Cardiovascular disease. A gendered view: literature review

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Abstract

Cardiovascular disease has become the leading cause of death in men and women in Colombia and worldwide. Its prevalence remains significant since there have been no notable changes in preventive or treatment trends in recent years. However, nowadays, the relationship with gender has been consolidating, so it is currently a relevant role, through which epidemiological, pathophysiological, and etiological differences between men and women have been elucidated, which could potentially mark differences in diagnosis, treatment, and hard outcomes. This article aims to describe the background and different factors that have been studied in cardiovascular disease and their relationship with gender, especially focused on women.

Keywords: cardiovascular diseases, women, primary prevention, acute coronary syndrome

Resumen

La enfermedad cardiovascular se ha constituido como la principal causa de muerte en hombres y mujeres en Colombia y a nivel mundial. Su prevalencia continúa siendo importante, pues en los últimos años no han existido cambios notables en las tendencias preventivas o de tratamiento. Sin embargo, en la actualidad la relación con el género se ha venido consolidando,

por lo que constituye actualmente un rol relevante, a través del cual se han dilucidado diferencias epidemiológicas, fisiopatológicas y etiológicas entre hombres y mujeres, que podrían potencialmente marcar diferencias en el diagnóstico, tratamiento y desenlaces duros. Este artículo tiene como objetivo describir los antecedentes y diferentes factores que se han estudiado en la enfermedad cardiovascular y su relación con el género, especialmente enfocado en mujeres.

Palabras clave: enfermedades cardiovasculares, mujeres, prevención primaria, síndrome coronario agudo.

CARDIOVASCULAR DISEASE. A GENDERED VIEW: LITERATURE REVIEW

Introduction

Cardiovascular disease (hereafter CVD) is the leading cause of death worldwide (1), and Colombia is no exception. According to DANE figures of the 242,609 deaths registered in 2019, 38,475 (16%) corresponded to ischemic heart disease and 15,543 (6%) to CVDs (2). Epidemiological, pathophysiological, and etiological differences have catalogued gender as a risk factor related to CVD, based especially on the gestational period, obstetric history, and hormonal differences with the corresponding protective role that has been attributed to estrogens (3).

Historically, CVD in the female gender is considered to be underrepresented, underdiagnosed, and undertreated in studies (4). Dr. Healy in 1991 coined the term Yentl's Syndrome, inspired by the story of a young woman posing as a man to gain access to education (5). Ayanian et al (6) demonstrated that women were less likely to undergo coronary angiography, angioplasty, or coronary surgery when they were admitted to hospitals in the context of an acute coronary syndrome.

The aim of this article is to provide a narrative review of the impact of traditional, emerging, and female-specific risk factors on the development of cardiovascular disease. It also aims to clarify the different pathophysiological mechanisms in women and the differences in terms of treatment, primary and secondary prevention.

Materials and methods

A narrative review of the literature was carried out by searching for scientific articles in Medline through Pubmed, SciELO and LILACS. The search strategy was developed using the terms Medical Subject Heading Terms (MeSH): Cardiovascular diseases, woman, Peripheral Arterial Disease, acute

myocardial infarction, Stroke. It was searched individually or in conjunction with the Boolean operators "AND" "OR". The bibliographic search was carried out on articles published from 1991 to 2022 and limited to articles in English and Spanish. The articles found by the preliminary search were analyzed by critical reading of the abstracts or full text.

Epidemiology

CVD affects 6.6 million women in the United States annually and is the leading cause of morbidity and mortality in this group (7). It causes 8.6 million deaths annually, comprising one third of all deaths among women worldwide (8). Coronary heart disease in women occurs 9 years later than in men (65 years vs. 59 years) (7) and is associated with a higher risk of morbidity and mortality from heart failure (9).

The representation of women in cardiovascular clinical trials has fluctuated over the last two decades, from 20% during the period 1966 to 1990, 25% from 1991 to 2000 (10), and in the last decade between 33% and 38% (11). The explanation for this phenomenon is probably due to the inclusion of patients whose mean age is 60 years or younger (11).

Anatomic, histologic, and physiologic gender differences

The gender difference starts from the cardiovascular morphology determined by the Hand1 and Hand2 genes on chromosome 4, which determine cardiac morphogenesis. Women's hearts have a smaller size, weight, and ventricular mass than men's; likewise, the coronary arteries are of smaller caliber, with greater tortuosity and a right dominance (12). Histologically, cardiomyocytes are of the same size; however, men tend to increase the number of binuclear cells and have a considerably higher rate of cell apoptosis per year, which represents greater fragility compared to women (12). Physiologically, women have a higher HR of 80lpm vs. 70lpm, a lower stroke volume and cardiac output of 4.5 vs. 5L/min compared to men and in premenopausal stage a higher arterial and left ventricular distensibility (13).

Sexual hormones and their cardiovascular benefit:

The premenopausal stage is clearly identified as a period of lower cardiovascular outcomes. Most of the effects of sexual hormones are based on gene expression (14); for example, at the vascular level, the expression of endothelial nitric oxide synthase (eNOS) favors vasodilatation, a decrease in blood pressure, and an increase in parasympathetic tone (15). Estrogens have been shown to have an antioxidant effect mediated by binding to the alpha-estrogen receptor, which enhances the expression of cystathionine-

γ-lyase (CSE), a hydrogen sulfide-generating enzyme, thus attenuating reactive oxygen species and cardiomyocyte apoptosis by suppression of ischemia/reperfusion (16). Blocking the pro-fibrotic effects of angiotensin II and endothelin-1 on metalloproteinases is another benefit of estrogens (17). In addition, the premenopausal stage has been associated with lower LDL cholesterol levels and higher HDL cholesterol levels compared to postmenopausal women (14).

Life expectancy of women is approximately 5 years longer than men, this statistic has been attributed mainly to the protective factor of estrogens during the female fertile period. In addition, it has been established that in this period women have levels of growth hormone (GH) up to twice as high as men, knowing the importance of this hormone in the regulation of apoptosis, cellular aging, and at the myocardial level, an increase in protein synthesis and a decrease in arterial lipid deposits (18).

In the post-menopausal stage, the predominant sex hormone is estrone, produced in the ovaries and fatty tissue. During this period, the previously mentioned benefits are lost, which favors the increase of the risk factors established as follows (14).

Traditional risk factors

The INTERHEART study demonstrated a different burden of risk factors between men and women for AMI. This allowed us to find that hypertension, diabetes mellitus, smoking, alcohol use, and physical inactivity were more strongly associated with AMI in women than men; and in addition, significant differences were found for psychosocial factors (4,19).

Dyslipidemia: constitutes the highest population-adjusted risk factor among women, with 41.7% compared with other known risk factors for CVD (20). However, this factor is observed in postmenopausal women, in whom decreased HDL cholesterol 2/3 ratio, increased APO B, triglycerides, and LDL cholesterol (21).

High blood pressure (HBP): remains the most common modifiable risk factor for CVD, with a current impact of 33.4% in adult women in the United States (21). It has been documented that systolic blood pressure rises more rapidly in older women compared with men, possibly because of decreased estrogen levels at menopause, overregulation of the renin angiotensin system with increased plasma renin activity, increased salt sensitivity, and increased sympathetic system activity in postmenopausal compared with premenopausal women (22). Likewise, moderate or borderline hypertension

causes more endothelial dysfunction and cardiovascular complications in women. It should be noted that it has been suggested that postmenopausal women have a dipping BP pattern during the night, which could explain the higher incidence of cardiovascular events attributed to BP during the night in women, demonstrating the importance and superior beneficial effect of BP control when ambulatory rather than conventional BP measurement is used (23).

Diabetes mellitus (DM): diabetes is a much more influential risk factor in women. Peters et al. (24), through a systematic review and meta-analysis, described that the relative risk (RR) for the incidence of coronary heart disease associated with diabetes compared with non-diabetes was 2.82 in women and 2.16 in men; moreover, the RR for coronary heart disease in women with diabetes was 1.44 (95% CI 1.27-1.63) compared with diabetic men. The risk of fatal coronary heart disease is 50% higher in those with a diagnosis of DM, which can be explained in part by a higher rate of coexisting risk factors in women with diabetes and a longer survival of women without diabetes (25).

Smoking: in women, smoking is more deleterious, with a 25% higher risk of coronary heart disease among smokers compared to men, regardless of the presence of other cardiovascular risk factors (26). It is especially important in women under 55 years of age, where it increases the risk of AMI up to 7-fold (25). In general, smoking decreases the generation and bioavailability of nitric oxide, increases oxidative stress and the inflammatory response, which explains its relationship with the initiation and progression of atherothrombotic disease; however, in premenopausal women, its consequences have been enhanced, considering its anti-estrogenic effect and the role of this hormone in increasing the release of nitric oxide (27).

Physical inactivity: The risk of CVD has a strong association, with the lowest risk in those with the highest levels of activity. It has been reported that after the age of 30, the risk of CVD attributed to physical inactivity outweighs the other factors in women (28).

Table 1 summarizes the traditional risk factors for CVD in women.

Table 1. Traditional risk factors for AMI according to gender

Risk Factor	Risk factor frequency	Odds ratio (95% IC)		P interaction
		Mujer	Hombre	
ApoB/ApoA1	24.3	3.3 (2.85-3.82)	2.87 (2.63-3.31)	0.20
Diabetes	7.97	4.26 (3.68-4.94)	2.67 (2.43-2.94)	<0.0001
HTA	28.3	2.95 (2.66-3.28)	2.32 (2.16-2.48)	0.0001
Waist-to-hip ratio	33.3	2.26 (1.98-2.57)	2.24 (2.08-2.42)	0.03
Psychosocial factors	88.6	3.49 (2.4-5.09)	2.58 (2.11-3.15)	0.02
Active smoking	9.2	2.86 (2.47-3.32)	3.04 (2.84-3.26)	0.06
Physical activity	16.5	2.07 (1.77-2.43)	1.3 (1.2-1.41)	<0.0001
Diet	17.9	1.78 (1.54-2.04)	1.68 (1.56-1.82)	0.20
Alcohol consumption	11.2	2.42 (2-2.93)	1.13 (1.06-1.21)	<0.0001

Note: Adapted from Kandasamy S, Anand, S. Can. J. Cardiol. 34, 450–457. (2018) (8)

Non-traditional risk factors:

Depression and anxiety: its relationship with CVD is due to multifactorial causes, among which is a change in behavioral habits (increased smoking, lack of exercise and dietary factors); as well as psychological mechanisms that lead to neuroendocrine alterations, inflammatory response, platelet reactivation and endothelial dysfunction (29). Depressed women show a higher risk of developing AMI or cerebrovascular accident (CVA) (29). At the same time, there is growing recognition of abuse of women as a public health determinant with recognized long-term effects on women's cardiovascular health (30). Recent evidence points to the proinflammatory state, alterations in the hypothalamic-pituitary-adrenal axis, the renin angiotensin aldosterone system, and the serotonin/kynurenine pathway, possibly contributing to the development of depression and CVD (31).

Specific risk factors for women:

Hormones, menopause, and hormone replacement therapy (HRT): after menopause, the incidence of CVD increases substantially, as well as mortality among those with early menopause; this showed in some studies that hormone replacement therapy for primary and secondary prevention increases the risk of coronary heart disease, breast cancer and venous thromboembolic events (21). Multiple current studies have attempted to elucidate the initiation of HRT and consider that the greatest value of initiation is just after the onset of menopause, when the heart and coronary arteries of women are still young and more receptive to the beneficial effects

of estrogens. Kim et al (32) conducted a recently published systematic review, including 26 randomized and 47 observational clinical trials, which documented an increased risk of venous thromboembolism, stroke, and a reduced risk of AMI in observational studies, with the clinical effects dependent on the time of HRT initiation, underlying disease, and route of administration. At this point, the benefit of HRT remains controversial, although it is recommended for control of hypoestrogenism symptoms, early initiation in early ovarian failure or early menopause for prevention of osteoporosis, CVD, and cognitive impairment (33,34).

Pregnancy: gestation is a stress test for women and provides a unique opportunity to analyze their future risk of developing CVD (21). Preeclampsia is independently related to a 4 times higher risk of incident heart failure, 2 times higher risk of coronary heart disease, and gestational diabetes is related to an 8 times higher risk of developing DM2 and 3 times higher risk of developing future cardiovascular events (35). A history of preterm delivery and small-for-gestational-age children is associated with a 1.4 to 2-fold increased risk of developing CVD (36).

Premature ovarian failure: when it is premature, that is, before the age of 40 or 45 years, it is related to an increase in CVR (35). It has been documented that women with this entity present with less favorable risk factors such as increased waist circumference and a high prevalence of hypertension and metabolic syndrome compared to women with a similar age and body mass index (37).

Inflammatory biomarkers, autoimmune disease: autoimmune diseases tend to be more common in women and constitute an additional risk factor that has been shown to confer an increase in CVR (38). This association has been reported in the literature for decades, and the strongest evidence available is found in systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). RA has been documented to result in 3 times the risk of CV mortality from events such as AMI or stroke, and even women with RA have a higher risk of AMI than men with the same diagnosis (39). Patients with SLE have markedly increased morbidity and mortality associated with CVD, including women between 35 and 45 years of age who have a particularly 50-fold increased risk of AMI compared to controls in the general population.

Other factors: it is important to consider them for risk stratification, such as early menstruation (under 10 years of age), polycystic ovary syndro-

me (PCOS), use of hormonal contraceptives, breast cancer, and abortions (35). Breastfeeding has been suggested as protective against future HT and CVD, especially if it is carried out for a minimum of 6 months (40).

Table 2 represents risk factors specific to women.

Table 2. Risk factors specific to women.

Risk factor	CVD	CAD	HT	CVA	DM2
PCOS	+	-	+	-	+++
POI	++	++	-	-	-
HTIP	++	+	+++	+	++
Preeclampsia	++	++	+++	++	++
GDM	++	++	+++	-	+++
Pregnancy PT <37 ss	++	+	+	++	++
Birth ≥1	++	-	-	-	-
Birth ≥5	+++	-	-	-	-
Abortion ≥1	-	+	-	-	-
Abortion 2+/3+	-	++	-	-	-
SGA <10th	++	++	-	++	-
Stillbirth	-	++	-	-	-

Conventions: CVD: cardiovascular disease, CAD: coronary artery disease, HT: arterial hypertension, CVA: cerebrovascular accident, DM2: diabetes mellitus type 2, PCOS: polycystic ovary syndrome. POI: primary ovarian insufficiency. HTIP: Hypertension induced by pregnancy. GDM: Gestational Diabetes Mellitus. PT: Preterm, SGA: small for gestational age. +: Weak association in cohort studies, RR: 1 - 1.5. ++: Moderate association, RR: 1.5 - 2.5 in cohort studies. +++: Strong association, RR>2.5 in cohort studies.

Note: Adapted from Gao, Z., Chen, Z, Med. Nov.Technol. Devices 4, 100025 (2019) (41)

Cardiovascular diseases in women:

Coronary artery disease (CAD):

CAD develops eight to ten years later in women (19), with a 2.6-fold higher incidence of cardiovascular events in postmenopausal compared with premenopausal women (41). The *Polaspire* study showed that women with CAD were older ($P < 0.001$) and higher in CV risk factors than men ($P = 0.036$) (42). Women outnumber men in incidence of ACS after the age of 75 years (43), however, those presenting below the age of 60 years are associated with mortality up to 2 times higher than that of a man of the same age (44). This could be related to the aforementioned: smaller coronary ves-

sels, lower diastolic distensibility, delayed diagnosis, lower probability of receiving reperfusion therapy, and optimal medical therapy.

Furthermore, women pathophysiologically generate plaque erosion with subsequent distal embolization, whereas men produce plaque rupture with local thrombosis (45). CAD in women is characterized by a more diffuse atherosclerotic burden often associated with microvascular and endothelial dysfunction, and there is more residual angina after myocardial revascularization (46). On the other hand, epicardial coronary stenosis is typical of men (40).

The Society of Cardiovascular Computed Tomography Consensus (hereafter SCCT) establishes recommendations for the use of coronary artery tomography angiography (CCTA) in patients with stable chest pain, where it has been shown to reduce testing following a normal CT scan. In the PROMISE trial, the MACE rate for women with a negative CCTA were similar to those of women with a negative stress test. On the other hand, women with an abnormal CCTA had higher rates of MACE than women with an abnormal stress test, suggesting that women may particularly benefit from a CCTA-guided approach because of its better prognostic value (47).

Takotsubo syndrome:

It is a condition in which there is a sudden, severe, and reversible dysfunction of the left ventricle, triggered by acute psychological or physical stress (48). One of the characteristics of this pathology, described for the first time in Japan in 1990, is its overwhelming preponderance in the female gender; although it constitutes 1 to 3% of the cases of ACS, its prevalence in the female gender ranges from 6 to 9.8%, while in men it is less than 0.5%, here the majority (90%) are postmenopausal adults, with an average age of 67 years (49). The prognosis is generally good for patients who survive the initial acute phase of heart failure, and it is not known whether outcomes differ by sex. In-hospital mortality varies from 0 to 8%, while 1-year mortality is 1 to 2%. Complications typically occur in the first phase, mainly related to heart failure, ventricular arrhythmias, left ventricular free wall rupture, mural thrombi and the risk of systemic embolization (50).

Spontaneous coronary artery dissection (SCAD):

It is the non-traumatic or iatrogenic separation of the coronary arterial walls, generally between the intima and the media or the media and the adventitia, which creates a false lumen, with intramural hematoma, which compresses the arterial lumen, decreasing blood flow and producing ische-

mia or infarction (51). Recent studies have described a prevalence of 0.07% to 1.1%, predominantly affecting young women, in whom it constitutes 81 to 92%. When it comes to ACS, SCAD is the etiology in up to 35% of cases in women younger than 50 years, and it is the most common etiology of pregnancy-associated AMI (52). It should be suspected in any premenopausal woman presenting with ACS without typical risk factors for atherosclerosis, absence of atherosclerotic lesions in coronary arteries, peripartum status, history of fibromuscular dysplasia, connective tissue disorders (Marfan syndrome, Ehler Danlos syndrome), relevant systemic inflammation (SLE, Chron's disease, sarcoidosis) or precipitating stressful events (emotional or physical such as intense exercise) (51). This type of lesion has been described most frequently in the anterior descending artery, although multivessel involvement has also been described (51).

Coronary Arterial Spasm:

It is a well-known phenomenon of recurrent chest pain at rest with transient ST-segment elevation. Its pathogenesis is multifactorial, including vascular smooth muscle hyperactivity, endothelial dysfunction, inflammation, oxidative stress, and an imbalance of the autonomic nervous system. The major risk factor is smoking, with possible triggers including the use of hallucinogens such as cocaine, ephedrine, and other drugs (53). The prevalence of vasospastic angina has been repeatedly reported to be higher in men than in women; however, Lee et al. (54) documented that women with coronary spasm were younger and showed a lower prevalence of smoking or fixed coronary stenosis compared to men. Likewise, the risk of adverse cardiovascular outcomes (MACE) was similar between both genders and in a multivariate model, high-sensitivity C-reactive protein was a significant predictor of MACE in men, but not in women.

Ischemia without obstructive coronary artery disease (INOCA) and infarction without obstructive coronary artery disease (MINOCA) in women:

15% of men and 30% of women with angina and ischemia in the stress test will not have coronary obstruction in invasive coronary angiography (INOCA). This being more common in women, between 45 and 65 years of age (55). The prevalence varies between 34-62% (56). The WISE study suggests that more than half of the patients with INOCA have coronary microvascular disease (CMD), indicated by an abnormal coronary flow reserve (CFR) (57,58). INOCA correlates with a major cardiovascular event rate of

2.5% per year (57), recurrent angina and repeat angiography, poor quality of life (QoL), and high cardiovascular costs similar to obstructive CAD (59,60).

On the other hand, up to 6% of patients with acute coronary syndrome (ACS) suffer myocardial infarction without obstructive coronary artery disease (MINOCA). The diagnosis of MINOCA is established in patients who meet AMI criteria according to the fourth definition of infarction with catheterization if evidence of lesions ≥50% (60). MINOCA faces reduced quality of life and adverse cardiac outcomes which includes a 4.7% all-cause mortality at 12 months. Patients in the CCTA arm of the PROMISE trial showed an increased risk of MACE in women with high-risk atherosclerotic plaques, defined as: positive remodeling, low attenuation, or napkin ring sign (61). In a study of women with MINOCA, the cause was identified in 85% of women when a combination of intracoronary optical coherence tomography (hereafter OCT) and cardiac magnetic resonance imaging (hereafter c-MRI) was implemented (62). Cardiac MRI plays a vital role in the exclusion of myocarditis and other cardiomyopathies (63). As well as vasoreactivity testing, thrombophilia detection and intravascular ultrasound could be involved in the diagnostic process of MINOCA (63). It was shown in a prospective Canadian study of patients with INOCA and MINOCA that attendance at a dedicated women's cardiovascular center improves diagnostic yield, and these long-term strategies could improve risk factor control, angina control, quality of life, fewer emergency department visits, and hospitalizations for angina per year in these highly symptomatic patients. Studies with long-term outcomes impacting cardiovascular outcomes are still pending (64).

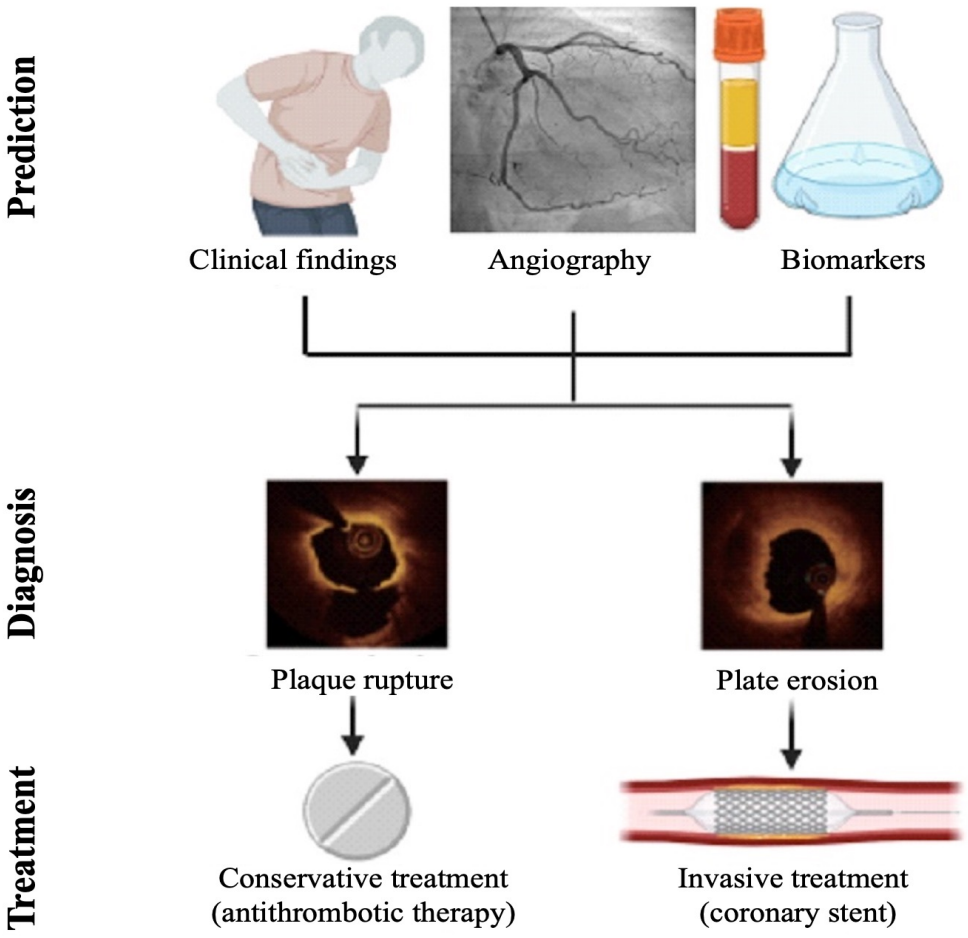
Treatment of ACS in women.

ACS is caused by different pathophysiological mechanisms as mentioned above and in women plaque rupture is not the main causal etiology. For this reason, management should be individualized.

It should be noted that even today, in terms of treatment, it has been found that women with coronary angiography showing single-vessel disease are less likely to undergo angioplasty and coronary bypass revascularization when they present 2- or 3-vessel disease compared to men (65). The use of tools such as OCT has had an impact on treatment, as it helps to identify thrombosis triggered by plaque erosion or rupture. This has allowed the selection of patients who can be treated with thrombus-reducing strategies such as catheter-directed lytic therapy (plasmin) without stent im-

plantation, which may be safer and more effective (66). This is possible, since rupture seems to involve luminal obstruction mechanisms, whereas erosion lesions exhibit less narrowing and therefore, after thrombus removal, treatment with antiplatelet agents may allow healing of the endothelial layer. Additionally, the role of antithrombin agents may be justified, as the risk of intraplaque hemorrhage is lower when the fibrous cap is intact. By avoiding stent implantation, the risks of both early (dissection, embolism, occlusive thrombosis) and late (restenosis, neoatherosclerosis and thrombosis) complications could be reduced (67). Hence, the EROSION study (68) demonstrated the success of treating patients with plaque erosion with aspirin plus ticagrelor, and its 1-year follow-up (69) continued to confirm a greater reduction in thrombus volume at follow-up and that 92.5% of patients with ACS remained free of major cardiovascular events. Figure 1 shows this approach.

Figura 1. Prediction, diagnosis and treatment of plaque erosion



Adapted from Crea, F & Vergallo, R. Int. J. Cardiol. 288, 22-24 (2029) 68

Regarding general pharmacotherapy, there are also significant differences according to gender, which may alter the therapeutic choices for women (7). Table 3 shows these differences.

Table 3. Pharmacological therapy in women.

Medication	Mortality risk for women	Adverse effects in women
Angiotensin-converting enzyme inhibitors	No benefit in mortality due to left ventricular dysfunction.	Drier cough
Aspirin	Greater protection against stroke. Less protection in AMI	Increased risk of bleeding
Beta-blockers	More dose-response sensitivity for blood pressure and heart rate	No differences identified
Digoxin	Increased mortality	No differences identified
Statins	No differences	Increased incidence of myopathy

Note: adapted from Leonard, E. A, Marshall, R. J Prim. Care Clin. Off. Pract. 45, 131–141 (2018) (7).

Prognosis

Women with atherosclerotic cardiovascular disease (hereafter ACVD) report a poorer experience, lower health-related quality of life, and a more unfavorable perception of their health compared to men; which has an important public health implication, as it requires more research towards understanding specific differences regarding gender-related quality of health care (70).

AMI in women deserves special attention because they have a worse in-hospital and long-term prognosis. They have twice the mortality compared to men, even in the thrombolytic era (71). Despite the improved prognosis in women treated with percutaneous intervention, they have a higher risk of in-hospital mortality, major bleeding, reinfarction and post-procedure readmission. Likewise, when they undergo myocardial revascularization surgery, they present more postoperative complications such as renal injury and postoperative AMI (25).

Similarly, complication rates after AMI are higher, such as mechanical complications, especially severe mitral regurgitation and symptoms of heart failure, possibly related to the presence of other concomitant comorbidities (25).

Prevention and counseling of CVR in women:

In this context, women are also more likely to be assigned to a lower CVD risk category and therefore receive less intensive medical therapy,

both pharmacological and invasive, as well as lifestyle recommendations, compared to men (11). Walli et al. (72) in a recent study documented that CVD treatment is more common in women than in men in primary prevention, with more favorable results in the female gender, but less intervention in terms of secondary prevention. CONCORDANCE study conducted in 43 Canadian hospitals showed that at 6 months after AMI there is already 29% more MACE than men, and at one year only 35% were undergoing cardiac rehabilitation and 16% receive less medication than men with respect to the recommendations of the guidelines (73). It is important to optimize risk factor control strategies, given that they are deficient in women. The EUROASPIRE V registry showed a 10% worse risk factor control compared to men in terms of smoking, physical activity, weight control, LDL cholesterol and HbA1c goals (74).

Statin use: Systematic reviews document that the inclusion of women and older adults in lipid-lowering medication, although increasing over time, continue to be underrepresented, limiting the evidence base for efficacy and safety in these subgroups (75). For this reason, although dyslipidemia drug therapy for secondary prevention has been shown to be equally effective in women and men in reducing recurrent cardiac events and mortality reduction(76), in primary prevention, the data are more limited with regard to the female gender, and it has even been found that it does not generate a significant reduction in mortality (77), and on the contrary may contribute to a greater probability of developing diabetes mellitus (DM) and myalgias in women (78).

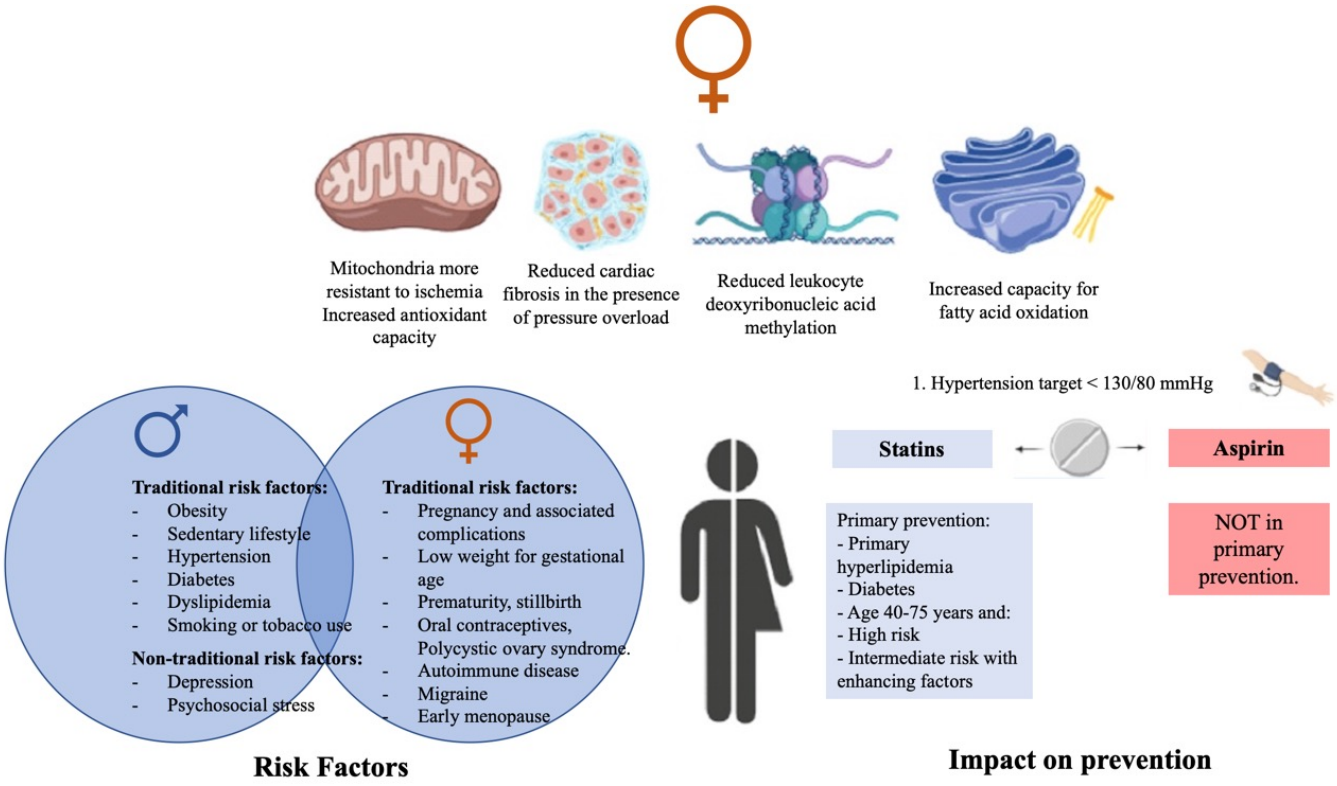
The recent review of primary prevention of CVD in women (23), considers that all women should receive statins in the context of secondary prevention, primary hyperlipidemia C-LDL ≥ 190mg/dL, DM, and in the case of primary prevention if the age is between 40 to 75 years and presents high CVR, or intermediate associated with potentiating risk factors among which are those specific to women (23).

Calcium Score for cardiovascular risk readjustment: in addition to the cardiovascular risk assessment strategies in primary and secondary prevention specified in the different clinical practice guidelines, the implementation of coronary calcium scoring is a marker of the extent of coronary artery disease (CAD) and can predict the presence of arterial stenosis, so it may be present before plaque burden occludes the lumen and leads to clinically

apparent CAD (79). It has been attributed a very high sensitivity (generally >95%) and negative predictive value of 99%. Women classified as intermediate-low risk by Framingham, who had a coronary artery calcium (CAC) score of 0, had a low mortality of 5% at 15 years compared with 23.5% for women with a score >400 (80). For CAC scores between 1-99 there is controversy, however, intermediate-dose statins could be initiated at an estimated risk >7.5%, otherwise a 10-year reassessment could be performed. Above this range, statin therapy would be clearly indicated, so the intermediate dose would vary between 100-300UA and high intensity >300 UA (81). This strategy has allowed better prediction of cardiovascular events and modification of intention-to-treat, especially in women at intermediate cardiovascular risk or when the risk score is inconsistent with that perceived by the clinician (79).

The use of aspirin is only recommended for secondary prevention. On some occasions, primary prevention is possible in the presence of current smoking, high calcium score, carotid atheromatosis, family history of premature CVD and low risk of hemorrhage (23). Figure 2 provides an approach to this subject.

Figure 2. General overview of cardiovascular disease in Women



Source: The authors

Cardiac rehabilitation programs in women:

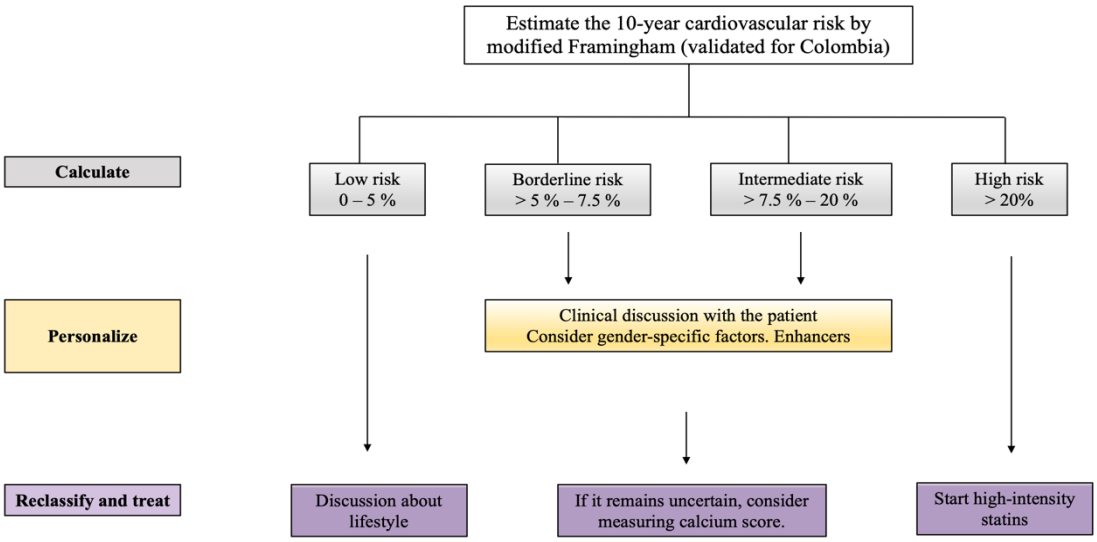
Mortality after acute coronary syndrome is estimated to be approximately 10%, which is why cardiac rehabilitation is a pillar in secondary prevention; however, there are records that specify that women are less referred, less adherent, and complete the programs less often (82). However, an Australian study of 25,000 patients documented that those women who successfully complete cardiac rehabilitation reduce mortality by 76% vs. 50% of men (83). Another study with a Swedish population showed that cardiac rehabilitation reduced mortality by 46% in women vs. 19% in men (84). There are records where a reduction of up to 3.1% has been achieved in rehabilitation programs; this demonstrates the importance of achieving adequate follow-up and treatment in women with established cardiovascular disease.

Depression: women with this diagnosis should be considered at risk for CVD and screened for cardiovascular risk factors (85).

Screening in women with hypertensive disorder of pregnancy: Recently, it was described that in women who had adverse events during pregnancy, by the age of 35 years, the number needed to screen in order to diagnose a woman with chronic hypertension is 9 and with dyslipidemia is 18. For this reason, it is essential to start screening soon after delivery (between 6 to 8 weeks), with a follow-up of 6 to 12 months after delivery, with annual follow-up every 5 years for blood pressure and metabolic factors. In this way, at 50 years of age, they will already apply to a usual risk assessment (86).

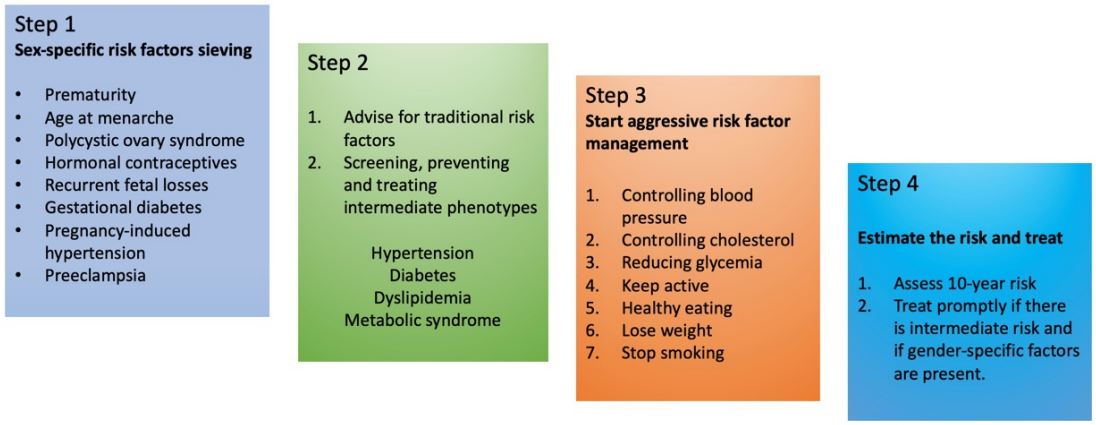
Approach to CVR in women: The tools for calculating CVR, especially in young women, did not include this specific population group, and therefore cannot accurately assess their risk, especially when considering the factors already mentioned that are not considered in women (87). Figures 3 and 4 show the approach to CVR in women.

Figure 3. Individualization of cardiovascular risk in women



Adapted from Freaney, P.M., Khan, S. Curr. Atheroscler. Rep. 22, (2020) 89

Figure 4. Steps for the reduction of cardiovascular desease in Women



Adapted from Agarwala, A., Michos, E. D. Circulation 121, 592-599 (2020) 35

Conclusions

Cardiovascular disease in women has become a subject of fundamental importance for the categorization, individualization, and specific management according to risk factors that are specific to the female gender. It has been shown that, in women, the pragmatic association between psychosocial factors, the cardiovascular protection offered by estrogens, and atypical forms of presentation constitutes a combination that has led to greater mortality in this population group by underdiagnosing ACS. It also allows us to continue research on a new perspective in the diagnostic and therapeu-

tic approach according to gender and, in turn, the importance of greater inclusion of women in clinical trials, in order to achieve an objective approach to adequate treatment that allows prioritization of women.

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