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Review Article

Acute Cardiovascular Medicine in Women: A Narrative Review on Disease States and Underlying Mechanisms

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INTRODUCTION

Cardiovascular Disease (CVD) is the leading cause of death globally in women and men, respectively 34.6% and 31.4% in 2019. The incidence of CVD is higher in men, yet worse prognosis and higher mortality after an acute cardiovascular event are seen in women. Advances in diagnosis and treatment have led to a reduction in mortality rates in both sexes over the last decades. This reduction, however, is less pronounced in younger women, women living in regions with a low to middle socio-demographic index, and women with a low socioeconomic status in high-income countries [1]. Furthermore, recent reports describe a rise of Acute Myocardial Infarction (AMI) in younger women [2]. Numerous cohort studies and registries have shown sex disparities in diagnosis, treatment, and outcomes, especially in acute cardiovascular care [3-6]. Women tend to be under-represented in clinical trials and gender differences are often not considered in the current guidelines. These concerns have prompted an international initiative to reduce the CVD burden in women by 2030 [2]. In this narrative review, we aim to highlight the main sex disparities in common acute cardiac diseases. Secondly, we discuss possible female-specific pathophysiological mechanisms and conjoint gaps in the knowledge on which future research can focus.

CARDIOVASCULAR RISK FACTORS

Traditional Risk Factors

Traditional risk factors like hypertension, diabetes, obesity, dyslipidemia, tobacco use, sedentary lifestyle, and family history of CVD are strong predictors for cardiovascular events in men. In women, these factors show a different prevalence and impact on cardiovascular health. In general, obesity and sedentary lifestyle are more prevalent. Women tend to be older when they present with CVD, and at presentation have more often metabolic syndrome, hypertension, and diabetes [3,7]. With hypertension, dyslipidemia, and diabetes being the most important modifiable risk factors in women, awareness should be raised about more drug-related side effects from antihypertensives, lower prevalence of controlled dyslipidemia and underuse of statins, and higher risk for delayed diagnosis of diabetes [2,8]. Additionally, the worldwide increase in tobacco use in young women is particularly concerning as smoking might be more deleterious in women [9]. Furthermore, a history of premature maternal AMI is a stronger risk factor for premature CVD in women than men [10].

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Sex-Specific Risk Factors

Pregnancy induced-hypertension, gestational diabetes, and pre-eclampsia increase metabolic stress during pregnancy and their occurrence encounters a long-term risk for development of CVD. Pre-eclampsia is associated with an increased risk of hypertension, Ischemic Heart Disease (IHD), stroke, and Venous Thromboembolism (VTE) in later life. Furthermore, CVD is the main cause of death in pregnancy and puerperium, mainly due to peripartum pulmonary embolism [11]. Additionally, cardiovascular toxicity from cancer treatment is a growing concern. Certainly, combination of chemotherapy and thoracic radiotherapy poses an increased risk for cardiac diseases like heart failure, coronary artery disease, arrhythmia, etc [2]. Finally, increased CVD risk from hormone-based contraceptives and hormone replacement therapies have been described, especially in smokers. However, its underlying mechanisms are incompletely understood and cardiovascular benefits in some subgroups remains debated [4,12].

Under-Recognized Risk Factors

Overall, non-traditional risk factors play a stronger role in women. In the VIRGO study, women with Acute Coronary Syndrome (ACS), were more likely to self-report as black, unemployed, divorced, separated, or widowed, with lower total household incomes and lower socioeconomic status than their male counterparts [3]. In both sexes, depression and history of attempted suicide are significant independent predictors of premature CVD and IHD mortality, though effects are far more pronounced in women. Additionally, women who experienced severe physical or sexual abuse in childhood have an almost 50% higher risks of cardiovascular events in early adulthood [13].

ACUTE CARDIOVASCULAR DISEASE STATES

Acute Myocardial Infarction

Cardinal symptom of ACS in both sexes is retrosternal pain or tightness. However, women present more frequently with other symptoms like pain in other body locations, fatigue, dyspnoea, or nausea, even without chest pain. These symptoms are regularly labeled as "atypical", however, they should rather be interpreted as characteristic for the underlying pathophysiology as women have a more pronounced vagal

response and more often have an alternative diagnosis such as coronary microvascular disease [4]. In acute myocardial ischemia or infarction due to obstructive Coronary Artery Disease (CAD), women, particularly premenopausal women, more often have endothelial cell denudation leading to plaque erosion than classic rupture in a thin-capped, lipid-rich plaque. Data from the PROSPECT study showed less extensive CAD, less necrotic plaque core, less plaque calcification, similar plaque burden, and smaller lumens in women. Moreover, thin-cap fibroatheroma was highly predictive of plaque vulnerability, more in women than men [14].

Women, in general, bear a longer delay in seeking medical care, face a higher risk of incorrect diagnosis, and delayed treatment. Women have fewer diagnostic findings on electrocardiogram, lower peak biomarkers at presentation, and symptom recognition is more difficult [3]. Younger women (under 55) presenting without chest discomfort pose the highest risk of misdiagnosis. In all age groups, women cluster more comorbidities including traditional and non-traditional risk factors at the time of ACS presentation than their male counterparts. Additionally, women are less likely to receive guideline-recommended therapy and more often experience side-effects and complications from medical treatment and interventions [4,7]. Multiple studies have consistently shown worse cardiovascular outcomes in women with ACS, even after adjustments for risk factors, medication, time to presentation and revascularization strategies. Again, outcome differences are most pronounced in young and middle-aged women compared to age-matched men [7].

Ischemia with Non-Obstructive Coronary Arteries

In suspected myocardial ischemia or infarction, up to two-third of women referred for coronary angiography have non-obstructive epicardial arteries (coronary stenosis < 50%) [15]. This condition has recently been termed (M) INOCA, which stands for ischemia or myocardial infarction with non-obstructive coronary arteries. Many different disease states can lead to (M) INOCA, ranging from epicardial coronary artery disorders (e.g. atherosclerotic plaque rupture, erosion or artery dissection with non-obstructive arteries), oxygen supply-demand mismatch (e.g. vasospasm, embolism) to endothelial dysfunction due to coronary microvascular dysfunction or vasospasm [5].

Several pathophysiological mechanisms have been recognized in INOCA, including coronary vasospasm and/or Coronary Microvascular Dysfunction (CMD) with changes in coronary blood flow regulation and vascular smooth muscle tone, altered cardiac autonomic nerve function, increased proinflammatory markers, platelet dysfunction, and/or presence of coronary atherosclerosis [15]. Vasospastic Angina (VSA) is the clinical presentation of myocardial ischemia caused by epicardial and/or microvascular vasospasm, whereas CMD manifests with so-called Microvascular Angina (MVA). Due to the heterogeneous character of INOCA, a stepwise approach with non-invasive and invasive testing and empirical therapy should lead the clinician in the diagnostic assessment. Although treatment is focused on modification of lifestyle factors and risk factor management, antianginal medication will differ for patients with VSA and MVA [5,15]. Clinicians should be aware that INOCA is about two times more prevalent in women than men and is often misdiagnosed. Coronary vasospasm and coronary microvascular dysfunction have been associated with impaired quality of life, increased major adverse cardiac events, overall mortality and healthcare costs [15].

Spontaneous Coronary Artery Dissection

SCAD is characterized by an acute nonatherosclerotic, nontraumatic coronary event with hematoma formation within the tunica media leading to true coronary lumen compression. With increasing disease recognition and advances in intracoronary imaging, SCAD is estimated at 1 to 4% of ACS in general, up to 35% in young women (≤ 50), and 43% of ACS during pregnancy [16]. The condition is about nine times more prevalent in women. Compared to men, women with SCAD more often have arteriopathies including fibromuscular dysplasia and systemic inflammatory disorders. Other risk factors are pregnancy, multiparity, and hormonal therapy. Preceded physical and emotional stress are more common in men. Sex differences in SCAD susceptibility and the role of sex hormones are still debated. High-level evidence-based guidance for treatment is lacking. Albeit, the majority show complete recovery of coronary architecture within 30 days with conservative medical management, about 14% requires urgent revascularization (PCI or CABG) with higher complication risk. In contrast to good long-term survival, SCAD patients often develop psychosocial distress, post-SCAD symptoms, and recurrent SCAD [16].

Acute Decompensated Heart Failure

In the spectrum of acute heart failure, Acute Decompensated Heart Failure (ADHF) is the most common clinical presentation. Its burden on health care systems is enormous and overall long-term outcomes remain poor. In general and as for hospitalization with ADHF, Heart Failure with reduced Ejection Fraction (HFrEF) mainly due to ischemic heart disease, is more common in males, while Heart Failure with preserved Ejection Fraction (HFpEF) is more prevalent in females [2,17]. Risk factors for women with acute decompensated HFpEF are older age, obesity, hypertension, chronic kidney disease, and depression. Prevalence of diabetes is similar in men but diabetes is associated with worse mortality in women [17]. Current guideline-recommended therapies ameliorate HFrEF outcomes, whereas medical treatment for HFpEF is limited. Furthermore, women with acute heart failure are less likely to be discharged on guideline-recommended therapy. Despite these differences, there seem to be comparable mortality rates in the year following hospitalization for ADHF [18].

Peripartum Cardiomyopathy

A rare, but sometimes fatal form of ADHF is Peripartum Cardiomyopathy (PPCM). PPCM is exclusive to women and is defined as idiopathic cardiomyopathy presenting with heart failure secondary to left ventricular systolic dysfunction towards the end of pregnancy or in the months following delivery, where no other cause of heart failure is found. The incidence ranges between 1:1300 and 1:4,000 births worldwide [2]. Main risk factors are African-American race, preeclampsia, multigestational pregnancies, hypertension, and age above 30 years. Outcomes are variable, covering complete recovery to cardiogenic shock in extremis, need for cardiac transplantation, or death [2,19]. Mortality rates vary widely (0 to 25%) based on geographic location. Pathophysiology remains incompletely understood, with current evidence supporting a vascular/hormonal hypothesis; PPCM is a vascular disease, triggered by hormonal changes during late gestation [20]. With respect to fetal safety, ADHF treatment in PPCM consists of heart failure therapy, anticoagulation, and inhibition of prolactin secretion [19].

Acute Myocarditis

Registries on acute myocarditis demonstrated a male sex dominance with a prevalence from 65 to 75%, most common in young men and postmenopausal women. Conduction abnormalities and ventricular arrhythmias were more frequently seen in women [21]. A recent large multicentric retrospective cohort study of adults hospitalized with acute myocarditis revealed higher rates of cardiogenic shock and cardiac arrest due to ventricular fibrillation in women. Additionally, female gender emerged as an independent predictor of in-hospital mortality. Despite a worst short-term outcome, one-year follow-up did not reveal any sex-related difference in mortality [22].

Takotsubo Syndrome

About 2% of patients presenting with suspected acute coronary syndrome have Takotsubo Syndrome (TTS). In women, this number goes up to approximately 10% and is it most frequently seen in postmenopausal women. Annualized recurrence rate has been estimated at around 1.5%. Its pathophysiology is incompletely understood, but an excessive cardiovascular response to a sudden catecholamines surge appears to be central. Psychological and/or physical stress often precedes the onset of TTS [23]. Whereas emotional stressors are more common in women, men appear to develop TTS as a complication of major non-cardiac illnesses or procedures. Moreover, male gender is burdened with a greater incidence of cardiogenic shock in TTS, ventricular arrhythmias, acute kidney injury, and higher in-hospital mortality risk [24]. While TTS is a reversible condition, in-hospital mortality rate is high (4-5%), which is in the same range as ACS STEMI patients. There are no prospective randomized clinical trials in patients with TTS [23].

Cardiogenic Shock

Women with cardiogenic shock are older and have a higher cardiovascular risk profile [27]. Analysis of the SHOCK registry and IABP-SHOCK II trial did not show any gender-related difference regarding in-hospital mortality and clinical outcome (1 year follow-up) in patients with AMI-related cardiogenic shock, despite a higher incidence of mechanical complications among women [25,26]. Interestingly, cardiogenic shock in women was less often related to acute coronary syndrome [27]. Lower rates of revascularization, invasive hemodynamic monitoring and use of mechanical circulatory support occurred in females. Besides this, a higher risk of 30-day readmission was observed in women with cardiogenic shock complicating AMI [6]. The EUROMACS registry enlightened that women who underwent VAD implantation were more often in an unstable hemodynamic condition (INTERMACS 1 and 2). Major bleeding, arrhythmias and RV failure were major complications in female patients [28].

Cardiac Arrest

Females tend to have less often witnessed cardiac arrest, a higher degree of comorbidities and present more likely with non-shockable rhythm. Multiple studies enlightened a gender difference in treatment of out-of-hospital cardiac arrest: women were less likely to receive bystander cardiopulmonary resuscitation and automatic external defibrillation, especially in public [29]. Some registries evidenced a sex disparity during post-resuscitation management with female receiving fewer revascularization, as well as less targeted temperature management [30,31]. Survival rate with a favorable neurologic outcome for women aged 30 to 49 years seems higher than that in men within the same age range. In general, however, higher overall mortality among women are observed [31].

UNDERLYING MECHANISMS

Anatomy and Physiology

Sex disparities in anatomy and organ function are present throughout the cardiovascular system, even after adjustment for body size. In healthy individuals, women have smaller heart cavities and a lower left ventricular mass. With higher age, left ventricular ejection fraction increases more in women than men, however, systolic myocardial strain and strain rate diminish more in aging women. Moreover, systolic and diastolic left ventricular elastance (stiffness) is higher than in men at the same age [17]. At rest, stroke volume is about 10% lower in women, though a higher baseline heart rate leads to a similar cardiac index in both sexes. During cardiovascular stress, men respond mainly by rising vascular resistance, while women create higher cardiac output by increasing their heart rate. It has been postulated that in repeated cardiovascular stress the heart rather than the large arterial vessels takes the burden in women [32]. However, this mechanism may shift in postmenopausal women, as systolic blood pressure rises more steeply in aging women [4]. Typical gender-related atherosclerotic coronary changes in ischemic heart disease have been discussed in section 3.1. Nevertheless, smaller coronary arteries, higher coronary blood flow, and higher endothelial shear stress are also believed to contribute to endothelial dysfunction and atherosclerosis [33].

Sex Hormones

The effects of sex hormones on cardiovascular health are incompletely understood. It has been argued that endogenous estrogens, namely estrone, 17-beta-estradiol, and estriol, play a protective role in CVD by its direct effects on vascular cells, regulation of lipid levels, recovery from vascular injury, mitigating of atherosclerosis formation during fertile age, protection from stress-induced cell death of cardiomyocytes, and myocyte regeneration. Estrogen acts through several pathways, within the cardiovascular system most importantly binding to the intranuclear estrogen receptor alfa leading to gene expression. More rapid effects are seen through "nongenomic" mechanisms. Herein, estrogen binds to plasma membrane receptors and subsequently increases levels of calcium and nitric oxide, and activation of kinases. After menopause, the decline in estrogen induces changes in endothelial mediators, endothelial dysfunction, enhanced sympathetic tone, more visceral adiposity, increased systemic inflammation, and elevated vascular stiffness [34].

The protective role of estrogen is ambiguous as estrogen supplementation in postmenopausal women has shown harmful effects, mainly increased risk of VTE and stroke. Nonetheless, hormone replacement therapy might be beneficial for CAD when it is initiated in younger women (< 60 years) or at an earlier stage of menopause [12]. Furthermore, hemostasis in women is influenced by hormonal fluctuations during the menstrual cycle, pregnancy, hormone-based contraceptives, hormone replacement therapy, and menopause. These fluctuations are associated with a higher thrombotic and hemorrhagic burden in acute cardiac diseases [4].

Men and postmenopausal women have higher levels of testosterone, which is postulated to enhance atherogenesis, vasoconstriction, hypertension, and coronary calcification [34]. Moreover, testosterone induces a relative natriuretic peptide deficiency which might be deleterious for cardiovascular health [35]. On the other hand, lower testosterone levels are associated with worse cardiovascular outcomes [12]. Animal data suggests that testosterone, rather than estrogen, acts protectively in myocardial ischemia-reperfusion injury [35]. Whereas estrogen is conventionally considered as cardioprotective, testosterone is often thought to have many deleterious effects on the cardiovascular system. Nevertheless, beneficial or noxious effects of estrogen and testosterone are rather context-specific.

Coronary Microvascular Dysfunction

Different pathophysiological mechanisms have been suggested in CMD, that involve structural, functional and extravascular abnormalities. As for functional disorders, endothelial coronary dysfunction is considered one of the main factors that lead to the development of CMD. In response to physiological stimuli, such as exercise or to intracoronary acetylcholine injection, the impaired endothelium may be unable to release vasoactive molecules, such as nitric oxide, that act on the vascular smooth muscle cells leading to vasodilatation and an increase coronary blood flow [36]. In addition, there may be a disproportion between the vasodilator nitric oxide and the vasoconstrictor endothelin-1, resulting in an abnormal microvascular tone. Endothelium-independent

mechanisms have also been proposed. In patients with CMD, a reduced Coronary Flow Reserve (CFR) in response to coronary reactivity testing with intracoronary adenosine administration is noted [5]. As for the structural abnormalities, coronary microcirculation is subjected to structural changes (microvascular remodeling), characterized by a reduction in capillary density and capillary diameter, intimal thickening, smooth muscle cell thickening and proliferation and perivascular fibrosis, resulting in a reduced microcirculatory conductance capacity [5,36]. Women have smaller size coronary arteries with laminar flow and higher endothelial shear stress, whereas men present most commonly with larger coronary arteries, disoriented flow and low shear stress. High shear stress conditions are associated with anti-atherosclerotic effects secondary to reduction in LDL transport, inflammation, platelet activation, atheroma formation and thrombosis. This may lead to the development of a more stable diffuse coronary artery disease in women, in contrast to more focal atherosclerotic narrowing typically seen in men [33].

Miscellaneous Effects

High amounts of iron in men and postmenopausal women have been associated with increased atherosclerosis severity and risk of CAD. Interestingly, it has been put forward that monthly iron loss has a protective effect on cardiovascular health [37]. Here, iron might inhibit calcification within atherosclerotic lesions, so calcification could work as a defense mechanism against iron-enhanced atherosclerosis. Furthermore, epigenetic mechanisms play a role in the pathogenesis of inflammatory diseases such as atherosclerosis. DNA methylation, histone modification, and microRNA alterations are the main epigenetic mechanisms which are activated by nutrition, smoking, pollution, stress, and the circadian rhythm. Other mechanisms such as oxidized lipids, cytokines and signalling molecules, hypoxia, and necrotic cells activate macrophages involved in pro- and anti-inflammatory signalling of atherosclerotic plaque [38].

GAPS IN KNOWLEDGE

As homeostasis in the cardiovascular system is achieved differently in both sexes, insights of the underlying mechanisms are vital to improve cardiovascular outcomes in women and men at risk. Differences in anatomy, physiological responses, hormone levels, endothelial function, hemostasis, concentration of mineral elements and epigenetics may have a subtle to profound influence on cardiovascular health. Moreover, effects may change over time due to alterations in other organ systems or external influences (e.g. smoking, sedentary lifestyle) (Figure 1A). One could question which changes in sex hormones, endothelial reactivity, and microvascular function influences the worsening cardiovascular outcomes after menopause. Also, what are the main compensatory physiological mechanisms before menopause? Future research should also focus on better understanding of the effects of testosterone in different clinical situations. Another, interesting topic is the possible role of free iron in acceleration of atherosclerosis after menopause (Figure 1B).

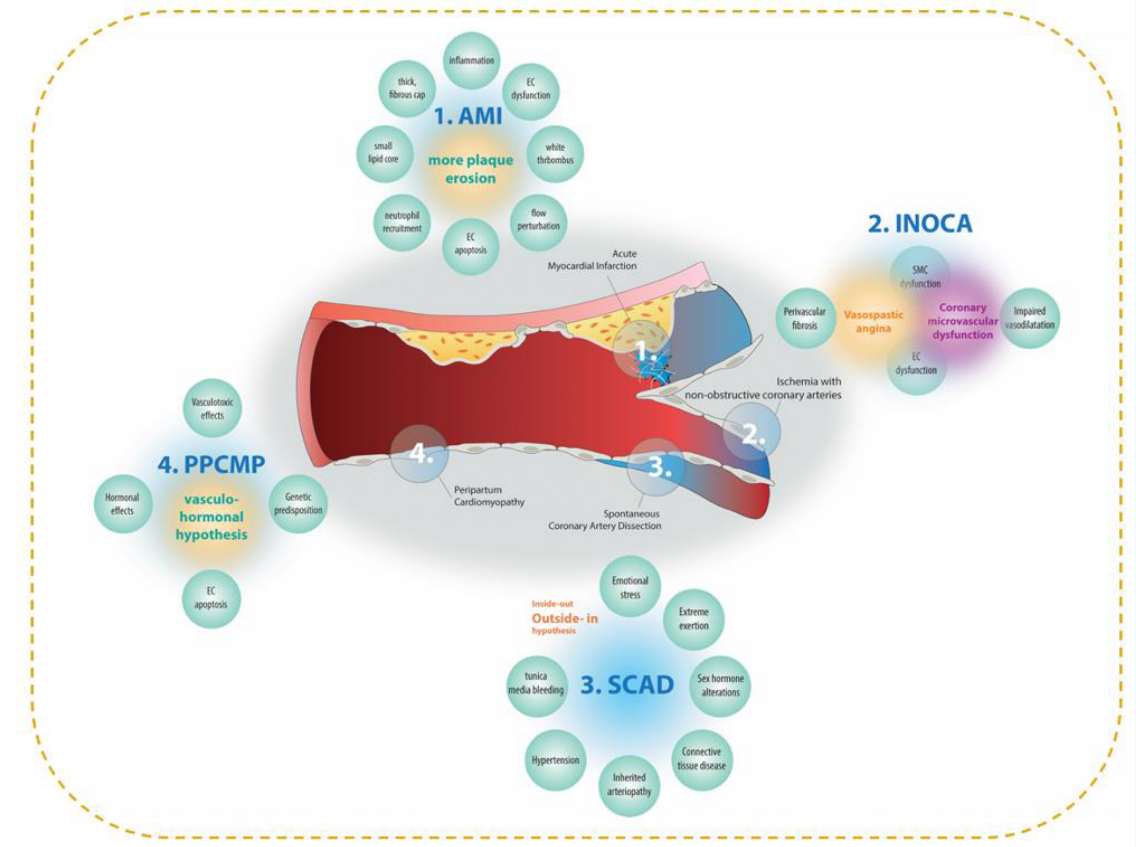

Figure 1A: Key drivers in pathophysiology of main acute cardiovascular diseases in women.
Abbreviations: AMI: Acute Myocardial Infarction; INOCA: Ischemia with Non-Obstructed Coronary Artery Disease; PPCMP: Peripartum Cardiomyopathy; SCAD: Spontaneous Coronary Artery Dissection; EC: Endothelial Cell; SMC: Smooth Muscle Cell.

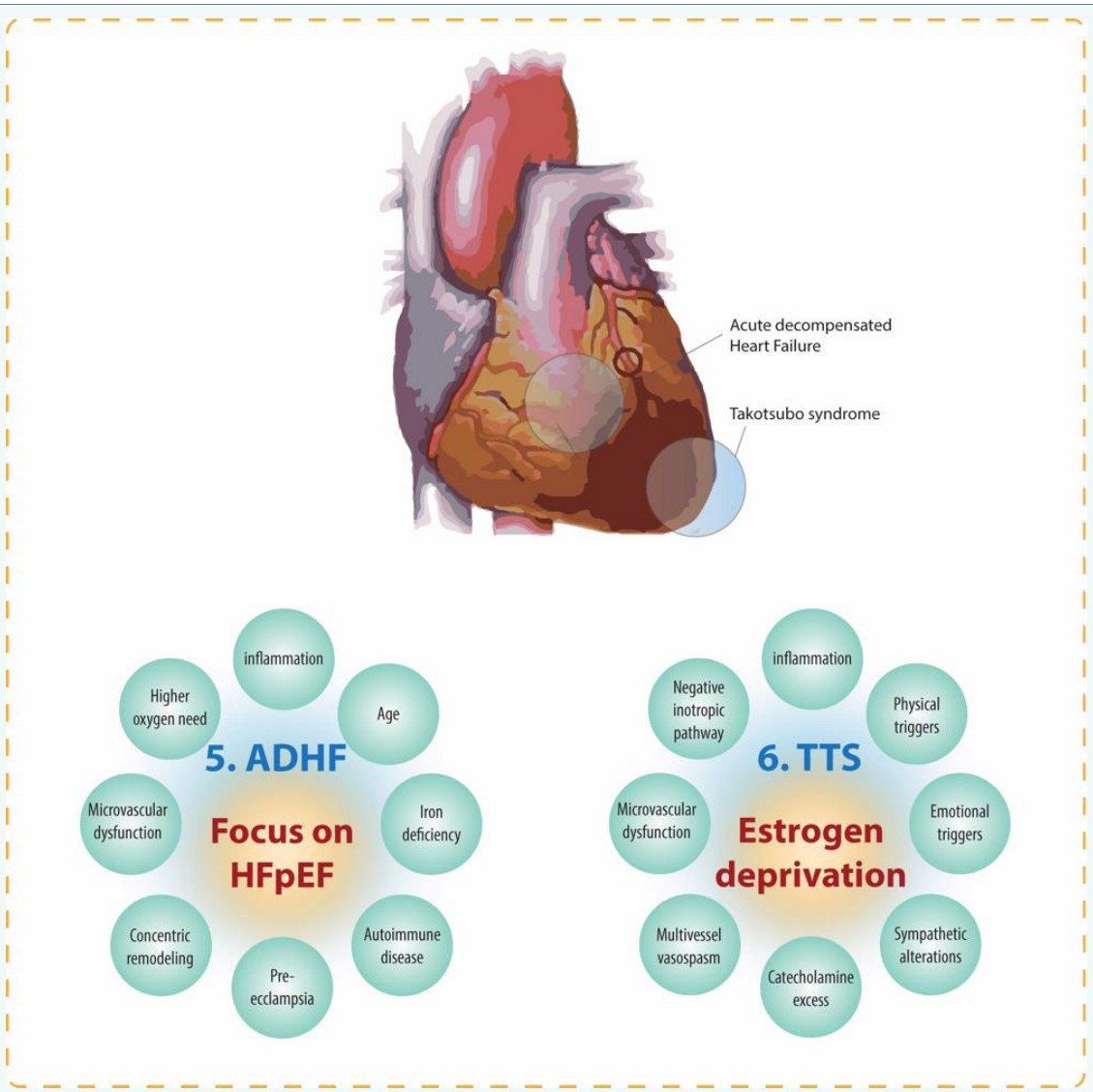

Figure 1B: Key drivers in pathophysiology of main acute cardiovascular diseases in women.
Abbreviations: ADHF: Acute Decompensated Heart Failure; TTS: Takotsubo Syndrome; HFpEF: Heart Failure with Preserved Ejection Fraction.

CONCLUSION

In summary, gender impacts pathophysiology, risk factors, prevalence, clinical symptoms, treatment, and outcomes in acute cardiovascular diseases. As female sex hormones have a protective effect on cardiovascular health, women, in general, are older and have more comorbidities on their presentation with an acute cardiac disease state. Presenting at younger age remains a tremendous risk factor for misdiagnosis and poor outcomes. Furthermore, women are less likely to receive guideline-recommended therapy and face a worse prognosis after an acute event. Also, diagnostic tests and treatment strategies are frequently based on clinical trials with male participants. Non-traditional risk factors are often underestimated, yet play an important role in the pathophysiology. In contrast to macrovascular coronary artery disease in men, women more often have coronary microvascular dysfunction and endothelial inflammation. Further unravelling of biological mechanisms, more enrollment of women in clinical trials, and enhanced awareness of cardiovascular health in women, should improve outcome differences.

REFERENCES

1. Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2019 (GBD 2019). Seattle, WA, USA: Institute for Health Metrics and Evaluation 2020.
2. Vogel B, Acevedo M, Appelman Y, Bairey Merz CN, Chieffo A, Figtree GA, et al. The Lancet women and cardiovascular disease Commission: reducing the global burden by 2030. Lancet. 2021; 397(10292): 2385-2438.
3. Bucholz EM, Strait KM, Dreyer RP, Lindau ST, D'Onofrio G, Geda M, et al. Editor's Choice-Sex differences in young patients with acute myocardial infarction: A VIRGO study analysis. Eur Heart J Acute Cardiovasc Care. 2017; 6(7): 610-622.
4. Maas AH, Appelman YE. Gender differences in coronary heart disease. Neth Heart J. 2010; 18(12): 598-602.

5. Kunadian V, Chieffo A, Camici PG, Berry C, Escaned J, Maas AHEM, et al. An EAPCI Expert Consensus Document on Ischaemia with Non-Obstructive Coronary Arteries in Collaboration with European Society of Cardiology Working Group on Coronary Pathophysiology & Microcirculation Endorsed by Coronary Vasomotor Disorders International Study Group. EuroIntervention. 2021; 16(13): 1049-1069.

6. Mahmoud AN, Elgendy IY. Gender Impact on 30-Day Readmissions after Hospitalization with Acute Myocardial Infarction Complicated by Cardiogenic Shock (from the 2013 to 2014 National Readmissions Database). Am J Cardiol. 2018; 121(5): 523-528.

7. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet. 2004; 364(9438): 937-952.

8. Wenger NK, Arnold A, Bairey Merz CN, Cooper-DeHoff RM, Ferdinand KC, Fleg JL, et al. Hypertension Across a Woman's Life Cycle. J Am Coll Cardiol. 2018; 71(16): 1797-1813.

9. Huxley RR, Woodward M. Cigarette smoking as a risk factor for coronary heart disease in women compared with men: a systematic review and meta-analysis of prospective cohort studies. Lancet. 2011; 378(9799): 1297-1305.

10. Banerjee A, Silver LE, Heneghan C, Welch SJ, Bull LM, Mehta Z, et al. Sex-specific familial clustering of myocardial infarction in patients with acute coronary syndromes. Circ Cardiovasc Genet. 2009; 2(2): 98-105.

11. Stuart JJ, Tanz LJ, Missmer SA, Rimm EB, Spiegelman D, James-Todd TM, et al. Hypertensive Disorders of Pregnancy and Maternal Cardiovascular Disease Risk Factor Development: An Observational Cohort Study. Ann Intern Med. 2018; 169(4): 224-232.

12. Lei L, Mao Y. Hormone treatments in congestive heart failure. J Int Med Res. 2018; 46(6): 2063-2081.

13. Rich-Edwards JW, Mason S, Rexrode K, Spiegelman D, Hibert E, Kawachi I, et al. Physical and sexual abuse in childhood as predictors of early-onset cardiovascular events in women. Circulation. 2012; 126(8): 920-927.

14. Lansky AJ, Ng VG, Maehara A, Weisz G, Lerman A, Mintz GS, et al. Gender and the extent of coronary atherosclerosis, plaque composition, and clinical outcomes in acute coronary syndromes. JACC Cardiovasc Imaging. 2012; 5(3 Suppl): S62-S72.

15. Bairey Merz CN, Pepine CJ, Walsh MN, Fleg JL. Ischemia and No Obstructive Coronary Artery Disease (INOCA): Developing Evidence-Based Therapies and Research Agenda for the Next Decade. Circulation. 2017; 135(11): 1075-1092.

16. Hayes SN, Tweet MS, Adlam D, Kim ESH, Gulati R, Price JE, et al. Spontaneous Coronary Artery Dissection: JACC State-of-the-Art Review. J Am Coll Cardiol. 2020; 76(8): 961-984.

17. Beale AL, Meyer P, Marwick TH, Lam CSP, Kaye DM. Sex Differences in Cardiovascular Pathophysiology: Why Women Are Overrepresented in Heart Failure With Preserved Ejection Fraction. Circulation. 2018; 138(2): 198-205.

18. Scrutinio D, Guida P, Passantino A, Lagioia R, Raimondo R, Venezia M, et al. Female gender and mortality risk in decompensated heart failure. Eur J Intern Med. 2018; 51: 34-40.

19. Davis MB, Arany Z, McNamara DM, Goland S, Elkayam U. Peripartum Cardiomyopathy: JACC State-of-the-Art Review. J Am Coll Cardiol. 2020; 75(2): 207-221.

20. Bello NA, Arany Z. Molecular mechanisms of peripartum cardiomyopathy: A vascular/hormonal hypothesis. Trends Cardiovasc Med. 2015; 25(6): 499-504.

21. Kytö V, Sipilä J, Rautava P. The effects of gender and age on occurrence of clinically suspected myocarditis in adulthood. Heart. 2013; 99(22): 1681-1684.

22. Younis A, Mulla W, Matetzky S, Masalha E, Afel Y, Fardman A, et al. Sex-Based Differences in Characteristics and In-Hospital Outcomes among Patients With Diagnosed Acute Myocarditis. Am J Cardiol. 2020; 125(11): 1694-1699.

23. Akashi YJ, Nef HM, Lyon AR. Epidemiology and pathophysiology of Takotsubo syndrome. Nat Rev Cardiol. 2015; 12(7): 387-397.

24. Lemor A, Ramos-Rodriguez AJ, De La Villa R, Hosseini Dehkordi SH, Vazquez de Lara F, Lee S, et al. Impact of gender on in-hospital outcomes in patients with Takotsubo syndrome: A nationwide analysis from 2006 to 2014. Clin Cardiol. 2019; 42(1): 13-18.

25. Fengler K, Fuernau G, Desch S, Eitel I, Neumann FJ, Olbrich HG, et al. Gender differences in patients with cardiogenic shock complicating myocardial infarction: a substudy of the IABP-SHOCK II-trial. Clin Res Cardiol. 2015; 104(1): 71-78.

26. Wong SC, Sleeper LA, Monrad ES, Menegus MA, Palazzo A, Dzavik V, et al. Absence of gender differences in clinical outcomes in patients with cardiogenic shock complicating acute myocardial infarction. A report from the SHOCK Trial Registry. J Am Coll Cardiol. 2001; 38(5): 1395-1401.

27. Collado-Lledó E, Llaó I, Rivas-Lasarte M, González-Fernández V, Noriega FJ, Hernández-Perez FJ, et al. Clinical picture, management and risk stratification in patients with cardiogenic shock: does gender matter? BMC Cardiovasc Disord. 2020; 20(1): 189.

28. Magnussen C, Bernhardt AM, Ojeda FM, Wagner FM, Gummert J, de By TMMH, et al. Gender differences and outcomes in left ventricular assist device support: The European Registry for Patients with Mechanical Circulatory Support. J Heart Lung Transplant. 2018; 37(1): 61-70.

29. Blewer AL, McGovern SK, Schmicker RH, May S, Morrison LJ, Aufderheide TP, et al. Gender Disparities Among Adult Recipients of Bystander Cardiopulmonary Resuscitation in the Public. Circ Cardiovasc Qual Outcomes. 2018; 11(8): e004710.

30. Winther-Jensen M, Hassager C, Kjaergaard J, Bro-Jeppesen J, Thomsen JH, Lippert FK, et al. Women have a worse prognosis and undergo fewer coronary angiographies after out-of-hospital cardiac arrest than men. Eur Heart J Acute Cardiovasc Care. 2018; 7(5): 414-422.

31. Zhang Q, Qi Z, Liu B, Li C. Predictors of survival and favorable neurological outcome in patients treated with targeted temperature management after cardiac arrest: A systematic review and meta-analysis. Heart Lung. 2018; 47(6): 602-609.

32. Huxley VH. Sex and the cardiovascular system: the intriguing tale of how women and men regulate cardiovascular function differently. Adv Physiol Educ. 2007; 31(1): 17-22.

33. Patel MB, Bui LP, Kirkeeide RL, Gould KL. Imaging Microvascular Dysfunction and Mechanisms for Female-Male Differences in CAD. JACC Cardiovasc Imaging. 2016; 9(4): 465-482.

34. Deroo BJ, Korach KS. Estrogen receptors and human disease. J Clin Invest. 2006; 116(3): 561-570.

35. Kuhar P, Lunder M, Drevensek G. The role of gender and sex hormones in ischemic-reperfusion injury in isolated rat hearts. Eur J Pharmacol. 2007; 561(1-3): 151-159.

36. Taqueti VR, Di Carli MF. Coronary Microvascular Disease Pathogenic Mechanisms and Therapeutic Options: JACC State-of-the-Art Review. J Am Coll Cardiol. 2018; 72(21): 2625-2641.

37. Raman SV, Sharkey-Toppen TP, Tran T, Liu JX, McCarthy B, He X, et al. Iron, inflammation and atherosclerosis risk in men vs. perimenopausal women. Atherosclerosis. 2015; 241(1): 249-254.

38. Kuznetsova T, Prange KHM, Glass CK, de Winther MPJ. Transcriptional and epigenetic regulation of macrophages in atherosclerosis. Nat Rev Cardiol. 2020; 17(4): 216-228.