# Women with Ischemic Heart Disease

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Cardiac diseases are the main cause of death for both sexes worldwide. Treatment varies widely according to the sex of a patient, as there are differences in physiopathology, epidemiology, clinical presentation and management.

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## 1. Introduction

Cardiovascular disease (CVD) is the leading cause of mortality worldwide, in both women and men. According to the Lancet Women and Cardiovascular Disease Commission, published in 2021 [1], cardiac disease represents 35% of all deaths in women worldwide, and 275 million women were diagnosed with CVD in 2019. However, as has been stated in this report, CVD in women is understudied, under-recognized, underdiagnosed, and undertreated, and women are still under-represented in clinical trials.

Thus, it is crucial to raise awareness of the importance of this health problem, as well as to consider of atherosclerotic risk factors -RFs- (both traditional and emergent female-specific) and the utilization of appropriate evidence-based guidelines with a female-specific approach in clinical practice.

## 2. Specific Features of Ischemic Heart Disease That Should Be Considered in the Clinical Assessment of Women with Suspected or Known IHD

### 2.1. Physiopathologic and Anatomic Differences

Compared to men, women show particular characteristics of IHD: there are physiopathologic differences, such as distal thrombus, plaque erosion, impaired coronary vasomotor function and microvascular dysfunction as main mechanisms explaining the development of IHD in women, contrary to plaque rupture in men [2]. Thus, women have less obstructive and extensive epicardial artery disease than men. Anatomically, women have smaller epicardial coronary arteries than men, which may complicate the precise evaluation of distal coronary arteries by coronary computed tomographic angiography (CCTA) [3]. In addition, women have thinner myocardial walls, which makes the assessment of non-transmural ischemia by cardiac magnetic resonance imaging (CMR) more difficult. Population-based studies have shown a lower calcium score [4] and atheroma volume [5] in women when compared to men. Women exhibit higher coronary blood flow at both rest and peak stress, but similar coronary flow reserve (CFR) [6].

### 2.2. Risk Factors

Although there are traditional atherosclerotic RFs present in both women and men, such as high blood pressure, diabetes mellitus (DM), dyslipidemia, smoking habits, obesity, physical inactivity, and family history of premature atherosclerosis, some atherosclerotic RFs present a higher risk in women than in men. For instance, DM confers a 45% higher risk of IHD [7], while smoking represents a 25% higher risk [8], and obesity a 64% higher risk [9] in women compared to men. Menopause is a traditional female-specific RF, which can be associated with higher levels of triglycerides, LDL-cholesterol and lower levels of HDL-cholesterol. Nevertheless, women are less likely to achieve lipid goals during treatment [10], mainly because they are not as aggressively treated as men.

Among the so-called emergent RFs, gynecologic and obstetric conditions merit special attention. Polycystic ovarian syndrome (PCOS) comprises hormonal and metabolic abnormalities such as impaired glucose tolerance, type 2 DM, vascular disease, dyslipidemia, and obstructive sleep apnea [11][12]. Early menopause is an independent risk factor for CVD, increasing risk by approximately 1.3-fold [13].

A detailed obstetric history should be registered for every woman being evaluated for a suspected IHD. Adverse pregnancy outcomes, such as hypertensive disorders, gestational diabetes, preterm delivery, multiparity (especially among women with five or more live births), and delivery of a small for gestational age infant, are now recognized as emerging risk factors for premature CVD in women [14][15][16][17]. A shared pathogenesis combining placental insufficiency and the development of a pro-inflammatory and antiangiogenic milieu has been suggested to explain the increased risk of developing a CVD in these patients [18].

Women with gestational diabetes have a higher CVD risk (twofold for stroke and fourfold for myocardial infarction (MI)) [19]. Regarding hypertensive disorders during pregnancy, Benschop et al. [20] reported that previously preeclamptic women have more modifiable cardiovascular RFs and develop coronary calcium approximately five years earlier, from the age of 45 years onwards, compared to women with normal blood pressure during pregnancy.

Other conditions that are not specific to women, but are more prevalent in women should also be considered, such as autoimmune diseases and depression/emotional stress.

Psychological stress is still an understudied and underappreciated cardiovascular RF that needs a tailored approach, particularly in women. The INTERHEART study showed the relationship between stress, depression and a woman's first MI [21]. Of note, the negative effects of stress and depression after an MI are more common in younger women compared to men and older patients [22][23]. Moreover, after MI young women have a twofold likelihood of developing mental stress-induced MI compared to men (22% vs. 11%, $p = 0.009$) [24].

A final case that should be considered is cardiac damage post-radiotherapy in the case of thoracic irradiation in women with breast cancer or lymphoma, with symptoms that develop decades after radiotherapy. In this case, two mechanisms can explain the coronary artery disease (CAD) [25]: a macrovascular injury that accelerates age-related atherosclerosis, or a microvascular injury that reduces myocardial capillary density and causes a reduction of collateral flow/vascular reserve resulting in myocardial ischemia, as well as an increased capillary permeability of the pericardium via thickening and adhesions.

### 2.3. Clinical Differences

From a clinical point of view [26], more women than men have a sudden cardiac death as a first manifestation of the disease. In addition, more women than men die during the first year after an MI and after a coronary artery bypass grafting (CABG), and younger women exhibit higher mortality rates than men.

Regarding the somewhat different clinical picture, it is important to consider that women's ischemic symptoms are more often precipitated by mental or emotional stress than by physical stress. Symptoms have been considered "atypical", because rather frequently women do not complain of an anginal chest pain, but of epigastric discomfort, as well as nausea, dyspnea and fatigue. In fact, these symptoms previously considered atypical have begun more recently to be contemplated as typical in women with IHD.

In addition, treatment following guideline-directed medical therapy and reperfusion strategies, either percutaneous coronary interventions (PCI) or CABG, are less applied in women compared to men [27].

## 3. Value of Different Imaging Techniques for Management of Women with IHD

The 2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR Guideline for the Evaluation and Diagnosis of Chest Pain made recommendations for a focus on the uniqueness of chest pain in women [28]. In this sense, the guideline considers the following as recommendation class I, level of evidence B-NR [28]:

> "Women who present with chest pain are at risk of underdiagnosis, and potential cardiac causes should always be considered.
>
> In women presenting with chest pain, it is recommended to obtain a history that emphasizes accompanying symptoms that are more common in women with acute coronary syndromes".

Considering the aforementioned pathophysiologic differences of IHD in women compared to men, as well as predominant plaque erosion, impaired coronary vasomotor function and microvascular dysfunction, it is crucial to identify in which scenarios the clinician should distinguish between women and men for an appropriate cardiovascular imaging approach

[29][30]. In this sense, although CCTA shows sensitivity and specificity with respect to detecting coronary stenosis and coronary dissections, its diagnostic accuracy can be limited in women due to the smaller diameter of vessels [31]. On the contrary, CMR and positron emission tomography (PET) are valid options to evaluate microvascular dysfunction thanks to their capacity to measure myocardial blood flow (MBF) and CFR.

## Diagnostic Algorithm for IHD in Women Considering the Pretest Probability of the Disease in a Multimodal Cardiac Imaging Approach

In case of suspected stable IHD, several tables for calculations of pretest probabilities of presenting an obstructive CAD in symptomatic patients have been applied. The 2021 ACC guideline [28] includes one table that is particularly useful because, in addition to chest pain characteristics, age and sex, it considers calcium scoring, which allows for refining the calculation according to the amount of coronary calcium, mainly in the case of patients with intermediate-high pretest probabilities.

Thus, in women with a suspected IHD, the first step should be to calculate the pretest probability of having an obstructive CAD. Accordingly, selection of the diagnostic test should also take into account the availability of tests, local expertise and patient characteristics and preferences (recommendation class I, level of evidence C, according to the 2019 ESC Guidelines for the Diagnosis and Management of Chronic Coronary Syndromes) [28].

According to the pretest probability of the disease:

- In patients with a very low probability of obstructive CAD, diagnostic tests can be deferred, although according to clinical evaluation, other options may be considered [32], such as: an exercise test (without imaging) if the electrocardiogram (ECG) at rest is interpretable and the patient can exercise (although this is less useful for women, considering the lower sensitivity of the test compared to men and the possibility of false positives), or a coronary calcium scoring for a better refinement of risk (if not included in the pretest probability analysis).

- In patients with a low to intermediate probability and considering that CCTA has a very high negative predictive value, an anatomic approach with CCTA is the most effective option, independent of sex.

- In those with an intermediate to high probability, an ischemia-provoking test with imaging should be considered: stress-echocardiography, nuclear (either single-photon emission computed tomography -SPECT- or PET), or stress CMR. The type of applied stress will depend on functional capacity, ECG at rest and the type of test selected.

- In those patients with a very high pretest probability, there is no doubt that invasive coronary angiography (preferably with fractional flow reserve measurement) is the most effective option to choose, independent of sex.

If an obstructive CAD is diagnosed, an appropriate management strategy should be applied that takes into consideration the extent and severity of ischemia and anatomic characteristics of coronaries, independent of sex. The possibility of a microvascular dysfunction and other causes of chest pain should also be considered.

According to the 2019 ESC Guidelines for the Diagnosis and Management of Chronic Coronary Syndromes [33], a non-invasive functional imaging test for myocardial ischemia or CCTA is recommended as the initial test to diagnose CAD in symptomatic patients in whom obstructive CAD cannot be excluded by clinical assessment alone (recommendation class I, level of evidence B).

**Table 1** shows a comparison of advantages and disadvantages of the different imaging techniques.

**Table 1.** Advantages and disadvantages of imaging tests.

| Imaging Test | Advantages | Disadvantages |
|---|---|---|
| **Stress echo** | **No radiation, high availability, lower costs** | **Poor acoustic windows, less reproducible** |
| **SPECT MPI** | **Good reproducibility, validated for ischemia detection. Uses stress-only protocols if possible** | **Radiation exposure, need for attenuation correction for anterior defects in women** |
| **PET MPI** | **Validated for ischemia detection, MBF and CFR can be measured** | **Radiation exposure, although less than SPECT MPI** |

| Imaging Test | Advantages | Disadvantages |
|---|---|---|
| CMR | Validated for ischemia detection, MBF and CFR can be measured. Standard measurement for ventricular function. No radiation | Less availability, higher costs, claustrophobia, patients with implantable cardiac devices |
| CCTA | High negative predictive value. Measurement of calcium score in addition to coronary anatomy | Radiation exposure |

SPECT: single photon emission computed tomography; PET: positron emission tomography; MPI: myocardial perfusion imaging; CMR: cardiac magnetic resonance; CCTA: cardiac computed tomography angiography.

The use of solid-state cadmium zinc telluride (CZT) cameras has allowed for improved spatial resolution and increased camera sensitivity that has allowed for a lower required dose of the radiotracer and therefore, lower radiation exposure. The use of hybrid imaging (SPECT/CT) allows for attenuated-corrected images.

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