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

Short title: Cardiovascular disease in women

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ABSTRACT

Cardiovascular disease (CVD) is the leading cause of death worldwide affecting both genders equally. However, in comparison to men, in women it often is underrecognized and undertreated in both the primary and secondary prevention settings. It is clear, that in the

healthy population, there are profound differences both anatomically and biochemically between woman and men and this may impact how both groups present when they become ill. Therefore, there are some diseases that affect more frequently in women than in men such us myocardial ischemia or infarction without obstructive coronary disease, Tako-subo syndrome, some atrial arrhythmias or the appearance of heart failure with preserved ejection fraction. Therefore, the diagnostic and therapeutic strategies that have been established based largely on clinical studies with a predominant 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 of woman with the most frequent cardiovascular pathologies including coronary artery disease, arrythmias, heart failure and valvopathies. In addition, we will describe diseases that exclusively affect to women related with the pregnancy some of them are life treating. Although the lack of research in women plays a role in the poorer outcomes in women specially in ischemic heart disease the results of some techniques such as transcathether aortic valve implantation and transcatheter edge to edge therapy seem to have better outcome in women.

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

INTRODUCTION

Cardiovascular disease (CVD) in women is the leading cause of death in women worldwide being responsible for 35% of total of death in 2019 [1]. Despite, 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 of women with cardiovascular pathologies at Medicine degree. 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 failure, arrhythmias and valvular disease and emphasize the importance of risk cardiovascular factors (RCVF) prevention.

HOW TO IMPROVE THE CARDIOVASCULAR RISK PREVENTION IN WOMEN?

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

Primary prevention in woman

Traditional risk factors such as diabetes, smoking, hypertension and low social status, confers 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 are 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) were 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 risk of cardiovascular disease [3].

Pregnancy is a predictor of future cardiovascular risk and may unmask different metabolic or latent vascular disorders [4]. Hypertensive disorders during the 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 have 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 red cells, intubation, and ventilation; Potential life-threatening conditions: severe hemorrhage, hypertensive disorders of pregnancy, intensive care unit admission. Maternal morbidity may be life-threatening condition and the incidence is increasing due to advanced maternal age and other risk factors. There is a lack of knowledge of the mechanisms linking severe maternal morbidity with cardiovascular disease.

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 the health CV in women [8].

Secondary prevention and cardiac rehabilitation in woman

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 a major adverse cardiovascular events (MACE) within 6 months of surviving an 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 the small gender differences in use of cardiovascular medication in EUROASPIRE V study [12]. In addition, women are less frequently referred to cardiac rehabilitation programs. This issue is especially important in woman, as referral and program attendance is clearly associated with a significant reduction in mortality which is more pronounced compared with men [13] (HR 0.54 vs. 0.81, respectively) as reported in the SWEDEHEART registry [14]. Moreover, all women who 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 as interscapular, jaw and epigastric regions [16].

Triggering factors such as emotional stress, 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, anguish [17–18]. Additionally, it has been reported that women typically minimize their symptoms [19]. External influences such as socioeconomic background, 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 it is imperative that physicians endeavor to avoid these failures. [20]. It has been speculated that limitations exist regarding the prognostic value of the 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 gender specific analysis was performed. These practice guidelines only consider classic CVRF when assessing the various diagnostic techniques and their probability of diagnosing coronary artery disease. These guidelines do not incorporate specific gender related factors such as early menopause or POS factors that 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 ECG (in particular when assessing functional capacity), due to its negative predictive value for the exclusion of events at 2 years. Undoubtedly, functional imaging tests such as stress echo or myocardial perfusion test (SPECT) are the 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 CTCA for both the 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 like 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 the 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 a sensitivity between 96%–100% and specificity between 40%–66%. [27] The currently available diagnostic tests for the diagnosis of IHD in women has been recently

analyzed, with CTCA standing out for its sensitivity and specificity (96%–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 are 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 echo may also be used. PET and 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 increased 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 similar age (13% vs 2.8%, respectively) [30]. INOCA is an important topic and well-designed further studies are urgently required to address a series of unanswered questions in 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 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 hospitalizations 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. Although 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 a 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].

Amongst patients who sought medical attention for cardiac symptoms prior to an ACS onset, women are more likely to have been reassured that the symptoms were non cardiac (53.4% vs. 36.4%; *P* <0.001) [18,37]. Chest pain has been reported to exist in approximately 90% of patients with an ACS regardless of sex [18]. Recent studies have showed that women are less likely to be transferred to a Primary PCI center and the development of primary PCI networks have achieved a decrease the in-hospital mortality in women [38]. It should be noted that hsTn thresholds for NSTEMI diagnosis may be less sensitive in women compared to male. 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 ESC guidelines have not incorporated these differences [40].

Management of ACS

Gender 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 an 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 a STEMI not receiving any reperfusion therapy in 2015 [36].

Regarding patients with NSTEMI, the ESC guidelines and AHA/ACC do not suggest stratification of risk based on gender [40]. Moreover, the GRACE 2.0 score, based on ACS threshold and based on predominantly male-based populations, also underestimates the risk of early mortality in women who were 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 the 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 RCTs 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 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 of 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. An intracoronary imaging such as intravascular ultra-sound or optical coherence tomographyto can help to detect a plaque erosion as well as coronary dissection or thrombosis, which may be overlooked during angiography. Additional investigations must include provocative 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 at discharge compared to patients with MI with obstructive IHD [47].

HOW TO MANAGE HEART FAILURE IN WOMEN

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

Women account for approximately 40% of heart failure with reduced ejection fraction (HFrEF) and 60% of patients with HF with preserved ejection fraction (HFpEF) [49]. There are fundamental differences in pathophysiology of HF in women compared to men. Women have 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 for the development of acute HF (AHF) *de novo* and at 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 checkpoints inhibitors-can present AHF due to various molecular mechanisms [52].

Assessment and diagnosis

Women typically develop high symptom burden, frequent hospitalizations, and have a more impaired quality of life, as well as higher incidence of depression, compared with men [52]. Echocardiographic studies in HFpEF have shown differences between both sexes, with women more likely having concentric 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 treated with ACEI, BB or MRA at admission and at hospital discharge. Considering the beneficial effects on the outcome of several drugs, gender-specific variability's were observed in many of the respective landmark trials [55]. Table 2 summarizes the different effects of drugs in both sexes in clinical trials. Recent data suggests that women with HF may need lower doses of key disease-modifying agents than men [71].

Peripartum cardiomyopathy

PPCM is defined as a 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 peptides-pro hormone BNP (NT-proBNP), are 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 ECMO/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 ESC guidelines and mortality have 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 is 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, PPMC and TTS are frequent causes of ACS in women and need special attention for its prompt diagnosis and treatment. The establishment of CS and ACS networks should offer similar beneficial effects in the care and outcomes of 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 in the effect of sexual 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 the appropriate treatment for each patient. The main diagnostic tool is the 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 the 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 panic attacks, have more symptoms and worse quality of life and are referred 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 comorbidities associated especially, hypertension and heart failure with preserved ejection fraction. Older age and female sex are independent predictor of atrial myopathy and fibrosis which in addition, is associated with a 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 the poorer outcome 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 women have 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 ICD trials showed lower likelihood of inducible sustained VT and lower overall mortality risk although, female have been historically under-represented in these trials.

Future studies with adequate representation of women will help understand the gender 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

An 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, 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% vs. 18.5%, respectively). When evaluating patients prior to TAVI, we must consider that women have distinct anatomical characteristics [87] (Figure 4) in which 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, the 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 ranged between 1-2% but increases with the age up to 9% in patients >75 years [89]. All-cause of mitral valve disease such as rheumatic, degenerative, or mitral prolapse is more frequent among woman compared to men [90]. It is interesting that 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, the more frequent development of pulmonary hypertension in women with mitral stenosis compared to men and 2nd, woman with prior myocardial infarction have a higher risk of the development of functional mitral regurgitation than 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 that suffer from this pathology as well as tricuspid disease may tolerate it better [96]. For primary or degenerative MR women undergoing mitral surgery were less likely than men to receive mitral repair rather than replacement and has a higher mortality [97]. For secondary MR treated with TEER female sex was independently associated with a lower adjusted risk of death at 2 years but the reduction of heart failure hospitalizations was less pronounced compared with men after the first year [98].

Tricuspid valve disease in woman

Tricuspid regurgitation 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 woman with the primary causes being isolated and left sided valvular disease whereas in men the main case was left ventricular dysfunction [107]. In a similar way to mitral valve disease, women tend to be diagnosed with more significant TR and at an older age in comparison to men.

CONCLUSIONS

In conclusion, this review highlights all the differences in the way a woman become ill with different CV pathologies, as well as their differences in diagnosis and treatment 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 different frequency in athymic disorders and valvulopathies. New treatment 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 acquired knowledge during the past years.

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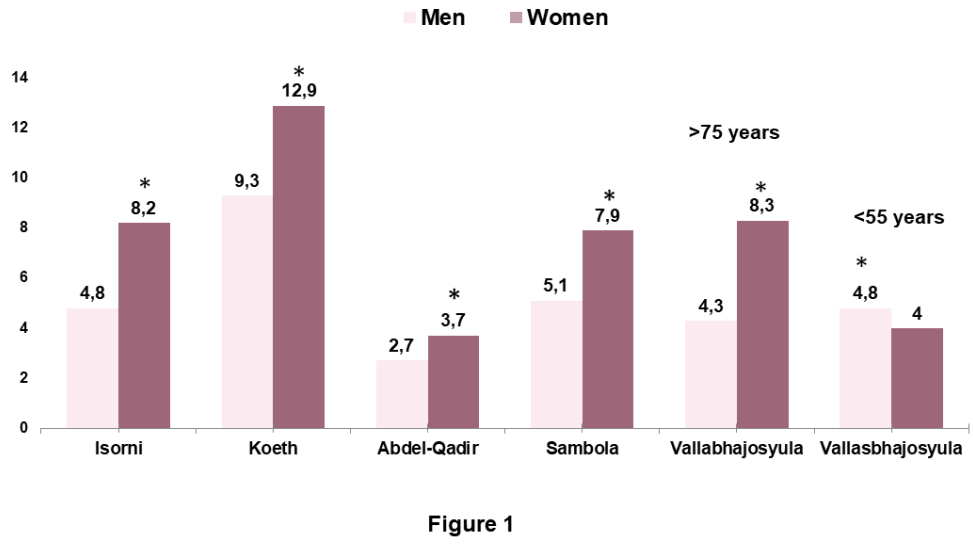

Figure 1

Figure 1. Studies investigating sex differences in the incidence of cardiogenic shock among

patients with acute myocardial infarction

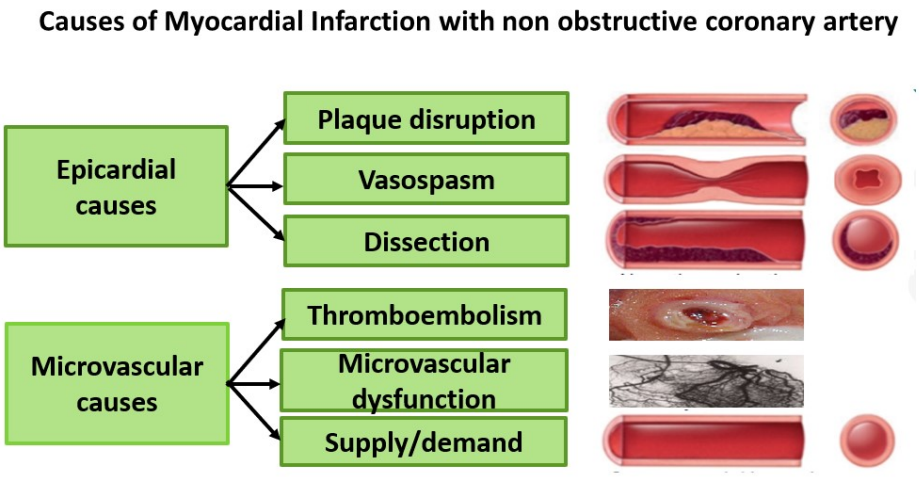

Figure 2. Causes of myocardial infarction with non-obstructive coronary disease

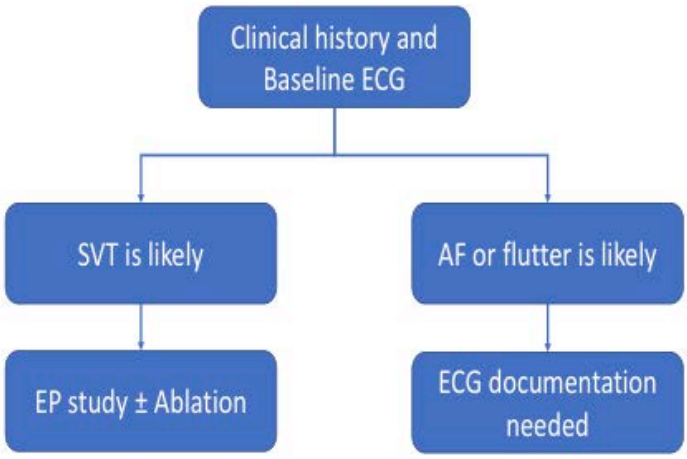

Figure 3. Diagnosis and therapeutic algorithm of cardiac arrhythmias

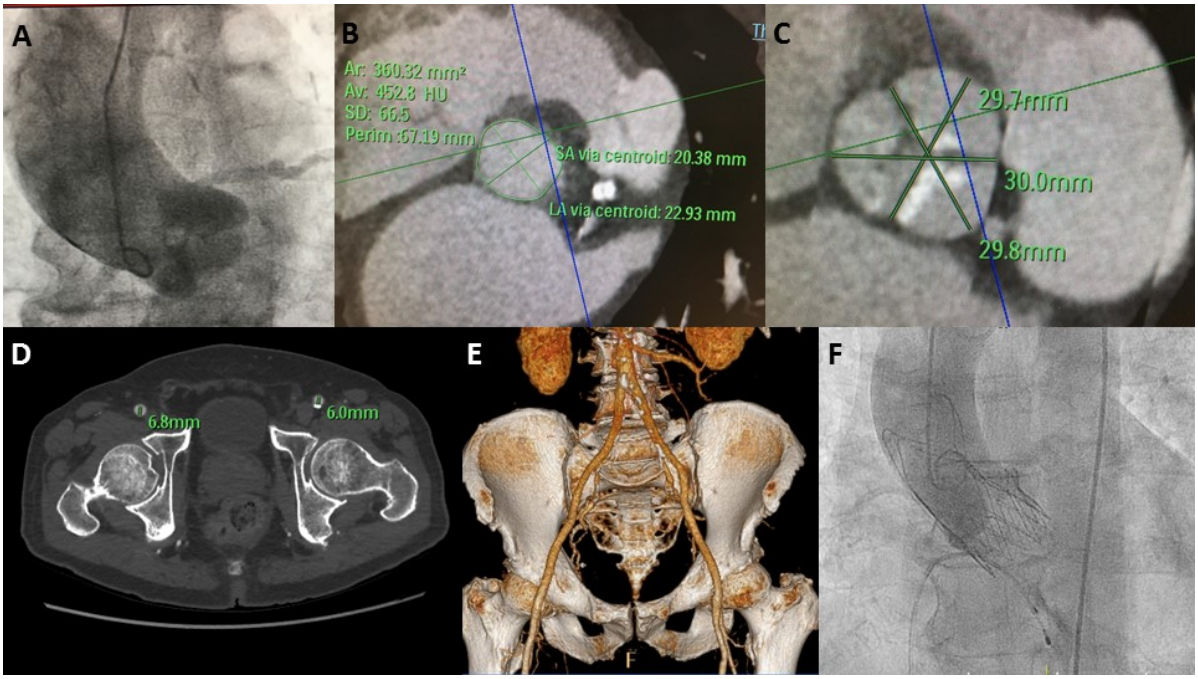

Figure 4. Typical characteristics of a female patient with severe aortic stenosis. **A.** Aortogram showing the three cusps projection which is usually used for valve implantation. **B.** Computerized tomography image showing the measurement of an aortic annulus. This measurement shows an area of 360 mm^2 and a perimeter of 67 m which is consistent with small annulus. **C.** Computerized tomography image showing the measurement of the sinus of Valsalva. The measurement is consistent with narrow sinus. **D.** Computerized tomography image from a common femoral artery It shows a moderate caliber of the artery enough for transfemoral access. **E.** Computerized tomography image showing 3D reconstruction of a non-tortuose iliofemoral axis. **F.** X-ray image showing the final aortogram after valve implantation showing a good result

Table 1. Female specific risk factors

Out of the pregnancy
Premature ovarian faliure: <40 y
Policystic ovarian syndrome
Hormonal contraceptive use
Menopause
Postmenopause homone therapy
During pregnancy
Preeclampsia
Gestacional hypertension
Gestacional diabetes

Preterm delivery

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

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

Abbreviations: RR, risk reduction; HF, heart failure