

Cardiovascular diseases in women: a differentiated view and risk stratification

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SUMMARY

Cardiovascular diseases are the main cause of mortality in men and women worldwide, surpassing mortality from all associated neoplasms. In women, its prevalence and mortality increase at menopause, but complications of reproductive age, such as preeclampsia and eclampsia, lead to increased cardiovascular risk throughout their lives. Coronary ischemic disease is the leading cause of death in Brazil and worldwide, with atherosclerotic disease being the principal pathophysiological mechanism. However, in women, other mechanisms are associated with myocardial ischemia, such as microcirculation disease and/or vasospasm, due to the anatomical and hormonal characteristics of women in different stages of their lives. Knowledge of the most prevalent cardiovascular diseases in women, as well as the specific risk factors, the traditional ones with the greatest impact, and the under-recognized ones, is of fundamental importance in their risk stratification, diagnosis, and management, fundamentally aiming at reducing mortality.

KEYWORDS: Cardiovascular diseases. Menopause. MINOCA. Heart disease risk factors.

INTRODUCTION

The most prevalent cardiovascular diseases (CVD) in women are ischemic heart disease (IHD), followed by cerebrovascular disease. IHD is the leading cause of death in Brazil, accounting for 12.03 and 12.2% of deaths in women and men, respectively; however, the percentage of deaths due to cerebrovascular accident (CVA) is higher in women than in men (10.39 and 8.41%, respectively)¹.

The main cause of IHD is coronary atherosclerotic disease (CAD) in men and women, but IHDs without obstructive lesions, such as microcirculation disease (CMD), vasospasm, coronary embolism/thrombosis, and spontaneous coronary artery dissection (SCAD), the latter more frequent during pregnancy, are more common in women and not infrequent in younger ones².

In the reproductive phase, hypertensive disorders of pregnancy (HDP) remain an important cause of complications and maternal-fetal mortality, being the second leading cause of mortality and disability-adjusted life years (DALYs)¹. Complications such

as preeclampsia (PE) and eclampsia (ECL), HELLP syndrome, gestational diabetes (GD), and acute kidney disease (AKD) increase a woman's cardiovascular risk (CVR) throughout her life cycle. Therefore, HDP, notably PE, ECL, and GD, are considered sex-specific cardiovascular risk factors (CVRFs)^{3,4}.

Heart failure with preserved ejection fraction (HFpEF), which is more prevalent in women, becomes more frequent with aging. Hormonal pathophysiological mechanisms, especially after menopause, lead to a higher prevalence of HFpEF, such as changes in the renin-angiotensin-aldosterone system, response to endothelial injury, left ventricular (LV) remodeling, and microcirculation dysfunction⁵.

Other HF phenotypes in women are Takotsubo cardiomyopathy and peripartum cardiomyopathy (PPCM). In Takotsubo cardiomyopathy, there is acute, reversible, LV failure, usually secondary to stress-induced adrenergic discharge, and 95% of cases are women who are affected mainly in the postmenopausal period. Most cases recover LV function within 3 months, with low recurrence (2–5%)⁶. PPCM is characterized by LV

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dysfunction at the end of pregnancy or in the first five postpartum months, especially in the first week, being a diagnosis of exclusion. The main risk factors (RFs) for PPCM are advanced age, PE, and multiple pregnancies. The prognosis is favorable, with the recovery of LV function within 6 months in more than 70% of cases⁶. Regarding mortality from HF, there are no differences in relation to men, although women are at greater risk (because they are older and have more comorbidities)².

CARDIOVASCULAR RISK FACTORS AND PECULIARITIES IN STRATIFICATION

Despite the importance of addressing CVRFs and their relationship with IHD in women, these are underrepresented in most clinical trials, and CVR stratification scores do not include RF inherent in women. The most current guidelines recommend that, in the evaluation of CVD, along with traditional and well-established RFs, gender-specific ones, such as polycystic ovary syndrome, use of hormonal contraceptives, HDP and its complications such as PE, ECL, and DG, menopausal hormone therapy, and the aggregate risks of inflammatory and autoimmune diseases, can be considered. It is important to remember that the traditional and most impacting RFs in

women are diabetes mellitus (DM), systemic arterial hypertension (SAH), dyslipidemia, smoking, obesity, and sedentary lifestyle. No less important in women are the under-recognized RFs, such as depressive disorders and social determinants of health, which contribute as potentiating risk factors (PFs) for better risk stratification and cardiovascular prevention. It is well described that, in women, these RFs interact with each other promoting inflammation, endothelial dysfunction, atherosclerosis, and autonomic and immune dysfunction, with a consequent increase in risk² (Figure 1).

The use of the classic Global Risk Score (GRS) associated with knowledge about specific RF, under-recognized RF, and PF allows us to reclassify women in terms of their risk. A more comprehensive and effective stratification leads to the possibility of earlier interventions, such as lifestyle change guidelines and the use of statins, seeking to achieve established goals for the control of CVD. In women stratified by GRS at intermediate or low risk, in the presence of PF, the assessment of the coronary calcium score (CAC) should be considered. If the CAC is zero, the statin should not be started unless DM, a family history of premature CAD, or smoking is present. A CAC between 1 and 99 favors the use of statins, especially in women over 55 years old. If the CAC is greater than 100 or above the 75th percentile for age and sex, the use of statins is indicated² (Figure 2).

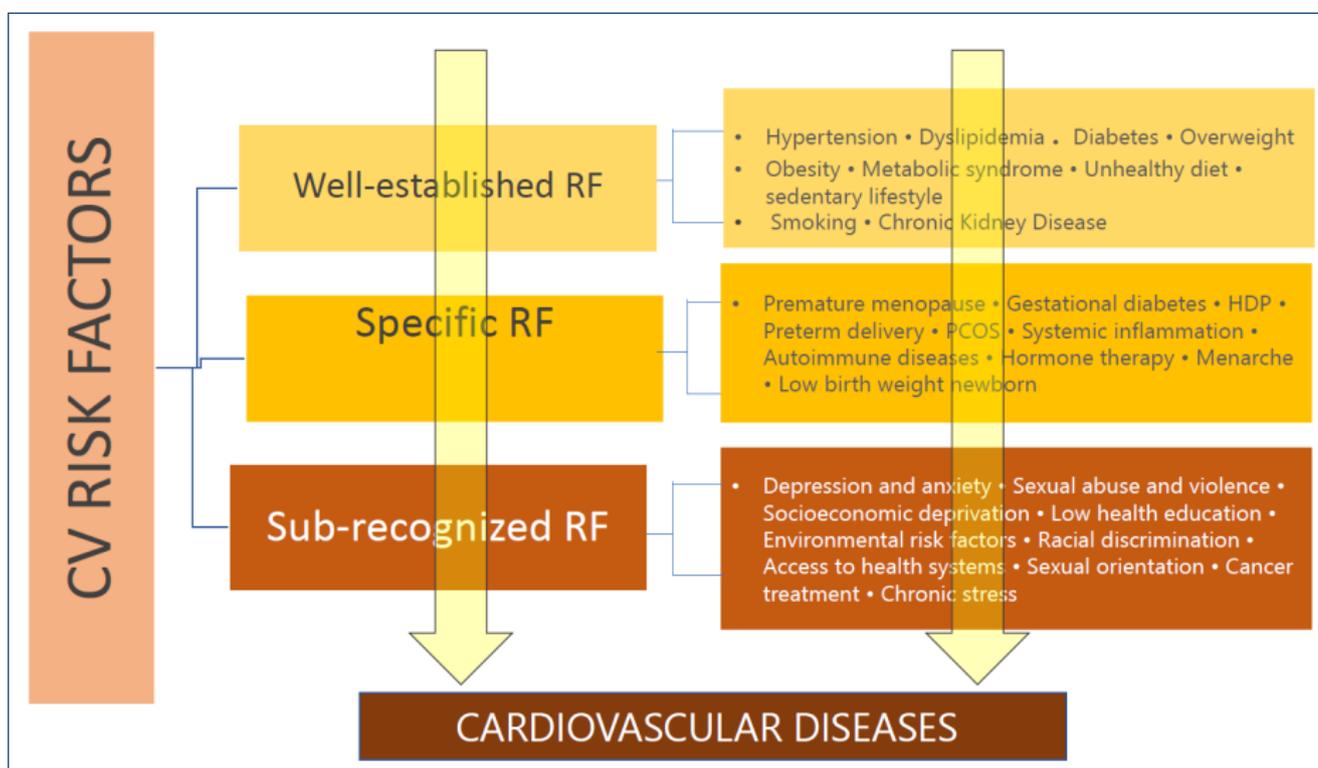


Figure 1. Cardiovascular risk factors in women (adapted from the Women's Cardiovascular Health Position 2022²). CV: cardiovascular; RF: risk factor; HDP: hypertensive disorders in pregnancy; PCOS: polycystic ovary syndrome.

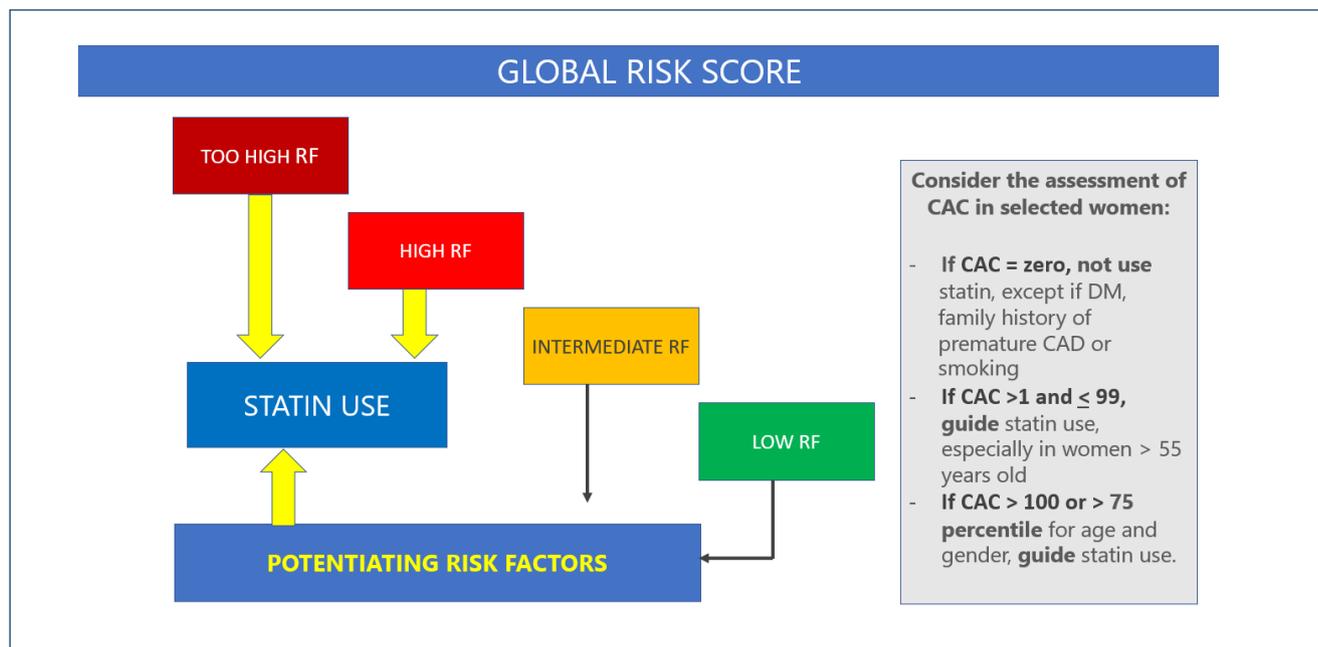


Figure 2. Stratification of cardiovascular risk in women (adapted from the Women's Cardiovascular Health Position 2022²). RF: risk factor; CAC: coronary calcium score; DM: diabetes mellitus; CAD: coronary artery disease.

CONSIDERATIONS ON DIAGNOSTIC METHODS IN DIC

Women with IHD behave differently from men due to the presence of peculiar pathophysiological characteristics, such as less caliber arteries and a higher prevalence of CMD. Coronary Ischemia without severe obstructive lesions (INOCA) and infarction without occlusive atherosclerotic lesions (MINOCA) are more frequent in women. Therefore, the sensitivity and specificity of the diagnostic tests are different, which deserves some consideration.

The baseline electrocardiogram (ECG) of women has its own characteristics such as a longer QT interval, changes in the ST-T segment, and flattening of the T wave. In addition, it can show changes that lead to misinterpretation, such as ST-T depression, T-wave inversion, and signs of LVH, which are described in up to 45% of women with breast implants⁷.

Exercise stress testing (ET) has a sensitivity of 62% and specificity of 68% with a positive predictive value of only 47%, but a high negative predictive value. Factors that may contribute to the inaccuracy of the ST response as a predictive tool include a lower prevalence of obstructive CAD in women compared to men and ST changes due to estrogen, mitral valve prolapse, coronary vasospasm, and CMD, which are more prevalent in women than in men. The association of ET with stress myocardial scintigraphy is an excellent strategy to increase the accuracy of the method^{8,9}.

Coronary angiography can be normal or present less severe obstructive lesions, even in the presence of ischemic symptoms, which leads to its non-appreciation, delaying the diagnosis and treatment of IHD. It is important to remember that women are at greater risk of developing AKD due to the contrast, in addition to presenting vascular complications because of the anatomical characteristics of their vessels¹⁰.

Coronary computed tomography angiography is important in the diagnosis of non-obstructive IHD. CAC is an important method in the therapeutic decision in women with low and intermediate risk stratification in the presence of PF (Figure 2). The presence of CAC greater than zero associated with mammary arterial calcification has a greater correlation with ischemic events in women than in men¹¹.

Cardiac magnetic resonance (CMR) provides data on perfusion and cell metabolism, with high sensitivity and specificity (89 and 80%) to detect IHD, and can be used in pregnant women, in addition to helping in the differential diagnosis of cardiomyopathies, and also in the analysis of cardiotoxicity in women undergoing treatment for breast cancer¹².

Measurement of carotid intima-media thickness by vascular ultrasound for risk reclassification is useful in women with at least two CVRFs. The presence of atheroma plaque in the carotid arteries is an aggravating factor for stratification in cases of intermediate risk¹¹.

FUTURE PERSPECTIVES

A clear understanding of disparities in morbimortality from CVD in women is essential for the development of measures to prevent and control these diseases, such as promoting a healthy lifestyle and controlling CVRFs deeply². Reducing the burden of CVD in women by 2030 is an ambitious goal, but an imperative, especially as most CVRFs can be modified and mitigated¹³. It is important to understand which mechanisms contribute to the worsening of the profile of women with emerging and non-traditional, exclusive or more common RFs, contributing to a better understanding of their mechanisms of CVD.

Recent studies demonstrate that epigenetic modifications play an important role in the occurrence and development of CVD and are differently associated with cardiometabolic characteristics in type 2 DM, stroke, and myocardial infarction (MI) in men and women¹⁴. In the future, with greater knowledge about the molecular mechanisms of epigenetics in the regulation of CVD, more strategies for its prevention may be implemented, in addition to the design of new sex-specific drugs, increasing their efficiency.

During pregnancy, women with or without heart disease are more vulnerable to adverse cardiovascular events. Today, heart diseases are the main cause of maternal death¹⁵, including HDP, more specifically PE, the main cause of maternal mortality and morbidity in Brazil and Latin America¹⁶. The Ministry of Health, despite having implemented several policies to strengthen and qualify actions in the care of pregnant women during prenatal care, childbirth, and the puerperium, did not reach the goal recommended by the WHO to reduce the maternal death rate, i.e., 35 maternal deaths for every 100,000 live births (2015)¹⁷. According to the data recorded in the Maternal Mortality Monitoring Panel in 2021, the country had an average of 107 deaths per 100,000 births¹⁸. Most cardiovascular complications that develop during pregnancy can be prevented and treated early. The development of combined cardio-obstetrics

care should be implemented as a model of antenatal care to improve maternal and fetal outcome^{19,20}.

CONCLUSION

Several measures have been developed by the Brazilian Society of Cardiology (SBC) through the Women's Department of Cardiology, such as the publication of Positionings and Guidelines^{2,3}, and the availability of educational, multidisciplinary lives, directed to the public²¹. These and other ongoing actions have the main purpose of expanding knowledge about the specificities related to WOMEN. A task force connecting other SBC departments and related clinical societies, together with measures in public health and private medicine, can generate impactful actions in reducing morbidity and mortality from CVD in this population with low representation in relevant clinical trials.

Raising awareness of an extremely relevant topic such as CVD in women involves academic training in the area of women's health, creating integrative programs in base communities, training community leaders as educators on health and well-being in women, acting both in the identification of those exposed not only to traditional CVRFs but also to the "new" CVRFs, such as psychosocial illnesses and socioeconomic aspects, less addressed at different levels of health²².

AUTHORS' CONTRIBUTIONS

MCCA: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Writing – original draft, Writing – review & editing. **MLC:** Data curation, Formal Analysis, Project administration, Supervision, Validation, Visualization, Writing – review & editing. **CMS:** Investigation, Methodology, Resources, Writing – original draft. **MENCC:** Investigation, Methodology, Resources, Writing – original draft. **RCMC:** Investigation, Methodology, Resources, Writing – original draft.

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