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REVIEW ARTICLE

Themed series on 'Gender-specific issues in cardiovascular therapy'

Gender-specific aspects in the clinical presentation of cardiovascular disease

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ABSTRACT

More than a quarter of a million women die each year in the industrialized countries from cardiovascular diseases (CVD), and current projections indicate that this number will continue to rise with our ageing population. Important sex-related differences in the prevalence, presentation, management and outcomes of different CVD have discovered in the last two decades of cardiovascular research. Nevertheless, much evidence supporting contemporary recommendations for testing, prevention and treatment of CVD in women is still extrapolated from studies conducted predominantly in men. The compendium of CVD indicates that current research and strategy development must focus on gender-specific issues to address the societal burden and costs related to these incremental shifts in female gender involvement. Indeed, this significant burden of CVD in women places unique diagnostic, treatment and financial encumbrances on our society that are only further intensified by a lack of public awareness about the disease on the part of patients and clinicians alike. This societal burden of the disease is, in part, related to our poor understanding of gender-specific pathophysiologic differences in the presentation and prognosis of CVD and the paucity of diagnostic and treatment guidelines tailored to phenotypic differences in women. In this, scenario is of outmost importance to know these differences to provide the best care for female patients, because under-recognition of CVD in women may contribute to a worse clinical outcome. This review will provide a synopsis of available evidence on gender-based differences in the initial presentation, pathophysiology and clinical outcomes of women affected by CVD.

INTRODUCTION

Cardiovascular diseases (CVD) are the leading cause of mortality and admission in hospital for women, accounting for a third of all deaths of women worldwide and half of all deaths of women over 50 years of age in developing countries [1,2]. By contrast, breast cancer accounts for just 3% of all deaths in the female adult population [3].

Recent advances in the field of cardiovascular medicine have not led to significant drops in case fatality rates for women, compared to the dramatic reductions achieved for men [4]. Such gender-specific difference in CVD mortality provides additional support for a lack of comparable progress in population-based risk reduction efforts for women [2] and is probably related to a knowledge gap about CVD in women.

In this context, several evidences demonstrated significant delays in health care–seeking behaviour, less intensive resource use patterns and longer diagnosis times for women than men. In this context, women are less likely to be referred for coronary angiography and revascularization procedures than men, and referral tends to occur at a later stage in the disease process [5]. Although a lower intensity of care may be, in part, related to a differential clinical history, symptoms profile and acuity of presentation, under-recognition of a cardiovascular involvement in women by caregivers may also be contributory to worsening outcome, especially in women with an established diagnosis of ischaemic heart disease or myocardial infarction [6]. Moreover, pharmacological therapy is hampered by defective evidence, as women are frequently underrepresented in clinical trials and there may be gender

differences in therapeutic response [3,7]. For example, women experience more bleeding than men regardless of whether they are treated with GP IIb/IIIa inhibitors, most likely because of frequent excess dosing in women [8].

In addition, despite many important studies over the past two decades have helped develop accurate clinical tests, risk factors, preventive interventions and effective therapies for CVD, the majority have either excluded women entirely or included only limited numbers of women and minorities. Thus, much of the evidence supporting contemporary recommendations for testing, prevention and treatment of CVD in women is extrapolated from studies conducted predominantly on middle-aged men [9]. Applying the findings of studies on male cohorts for the management of CVD in women may be inappropriate, because the symptoms of CVD, natural history and response to therapy are different in men and women [9,10].

Only recently, significant sex-related differences in prevalence, presentation, management and outcomes of CVD have been evaluated and discovered [2].

This review will briefly summarize gender-related differences in clinical presentation of several CVD, focusing at the same time on pathophysiologic explanation of such differences compared to men population. Knowing such gender differences may facilitate a rapid identification of cardiac warning signs and symptoms in health care givers promoting and facilitating the entry of women into the health care system for a better and faster treatment that can ultimately save a women's life.

GENDER-RELATED RISK FACTOR DIFFERENCES

Guidelines emphasize the importance of recognizing the full spectrum of CVD and thus classify women as being at high risk, intermediate risk, lower risk and optimal risk [11].

New findings support the concept of a multifactorial model, in which sex hormones interact with traditional and conditional risk markers, leading to an increase in the functional expression of atherosclerotic plaque deposition or vascular or metabolic alterations resulting in worsening outcomes for women [6]. Furthermore, whereas the major cardiovascular risk factors are the same in both sexes, gender-specific differences are noted [12,13], and these differences are related to different outcome. There is also substantial gender-related variability in the prevalence and outcome associated with traditional cardiac risk factors (*Table I*). That is, although overall rates of hypertension and smoking are higher in men, elderly hypertensive women and young female smokers are prominent at-risk subsets [14].

Population studies have noted that total cholesterol measurements are higher in men until the fifth decade of life but, beyond this age, women have greater values [2]. Furthermore, gender differences in high-density lipoprotein (HDL) values diminish with advancing age. Women typically experience a relatively mild decline in HDL cholesterol at the time of menopause [14,15]. In a comprehensive review of 25 population studies, Manolio et al. [16] reported that HDL cholesterol inversely predicted coronary artery disease (CAD) in younger women and men as well as older (65 years) women. Hypertriglyceridemia is also a more potent independent risk factor for CVD in women when compared with men [2]. A recent meta-analysis of 17 studies revealed that the CAD relative risk for hypertriglyceridemia was elevated 32% in men and 76% for women [17]. Although younger-aged diabetic women (i.e., <45 years) have an equally low prevalence of atherosclerosis [18], numerous studies have reported a significantly higher cardiovascular mortality for diabetic women when compared with diabetic men [19,20]. The latter is probably related to the fact that premenopausal diabetes eliminates the 'female advantage' of a predominately

Table I A Comparison of Gender Differences in Traditional Cardiac Risk Factors. Modified from reference (2).

	Men	Women
Risk factor threshold values		
Age threshold for ↑ disease risk	≥45	≥55
Family history of premature	<55	<65
Coronary heart disease		
HDL cholesterol		<50 mg/dl
Population average values		
Lipids		
Total cholesterol	↑	↑ for women after age ~50 years
HDL cholesterol		↑
Prevalence rates		
Hypertension	↑	
Smoking	↑	
Coronary disease or outcome risk		
Triglycerides		↑
Diabetes mellitus		↑
Obesity (e.g., BMI ≥30 kg/m^2)	↑	↑
Central obesity (≥35 kg/m^2)		↑

HDL = high-density lipoprotein.

lower CAD prevalence and outcome risk that exists for the female population in general [19]. Notably, the age-adjusted prevalence of CVD is nearly twofold higher in diabetic versus nondiabetic women [2].

Finally, the role that novel CVD risk factors and recently developed screening technologies (e.g., coronary calcium scoring) should play in guiding preventive interventions is as yet unclear. New-advent risk indicators such as inflammatory markers (for instance high-sensitivity C-reactive protein, IL-6, fibrinogen and acute phase protein), retinal artery narrowing, coronary artery calcification, endothelial dysfunction and anaemia are therefore now being studied in women [21].

CORONARY ARTERY DISEASE (CAD) IN WOMEN

Coronary artery disease is still considered to be a male disease, and it is likely to be under-diagnosed in women who often reported symptoms different from men. There are multidimensional factors such as psychosocial, physiological, anatomical and biological factors that contribute to different symptoms between men and women [22]. For example, women have smaller coronary artery lumens and less collateral circulation than men, which may lead to an increase in ischaemia, particularly during exertion or stress. In addition, the prevalence of obstructive coronary disease is particularly low in premenopausal women, whilst increases dramatically for a woman after age 50 [14]. In approximately 60% of cases of hospital admission, the initial presentation of CAD in women is acute myocardial infarction or sudden cardiac death and up to half of all women presenting with an acute myocardial infarction report no prior chest pain symptoms [6,14].

The higher mortality noted for younger women when compared with age-matched men could be due the higher frequency of plaque erosion when compared to more plaque rupture in men [23–25] (*Figure* 1).

In an autopsy series, women also had a greater frequency of distal microvascular embolization in the setting of a fatal epicardial thrombosis when compared to men, independently of the type of thrombus or presence of necrosis [26].

Another cause of acute myocardial infarction and sudden death in women is spontaneous coronary artery dissection. About 80% of the cases occurred in women, in absence of coronary atherosclerosis, and more than 25% of these usually occur in the peripartum period [27,28].

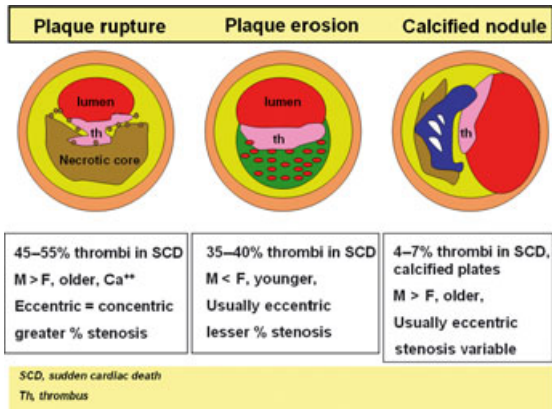

Figure 1 Gender differences in plaque morphologic features in an autoptic series of patients who died for sudden cardiac death. Modified from reference (25). SCD, sudden cardiac death; Th, thrombus.

The dissection can involve every coronary artery, but in women it frequently involves the left anterior descending coronary artery, whereas in men the right coronary artery is more frequently involved [28].

After sudden cardiac death, the most common presentation of obstructive CAD for women is atypical symptoms such as back pain, dyspnoea, indigestion, nausea/vomiting and weakness [12]. Frequently women reported pain in the jaw and neck [22] and describe their symptoms as more anguished and frightening (emotional component) compared with men [29] (*Table II*).

Furthermore, women had more acute than prodromal symptoms. The most frequent prodromal symptoms reported up to 1 month before the onset of AMI were unusual fatigue (70.7%), sleep disturbance (47.8%) and shortness of breath (42.1%) [30]. In this context, a small

Table II Signs and symptoms of coronary heart disease (adapted from the Harvard Medical School website—http://www.harvard.health.edu).

Traditional heart attack warning signs
Pressure, burning, squeezing in the centre of the chest
Discomfort in one or both arms, shoulders, neck, jaw, stomach or back
Shortness of breath
Fatigue, cold sweat, nausea, weakness
Symptoms of coronary heart disease can differ in women
Pain in upper back, jaw or neck
Shortness of breath
Flu-like symptoms: nausea or vomiting, cold sweats
Fatigue or weakness
Feelings of anxiety, loss of appetite, discomfort

proportion of patients (about 16%) with acute coronary syndrome seek medical assistance for prodromal symptoms in the 90 days before the event. Seeking treatment for these symptoms is associated with improved survival in women but not in men, because prodromes were associated with improved 1-year survival for women but not for men [31].

At the time of first experience of a myocardial infarction, women are often 7–10 years older and more likely to have diabetes mellitus or heart failure (HF) than men [32]. Particularly, diabetes is an independent predictor of 'atypical' presentation of acute myocardial infarction in women [33]. This atypical presentation of CAD causes a delay in diagnosis and treatment in women [34,35] and may lead to worse outcomes characterized by increased hospital morbidity, higher mortality and fewer evidence-based therapies, including revascularization, anticoagulation, β-blockade, statins and antiplatelet agents [36]. As demonstrated by the Global registry of Acute Coronary Events (GREECS) study, patients with ST-segment elevation myocardial infarction were less likely to receive percutaneous coronary intervention or fibrinolysis if their symptoms were atypical [34]. Furthermore, chest pain typical for angina pectoris is less likely to be associated with obstructive epicardial CAD in women than in men [2]. However, in the presence of obstructive coronary disease, women have an overall worse prognosis than men, conditioning by the acuity of presentation and the degree of comorbidity [37].

Despite women with chest pain in the absence of CAD are at low risk for adverse cardiac events, a majority continue to have symptoms that contribute to a poor quality of life and consumption of large amounts of health care resources because of repeated evaluations and hospitalizations [38,39]. Many of these women are diagnosed with 'noncardiac' chest pain. An alternative mechanism for their symptoms, present in approximately one-half of women with chest pain in the absence of angiographically documented obstructive CAD, could be a coronary microvascular dysfunction [40]. Differentiation between these mechanisms of chest pain is important, because 'noncardiac' chest pain is not associated with cardiovascular sequelae and may require further medical evaluation and treatment. By contrast, Syndrome X, which is thought to be caused by microvascular dysfunction, is associated with inducible metabolic ischaemia and can be treated by improving microvascular vasomotor tone with oral L-arginine, a precursor to vascular nitric oxide, and oestrogen [40].

HEART FAILURE IN WOMEN

Data from the Framingham study suggest that the lifetime risk of developing HF is about 20% for both men and women [41]. There are differences between men and women in clinical presentation, aetiology, treatment and outcome in HF, and these differences lead to different outcome. For example, women receive less life-prolonging treatment (ACE-I, beta-blockers and spironolactone) than men, in the presence of normal left ventricular function, whilst there no difference if aetiology of HF is CAD [42].

Typically, female patients with HF are older than males and more likely to be hypertensive and diabetic [43,44]. Usually, women tend to have better preserved systolic function, a lower prevalence of ischaemic aetiology and are less likely to have a history of prior MI [43]. In fact, they are less likely to have CAD, but more likely than men to have hypertension and valvular disease as the underlying aetiology.

Some studies showed that women with chronic HF have a better age-adjusted survival rate than men with the same condition [45,46]. This is because of the fact that women get underlying CVD at older age and they have different aetiology of HF. Such survival data are also confirmed in decompensated HF and in patients referred to cardiac transplantation. In fact, women with nonischaemic cardiomyopathy presented a better survival than men, irrespective of baseline characteristics, while there was no advantage in presence of ischaemic cause [47].

A peculiar type of left ventricular dysfunction and HF typical in women is Takotsubo cardiomyopathy. This disease is characterized by a left ventricular dysfunction, electrocardiographic changes like an acute myocardial infarction and release of cardiac biomarkers, in the absence of obstructive coronary disease [48]. The left ventricular dysfunction is usually reversible and it improves within weeks, despite a dramatic clinical presentation with substantial risk of complications in the acute setting. The aetiology of Takotsubo has not been clearly established. Many mechanisms have been postulated to explain the pathophysiology, as catecolamine-mediated cardiotoxicity, multivessels coronary vasospasm and abnormalities in coronary microvascular function [49]. Many studies showed a marked gender difference, because it is typically observed in postmenopausal women [49] with the highest frequency of occurrence between the seventh and eighth decade of life [50].

The reason for the much more common occurrence in postmenopausal women is unclear. This disease is often triggered by an emotionally stress or physical stress and it is known that men and women have different response to emotional stress [51].

Probably, it depends on the influence of sex hormones on the sympathetic neurohormonal axis and on coronary vasoreactivity [52]. Also menopause has been associated with endothelial dysfunction in response to reduced oestrogen levels [53]. This might add to the effect that mental stress exerts directly on endothelium [54].

ARRHYTHMIAS IN WOMEN

It has been demonstrated that women have higher heart rates at rest and longer corrected QT intervals than men, probably due to differences in exercise tolerance, autonomic modulation and intrinsic properties of the sinus node [55]. After achieving autonomic blockade with propanolol and atropine, Burke et al. [56] demonstrated that this gender difference in heart rate persisted, suggesting an intrinsic difference in the sinus node itself as the cause. Furthermore, there are many differences in incidence, prevalence, presentation and clinical course of many arrhythmias, such as atrial fibrillation (AF) or supraventricular arrhythmias (SVT) [57]. AF is the most common arrhythmia in the adult population and generally its incidence increases with age both in men and women, but it is more prevalent in men of all age groups. In addition to gender difference in prevalence, there are differences in outcomes and prognosis between men and women with AF as well. Women with AF are more symptomatic [57], older and have lower quality of life and more co-morbidities than men [58]. Also they present more likely a higher heart rate, longer episodes and increase incidence of embolic strokes compared to men [59]. Data from the Euro Heart Survey on Atrial Fibrillation demonstrated that women are usually treated less aggressively, with fewer cardioversions and catheter ablations. In this study, albeit both genders received anticoagulation therapy, women experienced a significantly higher rate of stroke and major bleeding events [58]. There are also differences in the incidence of SVT: atrioventricular nodal re-entry tachycardia has a 2 : 1 female-to-male predominance, while accessory pathways, including Wolf-Parkinson-White syndrome, are twice as frequent in men [60]. Some study demonstrated the evidence of hormonal effects on the triggers and timing of SVT. It seems that many episodes and symptomatic episodes are experienced by women during the luteal phase of the menstrual cycle (when progesterone is elevated). Particularly, it is demonstrated a cyclical variation in SVT inducibility during menstruation cycle. In fact, some patients were not inducible during electrophysiologic studies performed at midcycle but they became inducible when the studies repeated during menstruation [61]. Also episodes of SVT increase during pregnancy and during postpartum period [62]. The mechanisms for increase in this situation may be related to hormonal effects, increased intravascular volume and autonomic tone [63].

CONCLUSIONS

Several clinical observations clearly demonstrated the importance of gender-specific differences in the clinical presentation of CVD. For this reason, diagnosis and treatment in women should be formulated from data on women and not on data obtained from men. The ability of knowing and recognizing gender differences in CVD may facilitate a rapid identification of cardiac signs and symptoms of warning and may avoid significant delays in diagnosis and treatment in women. Continued efforts are necessary to improve both knowledge and early recognition of warning clinical presentation of CVD in women to reduce the risk of mortality related to the misleaded diagnosis that women are often still paying because of the peculiar presentation related to their gender.

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