INVITED REVIEW

Sex differences in acute cardiovascular care: a review and needs assessment

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Abstract	Despite significant progress in the care of patients suffering from cardiovascular disease, there remains a persistent sex disparity in the diagnosis, management, and outcomes of these patients. These sex disparities are seen across the spectrum of cardiovascular care, but, are especially pronounced in acute cardiovascular care. The spectrum of acute cardiovascular care encompasses critically ill or tenuous patients with cardiovascular conditions that require urgent or emergent decision-making and interventions. In this narrative review, the disparities in the clinical course, management, and outcomes of six commonly encountered acute cardiovascular conditions, some with a known sex-predilection will be discussed within the basis of underlying sex differences in physiology, anatomy, and pharmacology with the goal of identifying areas where improvement in clinical approaches are needed.
Keywords	Acute heart failure • Acute myocardial infarction • Cardiac arrest • Cardiogenic shock • Female • Sex differences • Spontaneous coronary artery dissection • Takotsubo cardiomyopathy

1. Introduction

Cardiovascular disease (CVD) is the leading cause of death worldwide with ischaemic heart disease (IHD) and coronary artery disease (CAD) being the most common conditions.[1–3] Despite significant progress in the care of patients suffering from CVD, there remains a persistent sex disparity in the diagnosis, management, and outcomes of these patients.[4–8] Results from the Prospective Urban Rural Epidemiological (PURE) study noted that the smallest difference in cardiovascular death and all-cause mortality in men and women was in high-income counties and the largest difference was reported in low-income countries.[9] However, for countries at all economic levels, women were less likely to have echocardiograms, stress tests, coronary angiograms, or revascularization procedures.[9] The sex disparity

seen across the spectrum of cardiovascular care is especially pronounced in acute cardiovascular care. The spectrum of acute cardiovascular care encompasses critically ill or tenuous patients with cardiovascular conditions that require urgent or emergent decision-making and interventions. The lack of consideration of sex as an essential biological variable in both preclinical and clinical studies has crucial downstream consequences on the development of therapeutic targets in CVD.[10] In this narrative review, the disparities in the clinical course, management, and outcomes of six commonly encountered acute cardiovascular conditions, some with a known sex-predilection will be discussed within the basis of underlying sex differences in physiology, anatomy, and pharmacology with the goal of identifying areas where improvement in clinical approaches is needed. Sex is a critical and easily addressable factor influencing healthcare disparities.

2. Acute cardiovascular care conditions

2.1 Acute myocardial infarction

Historically, CVD was considered to be a male-predominant disease, likely due to extrapolation from early trials that had a high proportion of male participants.[11–13] This extrapolation led to a sex bias in the diagnosis and standard of care provided by physicians.[12,14] Women presenting with acute myocardial infarction (AMI) represent a systematically different cohort with regards to comorbidities, age of onset, and outcomes.[15,16] Women often do not experience the same pattern of chest pain as men and physicians are less likely to attribute their symptoms to CAD.[17,18] Although there are no sex-based difference in the guideline recommendations for the management of ST-segment elevation (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI), the use of angiography, percutaneous coronary intervention (PCI), and prescription of medications for secondary prevention are lower in women than for men resulting in a higher risk of 30-day mortality among women.[6,19–25]

2.1.1 Distinct clinical profile of women

Women with AMI are more likely to present with dissimilar symptoms to men, delay to presentation, and have increased comorbidities and increased incidence of myocardial infarction with non-obstructive coronary arteries (MINOCA).[26] Obstructive atherosclerotic epicardial disease is the most common cause of AMI in both men and women, but other pathophysiological causes such as spontaneous coronary artery dissection (SCAD), Takotsubo cardiomyopathy (TTC), vasospastic angina, and microvascular dysfunction that can lead to AMI are more common in women.[14,27] Women experience fluctuations in their prothrombotic state because of menstrual cycles, pregnancy, use of oral contraceptive pills, menopause, and menopausal hormone treatments.[28,29] The 2019 American Heart Association (AHA) guidelines recommend the need to routinely assess a detailed history of pregnancy complications as a part of routine cardiovascular risk assessment for primary prevention.[30,31] The current European Society of Cardiology–European Atherosclerosis Society Dyslipidemia Guideline (ESC/EAS), however, do not list pregnancy complications such as pre-eclampsia, gestational diabetes, or premature menopause for women as risk enhancers for assessment of cardiovascular risk and primary prevention.[32] Pregnancy induced-hypertension, gestational diabetes, and preeclampsia increase metabolic stress during pregnancy and their occurrence present a long-term risk for development of CVD.[33,34] Systemic inflammatory diseases such as systemic lupus erythematosus and rheumatoid arthritis are more common in women and increase the risk of CHD. However, these differences in the cardiovascular profile of women do not fully explain the higher early mortality and lower long-term survival.[35] Women with AMI tend to have more comorbidities including metabolic syndrome and chronic kidney disease when compared to men.[36] Women presenting with AMI on average were older, more often had hypertension and diabetes but were less likely to be smokers. Women with AMI often have a lower prevalence of hypercholesterolaemia and peripheral vascular disease compared to men.[15,16,37,38] Women more frequently have NSTEMI and less frequently STEMI.[35]

2.1.2 Cardiovascular effects of oestrogen

Oestrogen improves vascular function, reduces atherosclerosis, ischaemia–reperfusion injury and impacts cardiovascular health by direct effects on the vascular cells and cardiomyocytes, as well as, indirect effects mediated systemically through altered autonomic and renal function.[39] In addition to oestrogen regulating gene transcription by binding to nuclear receptors (Erα, Erβ), oestrogen also binds to receptors located at the plasma membrane (G-protein-coupled oestrogen receptor, GPER) that activate membrane signalling cascades (Figure 1).[40] Oestrogen affects ion channels that modulate cardiac repolarization, intra-cellular calcium regulation that affects contractility, and reactive oxygen species that define oxidative stress.[39] Several preclinical studies provide evidence that females develop less cardiac hypertrophy and less ischaemia–reperfusion injury than males.[41,42] In non-human primates, oestrogen reduced formation of atherosclerotic plaque when administered soon after ovariectomy.[43] The mechanisms involve, in part, regulation of endothelium-derived nitric oxide through activation of Erα.[39,44,45] Other preclinical studies indicate that oestrogen also regulates angiotensin-converting enzyme, angiotensin receptors, and β-adrenergic receptors, thus, these regulatory pathways have important implications for sex differences in development and treatment for hypertension in women.[46–48] Oral forms of oestrogenic treatments, specifically conjugated equine oestrogen and micronized 17β oestradiol, reduce hepatic production of low-density lipoproteins, and, thus, reduce the lipid contribute to the development of atherosclerosis.[49–52] Large clinical trials to investigate whether the use of menopausal hormone treatments reduce cardiovascular risk have provided useful information. First, oral conjugated equine oestrogen did not provide secondary prevention for CVD [Heart and Estrogen/Progestin Replacement Study (HERS)].[53–55] Second, oral conjugated equine oestrogen reduced development of coronary calcification and carotid artery intima-medial thickening when treatment began within 5 years of menopause.[52,56] For women who underwent bilateral oophorectomy prior to the age of natural menopause, oestrogen treatments (oral and transdermal) reduced the risk of cardiovascular morality.[57,58]

2.1.3 Diagnostic and treatment disparities and outcomes

Despite advances in cardiovascular care, there exists a significant sex disparity in management and outcomes of AMI.[59,60] These sex disparities reflect the differences in age, comorbidities, and presentation that lead to delayed diagnosis and treatment. However, even after adjusting for demographics and cardiovascular risk profile women were noted to have an excess mortality suggesting that underlying basic physiological parameters that differ between female and males are not considered in diagnostic and treatment guidelines.[15,61] Several studies including the SWEDHEART (Swedish Web System for Enhancement and Development of Evidence Based Care in Heart Disease Evaluated According to Recommended Therapies) registry, CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the American College of Cardiology/American Heart Association Guidelines) quality improvement registry and AHA-Get with the Guidelines registry noted that women presenting with AMI were less likely to receive reperfusion and revascularization, a trend that was re-demonstrated by Wilkinson et al.[15,16,35,62] in their study of AMI in England and Wales. Wilkinson et al.[35] noted that provision of coronary angiography within 72 h for NSTEMI showed the highest sex discrepancy compared to other quality measures in AMI. AHA Get with the Guidelines registry noted a lower achievement of the guideline recommended 90-min door to balloon/door to PCI time among women <65 years of age compared to men of the same age group.[62] Evidence from the ARIC[63] community surveillance study,
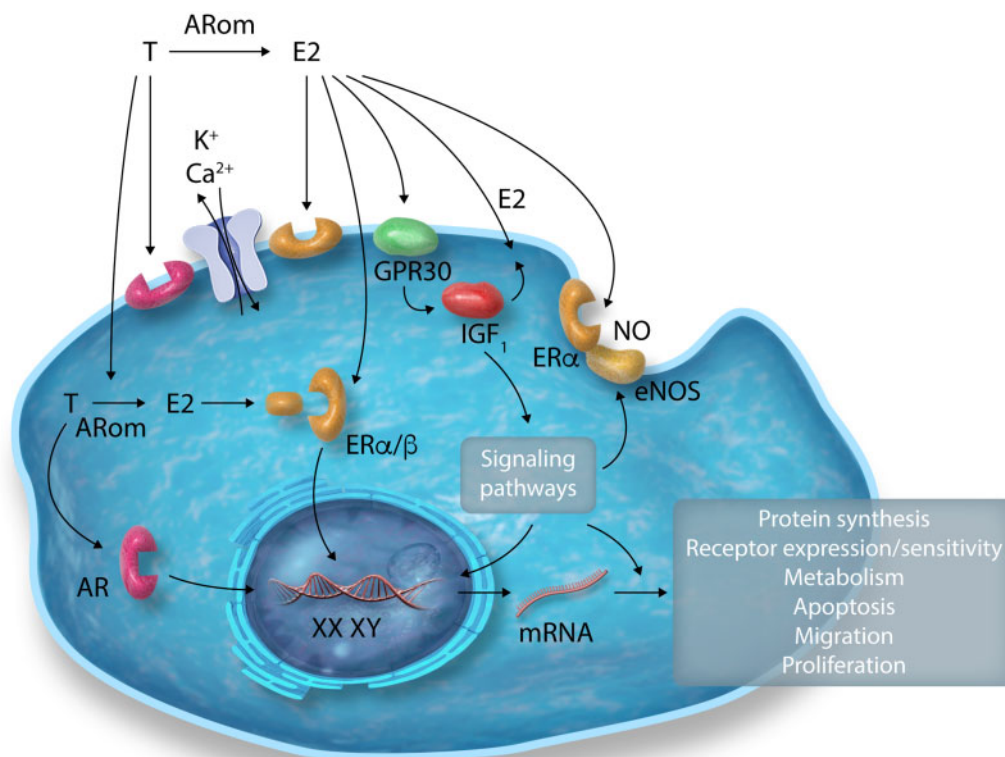
Figure 1 Summary schematic of potential mechanisms by which sex steroids affect cellular functions. At the genetic level, the basic difference between females and males are the presence of XX chromosomes in females and XY in males. The genes on these chromosomes direct the development of reproductive organs, affect gene transcription of functions related other physiological systems and can alter expression of genes on some autosomes. Sex steroids are produced from the gonads. Testosterone is aromatized to 17β oestradiol in males and females but circulating levels of testosterone are greater in males than females, while circulating levels of 17β oestradiol are greater in reproductively competent females than males. These sex steroids can diffuse into the cell to bind to cellular receptors which migrate to the nucleus to affect gene transcription, as well, as bind to surface receptors that affect ion channel function and initiate a cascade of signalling pathways that direct cell function or indirectly affect gene transcription. ARom: aromatase; E2: 17β oestradiol; eNOS: endothelium-derived nitric oxide; ERα: Oestrogen receptor alpha; ERα/β: either oestrogen receptor alpha or beta; GPR30: G-coupled protein receptor 30; IGF1: insulin-like growth factor 1; mRNA: messenger ribonucleic acid; NO: nitric oxide.

SWEADHEART registry, and CRUSADE registry demonstrated that women were less likely to be prescribed guideline indicated pharmacological therapies including aspirin, dual antiplatelet therapy, lipid-lowering medications, beta-blockers, and angiotensin-converting enzyme inhibitors (ACE-Is)/angiotensin receptor blockers (ARB).[15,16,35,62] Risk stratification is used to determine the need and timing for coronary angiography in NSTEMI. There is a risk of physicians underestimating the cardiovascular risk in women.[64] Women have unique risk factors for CVD such as poly-cystic ovarian disease, preeclampsia, preterm delivery, gestational diabetes mellitus, pregnancy loss, and early menopause.[31,65] Women should be considered as likely as men to have AMI and should receive the same standard of care as an age-adjusted male would in this setting. In a study using data from the Myocardial Ischemia National Audit Project (MINAP), implementing the provision of guideline-indicated care was noted to reduce excess mortality and potentially avoidable deaths.[66]

It is conceivable that the lower adherence to guideline therapy could partly be attributed to a higher incidence of MINOCA in women.[67,68] Patients with MINOCA have fewer conventional risk factors when compared with AMI patients and typically do not have plaque erosion or coronary thrombosis.[69–71] Despite recent data suggesting beneficial effects of statins and ACEI/ARB on long-term outcomes, these medications are typically under prescribed for women with MINOCA.[72]

2.1.4 Conclusion

The number of studies reporting sex-differences in risk factors and outcomes from AMI has grown in recent years. However, women's cardiovascular health and outcomes has yet to be optimized. In light of the results of the various studies, it is likely that sex differences in AMI mortality are potentially modifiable through improved concordance with guideline-indicated care. In addition, improved outcomes for women with AMI will result from better understanding of physiological factors influencing development and risk for disease, as well as elimination of bias in guidelines based on male models of disease. Inclusion of pregnancy-associated complications including preeclampsia, preterm delivery, and gestational diabetes as risk enhancers in the assessment of atherosclerotic CVD should be standard practice. Risk stratification scores

used in the emergency department and in-hospital to assess the need for angiography in patients presenting with NSTEMI should include female-specific risk factors. The first step in minimizing negative effects of bias is increasing awareness of implicit stereotypes and being motivated to counteract them to ensure that bias does not influence behaviour.[73,74] Therefore, efforts to ensure equity of care for women should be focused on improving the evidence base by including more women participants in future clinical trials and providing effective sex-specific guideline recommendations for management of AMI in women with a discrete focus on sex-specific risk factors and presentation.[37,73]

2.2 Cardiogenic shock

Cardiogenic shock (CS) occurs in about 5–10% of patients presenting with AMI and is more common in patients with STEMI than NSTEMI.[75,76] From nearly 100% in-hospital mortality, the use of emergent revascularization has decreased the overall in-hospital mortality to 30–40% in the contemporary era.[77,78] Among patients presenting with AMI, CS has been reported to occur more frequently in women when compared to men.[79–83]

In a series of studies that spanned data collected from 1995 to 2010, women presenting with STEMI had higher rates of acute heart failure, left ventricular dysfunction, and CS even after adjusting for age, type of MI and baseline characteristics.[79,82,84–87] In addition to the presence of obstructive CAD, female susceptibility to endothelial dysfunction, and microvascular disease could inherently, from a biological standpoint, increase the risk of females developing more frequent complications from AMI, including a higher incidence of CS.[88] Women with AMI often have atypical presentation and a delay in seeking medical care for their symptoms resulting in an increase in total ischaemic time with an associated risk for the development of prehospital CS.[15,26,61] Furthermore, women with AMI were less likely to receive reperfusion and revascularization and less frequently received guideline recommended pharmacological therapies at discharge.[35,37,62]

2.2.1 Patient characteristics

Both randomized controlled trials (RCT) and real-world data from registries and hospitals have consistently demonstrated women with CS tend to be older, with a higher prevalence of hypertension, diabetes, and other comorbidities.[4,79,89–97] While there are limited data on the effects of reproductive age on CS, the loss of oestrogen is likely to increase inflammatory processes associated with development of microvascular damage and inflammation as time progresses past menopause.[98]

2.2.2 In-hospital management and outcomes

In both female and male patients presenting with AMI-CS, the majority of infarcts involved the anterior ventricular wall. Coronary angiography, PCI, and surgical revascularization rates were similar in both men and women.[89] Haemodynamics did not differ by sex except for cardiac index measured on ionotropic support which was significantly lower in women.[89] In a study assessing sex differences in 173, 473 admissions of mechanical circulatory support (MCS) in AMI-CS using the NIS database, after adjusting for baseline and hospital characteristics, there was no sex disparity in the use of MCS or the timing of MCS placement.[99]

The lack of sex differences in treatment and in the 1, 6-months and 1-year outcomes are consistent in several contemporary studies.[87,89,90,94,95] There are only few contemporary observational studies that demonstrated female sex as an independent predictor of mortality. In a Dutch multicentre registry of 227 CS patients, Velders *et al.*[100] reported female sex as an independent effect modifier causing higher 1-year mortality after STEMI-CS. Studies analysing sex disparities in AMI-CS using the NIS database noted that women had a higher in-hospital mortality compared to men on multivariate analysis which extended to all racial and ethnic groups.[4,96,97,99] Despite compelling differences in the management and outcomes of AMI, in the setting of AMI-CS there seems to be an absence of sex disparities in treatment and outcome.[15,37,89,90,99] It is likely that the acuity in patients with CS influences decisions regarding management and long-term therapy.

2.2.3 Conclusion

Among patients with AMI, CS occurs more frequently in women when compared to men. This difference might reflect a higher cardiovascular risk profile and a prehospital delay for women than men.[90,95] Several studies have demonstrated a longer pre-hospital delay in female patients with AMI with and without CS.[90,94,100] Prompt revascularization has shown to improve survival and incidence of CS in patients with AMI.[101]

2.3 Cardiac arrest (CA)

Out-of-hospital CA (OHCA) is a major public health concern and there are approximately 420 000 cases in the United States and 275 000 cases in Europe annually.[102–104] Prior studies suggest that sex differences exist among CA victims with regards to witnessed arrests, resuscitation efforts, shockable rhythms, PCIs, survival and neurological outcomes.[105–107] Despite the Academic Emergency Medicine Consensus Conference Cardiovascular Resuscitation Working Group identifying sex- and gender-specific OHCA research as one of the research priorities in emergency medicine, there are limited studies.[108] Patients with OHCA depend on lay rescuers to recognize the patients arrest, call for help, and initiate cardiopulmonary resuscitation (CPR) and early defibrillation.[109,110]

2.3.1 Sex disparities in recipients of bystander CPR in OHCA

Recognition of CA and initiation of CPR are the most important links in the chain of survival for CA resuscitation.[110,111] For every minute delay in CPR in a person with OHCA, the chance of survival decreases by 7–10%.[112] Bystander CPR and automated external defibrillator (AED) use has a synergistic positive effect on outcome and when used together can more than double the rate of survival from OHCA.[113] Despite the robust evidence in favour of bystander CPR and the systematic efforts at promoting this by professional organizations, the number of OHCA patients who receive bystander CPR remains low at 10–65%.[114–116] Several studies have noted a disparity in bystander CPR between males and females.[117–119] Males were more likely to receive bystander CPR than females.[117–120] This disparity was particularly significant in CA occurring in the public environment, but it was not found in the home environment.[117] Understanding barriers and facilitators to provision of bystander CPR globally can help to further contextualize the differences that prevail when discussing why women receive less CPR.[121] Modesty and social norms regarding exposing/touching a woman's chest, bias created by educational programs, and under recognition of cardiac disease in women all contribute to lower bystander CPR in women.[122–126] In the home environment, responders may have increase motivation and less fear of legal implications of their actions.[117] In a national survey on public perceptions on why women receive lower bystander CPR,[121] three major themes emerged: (i) sexualization of women's bodies and fear of accusations regarding sexual harassment, (ii) women being weak and frail

and, therefore, prone to injury, and (iii) misperceptions about women in acute medical distress.[121] Several male respondents in the study expressed that their actions would be misconstrued as inappropriate or that it might have legal ramifications regarding accusations of sexual assault.[121] An elimination of bias in training by increasing the use of realistic female patient simulators in CPR training may alleviate some of this reluctance and help overcome the social stigma associated regarding the physical attributes of patient sex and thus improve bystander CPR.[122] In a study in Austria, it was found that women were less willing to provide bystander CPR or apply an AED to a person who had collapsed from CA.[127] Increase in encouragement, empowerment, and education of women to provide bystander CPR might help to mitigate this disparity.[121]

2.3.2 Baseline characteristics and prehospital care

Female patients with OHCA tend to be older with more comorbidities, have a higher probability of being in non-public locations, less often have witnessed arrests, more often have a non-shockable rhythm, and a lower probability of receiving resuscitation efforts during prehospital care than men.[119,128,129] The interval between collapse and arrival of the ambulance was similar in men and women.[130] The prevalence of non-atherosclerotic ischaemic as the cause of CA (28.3% vs. 24.3%) could be one of the reasons why women present more often with non-shockable rhythms.[128,131–133]

A higher early mortality in men is accentuated by a higher predilection for smoking and hyperlipidaemia leading to a higher risk for CAD and poorer outcomes after CA.[118,134] Effects of testosterone on the cardiovascular system are controversial. Much of the literature suggests that low testosterone levels are associated with increased CVD.[135,136] Deleterious effects of testosterone have been reported on vasoconstriction, on accelerating inflammation and the death cascade.[134,137–140] These contradictory effects suggests that testosterone may simultaneously benefit and harm the cardiovascular system by different pathways.[138] Although testosterone may also bind to surface and nuclear receptors, the aromatization of testosterone to oestrogen may counter balance the direct effects of testosterone on nuclear and membrane receptor binding. Additional studies are required to better understand the complex effects of testosterone on the cardiovascular system.

2.3.3 Childbearing age and effect of oestrogen

Women have increased chest wall compliance compared to men making chest compressions and resuscitation efforts easier and more effective.[118] Data from registry and prospective studies suggest that females of childbearing age are more likely to survive a CA event, despite being more likely to have arrest characteristics that are associated with poor outcomes (unwitnessed arrest, private location, non-shockable rhythm).[141–143] Preclinical studies showed that neurons and cardiac cells derived from female and male animals react differently to ischaemia and hypoxia.[144,145] This difference may reflect anti-inflammatory and antioxidant effects of oestrogen that contribute to reduced ischaemia–reperfusion-induced myocardial injuries in mice, cats and guinea pigs.[146–148] Furthermore, oestrogen also stabilizes the mitochondrial membrane, preventing influx of calcium and potassium into the cell that alleviates the death cascade initiated by CA.[149] In preclinical studies, oestrogen treatments reduced global ischaemia-induced neuronal death and cognitive deficits following cardiac arrest.[129,150,151]

2.3.4 In-hospital management

2.3.4.1 Coronary angiography and percutaneous coronary intervention. Immediate coronary angiography and PCI improve outcomes in CA with STEMI.[152,153] Thus, current guidelines from both the American College of Cardiology and European Society of Cardiology recommend emergent coronary angiography for patients with OHCA with ST-segment elevation or suspected AMI, as well, as for patients with haemodynamic or electric instability including shock and recurrent ventricular arrhythmias.[154,155] In spite of these recommendations, several studies continue to report and confirm that women undergo fewer coronary angiography procedures and PCI in post-resuscitation care (28% vs. 50% $P < 0.001$), PCI (17% vs. 30% $P < 0.001$) as well as coronary artery bypass grafting (0.4% vs. 30% $P < 0.001$).[128,152,156,157] However, revascularization in women is associated with ∼2-fold higher bleeding risk, which might influence the decision towards a lower use of angiography and PCI when the aetiology of CA is not known.[128]

2.3.4.2 Targeted temperature management. There is a wide variability in use of TTM though the rates of implementation of TTM have been steadily increasing.[128,158–160] Two RCTs demonstrated clinical benefit of TTM in patients with CA with shockable rhythms.[161–163] The 2015 Guidelines for Advanced Cardiac Life Support recommends TTM for all unresponsive adult post-cardiac arrest patients.[164] The ACC/AHA guidelines give a Class I recommendation for TTM in successfully resuscitated patients with VT/VF and a Class II b for other types of rhythms.[165] There is a paucity of literature that specifically addresses the question of sex disparities in application of TTM.[108] In a national database study in the USA, TTM was used less often in females in both VF/VT and non-shockable rhythms, but not in pulseless electrical activity (PEA)/asystole arrests.[128] A study from Columbia University Medical Center between September 2015 and July 2017 noted that only 37.5% of patients considered for TTM were female.[166] Winther-Jensen *et al.*[156] demonstrated that TTM was less frequently used in women (47% vs. 61% $P < 0.01$). It is concerning to see sex-discrepancies in the use of TTM. There needs to be increased awareness and earnest efforts by the medical community to close this sex-based gap in order to improve survival and neurological recovery in women post-CA.

2.3.5 Outcomes

2.3.5.1 Mortality. The association of sex with mortality from OHCA is controversial. Some studies report improved survival in females,[106,141,143,167] while others noted a lower survival in males.[118,120] A Korean study of 20 675 OHCA patients reported no sex-disparity in survival.[157] A Danish registry study and a registry from Japan noted that females had a lower unadjusted odds of survival, however, on multivariate analysis after adjusting for baseline characteristics and treatment, females were associated with increased odds of survival.[106,143] The greater survival on multivariate analysis is best explained by a difference in baseline characteristics as noted in the studies. Specifically, women were older, received less frequent bystander CPR and less often had an OHCA outside the home, had lower rates of coronary angiography, PCI and TTM, therefore, mitigating the signal of higher mortality in women.[167] Reports of sex-disparities in survival-to-hospital-admission in patients with OHCA have also been conflicting with demonstration of higher survival rates in women in a Swedish study and no sex-specific variation in survival in a Canadian study.[118,168] It is conceivable that the conflicting results on survival could be due to differences in demographics, risk factors, prehospital care, and healthcare systems in various countries.

Efforts to lower the incidence and mortality of CA in women needs to begin right from the level of primary preventive care that should focus at aggressively managing and reducing cardiovascular risk factors and comorbidities. Early diagnosis and timely revascularization with adherence to guideline-recommended medications for secondary prevention might help lower the incidence of CA in women. Women presenting with OHCA are older and have factors that have been associated with worse outcomes after CA such as lower rate of BCPR and lower use of AED, angiography and TTM. Increasing awareness of CVD in women, prehospital care and a strict adherence to guideline-recommended in-hospital management could mitigate the sex disparities in mortality and improve survival in women with CA.

2.3.5.2 Neurological outcomes. Clinical and demographic factors underlying the sex disparities are likely to be complex and the pre-hospital and clinical factors predisposing to sex disparities in neurological outcomes are unknown.[128] The influence of sex of the patient on response to TTM and neurological outcome has not been consistent in different clinical studies.[169] The mechanisms behind this can only be speculated on with likely reasons being males and females having differential level of neuronal injury following CPR, effect of sex hormones on ischaemic–reperfusion injury and the different ages of male and female patients included in the studies.[170,171] Kim et al.,[128] in a study from Korea, reported overall higher mortality in females and lower odds of having good neurological outcome. The lower mortality in men noted in that study is contradictory to most of the other studies which noted female sex to be associated with better survival. Studies have shown racial, ethnic, and regional disparities in OHCA.[172–174] It is conceivable that the conflicting results noted by Kim et al. could be due to racial and regional disparities, or to differences in the underlying risk of OHCA, local approach to organized emergency response, and post-resuscitation care. In a meta-analysis, Zhang et al.[169] demonstrated that male sex was associated with a higher rate of good neurological outcome, but it was not associated with a higher rate of survivors. A multicentre registry study demonstrated that sex did not influence the neurological outcomes of TTM-treated OHCA patients.[175]

2.3.6 Conclusion

There is an urgent need to identify causes and barriers to eliminate the sex disparities in post-CA care. The lay public associates CA with male sex, thereby risking a delay (or total absence) of CA recognition in females in situations of a collapse. Such lack of knowledge should be addressed in CPR training. Public health measures aimed at increasing bystander CPR for women and early referral of eligible women for internal defibrillator placement should be undertaken.[117,118] The absence of realistic female patient simulators may bias training for and research into patient care and increased use of female simulators should be implemented.[122] Aggressive post-resuscitation care, including emergent coronary angiography, and TTM should be emphasized upon irrespective of sex and is likely to result in favourable outcomes.

2.4 Acute decompensated heart failure

Acute decompensated heart failure (ADHF) is the most common presentation of heart failure (HF) and bodes a poor prognosis. Registries and national statistics show that slightly more than 50% of hospitalized HF patients are women. Of the 2 two broad phenotypes, women account for approximately 40% of heart failure with reduced ejection fraction (HFrEF) and 60% of patients with HF with preserved ejection fraction.[176,177] Even with improving trends there still is a low rate of sex-specific reporting in pre-clinical and clinical cardiovascular studies.[10,178] There continues to be substantial under-representation of women in most major HF RCTs likely causing reporting of underpowered sex–drug interaction.[179,180] This under-representation combined with the absence of sex-specific reporting has significant ramifications on the development, implementation, and outcomes of definitive HF therapies for women.[179]

2.4.1 Risk factors

The patient's biological sex is associated with significant differences in phenotype, aetiology, age of initial diagnosis, clinical presentations, management, and prognosis.[177,179,181] Compared with men, women hospitalized with acute HFpEF are older, are more likely to be obese, and to have hypertension disease, depression, and chronic kidney. Furthermore, women are less likely to have CAD (which is more frequently associated with HFrEF),[177,179,182] atrial fibrillation, chronic obstructive pulmonary disease, or smoking; and to have a similar prevalence of diabetes mellitus.[1,183,184] Diabetes is a strong mortality predictor in HF and confers worse outcomes in women compared to men.[185,186] Even though men and women being hospitalized for ADHF differ substantially in their baseline characteristics, they share similar in-hospital mortality[177,182,187] and length of stay, as well as comparable short-term outcomes post-discharge irrespective of the type of LV dysfunction.[188,189]

2.4.2 Anatomical and pathophysiological differences

Women have smaller ventricular chambers, higher LV elastance, and higher ejection fraction compared to age-matched men.[190,191] Ageing women have relatively attenuated decline in cardiomyocyte number and mass, as well as a lower tendency towards cardiomyocyte hypertrophy and eccentric LV remodelling compared to men.[191,192] Women are at a higher risk of developing HFpEF as cardiac ageing predisposes women more than men to develop LV concentric remodelling, LVDD and stiffening.[191–193] Women show a greater decline in arterial ventricular coupling ratio reserve with age[194] due to worsening arterial stiffness[195] and a higher LV diastolic elastance at any given age compared to men. Interestingly, in addition to fundamental structural differences in the normal heart, women with HFpEF show a greater degree of LV dysfunction not only at rest but also with exercise as evidenced by a lower e′ (early diastolic mitral annulus velocity), higher E/e′ ratio (E, trans-mitral early peak velocity) which is a surrogate for diastolic filling pressures, and a higher Ed (end-diastolic elastance) during exercise on echocardiography.[196] Additionally, lower systemic and vascular compliance and impaired oxygen utilization attributes to worse exercise intolerance in women with HFpEF as compared to men.[196]

On a cellular level, sex differences exist due to the combined genetic effects of the sex chromosomes and in steroid hormones. Oestrogen, through production of endothelium-derived nitric oxide promotes vasodilatation, the hormone also increases expression of heat shock proteins, acts as an antioxidant, and alters inflammation through cytokines associated with immune function.[191,192,197,198] Depletion of oestrogen, especially after menopause, contributes to the development of HFpEF in women through changes in mitochondrial function, which leads to increase in oxidative species and myocardial inflammation, myocardial fibrosis, and decreased calcium reuptake, which leads to prolonged relaxation of cardiomyocytes characterizing ventricular dysfunction.[199] Another mechanism predisposing women to HFpEF postulates the role of activated renin–angiotensin–aldosterone system as the decline in

oestrogen with menopause would increase reactive oxygen and collagen synthesis leading to ventricular stiffening and diastolic dysfunction.[197] Preclinical studies indicate that oestrogen regulates mitochondrial function and biogenesis by activating molecules such as mitochondrial transcription factor to activate gene expression.[199] LVDD appears to be closely dependent of mitochondrial energy production as it is observed that in ovariectomized mice, oestrogen replacement decreases E/A ratio (signifying restrictive LV diastolic filling pattern) and prolonged isovolumic relaxation time both of which are significantly correlated with mitochondrial ATP levels.[199] Sexually dimorphic gene expression has recently been identified in human hearts showing differential expression of mRNA for cytokines which promote proinflammatory signalling, myocardial hypertrophy, and mitochondrial dysfunction.[200]

Additionally, many genes encode inflammatory responses in cardiac tissue leading to enhanced inflammatory pathways are up-regulated in the female myocardium.[191] Furthermore, telomere shortening is not age-dependent phenomenon in healthy humans but it occurs regardless of chronological age in patients with HF, suggesting that cardiomyocyte cellular ageing is exacerbated in HF. Telomere length in the presence of the disease is better preserved in females than males, an effect that suggests that the telomere length required for the onset of HF may occur later in life in women than in men.[201]

2.4.3 Biomarkers

B-type natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP) is used clinically as a diagnostic and prognostic maker of the severity of HF. Prognostic value NT-proBNP by determining in-hospital mortality and HF readmission in all HF phenotypes is well known,[202,203] but sex differences in its prognostic value is still in question. Baseline levels of NT-proBNP levels are higher in women than men indicating a need for age and sex-specific levels in clinical guidelines.[204,205] Though some studies show that, NT-pro BNP levels were a more valuable marker of predicting long-term mortality and HF readmission in men,[203] other studies indicated that higher BNP levels were a more powerful predictor of death in women.[206] Nonetheless, there is no significant sex difference in the ability of BNP in predicting in hospital mortality.[207] Because of these differences, interpretation of NT-proBNP levels should be combined with other biomarkers, i.e. highly sensitive cardiac troponin-T, to provide a better estimation of prognosis than either biomarker alone.[208]

2.4.4 Women and heart failure with preserved and reduced ejection fraction

Women account for more than two-thirds of patient with HFpEF. The reason because of which women are overrepresented in this phenotype of HF is complex and multifold. First, as mentioned in Section 2.4.2, there are fundamental anatomical and pathophysiological differences between the two sexes which disproportionately predisposes women to develop HFpEF. After menopause higher free/total testosterone levels and higher testosterone/oestradiol ratio secondary to lower levels sex hormone binding globulin is associated with elevated LV mass in both men and women.[209] Nonetheless, not only does this androgenic pattern cause a higher mass to volume ratio (concentric hypertrophy) but also it increases HF events in postmenopausal women.[209,210] Since hypertension is more common in women with HFpEF and the fact that women respond differently to pressure overload with a more prominent remodelling of concentric nature than eccentric,[191] cardiac ageing predisposes women more than men to develop LVDD and stiffening which are

hallmarks HFpEF.[191,193,199] Along with the differences in LV, women also have lower right ventricular mass, smaller volumes and overall better right ventricular systolic function compared to men.[211] Oestrogen promotes pulmonary vascular remodelling and vasoconstriction which is one of the mechanisms for the development of pulmonary hypertension which a key pathophysiologic feature of HFpEF.[191,211] Paradoxically, even though there is markedly higher prevalence of pulmonary hypertension in women, in both preclinical and clinical studies oestrogen treatments reduced right ventricular failure in women with pulmonary hypertension.[211]

Second, myocardial metabolic response to obesity is modulated by sex. Female sex independently predicts greater fatty acid metabolism and relates to inefficiency in fatty acid metabolism.[212] Patients with 'obese HFpEF' exhibit increased plasma volume, more concentric LV hypertrophy, and greater right ventricular dilatation. Furthermore, higher global prevalence of obesity in women, obesity and metabolic syndrome contribute to development of HFpEF in women compared to men.[213]

Third, the higher prevalence of autoimmune disorders and an overall stronger immune response compared to inflammation in women may contribute to the progression of HFpEF.[191] Unlike men who have a higher incidence of obstructive CAD, women generally tend to have microvascular and endothelial dysfunction and non-obstructive CAD causing microvascular dysfunction leading to myocardial hypertrophy and fibrosis.[214] It is also thought that various comorbidities common to HFpEF (e.g. obesity, diabetes, chronic kidney disease) which are predominantly seen in women, lead to systemic inflammation and coronary endothelial inflammation and coronary microvascular dysfunction which eventually leads to LV diastolic stiffening and HFpEF.[214,215] Fifth, anaemia (with a lower blood haemoglobin cut off for females) is a strong prognostic factor in patients with heart failure. It is strongly predictive of all-cause mortality and cardiovascular death in women with HFpEF admitted for ADHF.[216] Finally, other special risk factors unique to women like pregnancy and preeclampsia may predispose to LV remodelling and LVDD and thus a 4-fold increase in future HF and hospitalizations.[217]

There is an important overlap between atrial fibrillation and heart failure. Though atrial fibrillation can be seen in patients with HFrEF, it is seen predominantly in patients with HFpEF[218] often leading to adverse cardiovascular outcomes in patients with HFpEF.[219] Atrial fibrillation is not only associated with a greater risk of hospitalization in women compared with men with HFpEF[219,220] but it is also associated with worse RV dysfunction in patients with HfpEF,[221] which may be contributing to the overall poor prognosis especially in women hospitalized for ADHF and atrial fibrillation.[183]

Compared to women, men have a higher lifetime risk of overall HF and HFrEF with a similar lifetime risk of HFpEF.[222] Though IHD is the most common cause of HFrEF in men, non-ischaemic cardiomyopathy, hypertension, and diabetes are major underlying comorbidities predisposing women to HFrEF. Advanced New York Heart Association symptoms and ischaemic aetiology confers worse outcome in women with ADHF due to HfrEF.[223] Other forms of non-ischaemic cardiomyopathy presenting as HFrEF are stress cardiomyopathy (Takotsubo cardiomyopathy) and peripartum cardiomyopathy.

Peripartum cardiomyopathy is a possibly fatal form of cardiomyopathy unique to females characterized by impaired systolic function and presents as ADHF in the last month of pregnancy or within 5 months postpartum with no pre-existing cardiac disease or identifiable cause.[178] Aetiology remains unknown, but potential causes include myocarditis, abnormal immune response to pregnancy, increased myocyte apoptosis, genetic predisposition, and proteolytic cleavage of prolactin during

oxidative stress. Risk factors include advanced maternal age, pre-eclampsia, and multiple gestations.[178,224] It is estimated that approximately half of peripartum cardiomyopathy patients recover normal systolic function within 6 months and another 20% deteriorate/die/require heart transplant.[178] There are limited data on the risk with subsequent pregnancies.

2.4.5 Management

Large RCTs have shown that ACEIs reduce mortality and morbidity in HF patients regardless of degree of symptoms.[179] Based on *post hoc* analyses of retrospective studies, β-blockers, aldosterone antagonists, angiotensin receptor blockers (ARBs), and ivabradine, a cardiotonic agent from a class of drugs that inhibits hyperpolarization-activated cyclic nucleotide-gated ion channels, seem beneficial in women with HFrEF.[225] The combination of hydralazine and isosorbide was studied in black women with HFrEF and found to reduce mortality, reduce hospitalizations, and improve quality of life.[225] Valsartan/sacubitril is a composite drug consisting of an ARB and a neprilysin inhibitor and recommended in replacement of ACEI or an ARB in HFrEF patients who remain symptomatic despite standard drug therapy. In spite of the lack of a sex-specific analysis, the *post hoc* analysis of the PARAGON-HF (Prospective Comparison of sacubitril-valsartan with ARB Global Outcomes in HFpEF) trial showed that patients with HFpEF who were recently hospitalized, particularly those with multiple recent hospitalizations, faced 2- to 3-fold higher risks of rehospitalization and cardiovascular death. Early initiation (<30 days post-discharge) of sacubitril/valsartan in patients with HFpEF recently hospitalized for ADHF were shown to have a 25–30% risk reduction for cardiovascular events like rehospitalization and cardiovascular death.[226] Clinical guidelines give recommendations on the management of HF based on major RCTs. Given the myriad of differences, women have an increased risk of developing adverse drug reactions and these adverse events are generally more serious in women than in men[179,227,228] due in part to different pharmacokinetics and pharmacodynamics properties between men and women, leading to up to 2.5-fold higher drug plasma levels of with same dose of the drug compared to men.[227] Women have a lower bodyweight, higher proportion of body fat, and lower plasma volume. These factors can contribute to a longer duration of action of lipophilic drugs and higher peak plasma concentrations of hydrophilic drugs in women.[227] Thus, in the era of 'individualized medicine', this kind of 'sex-uniform' guidelines needs to be addressed. On the other hand, it is also seen that women with HFrEF are less often treated with guideline-directed medical therapy, are less often admitted to cardiology wards, have a lower frequency of assessment of LV function,[181,229] and also continue to receive suboptimal treatment for, compared with men, with no obvious explanation for these disparities.[230]

Lastly, the use of guideline-directed cardiac resynchronization therapy (CRT) and implantable cardioverter-defibrillator[231] use was associated with substantially increased survival in eligible men and women with HFrEF.[232] Although there has been a sustained rise in the percentage of women getting ICD placements, there still exist is a significant disparity in the utilization of CRT and ICD between men and women with up to 2.5-fold higher utilization of device therapy by men in some studies.[233–236] This disparity remained even after adjusting for socioeconomic status as well as level of education.[236]

Female patients are underrepresented in the population of MCS patients and, when they are supported, left ventricle assist device (LVAD) implantation is more often under emergency circumstances.[237] Women tend to receive less ventricular assistive device support despite a more critical HF state at admission.[237,238] Both sexes differed for implanted device types with implantation of smaller device pumps in women while the overall survival in women was significantly worse.[238] Consistent with the earlier theme enrollment of women in trials with implantable pulsatile-flow devices has often been low because of the large volume-displacement chambers with inadequate space for the pump housing in small women.[237] Women are seen to have a higher incidence of major bleeding, arrhythmias, and a worse early and long-term survival.[238] Even though the incidence of LVAD complications are similar between the two sexes,[239] LVAD implantation as a bridge to transplantation is associated with longer duration of inotropic support and higher requirement for postoperative mechanical right ventricular support in women.[240] Nonetheless, women have similar postoperative and midterm survival, length of hospital stay, readmission rates, and postoperative complications.[239,240]

2.5 Spontaneous coronary artery dissection

SCAD is defined as an epicardial coronary artery dissection that is not associated with atherosclerosis or trauma and not iatrogenic.[241] True prevalence of SCAD is unknown mostly because it is vastly under-recognized and misdiagnosed.[241] A low suspicion of acute coronary syndrome (ACS) in young women even in the presence of classic presenting symptoms,[238] limitations of current coronary angiographic techniques, and lack of clinician familiarity with the condition and its different variants are all potential reasons for under diagnosis of SCAD in the contemporary era.[241,242] With the use of intracoronary imaging techniques, SCAD is now estimated to be the cause of approximately 1%–4% of ACS cases overall.[243] It is vastly more prevalent in women than men with >90% cases reported in women and predominantly affects young women. Data on men with SCAD are scarce, though one study reports that men may present at a slightly younger age than women (mean age, 48.6 ± 9.8 vs. 52.3 ± 9.2 years; $P = 0.05$).[241,244] It accounts for the cause of ACS in up to 43% and 35% of pregnant women and women ≤50 years old, respectively.[241]

2.5.1 Risk factors and pathophysiology

The natural history of disease progression in SCAD is multifaceted and is affected by hormonal influences, arteriopathies, genetic factors, and systemic inflammatory diseases; precipitated by environmental factors and stressors. Peri-partum SCAD or 'pregnancy-associated SCAD' is the most common cause of pregnancy-associated AMI.[241] It commonly occurs in the third trimester or early postpartum period, with the highest prevalence in the first postpartum month and, in particular, in the first postpartum week.[241,245] The cause of pregnancy-associated SCAD is not fully understood. It is thought that hormones and unique pregnancy-related complications like gestational hypertension and preeclampsia contribute. In addition, there is a higher use of fertility treatments and hormone replacement therapy in patients with SCAD than in general population.[243,245] One hypothesis is that oestrogen and progesterone receptors in the coronary arteries mediate structural changes in the arterial wall, culminating in rupture, IMH, and onset of clinical symptoms,[241] which may explain why SCAD is more frequent in multiparous women.[245] Women with pregnancy-associated SCAD seem to have a poorer prognosis than women with non-pregnancy-associated SCAD. Patients with pregnancy-associated SCAD have a more severe clinical presentation than those patients with non-pregnancy-associated SCAD, often with multivessel dissections and acute heart failure.[245]
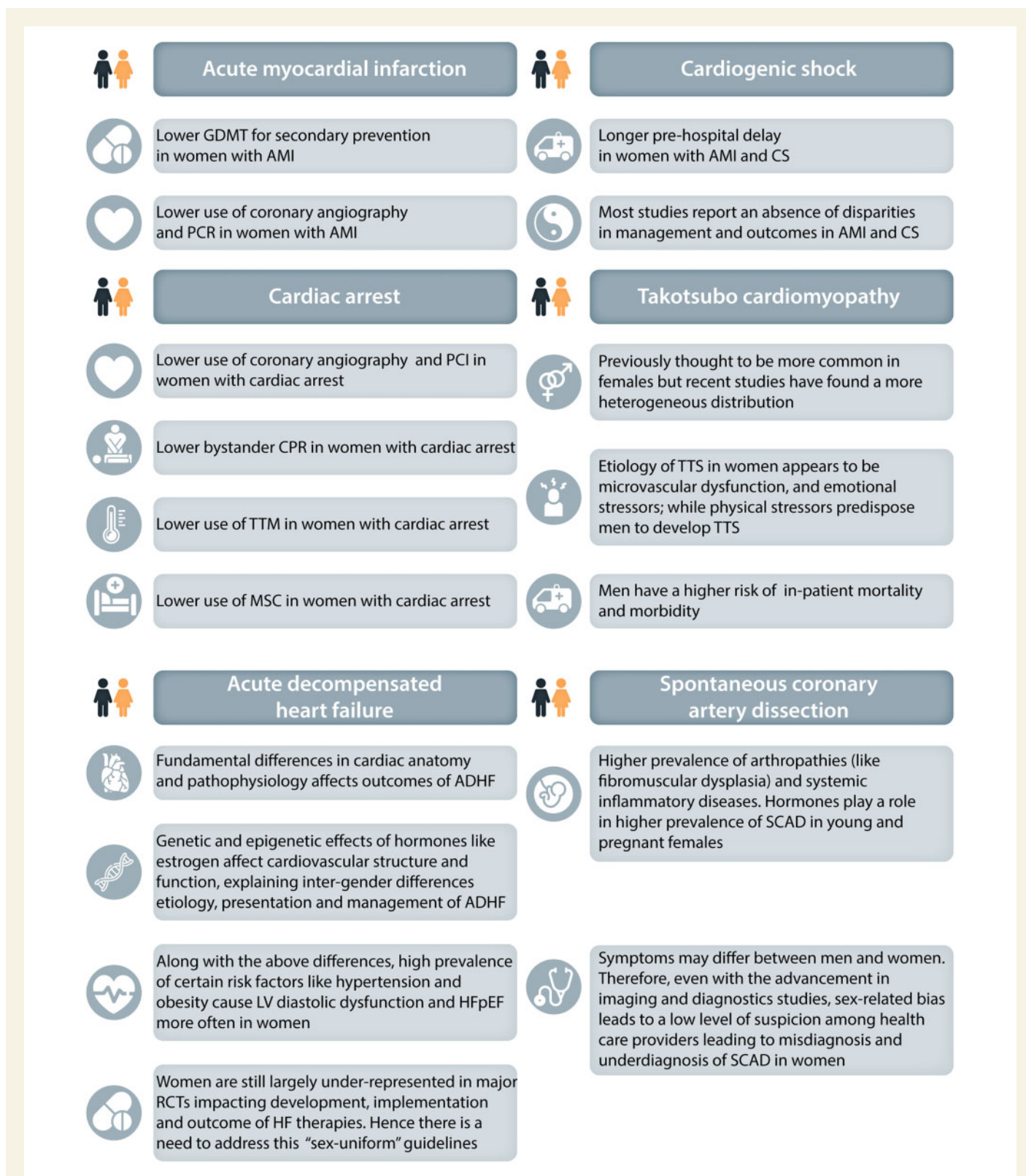
Figure 2 Gaps in care in acute cardiovascular conditions. ADHF: acute decompensated heart failure; AMI: acute myocardial infarction; CPR: cardiopulmonary resuscitation; CS: cardiogenic shock; GDMT: guideline-directed medical therapy; HF: heart failure; HFpEF: heart failure with preserved ejection fraction; LV: left ventricular; MCS: mechanical circulatory support; PCI: percutaneous coronary intervention; RCT: randomized controlled trials; SCAD: spontaneous coronary artery dissection; TTM: targeted temperature management; TTS: Takotsubo cardiomyopathy.

Arteriopathies such as fibromuscular dysplasia (FMD) which have a higher prevalence in women, are commonly associated with SCAD.[241,242] Structurally, women have a smaller vessel diameter, more coronary tortuosity compared to men that can lead to a higher dissection rate.[243,246]

In addition to the underlying diseases, SCAD is also precipitated by emotional and physical stressors.[241,243,244] SCAD is poorly studied in men as its prevalence is extremely low. Vigorous physical exercises such as weightlifting and body building, have been described as the most common SCAD precipitants in men.[241,242] In a prospective SCAD study, FMD was only present 48% of the time in men, yet was identified in 73% of the women in that cohort,[244] further suggesting sex differences in the pathophysiology of SCAD.

2.5.2 Clinical presentation

The clinical presentation of SCAD can range from classic angina to CS or sudden death. All patients present with elevated troponins and chest discomfort.[241,242] Middle and distal portions of the left anterior descending artery are the most commonly affected but other arteries can also be affected.[241] Unfortunately, even with the advancement in imaging and diagnostics studies, as well as increased awareness, sex-related bias leads to a low level of suspicion among healthcare providers. This disparity is driven by the fact that women present more often with symptoms like shortness of breath, fatigue, back pain and headaches, and have non-traditional cardiovascular risk factors. In a landmark study, researchers found that women under the age of 55 who experienced ACS type symptoms were seven times more likely to be misdiagnosed and discharged from the emergency department compared to their male counterparts presenting with identical symptoms with a non-diagnostic EKG being one main of the criteria for discharging.[247] Since only 13–69% patients with SCAD present with EKG changes[241] and one of the most common presentations includes angina there is a concern for underdiagnosing SCAD in women. Angiographically, type 1 SCAD variant is defined by a double lumen appearance and type 2 is characterized by diffuse stenosis of varying severity with changes in the arterial caliber.[248] Men are more likely to have Type 1 than Type 2 SCAD despite the higher prevalence of Type 2 dissection in the overall SCAD population.[243] Intracoronary imaging techniques such as intravascular ultrasound (IVUS) or optical coherence tomography[249] are also recommended to increase the diagnostic yield since angiography may miss the diagnosis of SCAD, especially type 2. Other imaging techniques like cardiac MRI and coronary CT angiography can also be useful to differentiate between ischaemic diseases like dissection from non-ischaemic diseases.[242]

Coexistence of SCAD and TTC has been reported in five case reports and one retrospective case series until today, including a totality of 14 patients.[250] Nonetheless, to avoid underdiagnosing SCAD, all patients diagnosed with TTC should be evaluated for SCAD and their angiograms reviewed thoroughly, preferably by an experienced interventionalist.

2.5.3 Management

Although American and European guidelines for the management of ACS advocate an early invasive strategy with revascularization of culprit lesions instead of conservative therapy alone,[241] conservative management is the mainstay for management. In the setting of underlying weak architecture of the coronary arteries in SCAD due to underlying arteriopathies as well as smaller coronary vessel diameter, greater tortuosity compared to men, studies have uniformly demonstrated that PCI increases risk of complications and renders poor outcomes by causing iatrogenic dissection and extension of dissections.[241,246,251] Hence, revascularization is reserved in patients who are haemodynamically unstable or having ongoing ischaemia or clinically stable patient with left main or severe proximal two-vessel dissection.[241] Effectiveness of coronary artery bypass graft (CABG) has only been studied in patients with SCAD of left main artery or proximal dissections, technical failure of attempted PCI or after complications occurring after attempted PCI.[241] On the other hand, conservative approach with medications like ACE inhibitors/ARBs and beta blockers as well as controversial therapies like anticoagulants or antiplatelet drugs and statins in SCAD alleviate symptoms, improve short- and long-term outcomes, and prevent recurrent SCAD.[241]

Management of SCAD during pregnancy requires multidisciplinary approach by including the cardiology and obstetric service to encompass maternal care as well as foetal wellbeing. Maintaining a strong suspicion to avoid missing a diagnosis and early diagnostic angiography to avoid iatrogenic dissection,[252] keeping into account foetal radiation exposure and finally aiming for conservative management if there is no evidence of ongoing ischaemia or infarction, haemodynamic instability, or particularly high-risk anatomy[253] are key components of pregnancy-associated SCAD management.

2.6 Takotsubo cardiomyopathy

Takotsubo cardiomyopathy[254] also known as stress cardiomyopathy, apical ballooning syndrome or broken heart syndrome, was first described in Japan in 1990 is characterized by transient systolic and diastolic left ventricular dysfunction accompanied with different wall motion abnormalities. There is a 9:1 female to male ratio in some studies,[255,256] but, in Japan, TTC is more prevalent among men.[255] TTC may be more heterogeneous than previously thought[7,212,224,255–257] as studies have shown higher incidence in men and younger population.[258] One study found that the mean age of diagnosis of TTC in males is lower in females (61.6 vs. 66.5 years; *P* < 0.001) and male predominance is typically seen in the younger population <35 years of age at the time of diagnosis (21.2% of males vs. 9.5% of females).[256] Though, approximately two-thirds of patients have identifiable triggering events like an emotional or a physical stressor,[255,257,258] its absence does not preclude its diagnosis.[255] Microvascular vasoconstriction of the coronary artery secondary to catecholamine excess may contribute to the development of TTC.[257,259] Autonomic dysfunction due to increased reactivity of sympathetic nervous system seen in subclinical hypothyroidism or hypothyroidism could explain the increased incidence of TTC in this subgroup.[260]

Interestingly, while emotional triggers are more prevalent in women, men usually present with physical stressors like medical conditions or procedures[261] which cause a higher heart rate, thus a greater sustained catecholamine surge causing cardiac dysfunction by increasing the risk of developing CS via pump failure due to large ballooning area and/or left ventricular outflow tract obstruction due to hyper contractility of the basal segment.[257,262] While, in women, low oestrogen may contribute to the excessive sympatho-adrenal and renin–angiotensin system activation and oxidative stress.[263,264] However, post-menopausal hormone therapy does not decrease the risk for developing TTC in females >50 years old,[265] eliciting the fact that the pathophysiology of TTC is much more complex and still poorly understood.

TTC and ACS have a similar presentation in clinical symptoms, ECG, and cardiac biomarker changes.[255] Even though coronary angiography with left ventriculography is considered gold standard, contrary to previous notion, it is essential to rule out only obstructive CAD, to diagnose
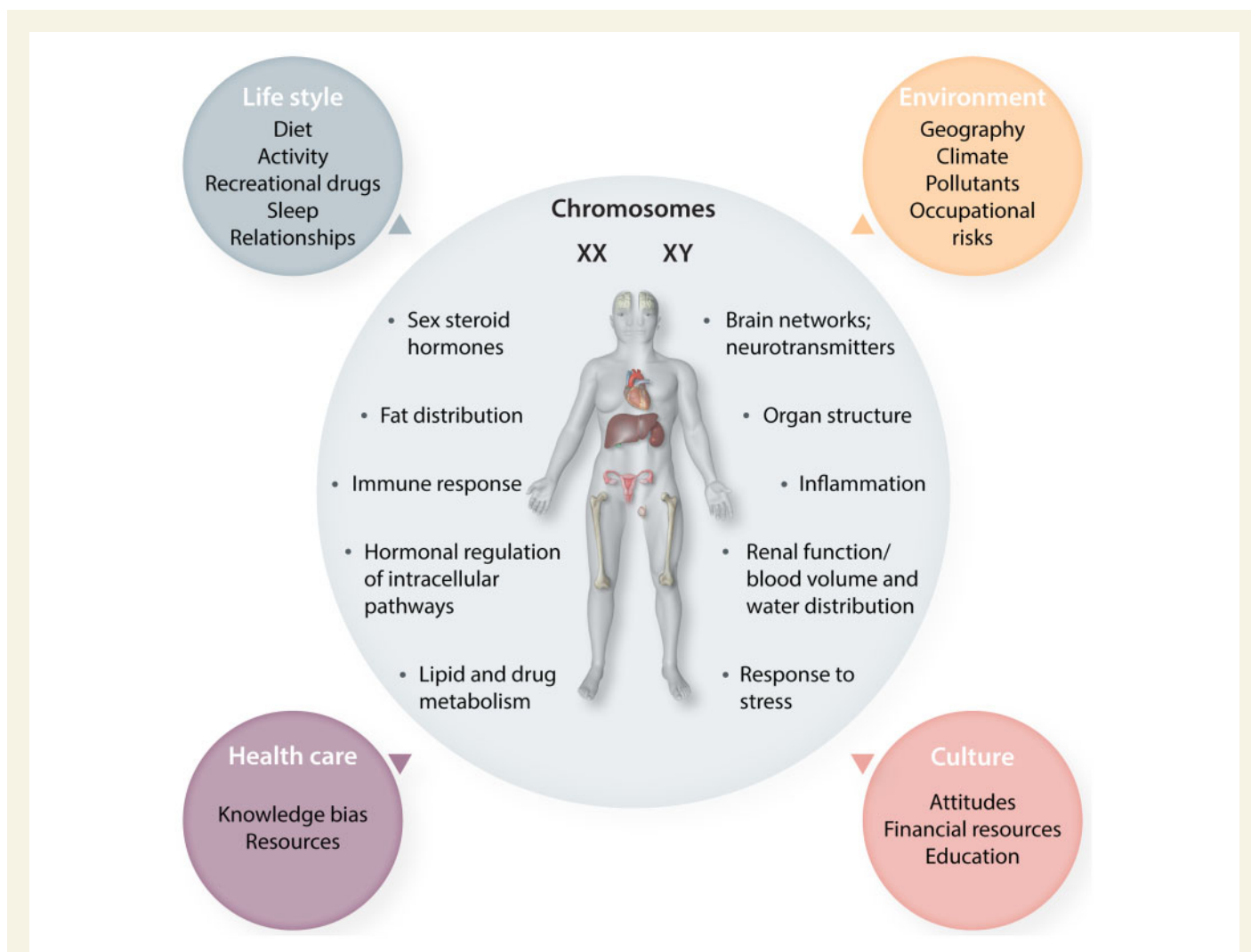
Figure 3 Influence of sex chromosomes in cardiovascular disease presentation, response to treatment and outcomes. The sex chromosomes direct development of some organs prior to the development of the reproductive organs and production of sex steroids hormones. The sex steroid hormones (oestrogen and testosterone) are present in both females and males, albeit in different proportions, and their concentrations changes with age from birth to puberty to reproductive senescence. The collective effect of the sex chromosome and hormones influence cellular regulatory pathways that influence organ structure and function, metabolism, and response to stress and reparative functions. Environmental, cultural, life style factors which contribute to the psychosocial construct of gender influence biology. Insufficient knowledge of sex differences in physiology and pathophysiology limit development of sex-specific care and treatment guidelines. Investigations into sex differences in physiological and pharmacological mechanisms, reporting clinical trial data by sex, identifying modifiable behaviours, and embedding concepts of sex differences into science and medical curricula will reduce sex disparities in treatment and outcomes.

TTC.[259] Concomitant CAD is reported with a prevalence ranging from 10 to 29%[255] and is reported CAD may itself trigger TTC.[259]

Male sex, Killip class 3–4 on admission, and diabetes mellitus were identified as independent predictors of long-term mortality in TTC patients.[266] A retrospective observational study of 406 patients from data collected from the InterTAK (International Takotsubo) registry demonstrated that a delayed resolution of wall motion abnormality was associated with a higher mortality at 1-year.[267] Males were found to have a longer recovery time for wall motion abnormality and presented with lower LVEF and higher troponin and inflammatory marker levels on admission and thus these results are clinically important because patients with these characteristics should be monitored closely after hospitalization, given the higher risk of potential clinical complications.[265,267] Although less common TTC in men is associated with a marked increase in in-hospital morbidity and mortality and a higher probability of acute complications such as ICU admissions, CS, ventricular fibrillation or tachycardia, and acute kidney injury along with longer length of hospital stay of more than 5 days and hospital costs compared to females.[256,268] This difference can be explained by the increased risk of death and overall short-term and long-term outcomes in patients with secondary TTC (presence of a physical trigger) compared with patients with primary TTC (emotional or no trigger).[257,266] Thus, more careful monitoring and intensive therapies may be required for men with TTC than for women with the same condition during hospitalization.

Table 1 Summary of sex-disparities in acute cardiovascular care

Condition	Epidemiology and risk factors	Management	Outcomes	Future directions
Acute myocardial infarction	Women tend to be older with a higher prevalence of hypertension, diabetes, metabolic syndrome, and a lower prevalence of hypercholesterolaemia and smoking More frequent non-ST-segment elevation and atypical presentation	Less likely to receive reperfusion, revascularization, lower achievement of 90-min door-to-balloon time	Higher mortality	Improve primary prevention, secondary prevention including GDMT and in-hospital management
Acute myocardial infarction with cardiogenic shock	Women tend to be older with a higher prevalence of hypertension and diabetes Higher rates of CS	Similar rates of angiography, PCI, CABG, MCS, and haemodynamics	Similar 1, 6-month and 1-year outcomes	Improve management of AMI to reduce incidence of CS. Continue sex equality management strategies
Cardiac arrest	Women are older, higher comorbidities, more often have a non-shockable rhythm. Lower rates of bystander CPR	Lower use of angiography, PCI, CABG, TTM	Conflicting results on mortality and neurological outcomes	Increase awareness, improve bystander CPR, increase female mannequins in CPR training, and reduce sex disparities in in-hospital management
Acute decompensated heart failure	Women tend to be older with comorbidities like hypertension, obesity, and kidney disease with higher prevalence of HFpEF Diabetes tends poor prognosis in women	Women are less likely to receive goal directed medical therapy Different pharmacokinetics/ dynamics has led to higher risk of women developing adverse reaction to drugs	Similar in-hospital morality, length of stay, and short-term post-hospital outcomes	Women are still largely under-represented in major RCTs impacts development, implementation and outcomes of HF therapies. Hence there is a need to address this 'sex-uniform' guidelines
Spontaneous coronary artery dissection	Women tend to younger, have arthropathies (like FMD) and systemic inflammatory diseases. Pregnancy is a major risk factor	Smaller coronary vessel diameter, greater tortuosity compared to men, leading to increased risk of complications with PCI and renders poor outcomes in women with SCAD	Higher mortality in females	Increase awareness of this disease and having a lower suspicion for SCAD especially in women
Takotsubo cardiomyopathy	Women tend to have microvascular dysfunction and emotional stress, while men tend to be younger and have emotional stress	More careful monitoring and intensive therapies may be required for men with TTC than for women during hospitalization	Higher mortality in males	Increase awareness of TTC in men and improving outcomes

3. Conclusions

In summary, there remain persistent sex disparities in the care and management of patients with acute cardiac conditions (*Figure 2*). In general, for all conditions, female patients typically receive less frequent guideline-directed care and have poor short- and long-term outcomes. Though significant success has been achieved in decreasing the in-hospital mortality in most acute cardiac emergencies, it is crucial to continue to address easily identifiable risk factors and to use the information regarding sex differences in physiology and pharmacology to guide treatment strategies (*Figure 3* and *Table 1*). Furthermore, there are limited data on the clinical outcomes in patients undergoing gender reassignment, and the heterogeneous timing for initiation of treatments, and types of treatments affecting the sex hormonal milieu present a challenging but crucial next steps in this field. Studies in cardiovascular medicine, specifically acute cardiovascular care, will benefit from additional preclinical studies of acute cardiovascular conditions, enrolment of similar proportion of men and women in clinical trials, sex-specific reporting of trial outcomes, and consideration of sex-hormones as effect-modifiers in healthcare delivery.

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