

Review Article **Cardiovascular**

## Difference of Coronary Artery Disease in Women and Men in Recent Trials

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### ABSTRACT

Coronary artery disease (CAD) is the leading cause of mortality worldwide, affecting both men and women, yet significant differences exist in how the disease manifests, progresses, and responds to treatment in the two genders. Men tend to develop CAD earlier, with classic symptoms such as chest pain, while women often experience atypical symptoms, including fatigue, shortness of breath, and back pain, which can delay diagnosis. Hormonal factors, particularly estrogen, offers protective effects to women before menopause, but the risk increases dramatically post-menopause. Men are more likely to have traditional risk factors like smoking, hypertension, and high cholesterol, whereas women often have additional risk factors, including pregnancy-related complications, early menopause, and autoimmune diseases. Diagnostic challenges in women are heightened by atypical presentations and higher rates of microvascular dysfunction, leading to frequent underdiagnosis. Treatment responses also differ, with women experiencing higher rates of complications and mortality after interventions such as stenting or bypass surgery. Psychosocial factors, including higher rates of depression and anxiety in women, further complicate outcomes. Understanding these gender-specific differences is crucial for improving prevention, early diagnosis, and tailored treatment approaches to reduce the global burden of CAD in both men and women.

**Keywords:** Coronary artery disease, Percutaneous intervention, Coronary artery bypass grafting, Gender differences

### INTRODUCTION

Coronary artery disease (CAD) remains one of the leading causes of death globally, affecting millions of individuals across genders. However, substantial differences exist in the incidence, presentation, risk factors, diagnosis, and treatment of CAD between men and women.<sup>[1]</sup> Historically, research and clinical trials have focused predominantly on men, leading to a gap in understanding gender-specific manifestations and outcomes in CAD. This oversight has contributed to under-recognition and misdiagnosis of CAD in women, who often exhibit atypical symptoms compared to men.<sup>[2]</sup>

### Pathophysiology and risk factors

Men are more likely to have obstructive CAD characterized by large calcified plaque formation in coronary arteries. Women, on the other hand, more frequently experience non-obstructive CAD, such as microvascular dysfunction and coronary artery spasms, which can lead to ischemia without

significant plaque buildup, spontaneous coronary artery dissection and Takotsubo cardiomyopathy. In men, plaques are typically more calcified and larger, with a greater likelihood of causing severe blockages and acute coronary events like heart attacks. Women's plaques are often smaller and more lipid-rich, and their vessel walls can be more prone to erosion rather than rupture [Figure 1]. Women exhibit more intense inflammatory responses, with higher levels of inflammatory markers like C-reactive protein. This can contribute to increased vascular damage and plaque instability.<sup>[3,4]</sup> The women's ischemia syndrome evaluation study is a landmark investigation initiated by the national heart, lung, and blood institute emphasized the importance of evaluating ischemia in women beyond obstructive CAD, challenging the assumption that non-obstructive CAD is benign.<sup>[5]</sup>

The study "Sex differences in the genetic and molecular mechanisms of CAD" by Sakkars *et al.* explores how genetic and molecular factors contribute to differences in CAD between men and women. It highlights that women may have distinct genetic risk factors and molecular pathways influencing CAD progression.<sup>[6]</sup>

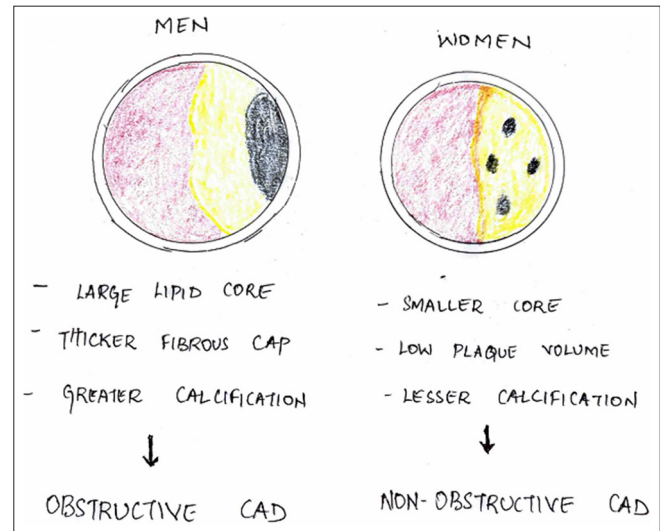
Sex-specific risk factors have also been identified. Testosterone, prevalent in men, has complex effects. While some studies suggest it may have protective roles in heart health, it is also associated with higher Low-density lipoprotein (bad cholesterol) levels, which contribute to plaque formation. Pre-menopausal women have higher estrogen levels, which are thought to provide a protective effect by maintaining the flexibility and function of the endothelial cells (cells lining blood vessels) and enhancing vasodilation. After menopause, when estrogen levels drop, women become more vulnerable to CAD.<sup>[7,8]</sup> The heart and estrogen/progestin replacement study (HERS) was a pivotal randomized controlled trial concluded that Hormone replacement therapy (HRT) with estrogen and progestin did not provide cardiovascular benefits for secondary prevention in postmenopausal women with CAD and posed significant risks of thromboembolic events.<sup>[9]</sup> The HERS study, along with subsequent trials like the Women's Health Initiative (WHI),<sup>[10]</sup> has been instrumental in reshaping recommendations for HRT, highlighting the importance of weighing risks versus benefits.

A meta-analysis revealed that women with a history of preeclampsia face a twofold increase in cardiovascular disease risk, including CAD, even decades after pregnancy. Similarly, women with Gestational diabetes mellitus (GDM) have a heightened risk of CAD and other cardiovascular complications later in life, with risk persisting up to 25 years postpartum.<sup>[8,11-13]</sup>

An editorial in frontiers in cardiovascular medicine (2023) discussed how chronic psychosocial stress can differentially affect men and women, contributing to CAD pathophysiology.<sup>[11]</sup> Studies have highlighted several

psychosocial stressors that uniquely affect women, including job strain, stressful life events, and social strain. For example, the WHI observational study found that high-stress life events, such as the loss of a spouse or experiences of abuse, were linked to a 12% increased risk of developing CAD. Similarly, social strain was associated with a 9% higher risk, and a combination of job and social strain led to a 21% increased risk of CAD in women.<sup>[14,15]</sup>

## GENDER DIFFERENCE IN PATHOLOGY OF ATHEROSCLEROTIC PLAQUE



**Figure 1:** Gender difference in pathology of atherosclerotic plaque

## Clinical presentation

Men typically present with "classic" symptoms of CAD, such as chest pain, while women often have atypical symptoms, including fatigue, shortness of breath, and nausea. Stress and emotional factors might impact women with CAD more profoundly, potentially triggering symptoms.<sup>[16,17]</sup> This can lead to symptom underreporting, as symptoms might be misinterpreted as stress or anxiety rather than CAD. As a result, CAD in women is more frequently misdiagnosed or diagnosed later in the disease process.<sup>[18-21]</sup>

The American College of Cardiology (2021) reviewed the clinical implications of these sex differences, noting that while men typically have obstructive CAD with larger plaque burdens, women often have non-obstructive disease, which can complicate diagnosis and treatment.

The Motivational Interviewing to Support Oral Anticoagulation in Atrial Fibrillation (MISOAC-AF) sub-study investigates sex-related differences in clinical outcomes in patients with atrial fibrillation and CAD. It reveals that women experience worse outcomes, particularly in thromboembolic events and cardiovascular mortality, compared to men.<sup>[22]</sup>

The study “Sex Differences in CAD: Insights From the KoRean wOMen’s chest pain rEgistry” explores sex-based disparities in CAD. It highlights that postmenopausal women experience a sharp increase in cardiovascular risk, primarily due to the decline in estrogen, which protects against cardiovascular issues. Women with CAD are typically older and have more cardiovascular risk factors than men. The study also notes that women are diagnosed later, as their symptoms tend to be more atypical. Furthermore, while in-hospital outcomes may be similar between sexes, women face more frequent bleeding complications after procedures like percutaneous coronary interventions (PCIs).<sup>[23]</sup>

### Diagnostic and imaging tools

A study by Awesat *et al.* highlights the unique challenges in diagnosing and managing acute coronary syndromes in women. These include delays in diagnosis, under-recognition of symptoms, and gender biases in treatment protocols.<sup>[24]</sup> Recent trials have shown that women are less likely to undergo invasive diagnostic procedures such as coronary angiography.<sup>[21,25,26]</sup> There is also a considerable delay in arriving at a diagnosis due to atypical symptoms.<sup>[27]</sup> Non-invasive imaging techniques, like coronary computed tomography angiography (CCTA) and stress echocardiography, are becoming more popular, especially for detecting microvascular disease and non-obstructive CAD in women. Women may have a higher rate of false negatives in exercise stress tests due to smaller heart size and differences in cardiac response.<sup>[28]</sup>

The prospective multicenter imaging study for evaluation of chest Pain trial that investigated the effectiveness of anatomical testing using CCTA versus functional testing methods like exercise electrocardiography and nuclear stress testing indicated that women had distinct demographic and clinical characteristics.<sup>[29]</sup>

### Treatment

Recent studies have highlighted the differences in response to pharmacotherapy, such as statins and antiplatelet therapy. Women may have a lower response to certain doses of statins and may experience more side effects, leading to lower adherence. On the other hand, both genders benefit from Angiotension converting enzyme (ACE) inhibitors and beta-blockers, though women may require dose adjustments based on body weight and kidney function.<sup>[30]</sup> A subgroup analysis of Ticagrelor With aspirin or aLone In hiGH risk patients after coronary inTervention (TWILIGT) trial, also established that women had higher bleeding risk compared to men on continuing ticagrelor with aspirin post PCI, hence suggests early withdrawal of aspirin post procedure.<sup>[31]</sup>

Studies also highlight that women tend to have worse outcomes after certain interventions, such as PCI<sup>[32]</sup>

and coronary artery bypass grafting (CABG). Women undergoing CABG generally experience higher mortality rates and complications compared to men, especially in the early postoperative period. This may be due to smaller vessel size, greater prevalence of comorbidities like diabetes and hypertension, and delayed diagnosis. However, long-term survival rates for women after CABG can be similar to men, particularly when advanced surgical techniques, such as off-pump CABG, are utilized.<sup>[33,34]</sup> Another study by Kim *et al.* (2024) investigates the impact of body mass index (BMI) on CAD and post PCI outcomes, focusing on sex differences in a Korean population. It found that BMI influenced CAD outcomes differently in men and women, with women showing a more complex relationship involving other metabolic and hormonal factors. High visceral fat was particularly associated with worse outcomes in women.<sup>[35]</sup> Women undergoing revascularization may have worse short-term outcomes (e.g., higher risk of bleeding, complications) but similar long-term mortality benefits compared to men. A recent study by Kang *et al.*, highlighted that even post-menopausal women may experience worse outcomes.<sup>[36]</sup>

In contrast, men often benefit more from traditional therapies like stents or medication due to their more prevalent obstructive disease patterns.

Women are under-referred to cardiac rehabilitation and less likely to complete programs, which may be linked to caregiving roles or underestimation of their cardiac risk. Studies highlight the need for tailored rehabilitation programs for women, addressing psychosocial factors and specific health concerns like anxiety and depression, which are more common in women post-CAD.<sup>[37]</sup>

## OVERALL OUTCOME

This gender disparity in CAD recognition contributes to increased mortality in women from cardiovascular events, as they often do not receive timely or appropriate interventions. These differences also leads to a higher burden of healthcare costs due to more frequent hospital readmissions, poorer quality of life, and prolonged recovery times for women. Women are underrepresented in cardiovascular research, leading to a lack of understanding of their specific needs. Women may face barriers in accessing healthcare, including transportation, childcare, and financial constraints.<sup>[20]</sup>

It also underscores the importance of public health campaigns to raise awareness about CAD symptoms in women, encouraging earlier diagnosis and gender-specific care strategies to improve outcomes.

In terms of policy and healthcare system adjustments, there is a growing need to integrate gender-specific guidelines into clinical practice, ensuring that women receive the same

**Table 1:** Comparative analysis of difference in CAD in men and women.

Features	Men	Women
Age of onset	<ul style="list-style-type: none"> <li>- Commonly occurs after age 45–55.</li> <li>- Higher prevalence before age 50.</li> </ul>	<ul style="list-style-type: none"> <li>- Commonly occurs after age 55–65.</li> <li>- Estrogen delays the onset until menopause, but the risk rises sharply afterward.</li> </ul>
Symptoms	<p>Classic presentation includes chest pain (angina), tightness, heaviness, or pressure.</p> <p>Symptoms often appear during physical exertion or stress.</p>	<p>More likely to present atypical symptoms: Fatigue, indigestion, dizziness, shortness of breath, back pain, nausea, or jaw pain.</p> <ul style="list-style-type: none"> <li>- Women often experience symptoms during rest or emotional stress.</li> </ul>
Risk factors	<p>Common risk factors include smoking, hypertension, high cholesterol, obesity, and diabetes.</p> <p>Family history of CAD plays a significant role.</p>	<p>Women share traditional risk factors like smoking, hypertension, obesity, and diabetes.</p> <ul style="list-style-type: none"> <li>- However, some unique risk factors in women include pregnancy-related complications (e.g., preeclampsia, gestational diabetes), early menopause, and autoimmune diseases (e.g., lupus, rheumatoid arthritis).</li> </ul>
Hormonal influence	<ul style="list-style-type: none"> <li>- Testosterone may contribute to higher risk by influencing lipid profiles and causing arterial inflammation.</li> </ul>	<ul style="list-style-type: none"> <li>- Estrogen provides protective effects by maintaining healthier blood vessels pre-menopause.</li> <li>- Post-menopause, the drop in estrogen increases the risk of CAD, with accelerated arterial plaque buildup.</li> </ul>
Psychological factors	<ul style="list-style-type: none"> <li>- Stress and depression are significant risk factors, though they are less emphasized compared to physical risk factors.</li> </ul>	<ul style="list-style-type: none"> <li>- Women have higher rates of depression and anxiety, which significantly increase CAD risk and affect outcomes post-diagnosis.</li> <li>- Social stressors, including caregiving responsibilities and socioeconomic factors, play a larger role in women's CAD risk.</li> </ul>
Pathophysiology	<ul style="list-style-type: none"> <li>- CAD in men is often due to larger epicardial coronary artery obstructions from plaque buildup (atherosclerosis).</li> </ul>	<ul style="list-style-type: none"> <li>- Women more commonly have microvascular dysfunction (affecting small coronary arteries), and plaque erosion, which may lead to ischemia without major blockages.</li> <li>- Endothelial dysfunction (lining of blood vessels) is more prevalent in women.</li> </ul>
Diagnosis	<p>Standard tests (e.g., ECG, stress tests, angiography) are generally effective for diagnosing CAD in men, as they often show typical patterns.</p>	<ul style="list-style-type: none"> <li>- Diagnosis can be more challenging due to atypical symptoms.</li> <li>- Women are more likely to experience false-negative results from standard tests, so additional tests (e.g., stress echocardiography, cardiac MRI) may be needed.</li> </ul>
	<ul style="list-style-type: none"> <li>- Men typically respond well to standard treatments like medications (e.g., statins, beta-blockers) and procedures (e.g., stents, CABG).</li> <li>- Mortality and complication rates from interventions are generally lower than in women.</li> </ul>	<ul style="list-style-type: none"> <li>- Women may have worse outcomes after treatments like angioplasty, stenting, or bypass surgery, often due to smaller vessel size, microvascular disease, or delayed diagnosis.</li> <li>- Post-procedure recovery can be more complicated for women, with higher rates of bleeding and vascular complications.</li> </ul>
Prognosis	<ul style="list-style-type: none"> <li>- Men tend to survive the first heart attack better and experience fewer complications in the short term.</li> <li>- However, long-term survival is affected by adherence to lifestyle changes and ongoing treatment.</li> </ul>	<ul style="list-style-type: none"> <li>- Women have a worse prognosis after a heart attack, with higher short-term mortality and complication rates (e.g., heart failure, stroke).</li> <li>- Post-heart attack, women are more likely to experience reduced quality of life and psychological stress, affecting recovery.</li> </ul>
Lifestyle modification and awareness	<ul style="list-style-type: none"> <li>- Men are often more responsive to lifestyle interventions like smoking cessation, diet, and exercise after a CAD diagnosis.</li> <li>- More public awareness and education campaigns focus on men's heart health.</li> </ul>	<ul style="list-style-type: none"> <li>- Women are less likely to be referred for cardiac rehabilitation or counseling post-diagnosis.</li> <li>- Awareness of heart disease in women remains lower, leading to underdiagnosis or undertreatment.</li> <li>- Women are also less likely to recognize early warning signs of a heart attack.</li> </ul>

CABG: Coronary artery bypass grafting, CAD: Coronary artery disease, ECG: Electrocardiograms, MRI: Magnetic resonance imaging

level of care and timely interventions as men. Improving research on sex-specific differences and expanding clinical trial participation for women will also play a crucial role in narrowing these outcome gaps. Table 1 elaborates on overall comparative analysis on these gender differences in CAD.

## STRATEGIES TO OVERCOME GENDER BIAS IN CAD

There have been efforts to address and improve gender bias in treating CAD in women. Research has identified gender bias in clinical decision-making for suspected CAD, with men undergoing more diagnostic procedures than women. Hence the following interventions can help reduce gender bias and improve outcomes for women with CAD.

### Increased awareness and education

Educating healthcare providers about the gender-specific presentation of CAD is crucial. Training clinicians to recognize these differences can lead to earlier diagnosis and intervention.<sup>[38]</sup> The European society of cardiology has called for increased public awareness campaigns specifically targeting women's cardiovascular health. Efforts to increase adherence to treatment and improve illness perception through tools like the illness perception questionnaire have also been beneficial in enhancing women's engagement with their own cardiovascular health.<sup>[37]</sup>

### Gender-specific diagnostic tools

Since women are more likely to experience non-obstructive CAD and microvascular dysfunction, the American college of cardiology advocates diagnostic tools like coronary flow reserve assessment, cardiac magnetic resonance imaging, and CCTA which offers more accurate detection of CAD in women without the risk of certain diagnostic artifacts that can affect women's imaging results.<sup>[39]</sup>

### Inclusion of women in clinical trials

Women have been often underrepresented in cardiovascular research, which limits the generalizability of trial outcomes to female patients. Globally, women comprise only around 34% of participants in CAD-related trials, which is notably below their proportion in the affected population. Factors contributing to this disparity include stringent enrollment criteria, gender bias in referrals, and the perception of CAD as a primarily male disease. These barriers lead to lower screening rates and enrollment for women compared to men. Encouraging greater participation of women in clinical trials helps ensure that the data reflects sex-specific responses to treatments and interventions. This will improve the development of tailored therapies for women.<sup>[40]</sup>

### Personalized treatment approaches

Given the differences in CAD pathophysiology between men and women, treatment strategies should be personalized. For example, women may benefit more from therapies targeting microvascular dysfunction, while men typically respond better to therapies for obstructive disease. Efforts to address women's unique CAD experiences have led to studies like the WARRIOR trial, which aims to find effective treatments for non-obstructive CAD.<sup>[41]</sup>

### Public health campaigns and screening programs

Raising public awareness about the risk of heart disease in women through health campaigns can help overcome misconceptions that CAD is primarily a male disease. Screening initiatives like the WISEWOMAN program have been pivotal. This program, managed by the CDC, focuses on screening underserved and low-income women and connecting participants to community resources for lifestyle support, which has demonstrated improved health outcomes for women at elevated risk of CAD. India is tackling CAD in women through initiatives like the population-based screening program under Ayushman Bharat. Healthcare workers, especially Accredited social health activist (ASHAs), are trained to support rural and low-income women. Awareness campaigns, often in partnership with WHO, educate women on unique CAD risks and preventive measures tailored to South Asian lifestyles.<sup>[42]</sup> Encouraging early screenings and regular heart health checkups for women, especially post-menopause, is essential in reducing gender disparities.

### Improving access to care

Barriers to healthcare access, including socioeconomic factors and geographic disparities, disproportionately affect women. Ensuring equal access to high-quality cardiovascular care, particularly for underserved populations, can improve outcomes by promoting earlier diagnosis and appropriate treatments.

## CONCLUSION

Recent trials underscore the importance of gender-specific approaches in the diagnosis, management, and treatment of CAD. While men tend to present with more classic obstructive CAD, women are more prone to non-obstructive disease and often exhibit atypical symptoms. Improved diagnostic strategies and personalized treatments are needed to address these disparities and improve outcomes for both sexes. Moreover, increased awareness and better inclusion of women in clinical trials are essential to address the underrepresentation of women in cardiovascular research, ensuring that treatments

are tailored to their specific needs. Overall, optimizing CAD care for women involves integrating gender-specific knowledge into clinical practice to improve detection, management, and outcomes. Continued research in this field will be crucial to optimizing care for women with CAD.

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