Cardiovascular Disease and Sex

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Abstract - One of the primary causes of death worldwide is cardiovascular disease (CVD). Women typically have a lower incidence of CVD than men, however after acute cardiovascular events, women have a higher mortality and worse prognosis. Different CVDs, such as coronary heart disease, stroke, heart failure, and aortic diseases, exhibit these sex variances. These differences have raised serious concerns so sex consideration is significant for the prevention, diagnosis, treatment, and management of CVD. In order to highlight the need of taking sex differences into account when determining cardiovascular risk, this study seeks to offer an overview of sex-related differences in numerous common CVDs as well as an analysis of potential factors linked with the disparities. Future studies should focus on how to define and include sex-related indicators into the methods currently used for cardiovascular risk assessment and management.

Key words: cardiovascular diseases; coronary disease; sex characteristics

Introduction

One of the primary causes of death in both women and men in the majority of developed countries is cardiovascular disease (CVD) [1]. In 2013, CVD was the cause of 35% of deaths in women and 32% of deaths in men worldwide [2]. Despite the fact that women typically have a lower incidence of CVD than males, a number of clinical studies have shown that after an acute cardiovascular (CV) event, women have a greater death rate and a worse prognosis [3]. Women still have inequities in diagnosis, treatment, and research for CVD, which is still underdiagnosed and undertreated in this population. Women’s risk is frequently underestimated because it is believed that they are “protected” against heart disease. Less aggressive treatment plans and a lower representation of women in clinical trials result from the underrecognition of cardiac disease and the disparities in clinical presentation in women. Women typically make up only 20% of patients, despite making up 40% to 50% of participants in longitudinal research and CVD registries [4]. Some of the mechanisms causing CVD disparities include ongoing discrepancies in risk factor prevalence, healthcare access, poor public and medical awareness leading to underdiagnosis, delayed adoption of evidence-based guidelines among women, and significant knowledge gaps [5].

The majority of CVD cases can be attributed to a group of classic risk factors, which include smoking, being overweight or obese, having high blood pressure, having diabetes, and having increased cholesterol. A new understanding of the mechanisms causing wors-
ening outcomes for women is made possible by increased awareness of the prevalence of traditional CVD risk factors and their differential impact on women, as well as emerging, non-traditional risk factors that are specific to or more prevalent in women [5].

Coronary artery disease

With a higher mortality rate in women under the age of 55, acute coronary syndrome (ACS) continues to be the leading cause of death in both men and women [6]. There are sex-related differences in baseline risk factors, coronary anatomy and physiology, clinical presentation, therapy, and outcomes of ACS patients. In comparison to men, women who present with ACS tend to be older and have more concomitant conditions. The most usual symptom of ACS is chest discomfort; however, women are more likely to report atypical symptoms. Women under the age of 55 are also more likely than men to experience prodromal symptoms [7]. On coronary angiography, women are more likely to have normal coronary arteries compared to men [8]. Due to an increased connection with major adverse cardiac events, angina, and hospitalizations for heart failure, the prevalence of CAD without obstructive coronary arteries (INOCA) is rising, which is associated with greater expenses. In order to meet the criteria for INOCA, a patient must have stable symptoms suggestive of IHD, objective evidence of myocardial ischemia from non-invasive testing, and no evidence of obstructive CAD. Prior research has demonstrated that women who present with ACS are less likely to have prompt revascularization, undergo coronary angiograms, or be treated with medical therapy that follows guidelines [4]. The sex differences in outcomes following ACS are more common in some population subgroups, especially those that are underprivileged in terms of age, race, and ethnicity. Young women with ACS are an understudied demographic that are at an increased mortality risk compared to men [5]. In general, factors leading to greater mortality in women with ACS include their older age at presentation, increased comorbidities such as diabetes, hypertension, and shock, as well as their frequently atypical presenting symptoms which can cause time delays. Recent studies have revealed that despite advancements in the recognition of sex differences over the previous few decades, there is still much to be learned about the individualization of treatment for men and women.

Possible pathogenesis

Inflammation is assumed as the root cause of atherosclerotic disease within the vascular endothelium. Sex variations in hemostasis and inflammatory indicators in ACS are suggested to exist. In contrast to women, men with STE-MI were shown to have significantly greater levels of fibrinogen, C-reactive protein, and interleukin-6, indicating a considerable inflammatory component of ACS in men. Overall, plaque rupture appears to be the most frequent cause of coronary thrombosis in both men and women, independent of presentation. This is to account for 76 % of male myocardial infarction deaths and 55 % of female deaths [9]. Plaque rupture was observed to be notably uncommon in younger females in prior research comparing the causes of ACS in men and women, possibly reflecting the preventive effects of oestrogen in premenopausal women [10]. Spontaneous coronary artery dissection (SCAD) is becoming more widely acknowledged as a significant cause of MI, particularly in women with low atherosclerotic risk.

Treatment & management

Women are more likely to significantly postpone seeking treatment for ACS symptoms [4]. Delays in obtaining ACS treatment can be explained by a variety of reasons, such as incorrect symptom attribution, a lack of self-risk awareness, and obstacles to self-care [11]. It is possible that the worse outcomes in women may be caused by the failure to seek immediate treatment for AMI. Also, women are less likely...
to be treated with guideline-directed medical therapy, to undergo invasive coronary revascularization procedures, or to be referred to cardiac rehabilitation. The ESC guidelines for treatment of STEMI and NSTEMI specify the indications for reperfusion and pharmacologic therapy, with no overt sex-specific recommendations, irrespective of the fact that many of the references are based on research underpowered to particularly address sex differences [12-13]. Angiotensin-converting enzyme inhibitors (ACEIs), beta-blockers, statins, and angiotensin receptor blockers (ARBs) have all been confirmed to be similarly effective in treating both sexes, resulting in lower morbidity and death after myocardial infarction. Despite the evidence of equal efficacy, women frequently receive fewer medications that are indicated by guidelines [14]. Following ACS, medication adherence has also been found to differ by sex, with women being related to lower adherence [15]. The use of ACEIs and ARB treatment during pregnancy is classified as category C during the first trimester and category D during the second and third trimesters. Category X during pregnancy is assigned to statins. When a young woman with reproductive potential undergoes ACS, these drugs might not be prescribed [5]. In one study, following CABG, women fared worse than men in terms of survival (65% and 31% at 10 and 20 years, respectively, vs. 74% and 41%, P 0.001). Age, delayed diagnosis and treatment, higher prevalence of comorbidities (diabetes, hypertension, and heart failure), and underuse of arterial grafts were all cited as contributing reasons to worse outcomes [16]. Another study examined how patients with significant coronary disease who were referred for PCI or CABG were affected by age and sex. Compared to men, women with one vessel CAD were more likely to get medical treatment and less likely to have PCI. This may be explained by an effort to prevent complications given that women experience greater in-hospital complications after PCI than men. Additionally, compared to men, women with left main disease or two- or three-vessel CAD were less likely to receive CABG. Serious bleeding problems were uncommon overall, but they occurred four times more frequently in women than in men. Despite the fact that women experience more hospital complications than men, this study’s ACS patients after PCI or CABG showed no discernible sex differences in 30-day mortality [17]. Despite improvement in PCI technology, clinical results in women following PCI continue to be inferior to those in men. Women continue to have higher rates of recurrent revascularization in addition to higher overall mortality. This may be partially explained by the fact that women tend to have more comorbid conditions, smaller vessels, and more coronary calcification than men. The selection of stents should take into account the fact that women are more prone than males to experience post-PCI bleeding. Uncertainty surrounds the ideal DAPT time frame following PCI. Despite the fact that women who complete cardiac rehabilitation may experience a higher reduction in mortality compared to men, women are frequently underreferred for cardiac rehabilitation and have lower completion rates [18]. Numerous patient-related factors, such as socioeconomic status, depression, obesity, the discomfort of exercise, and family duties, have previously been linked to low referral and completion rates; nevertheless, physicians’ lack of support is just as significant [19].

**Heart Failure**

**Heart Failure with Reduced Ejection Fraction**

50% fewer women than men experience heart failure (HF) with reduced ejection fraction (HFrEF), which is defined as clinical signs and symptoms of volume overload and/or low cardiac output with an ejection fraction (EF) of ≤ 40% [6,20]. In comparison to men, women with HFrEF have fewer comorbidities, lower hospitalization rates, and better survival rates, but they also have more symptoms, have worse functional status, and have lower health-
related quality of life (HRQOL) [21]. Women are still notably underrepresented in clinical HF trials, which further reduces the amount of information that may be used to guide prospective sex-specific treatment therapies [22]. The variations in presentation, results, and therapy are probably the result of a combination of biological and psychosocial variables.

**Heart Failure with Preserved Ejection Fraction**

The most prevalent form of heart failure (HF) in women is heart failure with preserved ejection fraction (HFpEF), and its frequency rises with age [23]. Numerous cardiovascular and non-cardiovascular conditions are linked to HFpEF [5]. HFpEF is difficult to diagnose, and there are no effective treatments that can change the course of the disease. Depending on population demographics, LVEF cut-offs, and study environment, it has been reported that mortality in patients with HFpEF is comparable to or lower than mortality in HFrEF [24].

**Arrhythmias**

**Atrial Fibrillation**

The most prevalent persistent arrhythmia, atrial fibrillation (AF), is becoming more and more prevalent as the population ages [25]. The diagnosis of AF entails a significant burden because of the associated medical expenses, patient symptoms, and reduced quality of life. Although there is no difference in the lifetime incidence of AF between the sexes, women often present when they are roughly 10 years older than males [26]. Women are more prone than men to have symptoms and to have more functional restrictions [27]. They are less likely to be referred for procedures like catheter ablation or electrical cardioversion since they have a higher mortality risk [28]. In spite of their increased risk of crippling stroke, elderly women are under-treated with therapeutic anticoagulation [29]. When taking anticoagulants, women are more likely than men to experience significant bleeding, experience more pharmaceutical side effects, and experience more procedural complications.

**Ventricular Arrhythmias**

The prevalence and presentation of ventricular arrhythmias and sudden cardiac arrest differ between the sexes [30]. Women have sudden cardiac arrest less frequently than men. When experiencing an out-of-hospital arrest, women are more likely than men to have pulseless electrical activity or asystole rather than ventricular fibrillation or ventricular tachycardia [31]. In comparison to men, women who receive an implanted cardioverter defibrillator (ICD) for primary prevention are less likely to develop ventricular arrhythmias over time [32]. There is a need for more research on the pathophysiology underpinnings of sex differences in arrhythmias.

**Women-specific cardiac disease**

**Peripartum cardiomyopathy**

Peripartum cardiomyopathy (PPCM) is a rare and severe form of cardiomyopathy that is frequently detected during the peripartum period and is characterized by heart failure and abnormal left ventricular systolic function. It is more common in older women and those who have a history of pregnancy-related hypertension [33]. Other risk factors include preeclampsia and twin gestations. Although the exact cause of PPCM is still unknown, genetic and vascular elements, as well as autoimmune inflammatory processes brought on by foetal or placental antigens, are thought to be contributing causes [34]. Most PPCM patients have newly developed heart failure, which is characterized by dyspnoea, orthopnoea, paroxysmal nocturnal dyspnoea, and lower extremities oedema. These symptoms might be mistaken for those of a typical pregnancy, which could lead to a missed or delayed diagnosis. Acute ischemic stroke brought on by an LV thrombus, ventricular tachycardia, or other forms of arterial thromboembolism are less
frequent early presentations of PPCM [35]. In the absence of pre-existing cardiac disease, systolic dysfunction with an EF 45 % or less is one of the echocardiographic criteria for PPCM [36]. LV dilatation, right ventricular dysfunction, increased pulmonary pressures, biatrial enlargement, and mitral and tricuspid regurgitation are further echocardiographic findings. The majority of women will regain cardiac function, although complications, both short- and long-term, are frequent [37]. The cornerstone of treatment for heart failure is heart failure-specific therapy, while bromocriptine is also being investigated in some clinical situations as a disease-specific therapy. When treating volume overload and pulmonary congestion, loop diuretics should be used cautiously to prevent over-diuresis during pregnancy, which could result in hypotension and hypoperfusion of the uterus.

**Takotsubo syndrome**

Takotsubo syndrome (TTS), also known as stress-induced cardiomyopathy, is a disorder that predominately affects postmenopausal women who have recently gone through a stressful situation, either physically or emotionally. A catecholamine storm brought on by the stressor, which starts a neurohormonal cascade, results in symptoms like those of acute coronary syndrome and heart failure [38]. Transient hypokinesis, akinesis, or dyskinesis of the LV mid-segments in the presence of a stressful trigger, with or without involvement of the apex (typically but not always), are included in the diagnostic criteria released by the Mayo Clinic in 2004 [39]. There are rare occurrences where regional wall motion anomalies are restricted to a region fed by a single epicardial vessel, but they must generally extend beyond a single epicardial vascular distribution. During the acute phase, serum natriuretic peptides (BNP or NT-proBNP) are markedly raised. Typically, the increase in troponin is disproportional to the amount of myocardium damaged (smaller). In order to maximize recovery, which typically takes a few weeks, the goal of management in TTS patients is to prevent any future complications such arrhythmias while providing supportive care. Along with treating heart failure during the acute period, vigilant monitoring for QT interval prolongation, conduction abnormalities, and arrhythmias is required [40]. TTS is not a benign syndrome, despite the fact that the majority of people with it have a good prognosis once ventricular dysfunction has resolved. There have been reports of left ventricular tract obstruction (LVOTO), severe mitral regurgitation, LV thrombus, cardiogenic shock, arrhythmias, including full heart block, and very rarely, death, as TTS side effects [41]. It was observed that the annual recurrence rate was 1 %. There is currently no corroborated definitive therapy for the prevention of recurrence [42].

**Chemotherapy-related cardiotoxicity**

Long-term survival rates for cancer patients have significantly improved as a result of advancements in cancer therapy. One of the main causes of morbidity and mortality among cancer survivors is cancer therapy-related cardiac dysfunction (CTRCD), which is on the rise as cancer patients survive longer. In the end, for many malignancies, the risk of death from cardiovascular disease (CVD) is greater than the chance of tumour recurrence [43]. CTRCD is defined as a decrease in left ventricular ejection fraction (LVEF) of > 10 % to less than 53 %, confirmed by repeat imaging 2–3 weeks after initial diagnosis [44]. Cardiotoxicity from breast cancer therapy, such as conduction abnormalities, arrhythmias, LV dysfunction, and myocardial ischemia, frequently occurs. Most CTRCD cases among women are associated with breast cancer treatment due to its prevalence. The first chemotherapy drugs to have been linked to CTRCD are anthracyclines. Numerous mechanisms have been hypothesized, yet the precise one is still unknown. Anthracycline cardiac toxicity can appear either quickly (within a week) or gradually after exposure. Early symptoms in-
clude myocarditis and pericarditis, which are caused by inflammation. On the other hand, late signs are linked to myocyte damage that really occurs, causing cardiac dysfunction and HF [43]. Cardiotoxicity risk appears to be dose-dependent. “Safe dosage” does not exist. Anthracyclines can cause cardiac toxicity at even lower doses, particularly in patients who already have cardiovascular risk factors. Alkylating agents, like cyclophosphamide and carboplatin, disrupt DNA by preventing transcription and compromising with protein synthesis. In 7 – 28% of patients, they have been associated with the onset of LV dysfunction [45]. The more recent cancer treatments target hormone receptors on breast cancer cells directly. Breast cancers that are HER2-positive are treated with HER2 drugs (trastuzumab and pertuzumab), which are monoclonal antibodies that bind to the extracellular domain of the ErbB2. Cardiotoxicity caused by trastuzumab is a well-studied phenomena that should be taken seriously, especially in patients who have a history of using anthracyclines concurrently or in the past [43]. Numerous risk factors can result in the development of chemotherapy as part of cancer treatment. Pre-existing LV dysfunction or HF, CAD, advanced age, female sex, and postmenopausal status are all patient-related risk factors. Treatment-related risk factors include concurrent administration of combination cancer therapies, the kind of chemotherapy, prior or ongoing radiotherapy treatment, and anthracyclines treatment in the past [46]. The current gold standard for imaging before, during, and after potentially cardiotoxic therapy is echocardiography. Although there is no universal agreement, the majority of studies use a drop in LVEF of 10% over time as a surrogate for cardiotoxicity and a signal of significant change in left ventricular function [47]. Beta-blockers, ACEIs, ARBs, statins, and aldosterone antagonists are examples of traditional heart failure drugs that show promise in preventing and lessening the severity of chemotherapy-induced cardiotoxicity. However, bigger randomized trials are necessary for further study.

**Conclusion**

Despite the fact that cardiovascular disease is the main cause of death for both sexes, there are differences in how ACS patients are managed and treated depending on their sex. Treatment delays in women may be partially explained by sex variations in ACS pathophysiology and clinical presentation. Additionally, compared to men who present with ACS, women are less likely to get pharmacological therapy suggested by guidelines or have coronary revascularization procedures, which has an impact on clinical outcomes. Women continue to be underrepresented in clinical studies, too. The public and medical communities can be educated, and women’s health centres can be developed to help alleviate these sex-specific care discrepancies.

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**References**


