Cardiovascular disease in women: Do we need new diagnostic and therapeutic strategies?

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ABSTRACT

Cardiovascular disease (CVD) is the leading cause of death worldwide affecting both sexes equally. However, in comparison to men, in women, it often is underrecognized and undertreated in both primary and secondary prevention settings. It is clear, that in the healthy population, there are profound differences both anatomically and biochemically between women and men, and this may impact how both groups present when they become ill. Moreover, some diseases affect more frequently women than men such as myocardial ischemia or infarction without obstructive coronary disease, Takotsubo syndrome, some atrial arrhythmias, or heart failure with preserved ejection fraction. Therefore, diagnostic and therapeutic strategies that have been established largely on the basis of clinical studies with a predominantly male population must be adapted before being applied to women. There is a paucity of data regarding cardiovascular disease in women. It is inadequate to only perform a subgroup analysis evaluating a specific treatment or invasive technique when women constitute fifty percent of the population. In this regard, this may affect the time of clinical diagnosis and severity assessments of some valvulopathies. In this review, we will focus on the differences in the diagnosis, management, and outcomes for women with the most frequent cardiovascular pathologies including coronary artery disease, arrhythmia, heart failure, and valvopathies. In addition, we will describe diseases that exclusively affect women that are related to pregnancy, and some of them are life-threatening. Although the lack of research on women plays a role in the poorer outcomes in women, especially in ischemic heart disease, some techniques such as transcatheter aortic valve implantation and transcatheter edge-to-edge therapy seem to have better outcomes in women.

Key words: acute coronary syndrome, arrhythmia, cardiovascular disease, valvulopathy, women

INTRODUCTION

Cardiovascular disease (CVD) in women is the leading cause of death in women worldwide responsible for 35% of all deaths in 2019 [1]. Despite this, CVD is underdiagnosed and undertreated in several clinical scenarios in women. We must make an effort not only to increase research focused specifically on women but improve teaching on the most important features in the diagnosis, management, and outcomes for women with regard to cardiovascular pathologies during undergraduate medical courses. In this review, we will focus on the most relevant differences between women and men in several areas of cardiovascular disease: coronary artery disease, heart

Table 1. Female-specific risk factors

Non-pregnancy
Premature ovarian failure, <40 years
Polycystic ovarian syndrome
Hormonal contraceptive use
Menopause
Postmenopausal hormone therapy
During pregnancy
Preeclampsia
Gestational hypertension
Gestational diabetes
Preterm delivery

failure, arrhythmias, and valvular disease, and emphasize the importance of the prevention of cardiovascular risk factors (CVRF).

HOW TO IMPROVE CARDIOVASCULAR RISK PREVENTION IN WOMEN?

Early detection and management of CVRF is the cornerstone of improving the CV health of women and reducing their mortality. Primary and secondary CVRF prevention is the cornerstone to improve the cardiovascular health in women.

Primary prevention in women

Traditional risk factors such as diabetes, smoking, hypertension, and low social status, confer a higher CVR in women compared with men [2]. There are also female-specific CVRF (Table 1). Despite hypertensive heart disease and its direct or indirect sequelae being one of the most common forms of cardiovascular disease, the description of this entity is outside of the scope of this review. Women with polycystic ovary syndrome (POS) are approximately twice as likely to have coronary artery calcification compared with women without POS. POS has been shown to be a marker of subclinical atherosclerosis and a predictor of cardiovascular disease risk [3].

Pregnancy is a predictor of future cardiovascular risk and may unmask different metabolic or latent vascular disorders [4]. Hypertensive disorders during pregnancy are a leading cause of maternal and fetal morbidity and mortality. In a nationwide cohort study using data from the French National Health Data System (CONCEPTION study), hypertensive disorders of pregnancy increased the risk of chronic hypertension almost 7-fold in the years following the birth [5]. On the other hand, a history of one or more pregnancies with gestational diabetes mellitus predicted an elevated risk of type 2 diabetes mellitus according to age, with a hazard ratio of 3.87 [6]. It is important to mention that maternal morbidity has been related to an increase in the risk of cardiovascular disease [7]. The World Health Organization has defined maternal morbidity as maternal near-miss based on clinical, laboratory, and management criteria: shock, hysterectomy, transfusion of ≥5 units of packed red cells, intubation, and ventilation. Potential life-threatening conditions include severe hemorrhage, hypertensive disorders of pregnancy, and intensive care unit admission. Maternal morbidity may be a life-threatening condition, and the incidence is increasing due to advanced maternal age and other risk factors. There is insufficient knowledge of the mechanisms linking severe maternal morbidity with cardiovascular disease.

The menopausal transition is also a period with an increased risk as it is associated with increased fat mass, insulin resistance, dyslipidemia, and endothelial dysfunction. Women with vasomotor symptoms during menopause appear to have an unfavorable cardiometabolic profile. Early management of traditional CVRF and daily exercise is essential to improve CV health in women [8].

Secondary prevention and cardiac rehabilitation in women

Women with ischemic heart disease (IHD) are at higher risk of stroke, heart failure, and all-cause mortality compared with men [9]. Despite this, data from the CONCORDANCE registry have shown that women attend cardiac rehabilitation programs less frequently and are more likely to suffer major adverse cardiovascular events (MACE) within 6 months of surviving acute coronary syndrome (ACS) [10]. Secondary prevention is poorer in younger women [11]. In addition, women's control of cardiovascular disease risk factors is almost 10% poorer compared to men despite small sex differences in use of cardiovascular medication in the EUROASPIRE V study [12]. In addition, women are less frequently referred to cardiac rehabilitation programs. This issue is especially important, as referral and program attendance are clearly associated with a significant reduction in mortality, which in women is more pronounced compared with men [13] (HR, 0.54 vs. 0.81) as reported in the SWEDEHEART registry [14]. Moreover, all women who have suffered a CV event should be referred to a rehabilitation program.

HOW TO IMPROVE THE MANAGEMENT OF CHRONIC ISCHEMIC HEART DISEASE

Angina pectoris is the most prevalent manifestation of IHD [15]. It has been previously reported that women experience more "atypical" symptoms, however, the evidence for this is conflicting. More recent studies have concluded that the most frequent symptoms reported by women are similar in most cases to their male counterparts, with central oppressive chest pain (80%–86%) being the most frequently reported location of anginal pain although other factors must be considered. In addition to centrally located chest pain, women frequently report pain in other locations such as interscapular, jaw, and epigastric regions [16].

Triggering factors, such as emotional rather than physical stress, are more frequent in women. In female patients, associated symptoms such as shortness of breath (dyspnea), in addition to the chest pain radiating to the jaw

and back, are a frequent occurrence [16]. A characteristic finding in women is a greater number of associated symptoms including dyspnea, tiredness, and anguish [17–18]. Additionally, it has been reported that women typically minimize their symptoms [19]. External influences such as socioeconomic background and educational factors may play a role in how women present and are subsequently evaluated. It has been shown that women are less frequently referred for further diagnostic testing, however, physicians must endeavor to avoid these failures [20]. It has been speculated that limitations exist regarding the prognostic value of various diagnostic tests in this clinical context in female patients. Whilst the European Guidelines for Chronic Coronary Syndromes [21] have reviewed the appropriateness of the various diagnostic tests, no sex-specific analysis was performed. These practice guidelines only consider classic CVRF when assessing various diagnostic techniques and their likelihood of diagnosing coronary artery disease. These guidelines do not incorporate specific sex-related factors such as early menopause or POS, which have a significant role in the development of coronary artery disease (CAD).

The consensus statement of the American Heart Association [22] has assessed the diagnostic value of various diagnostic tests in women. Despite the limitations of the conventional stress test, it still has a role in women at low-intermediate risk of CAD and normal baseline electrocardiography (ECG) (in particular when assessing functional capacity) due to its negative predictive value for exclusion of events at 2 years. Undoubtedly, functional imaging tests such as stress echocardiography or myocardial perfusion test (SPECT) are better alternatives for patients with intermediate-high risk of IHD. In patients with an intermediate-high risk of IHD, cardiac MRI with stress perfusion can also be considered. All of these techniques are effective for the diagnosis and estimation of the risk of MACE [23]; however, their availability may be limited.

Increasing evidence exists supporting the value of computed tomography coronary artery (CTCA) for both diagnosis and risk stratification of obstructive and non-obstructive coronary artery disease in women. CTCA has emerged as a first-line test, with both diagnostic and prognostic value. In the CONFIRM study [24], there was a clear correlation between the risk of mortality and the number of vessels affected, similar to the result of other studies: PROMISE and SCOT-HEART [25, 26]. In addition to coronary anatomy, CTCA provides valuable information including atherosclerotic plaque burden, the presence of myocardial bridges, and detection of coronary calcium, a useful marker of atherosclerosis. In premenopausal women, the prevalence of coronary calcium is low and typically develops 10 years after male patients. Coronary calcium in women (in large studies including over 1200 female patients) demonstrated a relevant diagnostic value for obstructive CAD with sensitivity between 96%–100% and specificity between 40%–66%. [27] The currently available diagnostic tests for the diagnosis of IHD in women have been recently analyzed, with CTCA standing out for its sensitivity and specificity (96% and 92%, respectively) and its predictive value [28].

It is worth mentioning the importance of the assessment of non-obstructive coronary disease due to its higher prevalence in females. Non-obstructive coronary disease (INOCA) is challenging for clinicians [29]. More than 70% of patients undergoing coronary angiography do not have obstructive coronary disease, and a large proportion are women. Physiopathologically, myocardial ischemia may be due to microvascular remodeling which causes conduction or vasomotor disturbances affecting arterioles and causing a dynamic obstruction. Furthermore, both mechanisms may coexist. The possibility of a microvascular origin of angina should be considered in patients with clear angina, abnormal noninvasive functional tests, and coronary vessels that are normal or have mild stenosis that is functionally non-significant on invasive angiography or CTCA. The diagnosis of microvascular disease can be confirmed using invasive tests during coronary angiography to determine the coronary flow reserve or the microcirculation resistance index. Non-invasive tests such as coronary flow velocity reserve (CFVR) on transthoracic Doppler echocardiography may also be used. Positron emission tomography (PET) and magnetic resonance imaging (MRI) are two excellent alternatives as non-invasive diagnostic tests but are limited by their availability. Current recommendations for diagnostic testing and treatment of microvascular disease are based on consensus documents. INOCA is not a benign condition as it is associated with an increase in the risk of events. In the WISE (Women's Ischemia Syndrome Evaluation) study, an increase in the risk of all-cause mortality in women with symptoms and signs of ischemia but without obstructive coronary disease was observed compared with a population at a similar age (13% vs. 2.8%, respectively) [30]. INOCA is an important topic and further well-designed studies are urgently required to address a series of unanswered questions about its diagnosis and management in this patient cohort. Currently, there are studies underway that may further our knowledge of this disease [31].

MANAGEMENT OF ACUTE CORONARY SYNDROMES IN WOMEN

ST-segment elevation myocardial infarction (STEMI) accounts for approximately 30% of acute coronary syndromes (ACS) with non-ST-segment elevation myocardial infarction (NSTEMI) accounting for 70% of ACS in women [32]. In the last decades, the incidence of ACS hospitalization has increased in younger women [33], and smoking and obesity are associated with this increase in young women [33].

The underlying mechanisms of ACS differ between both sexes although MI with obstructive coronary artery disease (CAD) is the most frequent cause of ACS in women. However, the pathophysiology of ACS in women has a broader spectrum of pathophysiological mechanisms. In

fact, myocardial infarction with non-obstructive coronary arteries (MINOCA) is more frequent in females compared to males (50%–70% vs. 30%–50%) [34].

Assessment and diagnosis

Women presenting with STEMI tend to seek medical attention later after symptom onset compared to men [35] and experience longer triage times in the emergency department with prolonged door-to-balloon times [35, 36].

In patients who sought medical attention for cardiac symptoms before ACS onset, women were more likely to have been reassured that the symptoms were noncardiac (53.4% vs. 36.4%; *P* <0.001) [18, 37]. Chest pain has been reported to exist in approximately 90% of ACS patients regardless of sex [18]. Recent studies have shown that women are less likely to be transferred to a primary percutaneous coronary intervention (PCI) center, and the development of primary PCI networks have reduced in-hospital mortality in women [38]. It should be noted that high ultrasensible troponin (hsTn) thresholds for NSTEMI diagnosis may be less sensitive in women compared to males. It has been reported that higher thresholds of hsTn for the confirmation of an ACS are required in female patients to confirm the diagnosis [39]. However, to date the European Society of Cardiology guidelines have not incorporated these differences [40].

Management of ACS

Sex differences in the invasive management of ACS have been described in previous studies [41]. Some authors reported that women are less likely to undergo reperfusion therapy following ACS [36]. Moreover, some studies have shown that reperfusion strategies are less common in women even after adjusting for age and comorbidities. In a Spanish study from 2003 to 2015, including 277821 patients (29% women), women were less likely than men to be treated with primary PCI, with this disparity noted over the 11-year study period, with 43% of women vs. 24% of men presenting with STEMI not receiving any reperfusion therapy in 2015 [36].

Regarding patients with NSTEMI, the ESC and American Heart Association/American College of Cardiology (AHA/ACC) guidelines do not suggest stratification of risk based on sex [40]. Moreover, the GRACE 2.0 score, based on the ACS threshold and predominantly male populations also underestimates the risk of early mortality in women who incorrectly received conservative treatment (GRACE 2.0 score <140). Recently, an updated version of this score (GRACE score 3.0) has been specifically created for assessing the mortality risk in women with NSTEMI, improving outcomes in this setting [42]. Moreover, there is a lack of knowledge regarding sex-specific dosing and metabolism of various drugs due to underrepresentation of women in clinical trials [43]. However, a meta-analysis of randomized controlled trials of potent $P2Y_{12}$ inhibitors (24 494 women and 63 346 men) showed that these antiplatelet agents significantly reduced the risk of MACE by 14% in women [44]. On the other hand, there is a need for dose adjustment of antithrombotic medication based on weight or renal function in females to reduce the incidence of bleeding events [44]. In terms of secondary prevention, women are less likely to receive statins, angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers at the time of discharge [45].

Myocardial infarction in the absence of obstructive coronary artery disease

The most recent diagnostic criteria for MINOCA incorporate the Fourth Universal Definition of Myocardial Infarction and exclude myocarditis and Takotsubo syndrome (TTS) from the final diagnosis of MINOCA (Figure 2). MINOCA is more common in women than men (15% vs. 3.5%) [46]. MINOCA is a working diagnosis and should lead the treating physician to investigate underlying causes. Cardiac magnetic resonance is advised to exclude myocarditis and Takotsubo syndrome. Intracoronary imaging such as intravascular ultra-

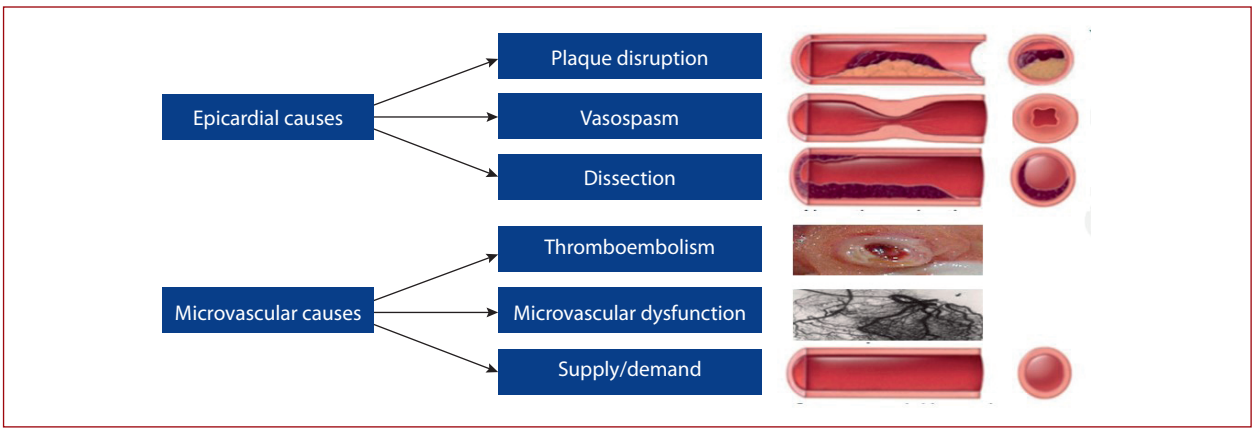

Figure 2. Causes of myocardial infarction with non-obstructive coronary disease

sound or optical coherence tomography can help to detect plaque erosion as well as coronary dissection or thrombosis, which may be overlooked during angiography. Additional investigations must include provocation vasospasm testing and screening for thrombophilia disorders to establish a specific diagnosis when necessary (Figure 2). A recent meta-analysis of >28 000 MINOCA patients showed higher rates of MACE in women compared to men (10.1% vs. 9.1%). In a recent study, regardless of age and sex, patients with MINOCA were less likely to receive guideline-directed medical therapy (GDMT) in-hospital and on discharge compared to patients with MI with obstructive IHD [47].

HOW TO MANAGE HEART FAILURE IN WOMEN

Heart failure (HF) is the leading cause of urgent hospital admission in patients over 65 years of age [48] with women constituting around 50% of those patients.

Women account for approximately 40% of patients with heart failure with reduced ejection fraction (HFrEF) and 60% of patients with HF with preserved ejection fraction (HFpEF) [49]. There are fundamental differences in the pathophysiology of HF in women compared to men. Women have a higher predisposition for coronary microvascular dysfunction, and this factor may be linked among HF syndromes that women are predisposed to TTS, peripartum cardiomyopathy (PPCM), and breast cancer radiotherapy-induced cardiomyopathy. Additionally, women are at greater risk of the development of de novo acute HF (AHF) and a higher incidence of cardiogenic shock (CS) during hospitalization for STEMI [50, 51]. TTS is an uncommon type of AHF, and the precise etiology remains unclear. Women with breast cancer treated with anthracyclines (<1%), radiotherapy, or immune checkpoint inhibitors can present AHF due to various molecular mechanisms [52].

Assessment and diagnosis

Women typically develop high symptom burden, experience frequent hospitalization, and have more impaired quality of life, as well as a higher incidence of depression, compared with men [52]. Echocardiographic studies in heart failure preserved ejection fraction (HFpEF) patients have shown differences between both sexes, with women more likely to have concentric left ventricular (LV) remodeling, more severe diastolic dysfunction, and higher LV filling pressures, compared with men [53].

Therapeutic management of HF

The management of AHF in women is in accordance with the current ESC guidelines [48]. Further consideration must be given to anatomical and physiological differences as these significantly alter pharmacokinetics/dynamics of drugs [54]. Data on the therapeutic effect of drugs used in the treatment of HF in women are very limited, as female patients are underrepresented in clinical trials. Women with a previous diagnosis of HF were less likely to be treated with antagonist converting enzyme inhibitor (ACEI), beta-blockers, or mineral antagonists (MRA) on admission and hospital discharge. Considering the beneficial effects on outcomes of several drugs, sex-specific variability was observed in many of the respective landmark trials [55]. Table 2 summarizes different effects of drugs on both

Table 2. Sex-specific differences in the treatment of heart failure trials

Beta-blockers	
CIBIS II [56]	Bisoprolol showed a beneficial effect on outcomes in both sexes
SENIORS [57]	Nebivolol showed a beneficial effect on outcomes in both sexes
MERIT-HF [58]	Metoprolol showed a significant risk reduction (RR) in men, without benefit in women
COPERNICUS [59]	Carvedilol showed a trend towards RR in women while a beneficial effect in men was achieved
Angiotensin receptor blockers	
CHARM [60]	Candesartan did not show sex-specific differences in the reduction of the primary endpoint
Val-HeFT [61]	Valsartan showed a RR in men, only a trend towards benefit in women
Angiotensin-converting-enzyme inhibitors	
SOLVD [62]	Enalapril showed a RR in men, but only a trend towards benefit in women
Mineralocorticoid receptor antagonists	
EMPHASIS-HF [63]	Eplerenone showed a similar RR in both sexes
RALES [64]	Spironolactone showed a similar RR in both sexes
Sodium-glucose co-transporter-2 inhibitors (SGLT2i)	
EMPEROR [65]	Empagliflozin showed similar benefits in both sexes
EMPULSE [66]	Empagliflozin was associated with RR of acute decompensated HF in both sexes
DAPA-HF [67]	Dapagliflozin showed a trend toward RR in women
Sacubitril/valsartan	
PARADIGM-HF [68]	Sacubitril/valsartan showed a RR in both sexes with HF
Digoxin	
DIG trial [69–70]	Digoxin was associated with an increased risk of death in women, but not men A retrospective analysis of the DIG trial indicates a beneficial effect of digoxin in HF and no excess mortality in women (serum contrentations 0.5 to 0.9 ng/ml), whereas ≥1.2 ng/ml are harmful

Abbreviations: RR, risk reduction; HF, heart failure

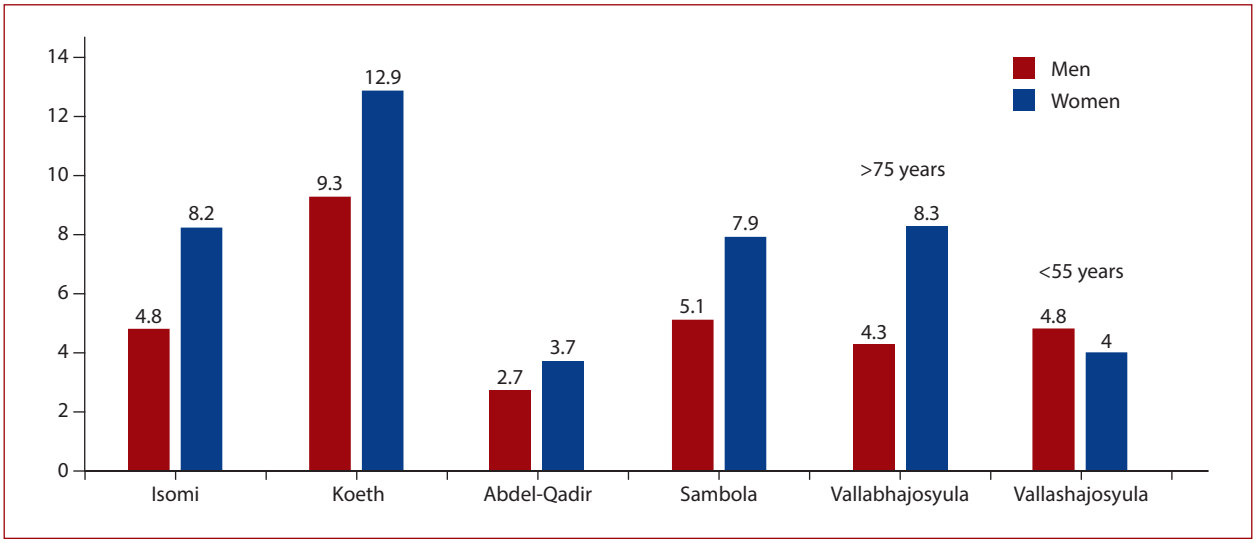

Figure 1. Studies investigating sex differences in the incidence of cardiogenic shock among patients with acute myocardial infarction

sexes in clinical trials. Recent data suggest that women with HF may need lower doses of key disease-modifying agents than men [71].

Peripartum cardiomyopathy

PPCM is defined as new-onset cardiomyopathy during the peripartum episode or up to 6 months postpartum, manifesting as reduced EF without any other cause of HF [72]. The presentation may vary from subtle/asymptomatic HF to cardiogenic shock. Natriuretic peptide-pro hormone BNP (NT-proBNP) is markedly elevated in newly diagnosed patients and facilitates diagnostic screening, in addition to electrocardiography, chest radiography, and echocardiography [72]. The management strategy should consider both mother and fetus and includes urgent hospital admission and transfer to an advanced HF center where venoarterial extracorporeal membrane oxygenation (ECMO)/left ventricular assist device (LVAD) and/or cardiac transplantation can be performed [53]. Bromocriptine should be considered in this clinical context although it always should be prescribed with anticoagulation due to the prothrombotic side effect of this drug [48].

Takotsubo syndrome

About 90% of patients with TTS are postmenopausal women [13]. There are no consistent differences between men and women regarding age, symptoms, prehospital delay, or clinical course. A diagnostic algorithm and management of TTS has been reported for both sexes in the ESC guidelines, and mortality has been reported to be higher in males (8.4% vs. 3.6%, respectively) [73]

Cardiogenic shock

The incidence of CS in the setting of AMI was higher among women in the majority of current studies [74, 75] (Figure 1). These differences are related to delays in diagnosis and failure to transfer to a primary PCI center or centers with a capacity for mechanical circulatory support. These disparities in treatment are associated with higher mortality in women with ACS [74–76]. Furthermore, PPCM and TTS are frequent causes of ACS in women and need special attention for prompt diagnosis and treatment. The establishment of CS and ACS networks should offer similar beneficial effects in care and outcomes for women and men.

How to improve the management of the most frequent arrhythmias in women

Sex differences in cardiac electrophysiology are a major determinant of the incidence, epidemiology, and clinical presentation of arrhythmias. The mechanisms behind these differences include differences in cardiac structure and the effect of sex hormones on cardiac ion channels and cardiac autonomic regulation [77]. However, there are also sex differences in access and response to medical therapies, which have an impact on prognosis.

The diagnosis of cardiac arrhythmias is essential to provide appropriate treatment for each patient. The main diagnostic tool is ECG. Therefore, patients with symptoms suggestive of arrhythmia should undergo ambulatory ECG monitoring. However, the clinical presentation as self-limited episodes often make it difficult to document arrhythmia on ECG. In these cases, clinical suspicion is based mainly on symptoms, and physicians must be aware that women with arrhythmias have more symptoms and may be more atypical.

Within supraventricular tachycardias (SVT), atrioventricular node reentrant tachycardia (AVNRT) has a prevalence twice as high in women than in men likely due to sex differences in electrophysiological properties, such as shorter slow pathway refractoriness in women [78]. Women with SVT are often misdiagnosed as having panic attacks, have more symptoms and worse quality of life, and are referred

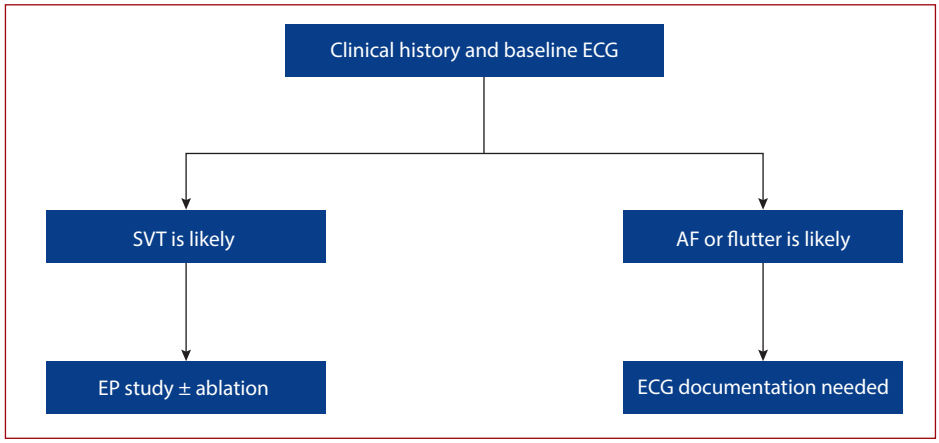

Figure 3. Diagnosis and therapeutic algorithm of cardiac arrhythmias
Abbreviations: AF, atrial fibrillation; ECG, electrocardiography; EP, electrophysiology; SVT, supraventricular tachycardias

later to an arrhythmia unit [79]. It is essential to emphasize that when symptoms are suggestive of SVT, early referral to an arrhythmia unit should be considered, and a diagnostic electrophysiological study should be offered even in the absence of documented arrhythmia (Figure 3). Catheter ablation is the treatment of choice in these cases with a very high success rate and practically no side effects [80].

Misdiagnosis of atrial fibrillation (AF) can have a negative impact on prognosis. Females with AF may be more symptomatic and in addition to this, these symptoms may be more atypical palpitations, fear/anxiety, fatigue, shortness of breath, and poor quality of life. Although the prevalence of atrial fibrillation is higher in men of all age groups, the lifetime risk of AF in females and males is similar because of longer life expectancy in females [81]. Women with AF are older and have more associated comorbidities especially, hypertension and heart failure with preserved ejection fraction. Older age and female sex are independent predictors of atrial myopathy and fibrosis, which, in addition, is associated with higher risk of stroke. AF is more likely to present as paroxysmal rather than persistent in women. However, females receive rhythm control strategies less often than males and are referred for ablation less often and later in the disease course [82]. This may explain poorer outcomes regarding freedom from AF post-ablation. In this regard, earlier AF ablation in women should be encouraged to improve outcomes. Complications related to the ablation procedure have been described more frequently in women, especially those related to vascular access. A proposed explanation is that even though women have a smaller body size, the same catheters are used in men and women.

Ventricular arrhythmias in the setting of structural heart disease have a lower incidence in women. Randomized primary prevention implantable cardioverter-defibrillator (ICD) trials showed a lower likelihood of inducible sustained ventricular tachycardia (VT) and lower overall mortality risk although females have been historically under-represented in these trials.

Future studies with adequate representation of women will help understand the sex difference in arrhythmias and improve clinical management to avoid disparities between women and men. Meanwhile, earlier diagnostic and therapeutic strategies should be encouraged to avoid disparities in clinical management that may affect prognosis.

Aortic stenosis in women

The phenomenon of the aging population has given rise to increased rates of degenerative aortic valve stenosis, and this issue will only increase in the coming years. When analyzing this disease, we must be aware of sex-based differences [83]. At the time of diagnosis, women are typically older, with more advanced symptoms, and have a higher prevalence of arterial hypertension and a lower prevalence of IHD. Anatomical differences also exist with a greater extent of valvular fibrosis notes rather than calcification, lower rates of bicuspid valve disease, and smaller aortic diameters. Differences have also been noted in left ventricular remodeling, with greater relative wall thickening and significant concentric hypertrophy, smaller ventricular cavities, and lower systolic and end-diastolic volumes noted in women. Left ventricular systolic function is typically preserved, with a higher prevalence of diastolic dysfunction observed in females. All these characteristics mean that women are referred more frequently to transcatheter aortic valve implantation (TAVI) than to surgical aortic valve replacement (SAVR). The results of TAVI in women are better than SAVR in high-, intermediate-, and low-risk women. This was demonstrated in the PARTNER studies: in PARTNER 1 [84] (2-year mortality 23.4% vs. 36.9%, respectively; $P = 0.02$), PARTNER 2 [85] (2-year mortality and stroke 16.8% vs. 20.4%, respectively; $P = 0.05$) and PARTNER 3 [86] (2-year mortality, stroke, rehospitalization 8.1%

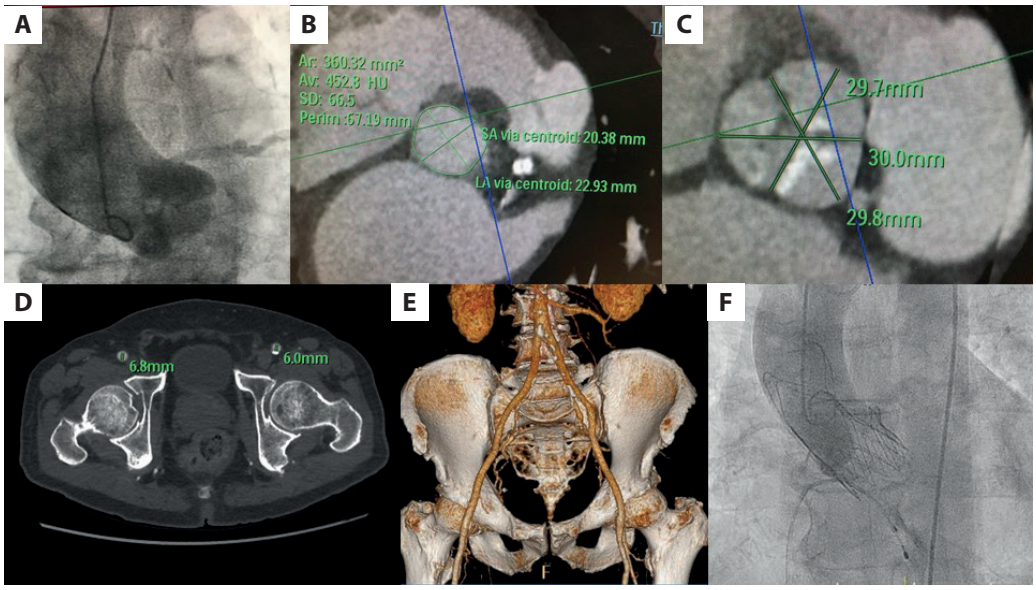

Figure 4. Typical characteristics of a female patient with severe aortic stenosis. **A.** Aortogram showing the three cusp projection, which is usually used for valve implantation. **B.** Computed tomography image showing the measurement of an aortic annulus. This measurement shows an area of 360 mm² and a perimeter of 67 mm, which is consistent with a small annulus. **C.** Computed tomography image showing the measurement of the sinus of Valsalva. The measurement is consistent with narrow sinus. **D.** Computed tomography image from the common femoral artery. It shows a moderate caliber of the artery adequate for transfemoral access. **E.** Computed tomography image showing 3D reconstruction of a non-tortuous iliofemoral axis. **F.** X-ray image showing the final aortogram after valve implantation showing a good result

vs. 18.5%, respectively). When evaluating patients before TAVI, we must consider distinct anatomical characteristics of women [87] (Figure 4), in whom we more frequently observe a smaller aortic annulus, lower height of the sinuses of Valsalva, lower origin of the coronary arteries, and peripheral vessels of smaller caliber and with more tortuosity. Although these characteristics may be more unfavorable, peri-procedural mortality is low. However, higher rates of coronary artery obstruction and peripheral vascular complications in women are reported. On the contrary, it has been demonstrated that there are lower rates of peri-valvular regurgitation and need for pacemaker implantation compared to male patients.

Mitral valve disease in women

Mitral valve disease (MVD) is the most common valvular heart disease worldwide [88]. The overall prevalence ranges between 1%–2% but increases with the age by up to 9% in patients >75 years [89]. All-cause mitral valve disease, such as rheumatic, degenerative, or mitral prolapse, is more frequent among women compared to men [90]. Interestingly, there are sex-related differences in valve morphology in patients with mitral valve prolapse [91]. Therefore, women are more prone to develop myxomatous valves affecting both leaflets, whereas men typically develop posterior valve prolapse. In addition, annulus calcification is more frequent in women than in men [92]. Other differential characteristics of mitral valve disease in women are, first, more frequent development of pulmonary hypertension in women with mitral stenosis compared to men and, second, women with prior myocardial infarction have a higher risk of the development of functional mitral regurgitation compared to men [93].

An important consideration is that women with cardiovascular disease are underrepresented in clinical trials, raising the question regarding the applicability of these results to women. Current guideline recommendations [88] are based on studies with predominantly male subjects. Cutoff points indicating the need for intervention of mitral valve disease may be potentially different in women, given that women typically have smaller hearts. This issue may have prognostic implications as it may provoke delays in referring women for treatment or influence the rates of under-treatment of women with mitral valve disease [94]. It has been demonstrated that women who are referred to surgery are more symptomatic compared to men, however, ventricular dimensions were noted to be smaller [95].

Special consideration needs to be taken for mitral valvopathy during pregnancy. The hemodynamic changes associated with the pregnancy may increase the gradient in mitral stenosis and as a result women poorly tolerate this and sometimes need to undergo percutaneous mitral balloon valvulotomy after 20 weeks of gestation. In contrast, the decrease in afterload observed during pregnancy may decrease the degree of mitral insufficiency, and therefore the patients who suffer from this pathology, as well as tricuspid disease, may tolerate it better [96]. For primary or degenerative mitral regurgitation (MR) women undergoing mitral surgery were less likely than men to receive mitral repair rather than replacement and have higher mortality [97]. For secondary MR treated with transcatheter edge-to-edge repair (TEER), female sex was independently

associated with lower adjusted risk of death at 2 years, but the reduction in heart failure hospitalization was less pronounced compared with men after the first year [98].

Tricuspid valve disease in woman

Tricuspid regurgitation (TR) is more prevalent and its progression more rapid in females compared to males. This may be explained by anatomical differences, with differences noted at the tricuspid annulus in women. Interestingly the risk of TR in patients with atrial fibrillation is higher in women. The cause of TR is also different in women with the primary causes being isolated left-sided valvular disease, whereas in men the main cause was left ventricular dysfunction [107]. In a similar way to mitral valve disease, women tend to be diagnosed with more significant TR at an older age in comparison to men.

CONCLUSIONS

In conclusion, this review highlights all the differences in the way women become ill with different CV pathologies, as well as differences in diagnosis and treatment of women compared with men. Unfortunately, these differences lead, in most cases, to a worse prognosis in women, especially young women with ischemic heart disease. Several cardiac anatomical differences lead to a different frequency in arrythmic disorders and valvulopathies. New treatments such as percutaneous treatment of severe aortic stenosis and mitral insufficiency showed better results in women. Therefore, an enormous effort must be made to promote teaching and research in this area and reduce the gap in the diffusion of knowledge acquired during the past years.

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