CAD or ejection fraction, but associated with higher risk of adverse outcomes; women with anemia were more likely to have renal dysfunction, diabetes, hypertension, and be non-white⁸¹. While anemia is a risk factor, one of the hypotheses as to why premenopausal women are protected from CAD implicates the monthly iron loss through menstruation as beneficial^{82, 83}.

C-reactive protein

Elevated levels of C-reactive protein (hs-CRP), a marker of inflammation, are associated with increased risk of cardiovascular events. The Reynolds Risk Score⁸⁴ incorporates hs-CRP and family history in an algorithm that improves on the FRS calculation. In the Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER)⁸⁵, rosuvastatin decreased CVD outcomes at 1.9 years in those with LDL <130 mg/dL and hs-CRP > 2 mg/L. Studies have reported a gender difference in hs-CRP prediction of CVD mortality; elevated hs-CRP levels are associated with higher mortality in men compared to women^{86,87}. In a subgroup analysis of JUPITER, the incidence of venous thromboembolism was also significantly reduced in women with the addition of rosuvastatin.

Lifestyle Factors

Alcohol—Alcohol intake has a J-shaped relationship with IHD risk in generally healthy populations, and healthy women are recommended to have no more than one drink per day on average. Excessive alcohol consumption is associated with hyperlipidemia, hypertension, vasoconstriction, hypercoagulability, and a lower ventricular fibrillation threshold⁸⁸. Moderate alcohol consumption is associated with reduced IHD risk, even in higher risk women with type 2 diabetes mellitus⁸⁹. The cardioprotective benefit of moderate alcohol intake may be due to increased HDL-C, increased endothelial vasorelaxation, decrease in platelet aggregation/function, and increased fibrinolysis⁸⁸.

Physical Activity and Cardiac Rehabilitation—Physical inactivity is higher among women than men, especially in non-Hispanic black and Hispanic adults¹¹. In one study of women the population risk of heart disease attributable to physical inactivity outweighed that of other traditional CVD risk factors⁹⁰. By enhancing coronary endothelial function, improving ventricular systolic and diastolic function, and decreasing CVD risk factors, exercise is important for the management of angina and prevention of MI⁹¹.

Cardiac rehabilitation is a cost-effective modality in the treatment of IHD^{92–94}; for improving CVD risk factors, functional capacity, and heart rate recovery^{95, 96}, and for rebuilding patient confidence and overall well-being. Participation in cardiac rehabilitation provides a mortality benefit above usual care alone⁹⁷. It is a Class I indication per ACC/AHA guidelines for stable IHD, MI, post percutaneous coronary intervention and coronary artery bypass grafting, heart failure, as well as valvular heart disease^{98–105}. A

comprehensive cardiac rehabilitation program includes a personalized exercise prescription, smoking cessation counseling, nutrition and weight management education, medication management strategies, and psychological support. Despite its known benefits, women and the elderly are less likely to be referred to cardiac rehabilitation and it is underutilized, particularly among low socioeconomic groups and in rural areas ^{106,92, 107, 108}.

Nutrition—Nutrition is a modifiable risk factor that influences atherogenesis and inflammation. The Mediterranean diet supplemented with extra-virgin olive oil or nuts reduced the incidence of major CV events by ~30% in people at high CV risk ¹⁰⁹. On the other hand, a traditional low-fat dietary approach did not result in CV benefit ¹¹⁰. Trans fatty acid intake has been associated with sudden cardiac death in women with clinical atherosclerosis, as well as overall all-cause mortality^{111, 112}. Adherence to the DASH diet appears to lower blood pressure and risk of heart failure, but does not reduce the risk of sudden cardiac death in postmenopausal women ¹¹³. Recent investigation of the relationship between the intestinal microbiome and IHD has led to improved understanding of the CVD risk of red meat consumption ¹¹⁴. Dietary L-carnitine and phosphatidylcholine are converted to trimethylamine-N-oxide (TMAO) by gut microflora, and increased TMAO levels are associated with CVD events. Atherosclerosis is suppressed in mice when TMAO levels are reduced by administration of antibiotics targeted at intestinal microbes ¹¹⁵. These findings introduce the intestinal microbiome as an exciting new potential therapeutic target for IHD.

Psychosocial Variables

Acute Mental Stress—Acute mental stress-related ischemia, infarction, and arrhythmias occur in both women and men as seen during disasters such as earthquakes and wars ¹¹⁶. A mental stress-associated acute syndrome, stress cardiomyopathy or Takotsubo-cardiomyopathy, is highly prevalent in post-menopausal women (80% of cases) ^{117–119}. It appears related to an abnormal response to a catecholamine surge in the setting of an acute emotional (i.e. death of a spouse) or a physical stressor (i.e. acute respiratory illness) ¹²⁰. Coronary endothelial and non-endothelial microvascular dysfunction (CMD), is a significant contributor to IHD in women, and has been associated with Takotsubo-cardiomyopathy ¹²¹. An important sex-based difference in IHD that has emerged in the past decade is that women and men differ in the degree of epicardial obstructive CAD noted on conventional angiography; coronary endothelial/non-endothelial microvascular dysfunction (CMD) has been proposed as playing a greater role in IHD in women with signs and symptoms of myocardial ischemia and no obstructive CAD. One recent study in women with CMD found that dyslipidemia and elevated BMI was related to CMD, and that the traditional risk factors modestly contribute to CMD (Agrawal M et al. Cardiovascular Diagnostics and Therapeutics 2013;3(3):146–52). It has been hypothesized that factors such as depression may play an important role in CMD and mechanistic links are under investigation. Ischemia from mental stress is more common in younger women (age < 50) post-MI compared to age-matched men ¹²².

Depression—Depression is associated with increased IHD risk and IHD mortality, but is currently not listed as an official risk factor in the guidelines, although recently depression has been proposed to be elevated to status of a CVD risk factor ¹²³. Particularly in young

women (age > 55), depressive symptoms were associated with increased risk of death compared to men > 55 years¹²⁴. Depression was associated with increased risk of CVD and was an independent predictor of CVD death in the Women's Health Initiative (WHI)¹²⁵. In the Nurses Health Study (NHS), depression was associated with fatal IHD events; use of anti-depressant medication was associated with an increased risk of sudden cardiac death¹²⁶. The mechanism by which depression impacts IHD risk is under investigation; while inflammatory biomarkers (CRP and IL-6) are elevated in women with depression, inflammation is felt to explain only a small portion of association between depression and CVD³. Depression is associated with decreased control of modifiable risk factors and lower medication adherence^{127, 128}.

No studies have shown that treatment of depression impacts cardiac mortality. In the ENRICH trial, treatment of depression with cognitive behavioral therapy and selective serotonin reuptake inhibitors did not reduce death or MI¹²⁹. Treatment with sertraline did not improve mortality in patients with heart disease in the Sertraline Antidepressant Heart Attack Randomized Trial (SADHART)¹³⁰. In a more recent trial on pharmacological and non-pharmacological treatment of depression, treatment did not reduce cardiac morbidity or mortality¹³¹. In the Stockholm Women's Intervention Trial for Coronary Heart Disease (SWITCHD), a randomized trial, group-based psychosocial intervention had a protective effect and prolonged life for women hospitalized for CHD¹³². Given that depression is a CVD risk factor, women should be screened for depression using the Patient Health Questionnaire (PHQ-2 or PHQ-9) during routine CVD preventive visits. Depression should be addressed and treated with a mental health provider, as recommended by the AHA and endorsed by the American Psychiatric Association¹³³.

Anxiety—Anxious patients post-MI are at increased risk of new cardiac events, cardiac mortality, and all-cause mortality. A meta-analysis reported that post-MI anxiety is associated with a 36% increased risk of adverse outcomes¹³⁴. In another meta-analysis, anxiety was an independent risk factor for IHD and cardiac mortality¹³⁵.

Anger—Anger is associated with adverse cardiac outcomes in both women and men. The pathogenesis of anger-related cardiac events implicates acute mental stress induced ischemia, coronary vasospasm, endothelial dysfunction in the setting of increased catecholamines, plaque instability, enhanced thrombogenicity, and arrhythmias. In the Atherosclerosis Risk in Communities (ARIC) study, those with normal BP prone to anger were at higher risk of acute MI, revascularization, and cardiac mortality compared to those with a low anger trait, although this association was not present in hypertensive patients¹³⁶. In a case-crossover analysis in the Stockholm Heart Epidemiology Program (SHEEP) of women and men, anger was associated with an increased risk of MI up to one hour after an outburst of anger¹³⁷. A more recent meta-analysis of the association of anger with MI, stroke, ruptured aneurysm, and ventricular arrhythmias, reported increased CV events within 2 hours of anger outburst¹³⁸.

Marital Status—In the Stockholm Female Coronary Risk (FemCorRisk) study cohort of community-based women with IHD, marital stress (but not work stress) predicted poor prognosis at a median follow up of 4.8 years. Women with severe marital stress had a 3x

increased risk of coronary events despite controlling for standard risk factors and left ventricular dysfunction¹³⁹.

Socioeconomic Status (SES)—Lower SES is associated with a slightly higher risk of IHD in women compared to men. Higher burden of modifiable risk factors is found in lower socio-economic status women; and a low SES is inversely related to body mass index¹⁴⁰. In the Women's Health Study, educated women were less likely to smoke, have hypertension, diabetes, or obesity; a decrease in incident CVD events was observed with increasing levels of education and income¹⁴¹. Low socioeconomic status and work stress also increased IHD risk in the FemCorRisk study¹⁴².

Hormones and CVD Risk

Oral Contraceptives (OCPs)—OCPs in young (age < 30 years) healthy women with no risk factors do not represent a major risk factor for IHD. Smoking combined with OCPs increases risk 7-fold¹⁴³. OCP use is associated with a significant increase in diastolic BP and poor hypertension control in hypertensive women, independent of age and weight¹⁴⁴. The fourth generation OCPs (containing drospirenone) can have a BP lowering effect as they have same mechanism of action as spironolactone; they are also associated with a slightly increased risk of VTE¹⁴⁵. The 2010 Centers for Disease Control guidelines recommend progestin-only OCP (level 1) over combined OCP (level 3) in women with controlled hypertension. The risk of MI is increased among second generation OCP (e.g. levonorgestrel) users aged 18–49, and this risk is similar among OCP users regardless of prothrombotic mutation¹⁴⁶.

Menopause and menopausal hormone therapy (MHT)—The incidence of IHD increases after menopause. Declining estrogen levels are implicated, but an altered unfavorable ratio of sex hormones (testosterone/estrogen) may contribute to the risk¹⁴⁷. IHD increases with age in both women and men, and menopause itself may not be an independent risk factor, as other risk factors such as diabetes, hypertension, and metabolic syndrome increase after menopause. Although observational data suggested that hormone therapy may reduce IHD risk, results from the randomized Women's Health Initiative (WHI) indicated that estrogen combined with progestin vs. placebo was associated with adverse outcomes in women. Menopausal hormone therapy is no longer recommended for primary or secondary prevention of IHD¹⁴⁸. Prior to WHI, The Heart and Estrogen/Progestin Replacement Study (HERS) did not report benefit of hormone therapy in women with IHD¹⁴⁹. In a younger middle-aged cohort of post-menopausal women 50–59 years, there was decreased coronary artery calcification in the estrogen arm vs. placebo¹⁵⁰; in the Kronos Early Estrogen Prevention (KEEPS) Study, although use of hormone therapy reduced vasomotor symptoms, there was no difference in coronary artery calcification or carotid intima-medial thickness after 4 years of follow up^{151, 152}. In women with a history of IHD who have significant vasomotor menopausal symptoms, non-hormonal options are available for management of these symptoms which include selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors (SNRI), life style and nutrition adjustments, sleep hygiene, and acupuncture¹⁵³. If an SNRI is initiated, blood pressure should be monitored as these agents can cause hypertension. There are no long-term follow

up data on the recently approved pharmacologic agent for menopause, bazedoxifene (an estrogen agonist and antagonist), to determine its impact on CVD risk.

Knowledge Gaps

While awareness of heart disease as a major health threat to women has increased among women over the past 15 years, awareness appears to have plateaued based on the AHA survey conducted in 2012. Awareness particularly lags behind in African American and Hispanic women. A better understanding of socioeconomic and cultural factors specific to women that pose as barriers for guideline-based preventive strategies is needed. There also remain extensive knowledge gaps in the pathogenesis of how psychosocial risk factors impact IHD in women, and regarding optimal treatment of those risk factors for risk reduction. Several clinically relevant questions regarding primary prevention also remain: Does pre-treatment with statin prevent radiation-induced accelerated atherosclerosis? Does early treatment of cardiac risk factors in women with adverse pregnancy outcomes lead to a significant impact on IHD mortality? Should preventive strategies such as aspirin be recommended in all patients with SLE and other autoimmune disorders if there are no contraindications?

Conclusion

IHD is a significant contributor to morbidity and mortality in women. Traditional Framingham risk factors such as hypertension, hyperlipidemia, diabetes, tobacco use, as well as lifestyle habits such as unhealthy diet and sedentary lifestyle are all modifiable. Health care providers should be aware of emerging risk factors in women such as metabolic syndrome, pregnancy related disorders, autoimmune disorders, sleep apnea, and chronic kidney disease; psychosocial factors such as depression, anxiety, low socioeconomic status, and work and marital stress play an important role in IHD in women. Education of women both in the medical office setting and in the community is important because timely treatment of risk factors can reduce the burden of IHD in women. Appropriate recognition, discussion, education, and treatment of risk factors is imperative given the expected growing burden of IHD in a healthcare system that focuses on delivering cost-effective, quality care for all patients.

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Figure. Ischemic Heart Disease Risk Factors in Women

Many traditional and novel risk factors contribute to the development of IHD through various mechanistic pathways.