Review Article

What do Cardiologists Expect from Imaging For Ischemic Heart Disease in Women

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Abstract

Ischemic heart disease (IHD) is an important cause of morbidity and mortality in women and men. This paper emphasizes the differences of IHD in women, focusing on the diagnostic investigation in its stable phase.

The higher prevalence of atypical symptoms, anatomical differences, and adverse psychosocial aspects, in addition to the association of specific risk factors regarding obstetrical history, requires an accurate clinical assessment and a targeted diagnostic investigation that consider the limitations, as well as the positive and negative predictive values of the methods. Because of breast exposure, tests involving radiation should be reconsidered in selected cases.

It is worth emphasizing that non-cardiological tests often performed in women, such as mammography, provide an opportunity to assess CVR at early ages or even in patients with few traditional risk factors.

Complementary tests for microcirculation assessment should be used in cases of proven ischemia in the absence of obstructive coronary artery disease, which is known to be more frequent in women.

Introduction

Despite the worldwide reduction in mortality from cardiovascular diseases (CVDs) in women and men in the past ten years, unfavorable outcomes, such as higher in-hospital mortality rates from ischemic heart disease (IHD) following percutaneous and surgical interventions, are more frequent among women.

Anatomical and pathophysiological differences, such as smaller epicardial coronary arteries adjusted for body surface, lower coronary vasomotor tonus with functional changes even in the absence of obstructive coronary artery disease, and higher microcirculation dysfunction, could explain the different IHD phenotypes in women.[1,2] Figure 1 shows the relevant differences of IHD between women and men.

The IHD clinical manifestations and characteristics of the complementary diagnostic methods are different in women, with false-negative or false-positive results, misinterpretations, and, consequently, inappropriate women's IHD management and treatment.[2,3] It is essential to consider the peculiarities of noninvasive imaging tests related to the female sex, assessing the advantages and disadvantages of each diagnostic modality to increase the accuracy of the tests that will impact on the IHD treatment and prognosis.[1]

Cardiovascular risk (CVR) stratification

CVD remains the major cause of death in adults, thus, the development of new strategies is required to mitigate CVR, mainly in women.

The difference in clinical presentation of IHD in women, whose symptoms are triggered by emotional or mental stress, the higher prevalence of symptoms other than chest pain, as well as the presence of nonclassical risk factors not considered in usual risk scores make CVR stratification a challenge in the female sex.

A growing body of evidence suggests that traditional cardiovascular risk factors (CVRFs), such as hypertension, diabetes, dyslipidemia, and obesity, pose a differential risk to women as compared to men. For example, diabetes poses a 40% higher risk of IHD to women as compared to men. Premenopausal women have a lower risk of CVD than men at the same age, but women lose that advantage in the menopausal transition.

For younger adults, CVDs account for 10.3% and 20.9% of the deaths in the age ranges of 25-44 years and 45-64 years, respectively. In young women, recognition of adverse pregnancy outcomes (APOs) as a women-specific CVRF is critical for CVR stratification. Women with history of pregnancies complicated by hypertension, gestational diabetes, premature delivery, low birth weight, and fetal growth restriction are at a higher risk for short- and long-term cardiovascular complications. Women with history of APOs can have increased risk for CVD even after achieving normoglycemia and standard control of postpartum blood pressure.[1] In addition, sex-specific or predominantly sexual risk markers, such as early menopause, polycystic ovary

Keywords

Women; Myocardial Ischemia; Multimodal Imaging; Risk

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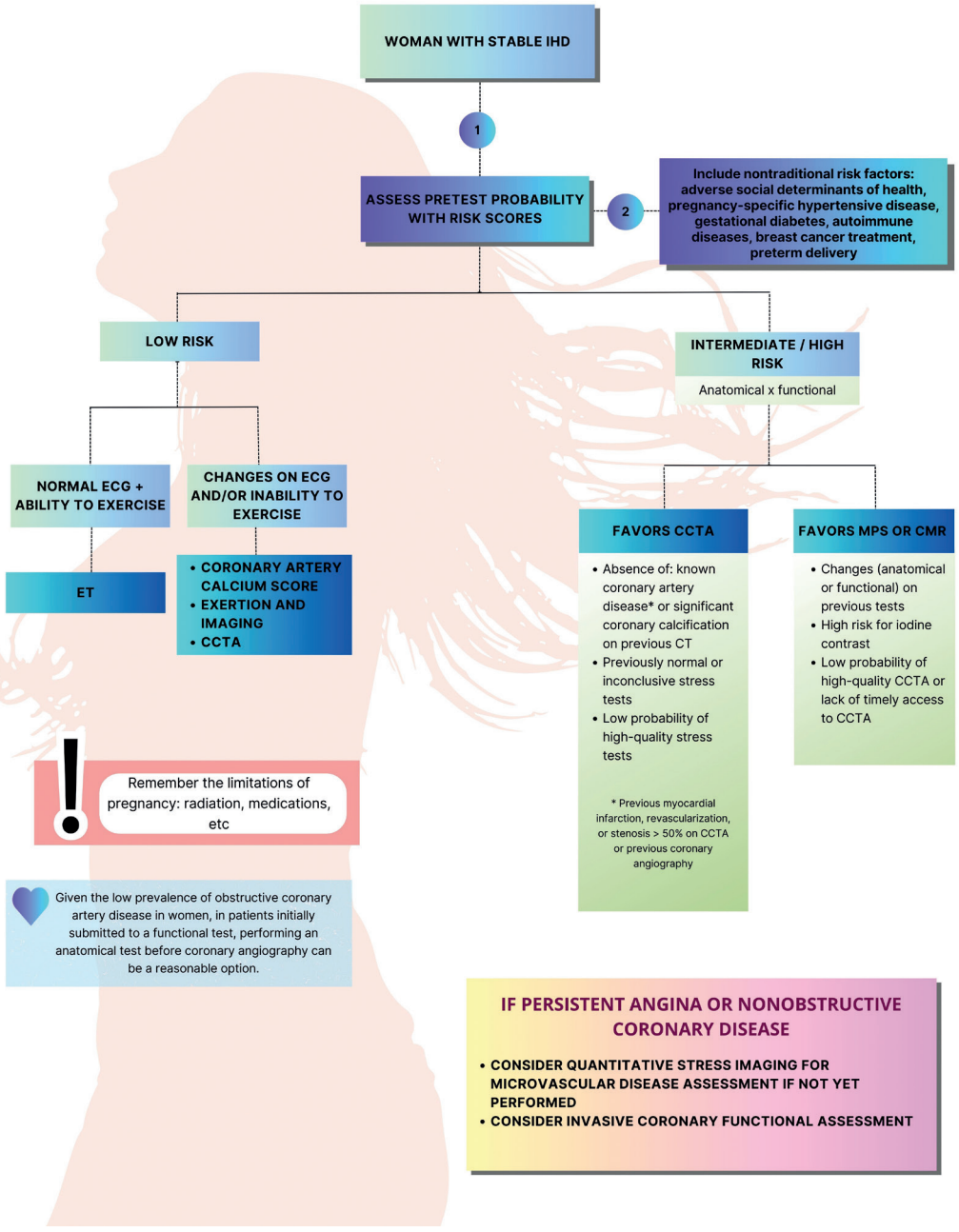
Central Illustration: Imaging For Ischemic Heart Disease in Women: What Cardiologists Expect



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Proposal of a diagnostic algorithm for women with suspected stable IHD. CCTA: coronary computed tomography angiography; MPS: myocardial perfusion scintigraphy; ECG: electrocardiogram; CMR: cardiac magnetic resonance; CT: computed tomography; ET: exercise test; IHD: Ischemic heart disease; CCTA: Coronary computed tomography angiography.

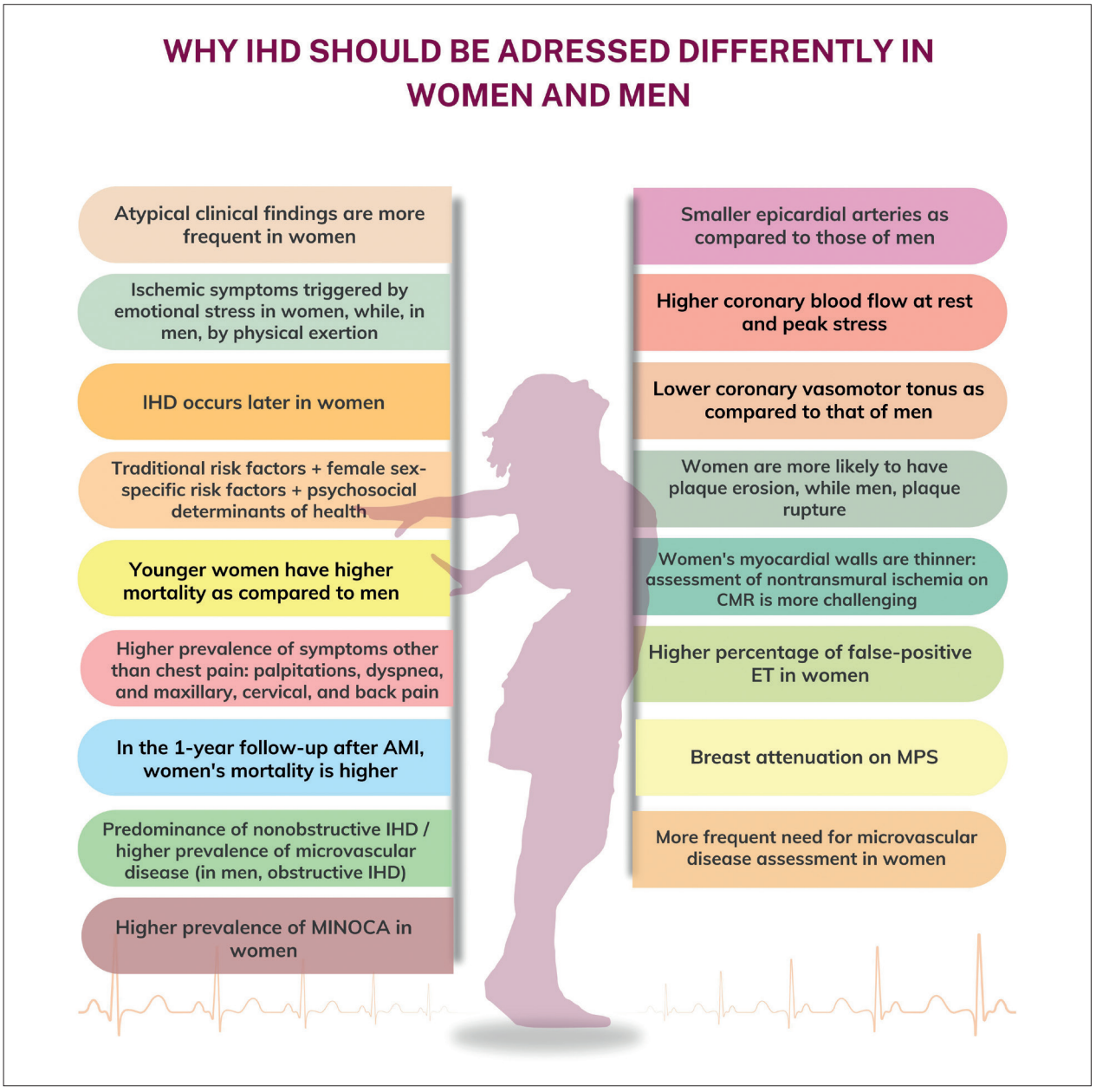

Figure 1 – *Relevant differences of IHD between women and men. IHD: ischemic heart disease; AMI: acute myocardial infarction; MINOCA: myocardial infarction with non-obstructive coronary arteries; ET: exercise test; MPS: myocardial perfusion scintigraphy; CMR: cardiac magnetic resonance.*

syndrome, rheumatological disorders, APOs, and presence of depression and adverse socioeconomic factors, are called enhancers of the traditional CVRFs, and pregnancy works as a "physical and metabolic exercise test (ET)" specific to women.[1]

At rest, coronary blood flow is maintained by autoregulation up to the development of critical stenosis, defined as the capacity to preserve blood flow during perfusion pressure changes, with constant metabolic needs. When an atherosclerotic plaque occludes more than 70% of the luminal cross-section, with a 50% reduction in the coronary diameter, it significantly increases proximal resistance and decreases distal coronary perfusion pressure. In that situation, autoregulation can maintain baseline coronary blood flow, but coronary reserve is impaired. Thus, at rest, the condition is asymptomatic, but, at high metabolic demands during physical exercise, the coronary flow is insufficient.

A large percentage of women with IHD has minimal or no epicardial coronary artery disease. Coronary microvascular disease, however, plays an important role in the etiology of IHD in the female sex, regulating blood flow and oxygen delivery and energetic substrates in the microcirculation-myocardium interaction. Myocardial ischemia is directly

dependent on a balance between myocardial energy *status* and coronary blood flow.[1-3] These changes are shown in Figure 2.[4]

Figure 3 describes the role of complementary tests for IHD stratification and diagnosis in women.

IHD diagnostic tests in women

A. ET

The ET is an accessible, safe, reproducible, low-cost, radiation-free functional test that provides information to support IHD diagnosis, CVR stratification, therapeutic assessment, and physical exercise prescription. It is recommended as the initial method to assess symptomatic women at low/intermediate CVR for IHD who have normal electrocardiogram (ECG) at rest and who can exercise.[1] The factors that contribute to reduce ET accuracy in women are as follows: lower prevalence of multivessel disease; less severe coronary lesions; women's ET performance below ideal (inappropriate physical capacity, shorter exercise duration, and lower achieved heart rate). The ET has sensitivity and specificity of 62% and 68%, respectively, with a positive predictive value of only 47%.[1,5]

B. Transthoracic echocardiography at rest and under stress

In addition to assessing segmental contractility abnormalities, transthoracic echocardiography is a valuable tool to screen for cardiomyopathies, such as hypertensive, hypertrophic, and Takotsubo cardiomyopathies, and other causes of chest pain.[2,3] Combined with exercise, more physiological, or pharmacological stress, it can be used for the IHD diagnosis and prognosis in symptomatic women at intermediate/high CVR. In abnormal stress echocardiography (SEC), the extension and severity of

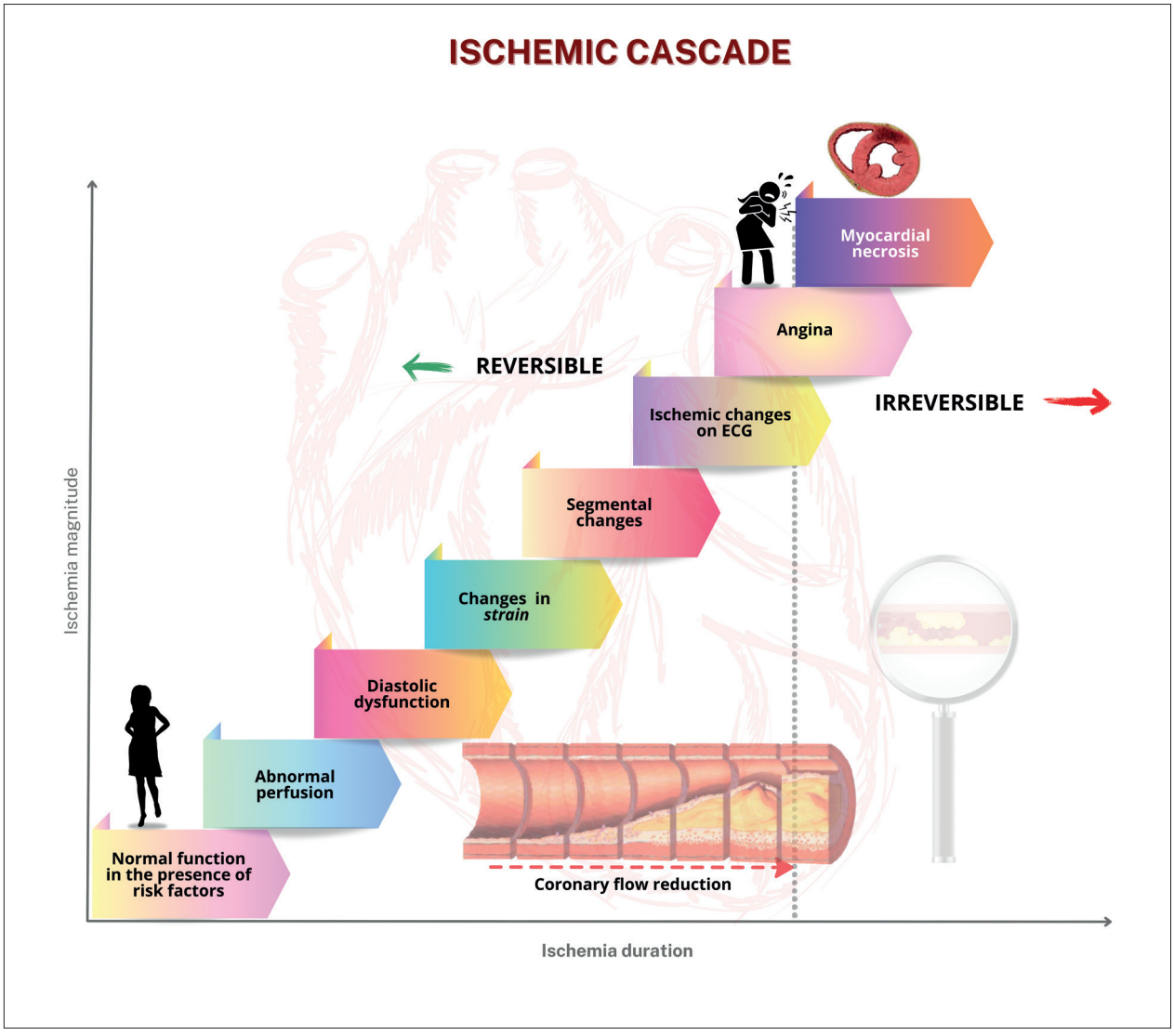

Figure 2 – *Ischemic cascade related to coronary flow reduction to detect IHD. ECG: electrocardiogram.*

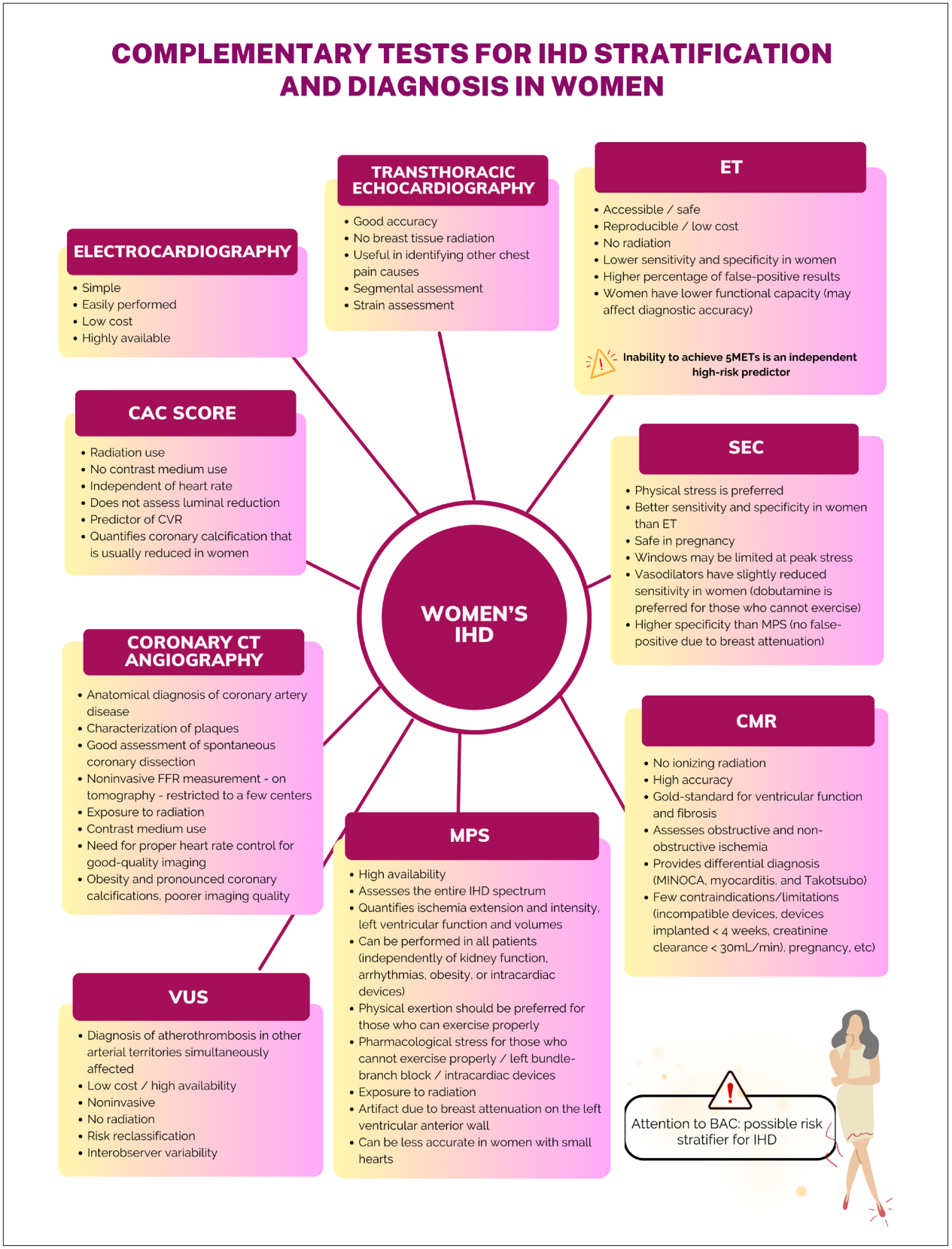

Figure 3 – *Complementary tests to assess IHD in women, with advantages and limitations. CVR: cardiovascular risk; IHD: ischemic heart disease; MINOCA: myocardial infarction with non-obstructive coronary arteries; FFR: fractional flow reserve; ET: exercise test; SEC: stress echocardiography; VUS: vascular ultrasound; MPS: myocardial perfusion scintigraphy; CT: computed tomography; CMR: cardiac magnetic resonance; BAC: breast arterial calcification; CAC: coronary artery calcium.*

contractility changes are associated with higher rates of cardiac events, even in the absence of obstructive IHD on invasive coronary angiography.[2,3] The markers of high CVR on SEC in women are: left ventricular ejection fraction (LVEF) at rest ≤ 40%; extensive wall contractility abnormalities at rest or extensive ischemia (≥ 4–5 left ventricular segments); right ventricular ischemia; increased left ventricular end-systolic diameter in the stress phase; and LVEF reduction with stress.[2,3]

The wall contractility abnormalities detected on echocardiography appear later in the ischemic cascade, being preceded by perfusion abnormalities detected on SPECT (Figure 2). Both techniques have comparable diagnostic accuracy and similar prognostic value. Thus, the local experience and equipment availability are crucial to select the imaging modality.[2,3]

C. Vascular ultrasound (VUS)

The investigation of atherothrombosis of the carotid system and femoral arteries with VUS has an excellent cost-benefit ratio for CVR stratification, because it is a noninvasive, widely available, and easily performed test.[5] The carotid VUS can detect subclinical atherosclerosis by measuring the intima-media thickness (IMT) of the common carotid artery and identify the presence of an atherosclerotic plaque (characteristics, quantification, and assessment of atherosclerotic burden).[6] A cohort study with a North American population[7] has shown a significant increase of IMT with age; however, the presence of atherosclerotic plaque is an aggravating factor in patients at intermediate CVR.[8,9] The ELSA study (Longitudinal Study of Adult Health) has shown that the IMT measure differed with sex, ethnicity, and age ranges in Brazilians, being important in CVR stratification in special subgroups.[10] The IMT measure or identification of a carotid plaque on VUS helps the CVR reclassification of women with at least two risk factors not considered in the usual risk scores or at intermediate risk.[11]

The carotid and femoral atherosclerosis assessment has been recently suggested to improve the early detection of the disease, and the presence of a femoral plaque in women is more indicative of IHD than that of a carotid plaque.[1]

D. Nuclear medicine tests

The myocardial perfusion tests SPECT and PET play an important role in the assessment of women with symptoms suggestive of IHD and at intermediate/high CVR,[1] mainly because of low radiation exposure (9-12mSv on SPECT). Regarding radiation exposure, the benefit-risk ratio favors benefit in IHD detection, as long as the indication is appropriate.

Stress myocardial perfusion scintigraphy (MPS) provides information on the perfusion deficit extension and severity, ischemic burden, and myocardium at risk, as well as the LVEF and wall motility at rest and under stress. For women at intermediate risk with ECG changes at rest or those who cannot exercise, MPS can be the first test requested. Technetium-99m is the radionuclide of choice because it involves less radiation exposure for the patient.

In the assessment of IHD in women, the MPS has shown sensitivity ranging from 78% to 88%, specificity, from 64% to 91%, and lower accuracy as compared to that in men.[12,13] Women have a smaller heart, and MPS has lower sensitivity to detect obstructive IHD because of the low resolution of conventional gamma cameras, in addition to breast attenuation that can result in false-positive tests, mainly in the anterior wall. Regarding breast attenuation, techniques of correction and pronation should be considered to improve the MPS SPECT specificity.[12,13] In women, LVEF can be overestimated with that technique, because of the methodology used for calculation in smaller and/or hypertrophic ventricular cavities.[12,13]

The MPS with pharmacological stress with vasodilators (dipyridamole, adenosine, regadenoson) is the best option for women who cannot exercise, with sensitivity of 91% and specificity of 86%.[3] The use of MPS could reclassify 36% of the patients, which was superior to the clinical and SEC results. The combination of MPS and PET has better resolution than SPECT and increases diagnostic accuracy by 20% in women (88% *versus* 67%), improving the detection of severe multivessel obstructive IHD.[14] A normal test result or of low risk (<5% of abnormal myocardium or equivalent to added stress score <4) is associated with an annual risk of death from IHD or nonfatal infarction < 1%[1,3] (Figure 4).

Women have a higher prevalence of microvascular disease and lower prevalence of obstructive coronary disease than men, and, for that analysis, complementary tests other than luminography are required. The combination of MPS and PET is a technique appropriate to assess coronary flow reserve (CFR), but it is not widely available. Evidence of reduced CFR (defined as <1.9–2.0) suggests underlying vascular dysfunction and can help detect microvascular IHD. Abnormal CFR is associated with diastolic dysfunction and can play a role in the assessment of heart failure with preserved ejection fraction (HFpEF), more prevalent in women. A study with 64.7% of women without obstructive IHD has shown an independent association of CFR reduction and diastolic dysfunction. Imaging protocols with hybrid equipment (PET/CT or SPECT/CT) add the assessment of anatomical changes to the coronary artery calcium score (CAC) quantification, thus increasing the sensitivity for the diagnosis of IHD in a single test.[1,12]

E. Coronary computed tomography (CT)

Symptomatic women with positive functional tests are often submitted to invasive methods, such as coronary angiography, that evidence no atherosclerotic plaque, which, when present, is not severe (stenosis < 50%).[2] Coronary CT is a noninvasive method that assesses the CAC in the presence of atheromatosis. Coronary computed tomography angiography (CCTA), despite its disadvantages, such as radiation emission and cost, provides the quantification and assessment of the characteristics and extension of atherosclerotic plaques, with an excellent accuracy when compared to coronary angiography for IHD

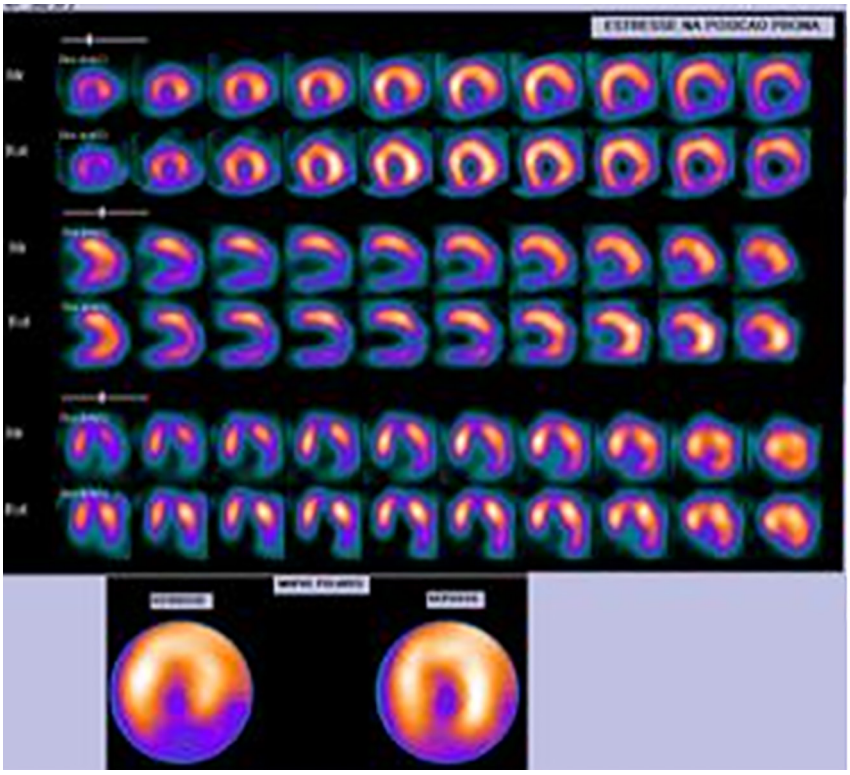

Figure 4 – *Abnormal MPS with a clear transient perfusion deficit in a patient with normal coronary angiography. Images provided by Dr. Viviane Parisotto Marino.*

diagnosis and treatment. Advanced diagnostic centers count on software that can noninvasively quantify CFR on CCTA, which has a good correlation with coronary angiography.[1,2]

The CAC plays an important role in CVR stratification, mainly in asymptomatic patients at low/intermediate risk. In symptomatic women, its role is controversial, because women's have fewer calcified vessels and/or plaques and lower coronary calcium volume. A CAC of 0 practically excludes obstructive IHD, with negative predictive value > 96.5% for lesions ≥ 50% (CONFIRM registry), in addition to indicating low CVR in both sexes (< 1%).[15] Mortality increases with the increase in CAC (0.8% and 9.8% with CAC of 0 and 400, respectively).[2] Although a CAC of 0 indicates low risk for cardiovascular events in women and men, women with any detectable CAC have a 1.3 higher relative risk of mortality from CVD as compared to men.[3]

CCTA has high diagnostic accuracy for obstructive IHD, even after sex-specific analysis. Sensitivity, specificity, and positive and negative predictive values increase with the increase in the stenosis degree. Because women's epicardial coronary arteries are thinner than those of men, the CCTA accuracy is lower (70% x 90%; p < 0.05), mainly in distal coronary arteries and branches.[3] However, in women, CCTA has higher accuracy to detect atherosclerotic disease as compared to stress tests. The CONFIRM study has shown an association of obstructive IHD, mortality, and major cardiovascular events (MACE), with odds ratio of 2.16 and 2.56 for women and men, respectively. In women, the presence of major coronary lesions and higher CAC increases the risk of mortality from CVD by 2.2 times as compared to men.[16]

In addition to detecting the presence of plaque, CCTA provides the assessment of calcium volume and load, presence of remodeling, and plaque vulnerability. Women have lower volumes of calcified or noncalcified plaques, regardless of age. The PROMISE study (n = 5007; 51% women) has compared anatomical and functional tests in patients with chest pain and low/intermediate risk, showing that, in women, positive *versus* negative CCTA was more strongly associated with subsequent clinical events (HR 5.9; 95% CI 3.3-10.4) than a positive *versus* negative stress test (HR 2.3; 95% CI 1.2-4.3). Because CT can detect nonobstructive IHD, its efficacy to predict events is better than that of the functional test, CT (CAC / CCTA) being more sensitive, while the functional test is more specific.[17]

Regarding the characteristics of atherosclerotic plaques, those with higher risk for MACE in women have low attenuation, positive remodeling, punctate calcification, and napkin-ring sign (suggesting a thin fibrous cap) (adjusted OR: 2.41; 95% CI 1.25-4.64).[3]

F. Cardiac magnetic resonance (CMR)

CMR plays an important role in the assessment of women with suspected or known IHD because it is noninvasive and involves neither ionizing radiation nor nephrotoxic contrast

media. In addition, it has high spatial resolution, wide visual field, excellent reproducibility, and provides the assessment of cardiac and vascular anatomy, ventricular function, ischemia, viability, and tissue characterization with high accuracy. CMR has been increasingly used in the assessment of suspected IHD in symptomatic women or those at intermediate/high risk.[18-19]

The CMR with stress has good accuracy for IHD diagnosis, risk stratification, and prognosis.[3,19] The CEMARC study (*Clinical Evaluation of Magnetic Resonance Imaging in Coronary Heart Disease*), with 5-year follow-up, has shown that women with false-positive MPS and negative CMR with dobutamine had low probability of MACE. In addition, that study has shown that the SPECT accuracy was significantly worse in women than in men, while CMR with stress was better than SPECT in women (AUC 0.90 x 0.67) and in men (AUC 0.89 x 0.74).[19]

CMR is an important strategy in suspected MINOCA (myocardial infarction with non-obstructive coronary artery), providing the location of inflammation, edema, and myocardial fibrosis, differentiating ischemic from nonischemic etiologies, identifying the underlying etiology in up to 87% of the cases, and providing the CVR stratification and management definition in women.[3,19] Subendocardial perfusion abnormalities have been described in patients with syndrome X and microvascular dysfunction confirmed by coronary reactivity testing (Figures 5, 6 and 7).[19]

One of the great advantages of CMR is its ability to overcome the technical limitations of other conventional stress imaging modalities, such as breast tissue, obesity, pulmonary disease, and low exercise capacity of the patients.[19]

G. Breast arterial calcifications (BACs)

Mammography can identify BACs or arteriosclerosis by showing radiopaque structures involving the entire circumference of the artery (Figures 8 and 9).

The estimated prevalence of BAC ranges from 8.2% to 12% in women aged over 50 years. There is an association between the presence of BAC and kidney disease, stroke, peripheral vascular disease, carotid artery disease, and IHD. The finding of BAC on mammographies of women under the age of 59 years has been reported to be an additional risk factor for CVD, mainly in women with diabetes, even asymptomatic.[20]

A retrospective cohort study of women assessed for breast cancer in a 23-year follow-up has estimated that those with BAC had higher relative risks as follows: 1.66 (95% CI 1.31–2.10) for cardiovascular events; 3.25 (95% CI 1.53–6.90) for IHD; 2.85 (95% CI 1.59–5.09) for hypertensive heart disease; 2.06 (95% CI 1.19–3.56) for congestive heart failure; 2.8 (95% CI 1.42–5.52) for peripheral vascular disease; 1.83 (95% CI 1.09–3.08) for atrial fibrillation; and 2.23 (95% CI 1.21–4.09) for lacunar infarction. Cox multivariate analysis, considering also the classical CVRFs, has shown a significant and independent association of BAC with both cardiovascular-event-free and specific survivals (1.94 - 95% CI 1.38–2.73).[20]

Another study has assessed 292 women by use of digital mammography and CCTA, and BAC and CAC were quantitatively assessed (0 to 12), correlated with each other and with the Framingham risk score. The sensitivity, specificity, positive and negative predictive values, and accuracy of BAC > 0 for CAC > 0 were 63%, 76%, 70%, 69%, and 70%, respectively. BAC > 0 had an area under the curve of 0.73 for the identification of women with CAC > 0. There was a strong quantitative association between BAC and CAC, and BAC was superior to the traditional CVRFs regarding CAC accuracy. The incorporation of BAC for the CVR assessment of peri- and postmenopausal women is premature, but BAC is an opportunity to identify women at high risk by using routine mammography analysis in breast cancer screening.[21]

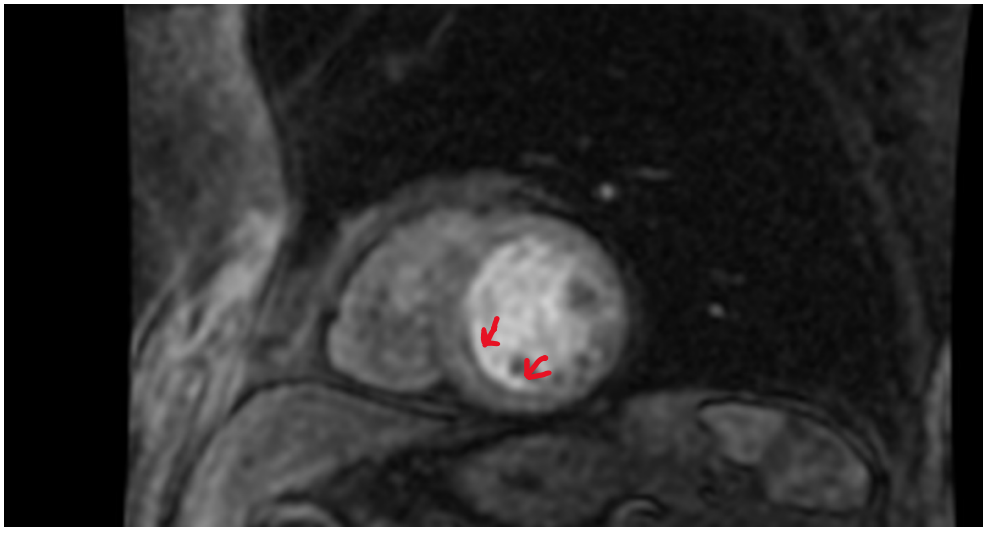

Figure 5 – *CMR imaging showing positive inferior subendocardial perfusion (red arrows). Images provided by Dr. Eduardo Belizário Falchetto.*

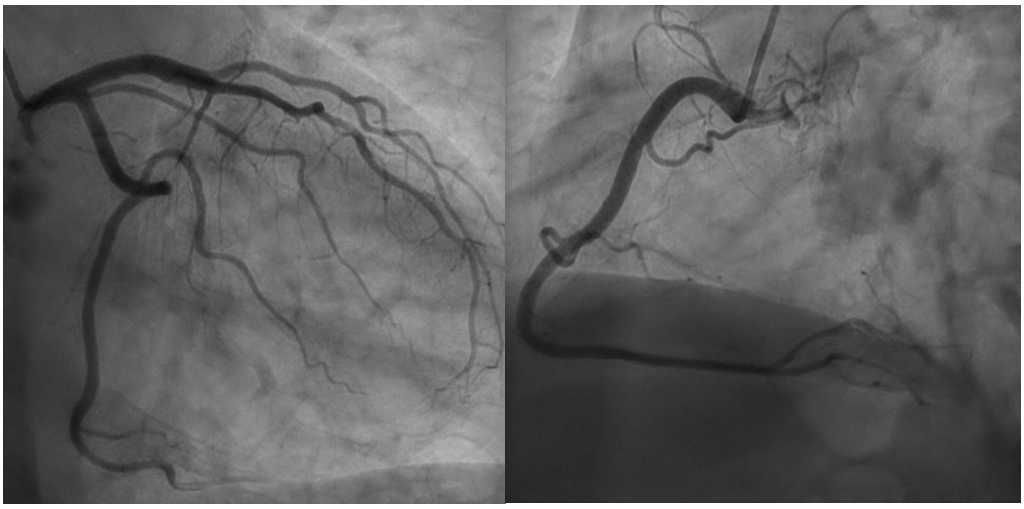

Figure 6 and 7 – *Normal coronary angiography of the left and right coronary arteries from a patient with changes on CMR imaging.*

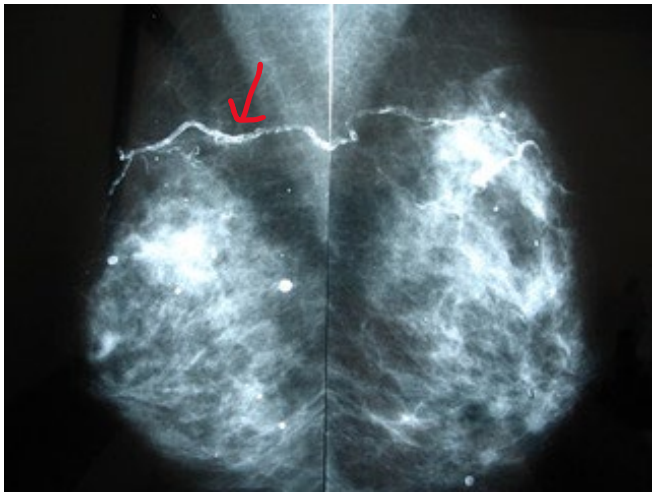

Figure 8 – *Calcified vascularization on the mammography of a 67-year-old woman (red arrow).*

Conclusion

IHD is an important cause of morbidity and mortality in women and men. This paper emphasizes the differences of IHD in women, focusing on the diagnostic investigation in its stable phase.

The higher prevalence of atypical symptoms, anatomical differences, and adverse psychosocial aspects, in addition to the association of specific risk factors regarding obstetrical history, requires an accurate clinical assessment and a targeted diagnostic investigation that consider the limitations, as well as the positive and negative predictive values of the methods. Because of breast exposure, tests involving radiation should be reconsidered in selected cases.

In addition, we emphasize that non-cardiological tests often performed in women, such as mammography, provide an opportunity to assess CVR at early ages or even in patients with few traditional risk factors.

There is no specific algorithm for risk assessment that considers such differences. Thus, this study presents the advantages and limitations of each complementary test (Figure 3) and provides an investigative suggestion, as briefly shown in the Central Illustration.

Complementary tests that assess the microcirculation should be used in cases of proven ischemia in the absence of obstructive coronary artery disease, which is known to be more frequent in women.

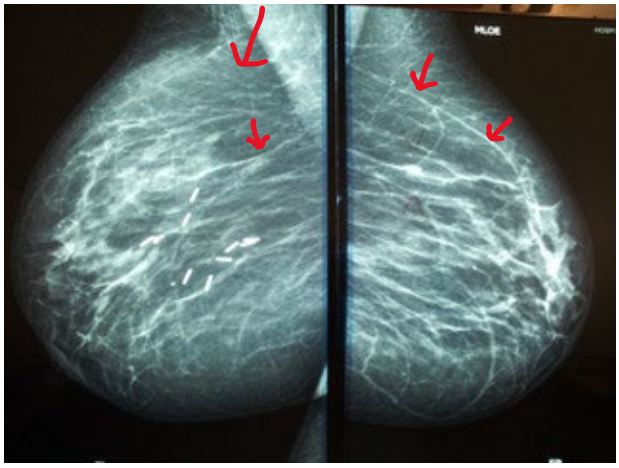

Figure 9 – *55-year-old patient with BACs (red arrows). Images provided by Prof. Washington Cançado Amorim.*

Author Contributions

Conception and design of the research; acquisition of data; analysis and interpretation of the data; writing of the manuscript and critical revision of the manuscript for intellectual content: Almeida MCC, Freire CMV, Espíndola LN, Oliveira GMM.

Potential Conflict of Interest

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Study Association

This study is not associated with any thesis or dissertation work.

Ethics Approval and Consent to Participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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