# Recent Insights in Coronary Artery Disease in Women

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## INTRODUCTION

Cardiovascular disease is the leading cause of death among women, regardless of race or ethnicity, accounting for deaths of 1 in 3 women. Mortality rates for coronary heart disease have fallen for both men and women but the rate of fall is much less in women than men.[1] A greater proportion of women (52 percent) than men (42 percent) with myocardial infarction die of sudden cardiac death before reaching the hospital. The worldwide INTERHEART Study, a large cohort study of more than 52,000 individuals with myocardial infarction, have revealed that women have their first presentation of coronary heart disease approximately 10 years later than men, most commonly after menopause. Despite this delay in onset, mortality from coronary heart disease is increasing more rapidly among women than men.[2]

## CORONARY ARTERY DISEASE RISK FACTORS IN WOMEN

### Age

Prior to the fifth decade of life, prevalence in men is greater than in women, but in the sixth decade, prevalence equalizes and in subsequent decades becomes greater in women.

### Family history

There is influence of sex on variation in the expression of various genes and in the downstream responses to the gene's products. stromelysin-1, a member of the matrix metalloproteinase family of enzymes that are believed to be involved in plaque rupture and plasminogen activator inhibitor-1 (PAI-1) are associated with myocardial infarction in women.[3] Differences in genetic expression by hormones ultimately account for observed differences in the pathophysiology of atherosclerosis including plaque composition (more cellular and fibrous tissue in women),[4] endothelial function (estrogen-induced coronary vasodilation), and hemostasis (higher fibrinogen and factor VII levels in women). Women are twice as likely to have plaque erosion (37 percent in women versus 18 percent in men), and men more frequently have plaque rupture as the underlying inciting event (82 percent in men versus 63 percent in women).[5]

### Race - CAD risk in Asian Indian women

The CAD rates among overseas Asian Indians worldwide are 50% to 400% higher than people of other ethnic origin irrespective of gender, religion, or social class. India is now in the middle of a CAD epidemic with urban Indians having CAD rates similar to overseas Indians, which is 4-fold higher than Americans. Whereas the CAD rates halved in the West in the past 30 years, the rates doubled in India with no signs of a downturn yet. The average age of first myocardial infarction (MI) has decreased by 20 years in India. Among Asian Indian men, about half of all MI occur under the age of 50 and 25% under the age of 40. Apart from glucose intolerance, they have no excess of conventional risk factors such as cigarette smoking, hypertension, and high cholesterol levels. Nearly half of them are life-long vegetarians. This excess burden of premature CAD in Asian Indians is due to a genetic susceptibility, mediated through elevated levels of lipoprotein(a) {Lp(a)}, which magnifies the adverse effects of lifestyle factors associated with urbanization, affluence, and changes in diet. It appears that at a given level of any single or combination of conventional risk factor(s), the CAD rates among Asian Indians are at least double that of Whites.

The excess CAD mortality among Asian Indians is greater in women than in men.[6] Among those studied by coronary

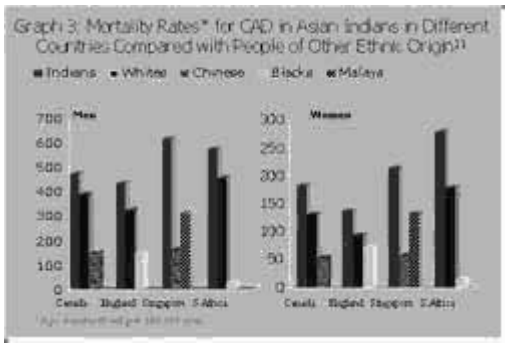


***Fig.1: Mortality rates for CAD in Asian Indians.***[6]

angiogram, three-vessel disease is seen among half of all Asian Indians and one third of premenopausal women. In the U.S., CAD mortality rates are 2-fold higher in Asian Indian women 45-64 years of age than in Whites. In Singapore, CAD mortality among Asian Indian women 30-39 years of age is 8-fold higher than Chinese women of the same age.

**Hypertension**

Women had a 15 percent higher prevalence of hypertension than that in men. The prevalence of increased hypertension reached a significant statistical difference from men beyond 75 years of age.[7] Women with hypertension have more under treatment and poor control than men.

**Diabetes and Metabolic Syndrome**

Both diabetes and metabolic syndrome are equally prevalent in women. Cardiovascular disease is twice as common among women with diabetes as those without, they are four times as likely to be hospitalized, and women have a higher risk for most clinical events than men. The INTERHEART Study confirmed a markedly stronger association of diabetes with myocardial infarction among women compared with men.[2]

**Hyperlipidemia**

The cutoff value for normal HDL levels are higher in women at 50mg/dl compared to men 40mg/dl. There is a rise in triglyceride and LDL cholesterol with menopause.[8]

**Obesity and physical activity**

There is increased prevalence of obesity among females. Most females did not engage in leisure-time physical activity and 18.5 percent were smokers.[9]

**Psychosocial Factors**

Psychosocial factors also tended to associate more strongly with increased risk among women. In addition, healthy life-style choices including regular exercise, fruit and vegetable intake and modest alcohol consumption provided stronger protection among women than men.

| Risk factor | Sex | Control (%) | Case (%) | Odds ratio (99% CI) | PAR (99% CI) |
|---|---|---|---|---|---|
| Current smoking | F | 9.3 | 20.1 | 2.86 (2.36-3.48) | 15.8% (12.9-19.3) |
| | M | 33.0 | 53.1 | 3.05 (2.78-3.33) | 44.0% (40.9-47.2) |
| Diabetes | F | 7.9 | 25.5 | 4.26 (3.51-5.18) | 19.1% (16.8-21.7) |
| | M | 7.4 | 16.2 | 2.67 (2.36-3.02) | 10.1% (8.9-11.4) |
| Hypertension | F | 28.3 | 53.0 | 2.95 (2.57-3.39) | 35.8% (32.1-39.6) |
| | M | 19.7 | 34.6 | 2.32 (2.12-2.53) | 19.5% (17.7-21.5) |
| Abdominal obesity | F | 33.3 | 45.6 | 2.26 (1.90-2.68) | 35.9% (28.9-43.6) |
| | M | 33.3 | 46.5 | 2.24 (2.03-2.47) | 32.1% (28.0-36.5) |
| Psychosocial index | F | - | - | 3.49 (2.41-5.04) | 40.0% (28.6-52.6) |
| | M | - | - | 2.58 (2.11-3.14) | 25.3% (18.2-34.) |
| Fruits/veg | F | 50.3 | 39.4 | 0.58 (0.48-0.71) | 17.8% (12.9-24.1) |
| | M | 39.6 | 34.7 | 0.74 (0.66-0.83) | 10.3% (6.9-15.2) |
| Exercise | F | 16.5 | 9.3 | 0.48 (0.39-0.59) | 37.3% (26.1-50.0) |
| | M | 20.3 | 15.8 | 0.77 (0.69-0.85) | 22.9% (16.9-30.2) |
| Alcohol | F | 11.2 | 6.3 | 0.41 (0.32-0.53) | 46.9% (34.3-60.0) |
| | M | 29.1 | 29.6 | 0.88 (0.81-0.96) | 10.5% (6.1-17.5) |
| ApoB/ApoA1 ratio | F | 14.1 | 27.0 | 4.42 (3.43-5.70) | 52.1% (44.0-60.2) |
| | M | 21.9 | 35.5 | 3.76 (3.23-4.38) | 53.8% (48.3-59.2) |

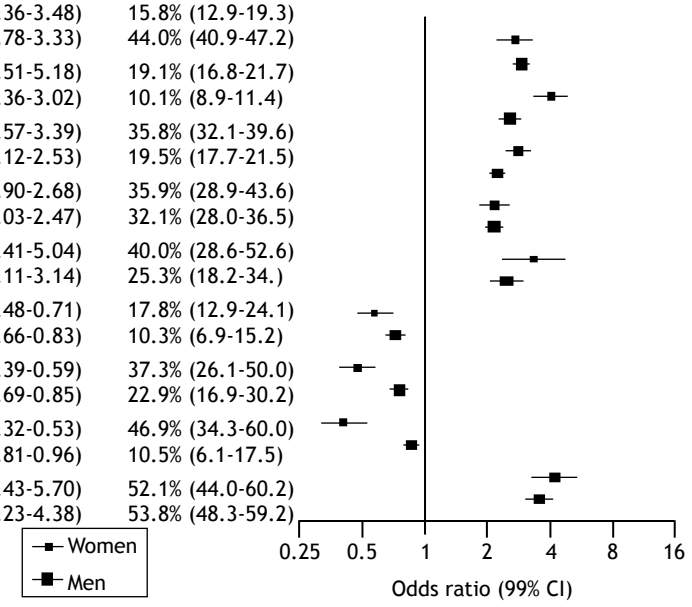


***Fig.2: Relative risks associated with various cardiac risk factors among men (M) and women (F) in the INTERHEART Study.***[2]

## PATTERNS OF PRESENTATION

### Stable Angina

The presentation is with effort-induced angina pectoris, due to reversible myocardial ischemia, caused by obstructive CAD that limits blood flow during periods of increased myocardial oxygen demand. This syndrome did not appear to afflict women until they became elderly with the exception of diabetic women.[10]

### Syndrome X and Microvascular Dysfunction

A more contemporary view includes variable thresholds for ischemia and symptoms that may vary. This view involves ischemia due to dynamic changes in coronary size that also compromise the microcirculation.[11] Endothelial dysfunction, and higher risk of atherosclerosis is prevalent in women with hypertension, diabetes, and dyslipidemia. Coronary angiography has limited symptom assessment, since it depends on the prevalence of obstructive CAD. In the WISE study, only 39% of the women had CAD, defined as over 50% stenosis, in more than one coronary artery. WISE investigators found that the typical angina classification missed 65% of women who actually had CAD.[12] Symptoms experienced by women without CAD may be related to microvascular ischemia or vasospasm of coronary arteries.

### Acute Coronary Syndromes

A study of 127 men and 90 women by Milner and colleagues[13] showed that among patients who presented to the emergency department with symptoms of coronary disease other than chest pain, there were several sex-related differences in symptoms. Dyspnea, nausea/vomiting, indigestion, fatigue, sweating, and arm or shoulder pain as presenting symptoms in the absence of chest pain were all more frequent among women than men.

## INVESTIGATIONS

The American Heart Association (AHA) approved, in 2003, the publication of a summary that points out new methods in evaluating women with chest pain.[14] According to this article, several studies demonstrate the limited value in women undergoing evaluation for CAD of standard stress testing and evaluation of electrocardiographic changes, myocardial perfusion defects, and regional wall motion abnormalities. The document determines perfusion imaging with magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS) as feasible methods for chest pain evaluation. The first method has shown evidence of subendocardial hypoperfusion in the absence of large-vessel obstruction, whereas the MRS also has the potential to detect myocardial ischemia by demonstrating transient reduction in myocardial high energy phosphates and increases in organic phosphate during stress testing. Nevertheless, the Association proposes additional studies to determine their diagnostic accuracy.

Carotid ultrasound, MRI, and test on the functionalty of endothelium have advantages over other invasive techniques in detecting atherosclerosis in its earliest stages. On the other hand, such screening requires sophisticated equipment and skillful expertise.[14] Regarding the invasive techniques, intravascular ultrasound (IVUS) not only visualizes coronary lumen, as does coronary angiography, but also arterial wall characteristics. The WISE IVUS substudy has released preliminary data suggesting that the majority of women without flow limiting lesions had abnormalities of endothelial function and/or microvascular flow reserve, with the potential to limit coronary perfusion.[15]

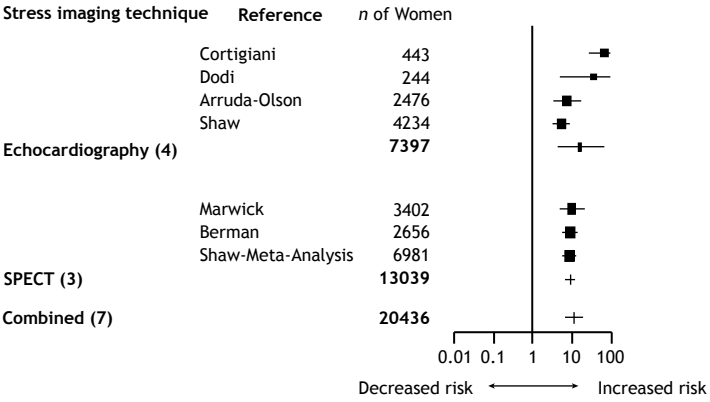


***Fig.3: Prognostic utility of echocardiographic and nuclear stress imaging among women. SPECT = single-photon emission computed tomography.***[16]

## EVIDENCE BASED THERAPY IN WOMEN

The Women's Health Study (WHS) randomized 39,876 healthy women older than 45 years to low-dose aspirin (100 mg on alternate days) and provided important insights into the use of aspirin for primary prevention in women. Whereas the benefit of aspirin in reducing ischemic stroke was consistent across all age groups, only in those older than 65 years did aspirin significantly reduce the risk of nonfatal myocardial infarction.[17]

The Pravastatin or Atorvastatin Evaluation and Infection Trial-Thrombolysis in Myocardial Infarction 22 trial demonstrated the safety and effectiveness of an intensive regimen of 80 mg of atorvastatin to reduce LDL cholesterol to a median of 62 mg/dl in both men and women.[18]

The Women's Health Initiative estrogen-only trial showed that use of hormone replacement therapy in postmenopausal women to prevent first coronary disease event showed no cardiovascular benefit and potential harm with increased incidence of stroke and pulmonary embolus in the estrogen arm.[19]

The ST-segment elevation myocardial infarction (STEMI) guidelines are silent on sex-specific recommendations, providing completely sex- and gender-neutral treatment recommendations.[20] The unstable angina/non-ST-segment elevation myocardial infarction (UA/NSTEMI) guidelines state that women with UA/NSTEMI should be managed in a manner similar to men. Indications for noninvasive and invasive testing are similar in women and men.[21]

A recent meta-analysis of trials of percutaneous coronary intervention (PCI) confirmed that women more frequently suffer vascular complications of their procedures compared with men. Many studies of both elective and primary PCI demonstrate a tendency to higher in-hospital mortality among women than men. However, late mortality was similar between the sexes.[22] Three randomized clinical trials of early invasive strategies for management of NSTEMI showed conflicting results with regard to treatment benefit in women. The FRISC II trial showed that women did worse with the early invasive strategy.[23] The RITA 3 trial showed that results were neutral among women,[24] but the TACTICS-TIMI 18 trial showed that women appeared to benefit from the early invasive strategy.

Women undergoing CABG have a higher risk for perioperative morbidity and mortality. Women have more postoperative depression than men. However, if indicated, CABG should not be delayed or denied to women.[25]

With glycoprotein IIb/IIIa inhibitors, treatment benefit extended to both men and women at high risk for adverse outcomes and that adverse outcomes occurred mostly in low-risk individuals. Women had more bleeding risk compared to men because of advanced age, associated renal impairment as well as lower body weight.[26]

## PROBLEMS OF MANAGING CAD IN WOMEN

Despite CAD being a leading cause of death and morbidity in females, a lot of fallacies remain in treatment and prevention of ischemic heart disease in women. Both the CRUSADE registry in UA/NSTEMI[27] and NRMI-1 investigators[28] in STEMI showed lower rates of use of aspirin, beta blockers, and heparin among women compared with men and later administration of fibrinolytic therapy among women.

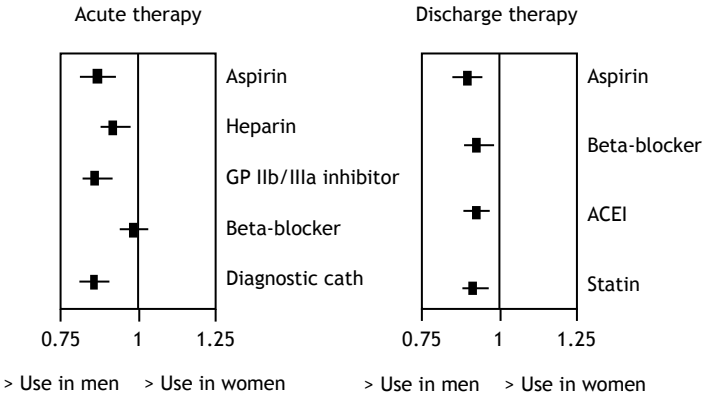


***Fig.4: Use of guidelines-recommended therapies among women compared with men in the CRUSADE registry.***[27]

Women have been under-represented in clinical outcome trials. Women also had nonadherence to long-term use of evidence-based medications in secondary prevention, particularly aspirin, statins, and angiotensin-converting enzyme (ACE) inhibitors. Both women's awareness of disease risk and physicians' awareness about coronary artery disease in women were low. Women are often misdiagnosed when their presenting symptoms differ from those observed in men.[29] Women are less likely than men to participate in cardiac rehabilitation after acute myocardial infarction. More social awareness and guideline recommendations are needed to eradicate this problem.

## CONCLUSION

CAD in women continues to be a major public health problem that represents a leading cause of death and disability. Women have a higher frequency of angina/chest pain than men; however, women have a lower prevalence of obstructive CAD compared with men with similar symptoms. Nevertheless, young women with obstructive CAD experience a significantly worse outcome compared with men with regard to prognosis after myocardial infarction, and older women with obstructive CAD often have greater comorbidities that influence their outcome adversely after acute myocardial infarction or myocardial revascularization than do men. Women presenting with acute coronary syndromes (ACS) are also less likely to receive effective acute diagnostic and treatment strategies than men. Diagnostic evaluation of women with suspected myocardial ischemia and CAD continues to be a major challenge. Gender differences in endogenous pain-modulatory systems may contribute to differences in pain perception. Magnetic

resonance spectroscopy and gadolinium cardiac magnetic resonance imaging may identify patients whose chest pain is due to myocardial ischemia without obstructive CAD. The WISE study and others have suggested that chest pain without flow-limiting lesions by angiography may be associated with endothelial dysfunction and impaired coronary flow reserve.

Better understanding of gender differences in manifestation and detection of myocardial ischemia is a critical initial step to improve outcomes for women. National Heart, Lung and Blood Institute-supported studies such as WISE offer opportunities for both translation and charting new research and educational strategies. Improved understanding of gender differences in ischemic presentation, diagnosis, and management is needed to communicate meaningful messages to the public, patients, and the healthcare community.

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