

Review Article **Cardiovascular**

Sex Differences in Cardiomyopathies

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Received: 21 July 2025

Accepted: 22 November 2025

Epub Ahead of Print: 27 January 2026

Published:

DOI

10.25259/IJCDW_41_2025

Quick Response Code:



ABSTRACT

Cardiomyopathies are a group of diseases involving primary abnormalities of the myocardium, which can be genetically determined or acquired. They are classified as hypertrophic cardiomyopathy, dilated cardiomyopathy, restrictive cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, and unclassified. Biological sex has a great impact on the prevalence, clinical manifestations, and prognosis of cardiomyopathies, through sex hormones, genetic variations, variations in pathobiology, pathophysiology, pharmacogenomics, and socioeconomic factors. The underlying mechanisms are not completely understood. Further research is necessary to understand these mechanisms and develop sex-specific therapeutic targets and treatments. This review aims to provide a summary of the current evidence on sex differences in cardiomyopathies and highlight the knowledge gaps.

Keywords: Biological sex, Cardiomyopathies, Phenotype, Pathophysiology, Outcomes

INTRODUCTION

Biological sex is a principal determinant of cardiovascular disease.^[1] The complex molecular mechanisms underlying sex differences in cardiomyopathies remain incompletely elucidated. A comprehensive understanding of the influence of biological sex on the prevalence, pathophysiology, clinical manifestations, therapeutic response, and prognosis of cardiomyopathies will facilitate the development of targeted diagnostic and therapeutic strategies, ultimately improving the outcomes. This review aims to provide a comprehensive summary of the current evidence and identify the knowledge gaps in sex differences in cardiomyopathies.

The factors contributing to sexual dimorphism in cardiomyopathies are shown in Figure 1.

Effects of sex hormones

Cardiomyocytes express receptors of all sex steroid hormones and, hence, are susceptible to their modulating effects. Variations in the synthesis and metabolism of sex hormones, genetic deletion or overexpression of sex hormone receptors, and genomic or nongenomic effects of sex hormone receptor activation contribute to sexual dimorphism.

Estrogen (E2) and its receptors, estrogen receptor alpha, estrogen receptor beta, and membrane G protein-coupled receptor exert important effects on the cardiovascular system through genomic and non-genomic pathways. The E2/estrogen receptor (ER) axis inhibits apoptotic pathways, modulates cardiac bioenergetics through various mechanisms, and mitigates pathological myocardial hypertrophy. The regulation of calcium homeostasis by the E2/ER axis results in

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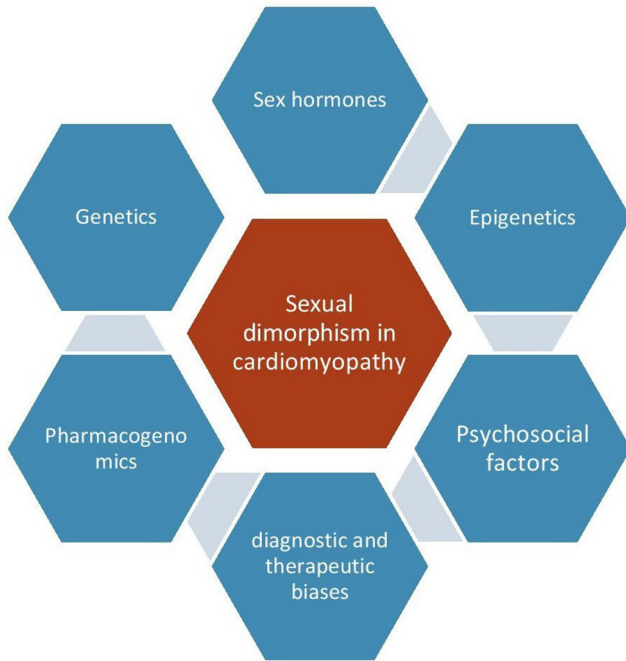


Figure 1: Factors contributing to sexual dimorphism in cardiomyopathies.

substantial gender differences in the electrophysiological and contractile properties of cardiomyocytes. Recent research suggests that it also may stimulate cardiac regeneration.^[2]

The influence of testosterone on the cardiovascular system is less clear. It appears to have both cardioprotective and negative effects on the cardiovascular system through various mechanisms. While testosterone is deficient in men with heart failure from different cardiomyopathies, such as dilated cardiomyopathy, endomyocardial fibrosis, and takotsubo cardiomyopathy (TTC), and is associated with poor cardiovascular outcomes, testosterone levels are higher in males with arrhythmogenic right ventricular dysplasia and are associated with major arrhythmic events^[3] Other studies show that testosterone is an important inducer of pathological hypertrophy.^[4]

Genetic factors

The impact of sex chromosome-linked gene abnormalities, such as X-linked dilated cardiomyopathy, Fabry's disease, and Barth's syndrome, is obvious. Sex-specific effects on the penetrance and severity of the autosomal genetic variants, and differences in transcriptomic profiles, lead to significant sex differences in cardiomyopathies.

Genetic cardiomyopathies, such as hypertrophic cardiomyopathy (HCM), genetic dilated cardiomyopathy (DCM), and arrhythmogenic right ventricular cardiomyopathy (ARVC), are more prevalent in men, despite autosomal inheritance.^[5-7]

Probable causes could be the significant sex differences in genetic variation-disease associations,^[8,9] variable penetrance, the effect of sex hormones, or underdiagnosis in women. The male predominance of most of the subtypes of cardiomyopathy in the pediatric age group,^[10] suggests that genetic and epigenetic factors play a significant role, apart from the sex hormones.

Sex differences in biological processes in cardiovascular cells

There are substantial differences between the sexes in ion handling, excitation-contraction coupling^[11] and rhythmicity, mitochondrial function, and energy metabolism, such as higher antioxidant gene expression in female mitochondria and cardiac lipid and carbohydrate metabolism pathways.^[12] Apoptosis also occurs differentially. In healthy hearts, the rate of cardiomyocyte apoptosis is 3 times higher in men. The cardiomyocyte death is found to be higher in the male failing heart.^[13] Differences also exist in the activation of the adaptive and innate immune system, levels of fibrosis mediators, fibrotic pathways, and pathological and electrophysiological remodeling [Figure 2].

Epigenetic mechanisms

Sex may influence cardiovascular epigenetics, leading to differences in cardiovascular disease manifestations through various mechanisms, including the effects of sex hormones on DNA methylation, histone modification, chromatin architecture, and microRNAs; the increased expression of X-chromosomal escape genes; and the expression of non-pseudo autosomal Y-chromosomal epigenetic modifiers in men.

Differences in pharmacogenomics

Women have a smaller volume of distribution, higher body fat content, larger free fraction of the drug, and slower renal clearance. These factors often result in higher drug concentrations and higher adverse effects in women. Other factors, such as variations in drug bioavailability, receptor number, receptor binding, and plasma protein binding, contribute to disparities in treatment outcomes between the sexes.

Diagnostic and treatment biases

The established diagnostic criteria for different cardiomyopathies, such as ventricular wall thickness, dimensions, and volumes, are non-indexed, which may result in delayed diagnosis of conditions such as HCM and cardiac amyloidosis. Underutilization of therapeutic interventions and cardiac rehabilitation in women leads to differences in therapeutic outcomes.

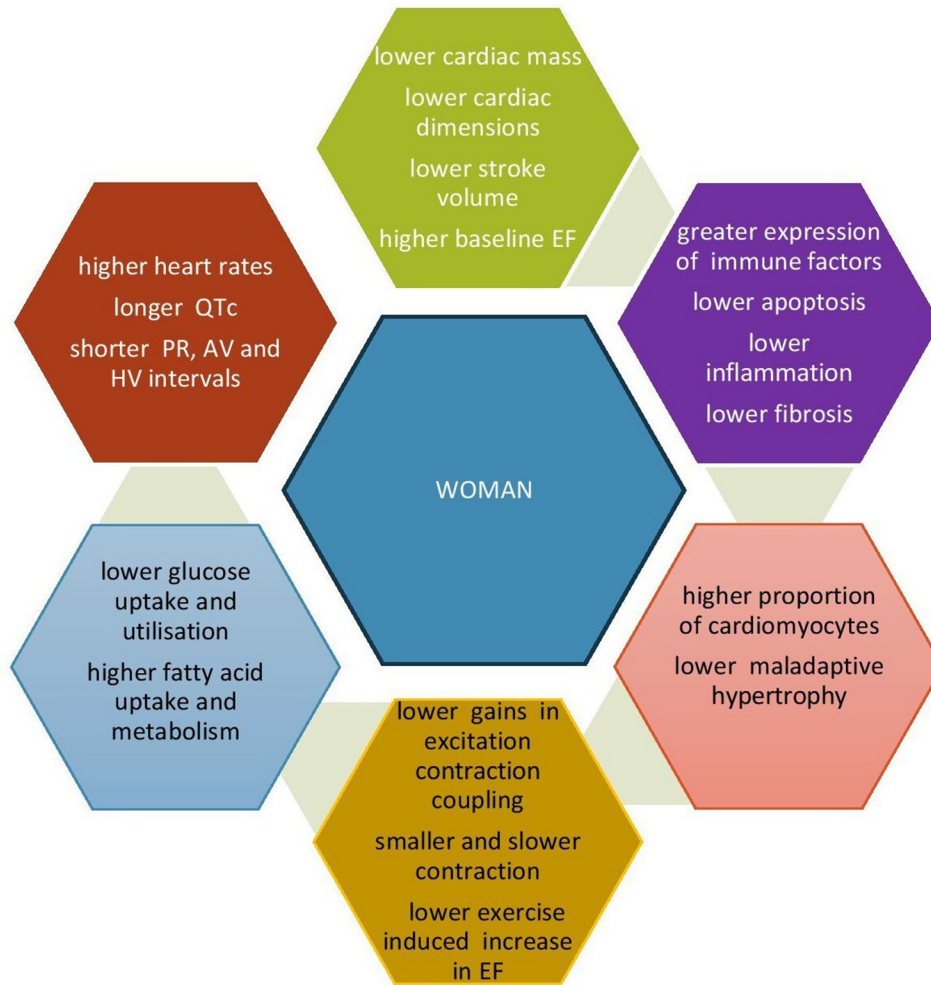


Figure 2: Cardiac biology in women compared to men. (QTc: corrected QT Interval, AV Interval: atrioventricular interval, EF: Ejection fraction, HV Interval: His Ventricular interval)

HYPERTROPHIC CARDIOMYOPATHY (HCM)

Although HCM classically has an autosomal dominant inheritance, recent evidence suggests that 40% of HCM could be non-familial. HCM is predominant in males. Men constitute approximately 60% of the study populations.^[14,15] This may be due to the lower penetrance of sarcomere variants in women, as well as delayed diagnosis and under-recognition of HCM in women. Disease penetrance is higher in men.^[16] More women are sarcomere-positive than men, and sarcomere-positive men have a higher risk of developing HCM.^[17] In a study of Indian women, 21 variations, including 7 new mutations, were identified in the beta *MYH7* gene. The mutation at Val 431 Met results in an abnormal hydrophobic interaction with Leu 352 Met and is presumably involved in cardiac remodeling and cardiomyopathy.^[18]

Women present approximately 6–7 years later than men.^[19] Females have a greater diastolic dysfunction and present with more advanced heart failure symptoms.^[14,15] Despite a similar

extent of hypertrophy, females have a greater incidence of dynamic left ventricular outflow tract (LVOT) obstruction, greater LVOT gradients, a higher incidence of resting obstruction, and higher grades of mitral regurgitation compared to men.^[20] However, the difference in LVOT obstruction was abolished after controlling for left ventricular (LV) end-diastolic diameter in the SHaRe registry.^[14] Hence, it is speculated to be due to the smaller LV chamber size in females.

Women with HCM have significantly higher rates of progression to advanced refractory heart failure than men.^[15] This difference was observed even in the pediatric age group.^[21] The all-cause mortality rate is higher, and the survival rate is worse in females.^[20,22,23] There is no difference in the incidence of atrial and ventricular arrhythmias, sudden cardiac death (SCD) events, or in implantable cardioverter-defibrillator (ICD) insertion for primary prevention between the sexes.

Females have a smaller body surface area (BSA)-corrected cardiac size than males.^[24] The current diagnostic criterion for HCM, of ≥ 15 -mm maximal LV wall thickness, is non-indexed. Hence, women require relatively greater hypertrophy to meet the criterion.^[25,26] This could account for the delay in diagnosis and advanced symptoms at presentation seen in women. Hence, sex-specific indexed criteria should be developed.

Females exhibit greater indexed-maximal LV wall thickness, smaller LV chamber size, and a significantly greater left atrial (LA) diameter.^[17] Indexed interventricular septum diameter, LV, and LA remodeling indices are greater in women. Severe hypertrophy of LV, i.e., wall thickness ≥ 30 mm, is similarly prevalent. Females exhibit more interstitial fibrosis, higher compliant titin, and lower expression of calcium-handling proteins such as phospholamban and sarcoplasmic reticulum calcium pump 2, in the cardiomyocytes.^[27]

On cardiac magnetic resonance (CMR) analysis,^[28] the LV Remodeling index and the extent of late gadolinium enhancement (LGE) are significantly greater in women compared with men. The diastolic function indices, such as peak flow rate and time to peak flow rate, were substantially lower in women than in men. In a study by Xuanye *et al.*,^[29] functional impairment of the LA and myocardial fibrosis were more common in female patients with HCM.

In a single-center study,^[30] women had better survival and a greater reduction in the mean LA pressure after alcohol septal ablation. However, other studies showed worse post procedural outcomes in women. A meta-analysis,^[31] which included 31,907 HCM patients, showed that women had a higher mortality rate, higher incidence of atrioventricular block, and higher rates of pacemaker implantation with either alcohol septal ablation or septal myectomy. In a large Chinese cohort,^[23] which included 1613 obstructive HCM patients undergoing septal myectomy, the operative mortality was significantly higher in women than in men. Five-year mortality rates were similar, but there was a higher risk of cardiovascular hospitalization in women. Hence, a gender-specific approach is needed in the perioperative care and monitoring to improve procedural outcomes in HCM.

In the Explorer HCM trial,^[32] after 30 weeks of treatment with Mavacamten, improvement in the primary composite functional endpoint, post-exercise LVOT gradient, the New York Heart Association (NYHA) class, and the increase in peak oxygen consumption were similar. However, there was a greater improvement in NTPro-BNP levels in women. The differences in HCM between the sexes are summarized in Table 1.

Fabry's disease

In Fabry's disease, men are more severely affected.^[33] In

Table 1: Gender differences in hypertrophic cardiomyopathy.

Characteristic feature	Male	Female
Sarcomere positive	Less likely	More likely to be sarcomere positive
Disease penetrance	More	lower
Age at presentation	Earlier	6–7 years older at presentation
Prevalence of obstructive phenotype	lower	Higher
Severity of symptoms	Less advanced	More advanced symptoms
Diastolic dysfunction	lower	Worse diastolic function
Mitral regurgitation	Lower degree	Higher degree
Survival rate	Better survival	Lower survival rate
Remodelling	Lower LV and LA remodelling indices	Higher LV and LA remodelling indices
Interstitial fibrosis	Less	More interstitial fibrosis
Post-procedure outcomes	lower	Higher mortality and complications after alcohol septal ablation and myectomy.

LV: Left ventricular, LA: Left atrial

women, symptoms may range from asymptomatic to severely symptomatic, depending on the pathogenic variant and X chromosomal inactivation. The milder phenotype, however, is more common, and disease progression is slower, which might account for an observed delay in the diagnosis of approximately 10 years. In the classic Fabry mutation, the treatment recommendations also vary between the sexes. In males, enzyme replacement therapy is recommended for all patients at any age of presentation, whereas in females, it is only recommended when symptomatic or definitive evidence of injury, demonstrated by imaging or histology, is available.

DILATED CARDIOMYOPATHY

DCM is more prevalent in men, with a male-to-female ratio of approximately 3:1.^[34] The impact of X-linked variants of dilated cardiomyopathy, such as Duchenne and Becker muscular dystrophy, on varied presentations in males and females is obvious. Recent research shows that variants in desmoplakin exhibit higher penetrance in females, and truncating variants in titin exhibit higher penetrance in males.^[35] Some studies have reported a higher frequency of Z-disc gene variants in women and truncating variants in the titin gene in men.^[36] On the contrary, Owen *et al.* reported that no such differences were found.^[37]

Females typically have a milder phenotype. In a study of 604 patients with DCM confirmed by CMR,^[37] females had higher LV ejection fractions (LVEF), lower indexed LV volumes, less myocardial fibrosis, and lower serum hs-cTnI levels. Despite the milder phenotype, females showed worse functional status at presentation and a greater incidence of congestive complications and heart failure hospitalizations. The factors that may contribute to this paradox warrant further investigation.

Survival rate is higher in women with DCM compared to men. The rates of all-cause, cardiovascular, or sudden death-related mortality are lower in women compared to men.^[38] This difference may be due to the higher LV function and a lower scar volume in females.^[39] While atrial fibrillation (AF) is more frequent in women with DCM, the incidence of ventricular arrhythmias is higher in males.

The current guidelines give gender neutral recommendations for the dosage of heart failure medications. However, differences in pharmacogenomics result in higher serum concentrations of drugs in females. In women, the reduction in mortality and heart failure hospitalization is observed at 30–50% of the recommended doses of angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), and beta blockers. Further increase in doses seems to increase the adverse events. Hence, gender-specific recommendations should be developed. Beta blockers, mineralocorticoid receptor antagonists, and sodium-glucose cotransporter-2 inhibitors show a similar improvement in heart failure outcomes in men and women. Large meta-analyses^[40] have shown that ACEIs have more favorable effects in men. On the contrary, other studies observed that women benefit more from ARBs than men. Females have a greater improvement in functional class with angiotensin receptor-neprilysin inhibitors, though other outcomes appear to be similar.

In a study of 4506 patients with ICD,^[41] life-threatening ventricular arrhythmias were significantly lower in women than in men. Women experienced significantly fewer appropriate ICD interventions. However, women are underrepresented in ICD trials. Future trials should increase women's representation. The response to cardiac resynchronization therapy is greater in women, with a larger increase in LVEF and better clinical outcomes.^[42] The frequency of LVAD implantation has risen substantially recently. In the pulsatile flow era, mortality and neurological complications, such as hemorrhagic and ischemic stroke, were higher in females. However, no significant differences in mortality or neurologic outcomes were observed with continuous flow LVADs. The referral rate for cardiac transplantation remains lower in women, and efforts are ongoing to address this gender imbalance by developing new allocation systems [Table 2].

Further prospective, comprehensive data are essential to understand the influence of biological sex on the genetics, pathophysiology, natural history, and response to various therapeutic modalities in dilated cardiomyopathy.

Alcoholic cardiomyopathy

The prevalence of alcoholic cardiomyopathy is higher in men owing to their greater alcohol consumption. However, the deleterious effects of alcohol are more pronounced in women, leading to cardiomyopathy at lower levels of alcohol consumption^[43] [Figure 3].

Phospholamban cardiomyopathy

Phospholamban cardiomyopathy is typically a severe form of cardiomyopathy, with advanced heart failure and a high risk of arrhythmia. Sustained ventricular arrhythmias are more prevalent in males than in females. De Brouwer *et al.*^[44] showed that low-voltage electrocardiogram (ECG) is a reliable predictor of sustained ventricular tachycardia (VT),

Table 2: Sex differences in dilated cardiomyopathy.

Men	Women
Higher prevalence	
Higher mortality	Better survival
Higher incidence of ventricular arrhythmias	Milder phenotype
More likely to receive an ICD and a heart transplant	Higher NYHA class at presentation
	More likely to respond to CRT

ICD: Implantable cardioverter-defibrillator, NYHA: New York Heart Association, CRT: Cardiac resynchronization therapy

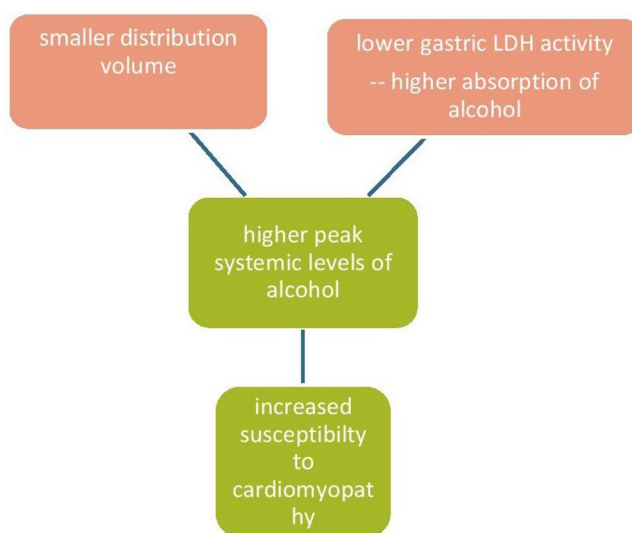


Figure 3: Increased susceptibility of alcoholic cardiomyopathy in women. (LDH: Lactate dehydrogenase)

and males with low-voltage ECGs have the lowest sustained VT-free survival.

Peripartum cardiomyopathy

Prior studies postulated viral myocarditis, fetal microchimerism, and nutritional deficiencies as the underlying mechanisms. However, recent research suggests vasculotoxicity due to a vascular hormonal interaction. The angiogenic imbalance due to the oxidative stress-induced cleavage of prolactin to a vasculotoxic and proapoptotic 16-kDa prolactin fragment, secretion of soluble fms-like tyrosine kinase 1 by the placenta, and decreased expression of vascular endothelial growth factor appears to be the central mechanism. A genetic predisposition may be the underlying trigger. Coronary microvascular endothelial damage is also implicated in the pathogenesis of TTC and radiotherapy-induced cardiomyopathy.^[45]

RESTRICTIVE CARDIOMYOPATHY

Cardiac sarcoidosis

Cardiac sarcoidosis appears to be more common in men. Females are more likely to have systemic sarcoidosis, while cardiac involvement is the first to occur in men.^[46,47] In Kalra *et al.*'s study,^[48] females presented at a later age. Chest pain and palpitations were more common in women. The incidence of dyspnea, presyncope, syncope, or arrhythmias at presentation was similar. In a large prospective registry, the cardiac sarcoidosis consortium,^[49] chest pain, hypertension, and heart failure at presentation were more common in females [Table 3].

Some studies observed that males are at significantly increased risk of ventricular arrhythmias.^[46,50] Females







and males had similar rates of ICD implantation, but males experienced significantly greater, appropriate ICD therapies than females.^[50] Kalra *et al.*,^[48] in their study of cardiac sarcoidosis by CMR, observed that female patients had significantly higher LV and RV ejection fractions, lower BSA-indexed RV and LV volumes, and a lower prevalence of LV LGE compared to male patients. They observed that the incidence of significant ventricular arrhythmias is lower in females. However, the prevalence of supraventricular arrhythmias, atrioventricular block, and the incidence of long-term all-cause mortality were similar between males and females. In another large study^[51] including 760 cardiac sarcoidosis patients, males were younger and had higher rates of ventricular arrhythmias and ICD implantation. Diabetes, major adverse cardiac events, acute kidney injury, and chronic kidney disease were more common in males, but AF and sick sinus syndrome were less prevalent.

In the cardiac sarcoidosis consortium, the requirement of immunosuppression was higher in females; however, in Kalra *et al.*'s^[48] study, no such difference was observed. Significant deficits in knowledge exist regarding the gender differences in cardiac sarcoidosis, which warrants further research.

Amyloidosis

Both wild-type and hereditary transthyretin amyloidosis predominantly affect men, accounting for more than 80% of the cases, with significantly greater incidence in patients above 80 years of age.^[52] However, the true prevalence of transthyretin cardiac amyloidosis (ATTR-CA) might be higher in women, as active screening for ATTR-CA in persons older than 60 years of age, with heart failure and LV hypertrophy, identified more women, with earlier echo

Table 3: Sex differences in restrictive cardiomyopathy.

Amyloidosis		Sarcoidosis		Hemochromatosis	
					
Higher incidence	Lower prevalence HFPEF is more prevalent	cardiac sarcoidosis is more common	Systemic involvement is more common	Higher prevalence	Lower prevalence
	Red flags are more common		Presentation with heart failure	Younger	Older
	Worse functional class at presentation	More LGE	Less LGE	Myocardial injury more	Myocardial injury less
Overall prognosis similar		Arrhythmias more common	Arrhythmias less common	worse outcomes	Better outcomes
HFPEF: Heart failure with preserved ejection fraction, LGE: Late gadolinium enhancement					

phenotypes.^[53] Hence, efforts should be made for early diagnosis in women to reduce the gender disparities.

Most women present with milder hypertrophic phenotypes.^[54] Nevertheless, the frequency of Heart failure with preserved ejection fraction is higher in females than in males,^[55] and women present with a more advanced new york heart association (NYHA) functional class.^[56] Carpal tunnel syndrome, an early sign of ATTR-CA, is more prevalent in females in the general population.^[57] Severe aortic stenosis as a coexistent finding in ATTR-CA is more frequently observed in women than in men.^[55]

On echocardiographic evaluation, females exhibit an almost equal indexed LV wall thickness, lower LV volumes, greater ejection fractions, lower diastolic function, and lower right ventricular function. Inconsistent differences are seen in Electrocardiography (ECG), CMR, and biomarker levels.^[58] The cardiac bone tracer uptake studies using 99mTc-labeled pyrophosphate showed a significantly lower mean heart-to-contralateral ratio in women.^[57]

There are no available data regarding the gender differences in the therapeutic response to medications in amyloidosis, due to the underrepresentation of women in the drug trials. The overall prognosis is similar^[59] [Table 3].

Sex-specific penetrance and variations in phenotype are seen in certain mutations. Val30Met cardiac mutations are more prevalent in males.^[54] Both estrogen and androgens seem to directly influence the transthyretin levels. Estrogen may be protective against the deleterious effects of amyloid fibrils on cardiac function.^[60,61] The composition of amyloid deposits also exhibits significant differences. Males have higher levels of Quiescin sulphydryl oxidase 1 and serpine 2, but lower apolipoprotein A1, compared to females.^[62] There are differences in immune responses, inflammatory signaling,^[63] autophagy and lysosomal function, thus affecting the clearance of amyloid deposits^[64] and differences in proteostatic pathways which affect the stability and degradation of amyloid fibrils.^[65] Further research is needed to elucidate the mechanisms underlying these differences.

Hemochromatosis

Men are more frequently affected than women. Myocardial injury due to iron overload is lower in women than in men.^[66] The underlying mechanism is still unconfirmed, though the protective effects of estrogen and regular loss of iron during menstruation are thought to be the causes. Compared to women, men present at a younger age and have worse outcomes [Table 3].

ARVC

ARVC predominantly occurs in males, despite the autosomal dominant inheritance.^[67] Disease penetrance is higher in

males, leading to prognostic differences. Among the PKP2 mutation carriers, more males fulfill the Task Force Criteria for diagnosis,^[68] and males with pathogenic variants in TMEM43 have an increased incidence of SCD and other adverse outcomes.^[69,70]

Male sex is associated with increased disease severity and adverse outcomes.^[71] The severity of arrhythmias is higher in males.^[71,72] Some studies^[73-75] reported that more intense and frequent exercise increases the risk of ARVC development, ventricular arrhythmias, and heart failure. They hypothesized that ARVC, being a desmosomal disease, the exercise-induced increase in the preload may have deleterious effects on the mechanical and electrophysiological properties of the myocardium. As exercise performance is higher in men, men with ARVC may have worse outcomes. In a study by Rootwelt-Norberg *et al.*,^[76] although the disease severity is higher in males at baseline, the structural and functional disease progression is similar after the cessation of exercise, and male sex ceases to be a risk marker for ventricular arrhythmias.

On the contrary, in a study by Kimura *et al.*,^[77] which included 109 Japanese ARVC patients, the risk of heart failure hospitalizations, death, and cardiac transplantation was higher in females. This was attributed to the lower BSA of the Asian study population, as the investigators found that a BSA below 1.50 m² is associated with a significantly worse outcome.

In a study by Lin *et al.*,^[78] men had a higher incidence of sustained VT, VF, or SCD as the initial presentation. Male patients had long-duration abnormal electrograms, larger endocardial and epicardial areas with late potentials, and larger epicardial unipolar low voltage zones. Male gender and a larger area of long-duration abnormal electrograms independently predicted the recurrence of ventricular arrhythmia after radiofrequency catheter ablation.

In the 2020 task force criteria for diagnosis,^[79] values based on sex-specific indexed volumetric measurements of end-diastolic volume and ejection fraction for both LV and RV were included.

Previous studies, which used non-indexed values, reported that men had larger ventricular volumes and lower ejection fractions when compared to women.^[67] Nevertheless, the North American ARVC Registry,^[75] which used indexed values, did not find a significant difference. The frequency of abnormal signal-averaged ECGs (SAECGs), inducible VT/ventricular fibrillation (VF), and positive cardiac biopsies was higher in men. The detection of intramyocardial fat on CMR imaging and abnormal SAECG was associated with adverse cardiac events in males. Nevertheless, this association was not found in women.^[75] The risk of fast VT/VF and death was lower in women [Figure 4]. In this

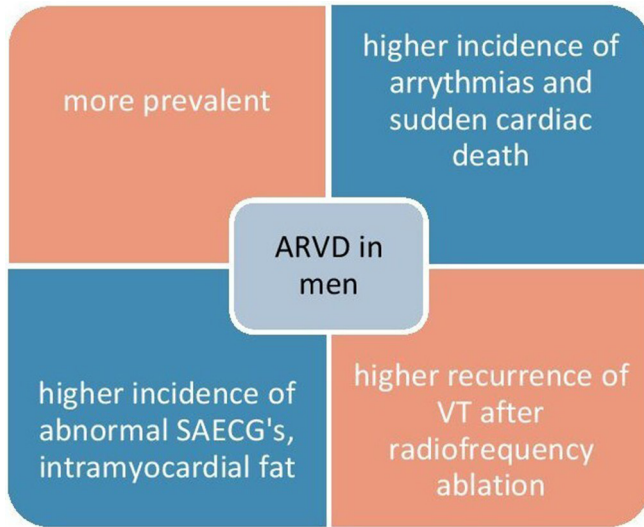


Figure 4: Arrhythmogenic right ventricular dysplasia in men. (SAECG: Signal averaged ECG, VT: ventricular tachycardia)

registry, the prevalence of the disease was similar between the sexes. In an analysis of the effect of sex hormones on the outcomes, increased serum testosterone in males and decreased estradiol levels in women are associated with adverse events.^[80]

There are variations among studies about the differences in prevalence and outcomes between the sexes. The role of referral bias, underdiagnosis, and other unrecognised factors should be studied further. Technologies that can better predict arrhythmias in females should be developed.

TTC

TTC is predominant in females, the proportion varying in different countries. In the Inter TAK registry (ITR),^[81] from the USA and Europe, the proportion of females is 89.8% and the Tokyo Cardiovascular Care Unit (CCU) Network reported a 72% of females. The mean age of the patients from Japan is between 70 and 80 years, and in Europe and the US, it is between 60 and 70 years.^[82] Affected men appear to be younger than women. The incidence of TTC is particularly high in post-menopausal women.^[83]

Physical and emotional triggers are the main triggers in males and females, respectively.^[84] Both negative and positive emotions can cause TTC, called broken heart syndrome and happy heart syndrome, respectively. Physical stressors include acute infections, trauma, sepsis, carcinoma, cerebrovascular accidents, postoperative state, and respiratory failure.^[85]

The incidence of chest pain is slightly higher in females. The rate of in-hospital complications, cardiogenic shock, heart failure requiring supportive therapy, and in-hospital mortality is higher in males than in females.^[86-88] White blood

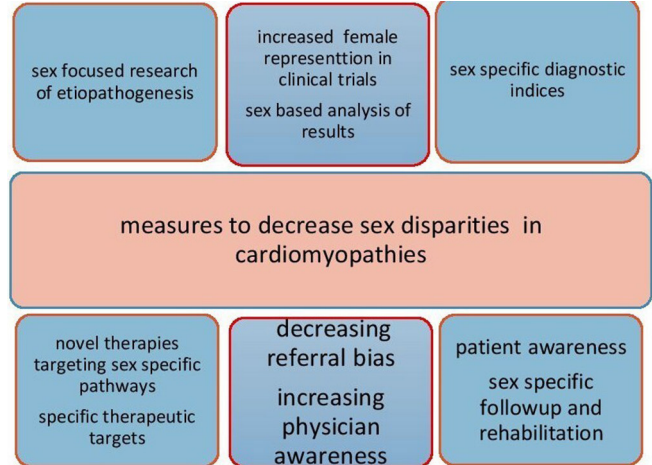




Figure 5: Measures to address sex disparities in cardiomyopathy.

Table 4: Sex differences in takotsubo cardiomyopathy.

		
Prevalence	+	+++
Age	Younger	Older, post-menopausal
Common triggers	Physical triggers	Emotional
Mortality	++	+
In-hospital complications	++	+
LV dysfunction	Higher	Lower
Recurrence	+	+++
Histopathology	Broad bands of necrosis, lymphocytic infiltrates	Few necrotic areas, no lymphocytic infiltrates

It denotes a comparative incidence. ++ means approximately twice that of +. +++ means more than thrice of +.

cell count and high-sensitivity C-reactive protein are also higher in males. The ITR reported that cardiac dysfunction is significantly greater in males than in females. Tokyo CCU Network reported an increased incidence of LV apical thrombus in males.

Recurrent TTC occurs uncommonly, with a varying rate of 4–10%. Recurrence is predominantly seen in females [Table 4]. The clinical presentation is observed to be similar between the initial and the later episodes; however, the triggers and patterns of regional wall motion abnormality on echocardiography vary.^[89,90]

The therapeutic effect of medications is similar between the

sexes. The utility of intra-aortic balloon counter pulsation and mechanical ventilation is higher in males, as the incidence of cardiogenic shock is higher.^[91]

Histopathology of the LV tissue exhibits broad areas of contraction band necrosis with lymphocytic infiltration in males. Whereas, in females, a few necrotic areas without lymphocytic infiltration were observed.^[87]

Many questions remain unanswered about the pathophysiology of TTC and the cause for female preponderance, etc., which need further study. The contribution of the hypoestrogenic state needs further investigation, as the serum estrogen concentrations in postmenopausal women are still higher than in males.^[92] It is speculated that the decreased susceptibility of the ERs to estrogen in postmenopausal women could be contributory and is being investigated. Measures to reduce sex disparities in cardiomyopathies are summarised in Figure 5.

CONCLUSION

The complex interaction of genetic, hormonal, biological, and social factors results in differences in the prevalence, pathophysiology, presentation, and outcomes of cardiomyopathies between the sexes. Further research is needed for a comprehensive understanding of the role of sex in the varied manifestations and response to therapy. Inadequate representation of women in clinical trials and gender neutral analysis of the results leads to incorrect representation of the disease manifestations and the treatment outcomes. Hence, it is crucial to increase the representation of women in future clinical trials with sex-based analysis and to develop sex-specific diagnostic indices and tailored therapies to improve the outcomes. Heightened awareness and a gender-based approach may decrease the disparities in clinical care.

Ethical approval: Institutional Review Board approval is not required.

Declaration of patient consent: Patient's consent not required as there are no patients in this study.

Financial support and sponsorship: Nil.

Conflicts of interest: There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation: The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript, and no images were manipulated using AI.

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How to cite this article: Lakshmi VSB, Ampabathuni G, Rongali P. Sex Differences in Cardiomyopathies. *Indian J Cardiovasc Dis Women*. doi: 10.25259/IJCDW_41_2025