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Review

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# Women and Heart Disease: Understanding Risk Factors for Coronary Artery Disease

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## ABSTRACT

Cardiovascular disease (CVD) is the leading cause of death in women in the US. Although the overall death rate due to CVD has decreased recently, it has actually increased in young women. Coronary Artery Disease (CAD), which may lead to myocardial infarction, congestive heart failure, and death, is an important focus for preventive efforts. The impact of traditional cardiovascular risk factors such as family history, diabetes mellitus, hypertension, hyperlipidemia, and smoking differs with gender. Women face unique risks related to pregnancy, menopause, and exogenous estrogen, and are more likely to develop other diseases (e.g autoimmune diseases, breast cancer) whose course or treatment may be complicated by CAD. This article will review CAD risk factors in women, tools to quantify that risk, and interventions to decrease it.

**KEYWORDS:** Women; Cardiovascular disease; Coronary Artery Disease; Risk factors.

**ABBREVIATIONS:** CAD: Coronary Artery Disease; CV: Cardiovascular; CVD: Cardiovascular disease**;** CAC: Coronary Artery Calcium**;** DM: Diabetes Mellitus; HDL: High Density Lipoproteins; hs-CRP: high sensitivity C-reactive protein; LDL: Low Density Lipoprotein; MI: Myocardial Infarction; OSA: Obstructive Sleep Apnea; PCOS: Polycystic ovarian syndrome.

## INTRODUCTION

Cardiovascular disease (CVD), which includes structural and functional disorders of the heart and blood vessels, is the leading cause of death in both men and women in the United States. It causes 25% of overall mortality in women.[1] The number of CVD deaths in the last three decades was higher in women than in men,[2] and the mortality rate attributable to Coronary Artery Disease (CAD) in young women actually increased despite decreased mortality in the general population.[3] Reasons for these trends are complex. Typical symptoms of CAD are sometimes absent or subtle in women. Studies have shown that nearly two-thirds of women who die suddenly of CAD had no previous symptoms that might have triggered treatment.[4] Many CVD risk factors, such as Diabetes Mellitus (DM), High Density Lipoproteins (HDL) and triglyceride levels have greater impact on women than men.[5] Women face unique risks related to pregnancy, menopause, and use of exogenous estrogen for hormone replacement therapy or contraception.[6] Use and efficacy of primary prevention measures may vary in women.[7] Finally, women continue to receive less-aggressive therapy for established CVD despite evidence that they benefit from the same therapies as men.[8] This article will review the risk factors for CAD in women, and interventions to decrease that risk.

## RISK OF CVD RELATED TO SOCIAL FACTORS AND FAMILY HISTORY

### Family History

Clinicians routinely enquire about family history of premature CAD (younger than 50

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years in male first degree relatives or 65 years in female first degree relatives).[9] Yet in a multivariate analysis of traditional risk factors, family history was predictive only in women. Analysis of two large cohorts in the Physician's Health Study and Women's Health Study showed complex relationships. History of maternal Myocardial Infarction (MI) was associated with increased risk for men and women. Paternal MI at any age was associated with increased risk in men, but only premature paternal MI increased risk for women.[10,11]

### Smoking

Smoking tobacco significantly increases Cardiovascular (CV) risk, even in those who smoke fewer than five cigarettes a day.[12] The effect of smoking may be greater in women due to the interactions between components of tobacco smoke and hormonal factors.[13] Since the risk in second hand smokers increases by 25-30%,[14] history of smoking should include these exposures as well. Some markers such as toenail nicotine levels can be used as an objective tool to estimate the average nicotine exposure. One study showed that toenail nicotine levels are predictive of CVD among women, independent of other risk factors.[15]

### Alcohol Consumption

Although moderate consumption of alcohol (no more than one drink a day in women) may be beneficial for the heart health, heavy drinkers are at increased risk of DM, elevated triglycerides, weight gain, hypertension, stroke, heart failure and other cardiovascular diseases. Thus, the American Heart Association recommends against initiating or increasing alcohol consumption to lower CV risk.[16]

### Physical Activity

Sedentary life is associated with increased risk of CVD in women. The Women's Health Initiative study showed that postmenopausal women who sit 10 hours or more a day have a greater incidence of CVD compared with women who sit 5 hours a day or less, regardless of leisure-time physical activity. This risk is significantly augmented in women with both low levels of physical activity and prolonged sitting.[17]

## RISK OF CAD RELATED TO OTHER MEDICAL CONDITIONS

### Hyperlipidemia

Hyperlipidemia is very important risk factor for CAD in both men and women. Higher levels of HDL are associated with lower risk of CAD, but the protective effect varies with gender. Women need higher levels of HDL to have the same level of protection; their threshold is 50 mg/dL, compared with 40 mg/dL in men.[18] While the role of triglycerides in CVD is more controversial, studies have shown that elevated triglycerides and low HDL levels were independent predictors of CVD mortality in elderly women, and that risk quadrupled in women with both conditions.[19]

### Hypertension

The prevalence of hypertension increases with age, particularly for women. In young adults, hypertension is more common in men, but the prevalence equalizes during middle age (45-65 years). After age 65 years, it is more common in women.[20,21] Elderly women also have the lowest rates of hypertension control.[22] Bearing in mind that women live longer than men on average, more attention should be paid to this risk factor to prevent MI, stroke, and heart failure.

### Obstructive Sleep Apnea (OSA)

Obstructive Sleep Apnea (OSA) is defined as recurrent episodes of apnea (lack of breaths) or hypopnea (smaller breaths) during sleep because of soft tissue obstruction of the upper airway. Most frequently this is related to increased neck circumference, but tonsil enlargement and other maxillofacial factors may contribute as well. OSA has been linked to hypertension and arrhythmias, particularly with more frequent and prolonged episodes of apnea.[23] Research has linked OSA to endothelial dysfunction,[24] which can occur with even moderate OSA in women.[25] Severe OSA has been linked with higher mortality from CVD in women.[26]

### Autoimmune Disease

Rheumatoid arthritis and systemic lupus erythematosus, which are more common in women, are associated with increased risk of CVD. In turn, CVD is an important cause of morbidity (e.g. myocardial infarctions) and death in these patients, even controlling for other risk factors.[27] The reasons for these associations are not well understood.

### Obesity

It is estimated that about 64% of American women are now either overweight or obese.[17] For many years, the relationship between obesity and CVD was thought to be due to higher rates of hypertension and DM. However, a 26 year follow-up of participants in the Framingham Heart Study indicated that obesity was a significant independent predictor of CVD, particularly among women.[28]

There are many measures to identify obesity. The most commonly used is the Body Mass Index (BMI), which is calculated using measurements of weight and height. However, other measures that reflect intra-abdominal obesity, such as waist/height ratio and waist/hip ratio, have been found to be better predictors of CVD among middle-aged and older women.[29] Current joint guidelines issued by the American College of Cardiology, American Heart Association, and The Obesity Society recommend that waist circumference and BMI should be obtained at

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least annually. Women with BMI 25 or greater or waist circumference greater than 35 inches (88 cm) should be counseled regarding their elevated CVD risk.[30]

#### Diabetes Mellitus

DM affects about 11% of women in the US.[31] It is considered a "coronary equivalent" – that is, individuals with established diabetes have risk for CAD approaching that of people who have already had an MI. Among people with DM, the risk of CVD is greater for women than men.[32] Furthermore, diabetic women have higher mortality from MI compared to non-diabetic women and men with or without diabetes.[33]

#### Metabolic Syndrome

The metabolic syndrome is a clinical entity defined by the presence of at least three of the following: elevated systolic blood pressure (or treatment for hypertension), elevated blood glucose (or treatment for DM), low HDL cholesterol, high triglycerides, and increased waist circumference.[33] Metabolic syndrome is common, and prevalence increases in women after menopause.[34] A meta-analysis of 37 studies found that metabolic syndrome increases CV risk beyond that associated with its component risk factors, and that CV events and death were higher among women with metabolic syndrome than men.[35]

#### Polycystic ovarian syndrome (PCOS)

PCOS is a clinical syndrome defined by presence of two or more of the following: ovulatory dysfunction, hyperandrogenism, and polycystic ovaries. Between 6-20% of reproductive aged females are affected.[36] Women with PCOS may also meet diagnostic criteria for DM or metabolic syndrome. Controlling for BMI, PCOS has been linked to two-fold higher risk of CVD.[37]

#### Depression

There is a complex relationship between depression, stress, and heart disease that appears to be independent of self-care and adherence to medical therapy. A higher burden of stressors has been associated with worsening atherosclerosis, the underlying pathologic change in CAD.[38] Major depression is associated with changes in the hypothalamic-pituitary-adrenal axis, resulting in elevations of cortisol, a stress hormone that antagonizes insulin, influences fat distribution, and may affect fluid retention.[39] Studies have shown that major depression is a risk factor for congestive heart failure in older women, but not men.[40] Depression is also more common after MI in women than in men.[41]

#### Complications of Pregnancy

A history of certain complications during pregnancy confers long term CV risk. Women with pre-eclampsia and eclampsia may continue to have marked elevations in blood pressure even years after delivery.[42] They have a four-fold higher risk of hypertension and two-fold higher risk of CVD.[42] Similarly, roughly half of women with gestational diabetes develop DM in the future.[43] The placenta is a highly vascular structure; abruption and infarction of it predict future vascular disease like hypertension.[44]

#### Exogenous Estrogen and Progesterone

Use of exogenous estrogen has been linked to elevations in diastolic and systolic blood pressure, particularly at higher doses, and can be prothrombotic.[45,46] Estrogen-containing oral contraceptives should generally be avoided in women with known hypertension, and should not be used in women aged 35 years and older who smoke, as they increase the risk of MI in this population.[47] On the other hand, post-menopausal hormone replacement with estrogen, at doses lower than in oral contraceptives, was once thought to lower the risk for CAD.[48] The Women's Health Initiative, however, found a small increase in the absolute risk for CVD with combined therapy.[49] Due to the side effects associated with using hormonal replacement therapy, the harm of combined therapy, and the small overall net benefit of estrogen alone, the American Heart Association (AHA) has recommended against using hormonal replacement therapy for CVD prevention.[18]

#### Left Chest Wall Irradiation

Breast cancer is the most common cancer in women and localized disease is routinely treated with excision and chest wall irradiation. Other neoplastic conditions, such as esophageal cancer, lung cancer, and lymphoma, can also be treated with thoracic irradiation. Unfortunately, radiation to the left chest wall has been associated with increased risk of cardiac complications because of resulting fibrotic changes within the coronary arteries and other structures. Risk is related to cumulative radiation doses, and is further modified by the presence of other cardiovascular risk factors.[50]

### PREDICTIVE VALUE OF SCREENING TESTS

#### Exercise Stress Testing

Exercise stress testing can provide significant prognostic information in men and women.[51] Two specific abnormalities – reduced exercise capacity and poor heart rate recovery – have been shown to be independent predictors of death in asymptomatic women.[52,53] At this time, however, there is insufficient evidence to support routine screening for asymptomatic or low-risk patients.[54]

#### Coronary Computed Tomography Angiography (CTA)

Coronary CTA is a newer non-invasive test that detects calcium deposition within coronary arteries. The Coronary

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Artery Calcium (CAC) score predicts adverse cardiovascular events,[55] improving assessment of women otherwise classified as low or intermediate risk using traditional risk calculators. It can be used to target statin therapy to those individuals most likely to benefit for primary prevention of CAD, which may have economic benefits.[56] There is also an association between high sensitivity C-reactive protein (hs-CRP) and CAC score in women, but not men.[57]

### hs-CRP

hs-CRP is a marker of inflammation. Elevated hs-CRP levels are associated with increased cardiac risk in older men and women, and higher CV mortality in men but not women.[58] The American Heart Association (AHA) does not endorse its routine use, however, since reducing hs-CRP has not been shown to improve clinical outcomes.[18]

### Uric Acid Level

Uric acid is another biomarker may be useful in identifying women at high risk of CV events. Elevated uric acid levels may negatively affect endothelial function and oxidative metabolism.[59] In a cross-sectional retrospective study of 607 premenopausal women who had undergone coronary angiography, serum uric acid levels were associated with the presence of CAD.[60] This finding was confirmed in patients with transient ischemic attacks or stroke; an elevated uric acid level independently predicted long-term CAD in women but not men.[61] It is as yet unclear whether lowering uric acid levels reduces CVD risk.[62]

## RISK CALCULATORS

It is difficult for busy clinicians to quantify the cumulative risk of multiple predisposing factors in individual patients. Therefore, algorithms have been developed to do so. Overall risk has then guided the use of preventive measures like statin and aspirin therapy in individuals.

The Framingham and American Heart Association (AHA) Risk Scores are the best known and most widely used in the United States. The Framingham score incorporates age, hypertension, hyperlipidemia, diabetes, smoking, and aspects of lifestyle like unhealthy diet and sedentary lifestyle. It does not account for menopausal status or pregnancy.[63] Old American Heart Association guidelines classified women into three risk categories based on the presence of comorbidities (e.g chronic kidney disease, diabetes, hypertension, hyperlipidemia, metabolic syndrome, subclinical atherosclerosis, and systemic autoimmune disease), central adiposity, lifestyle factors (e.g diet, physical inactivity, and exercise tolerance), family history of premature CAD, and history of pregnancy complications (Table 1).[18]

| **High risk (>=1 high-risk states)** |
|---|
| • Clinically manifest CVD<br>• Clinically manifest cerebrovascular disease<br>• Clinically manifest peripheral arterial disease<br>• Abdominal aortic aneurysm<br>• End-stage or chronic kidney disease<br>• Diabetes mellitus<br>• 10-y Predicted CVD risk 10% |
| **At risk (>=1 major risk factor[s])** |
| • Cigarette smoking<br>SBP>120 mm Hg, DBP>80 mm Hg, or treated hypertension<br>• Total cholesterol >200 mg/dL, HDL-C<50 mg/dL, or treated for dyslipidemia<br>• Obesity, particularly central adiposity<br>• Poor diet<br>• Physical inactivity<br>• Family history of premature CVD occurring in first-degree relatives in men <55 y of age or in women<65 y of age<br>• Metabolic syndrome<br>• Evidence of advanced subclinical atherosclerosis (e.g coronary calcification, carotid plaque, or thickened IMT)<br>• Poor exercise capacity on treadmill test and/or abnormal heart rate recovery after stopping exercise<br>• Systemic autoimmune collagen-vascular disease (e.g lupus or rheumatoid arthritis)<br>• History of preeclampsia, gestational diabetes, or pregnancy-induced hypertension |
| **Ideal cardiovascular health (all of these)** |
| • Total cholesterol <200 mg/dL (untreated)<br>• BP <120/80 mm Hg (untreated)<br>• Fasting blood glucose <100 mg/dL (untreated)<br>• Body mass index <25 kg/m2<br>• Abstinence from smoking<br>• Physical activity at goal for adults >20 y of age:<br>150 min/wk moderate intensity,75 min/wk vigorous intensity, or combination<br>• Healthy (DASH-like) diet |

**Table 1:** AHA Classification of CVD Risk in Women.

The new American Heart Association CV risk calculator was introduced in 2014, and includes only age, gender, smoking status, systolic blood pressure, total cholesterol, HDL cholesterol, and DM.[64] Its use has been validated only for whites and blacks, not other ethnic and racial groups.

The Reynolds Risk Score (RRS), unlike the others, was developed using data specifically for women. It adds hs-CRP and parental history of MI before age 60 years to the variables used in the Framingham risk score in an attempt to better risk stratify women.[65]

Unfortunately, none of these tools is perfect. A recent analysis found that Framingham and American Heart Association scores overestimate CV risk in women, while the Reynolds score underestimates it.[66] These scores may help clinicians initiate discussions about CV risk, but their limitations should be acknowledged as part of shared decision making.

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## PREVENTION OF CVD IN WOMEN

Some risk factors are clearly modifiable. Smoking cessation and avoidance of environmental tobacco smoke are well-accepted approaches for preventing MI.[18] Developing healthy lifestyles among young women and maintaining these behaviours through mid life may substantially lower the incidence of CVD.[67] Management of hypertension also lowers CVD risk, although the newest guidelines for blood pressure targets are controversial (Table 2).[68]

| |
|---|
| **High-risk women** |
| • Aspirin therapy (75–325 mg/d) should be used in women with CVD unless contraindicated (Class I; Level of Evidence A). |
| • Aspirin therapy (75–325 mg/d) is reasonable in women with diabetes mellitus unless contraindicated (Class IIa; Level of Evidence B). |
| • If a high-risk woman has an indication but is intolerant of aspirin therapy, clopidogrel should be substituted (Class I; Level of Evidence B). |
| **Other at-risk or healthy women** |
| • Aspirin therapy can be useful in women >65 y of age (81 mg daily or 100 mg every other day) if blood pressure is controlled and benefit for ischemic stroke and MI prevention is likely to outweigh risk of gastrointestinal bleeding and hemorrhagic stroke (Class IIa; Level of Evidence B) |
| • Routine use of aspirin in healthy women<65 years of age is not recommended to prevent MI. (Class III, Level of Evidence B) |

**Table 2:** Use of Aspirin in prevention of CVD in women.

Aspirin has been the cornerstone of prevention for atherosclerotic diseases like MI and stroke for many years, but comes at a price. While aspirin at doses of 81 mg daily or 325 mg every other day[69] lowers risk of MI in men, in women it only lowers risk of thrombotic stroke.[70] Benefits of therapy are partially offset by an increased risk for bleeding.[71]

LDL cholesterol has been a target for CV prevention for several decades. Statin therapy lowers the incidence of CV events, even in people with normal LDL cholesterol levels.[72] Research suggests that this class of medications has beneficial actions that extend beyond its lipid-lowering effects.[73]

Interventions for other metabolic risk factors are variably effective. Tight glycemic control in patients with DM has not been associated with CVD risk reduction.[74] On the other hand, early lifestyle interventions aimed at treating obesity and hyperlipidemia in women with PCOS impact the development and progression of atherosclerosis.[75] For patients with autoimmune disorders, disease modifying agents are preferred over corticosteroids, which have been linked to development of metabolic syndrome and premature atherosclerosis.[76] Biologics such as tumor necrosis factor antagonists and anti-CD40 agents are associated with lower rates of CVD.[77]

## CONCLUSION

The prevention and diagnosis of CVD in women are clinically challenging. Women have unique risk factors that are often underappreciated, including polycystic ovarian syndrome and connective tissue diseases. Other traditional risk factors, such as family history and comorbid conditions, have different predictive values in women. Existing risk calculators can under or overestimate the risk of individual women. Of these, the Reynolds Risk Score (RRS) appears to be the most accurate, but requires an additional laboratory test (hs-CRP). Additional research to refine our risk calculators is needed.

Women at risk for CVD derive benefit from some standard pre ventive therapies, like statins. Current evidence does not support use of aspirin for primary prevention of myocardial infarction in women, and the benefits for ischemic stroke are counter balanced by an increased risk in hemorrhagic stroke.

Women with CAD events may have subtle or atypical symptoms; the majority present with sudden cardiac death as their first event. This finding highlights the need for better primary prevention efforts and for public health outreach and education directed specifically at women.

In summary, CVD is an increasingly important cause of morbidity and mortality in women. Clinical and public health approaches to women at risk for and with CAD should be informed by the known differences of risk, clinical presentation, and response to preventive therapies of women compared to men. Additional research is needed that includes women of child bearing age and the elderly, if we are going to effectively improve health care and outcomes.

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