JACC
© 2026 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
PUBLISHED BY ELSEVIER

JACC STATE-OF-THE-ART REVIEW

Sex Differences in Dilated Cardiomyopathy

Evidence Gaps and Future Directions

Sophie L.V.M. Stroeks, MD,[a,b,c,d] Shanelle Oko-Osi, MSc,[e,f] Arianna Arasu, MSc,[e,f] Jane E. Hirst, MD, PhD,[g] Upasana (Paz) Tayal, BMBCh, PhD[e,f]

ABSTRACT

Dilated cardiomyopathy (DCM), which affects 1 in 250 people, is a leading global cause of heart failure and the most common indication for heart transplantation. Evidence suggests that DCM is more prevalent in men, but whether this reflects biological differences or underdiagnosis in women remains uncertain. This review explores the impact of sex on DCM, examining differences in epidemiology, etiology, clinical presentation, treatment response, and outcomes. Women often present with less severe cardiac phenotypes, including lower levels of fibrosis and better left ventricular function, yet the long-term prognosis of DCM in women is less clear. Through a systematic review and meta-analysis, we found that male DCM patients with variants in *PLN*, *DSP*, and *LMNA* had higher arrhythmic event rates compared with TTNtv and *BAG3* carriers. In female patients with DCM, those with *RBM20*, *DSP*, and *PLN* variants faced the highest arrhythmic risk, and TTNtv carriers the lowest. *PLN* and *LMNA* variants had the highest heart failure risk in both sexes, whereas *BAG3*, *RBM20*, and *TTN* variants had lower heart failure rates in female compared with male carriers. These findings highlight the influence of sex and genotype on clinical outcomes. Current risk-stratification tools, such as those used for implantable cardioverter-defibrillators, may undertreat women owing to reliance on sex-neutral thresholds. We highlight the role of genetic, environmental, and reproductive factors in shaping these disparities, including the influence of pregnancy, pregnancy complications, and menopause. This review identifies key gaps in knowledge and calls for expanded representation of women in DCM studies and the development of sex-specific risk models. Addressing these gaps is essential to improving outcomes and advancing equitable personalized care for all DCM patients.
(JACC. 2026;87:723–735) © 2026 by the American College of Cardiology Foundation.

Dilated cardiomyopathy (DCM) is a common heart muscle disease, affecting roughly 1 in every 250 individuals, and is a leading cause of heart transplants and mortality.[1] The etiology of DCM is diverse and includes genetics, infectious and inflammatory diseases, and toxins, although many cases remain unexplained after extensive evaluation.[2] The literature on DCM presents a complex and often contradictory narrative when it comes to comparing the sexes. We have recently shown that DCM is more prevalent in men than in women, partly because of underdiagnosis in women and partly because of increased penetrance in men.[3] Factors influencing these sex biases in

Listen to this manuscript's audio summary by Editor-in-Chief Dr Harlan M. Krumholz on www.jacc.org/journal/jacc/podcasts.

From the [a]Department of Cardiology, Maastricht University, Cardiovascular Research Institute Maastricht, Maastricht, the Netherlands; [b]KU Leuven, Cardiovascular Sciences, Leuven, Belgium; [c]Department of Clinical Genetics, Maastricht University Medical Center, Maastricht, the Netherlands; [d]European Reference Network for Rare, Low Prevalence and Complex Diseases of the Heart (ERN GUARD-Heart), Amsterdam, the Netherlands; [e]National Heart Lung Institute, Imperial College London, London, United Kingdom; [f]Royal Brompton & Harefield Hospitals, Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom; and the [g]George Institute for Global Health, Imperial College London, London, United Kingdom.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received July 18, 2025; revised manuscript received September 3, 2025, accepted September 5, 2025.

ISSN 0735-1097/$36.00 https://doi.org/10.1016/j.jacc.2025.09.1603

ABBREVIATIONS AND ACRONYMS

DCM = dilated cardiomyopathy

DSP = desmoplakin gene

HF = heart failure

HFrEF = heart failure with reduced ejection fraction

ICD = implantable cardioverter-defibrillator

LMNA = lamin gene

LVEF = left ventricular ejection fraction

RBM20 = RNA-binding motif protein 20

TTN = titin gene

penetrance are incompletely understood. Our understanding of the different causes, risk factors, clinical presentation, and prognosis between men and women is rapidly evolving, although this is not currently accounted for in clinical care. This variability underscores the pressing need for research dedicated to exploring the sex-specific elements of DCM. These efforts are crucial in establishing if sex-specific strategies are needed for diagnosing, treating, and managing DCM.

The present review aims to synthesize current knowledge on sex differences in the epidemiology, etiology, clinical presentation, treatment response, and outcomes of genetic DCM, while highlighting gaps in understanding and suggesting directions for future research (**Central Illustration**). Although DCM can result from various causes, this review focuses primarily on genetic forms of DCM and the sex-specific differences associated with them. Sex differences in other causes of DCM are discussed if sex-stratified data in genetic DCM are not available, for example, heart failure (HF) treatment responses. Sex differences in broader causes of nonischemic cardiomyopathy and all-cause HF are not specifically evaluated.

EPIDEMIOLOGY

DCM is one of the most common causes of HF, with an estimated prevalence of approximately 1:250 to 1:400.[4] The incidence of DCM is reported as 5 to 7 cases per 100,000 persons per year, though there is considerable geographic variation in this because confirmation of disease requires cardiovascular imaging, which may not be as available in resource-poor settings.[5]

Sex differences are a notable feature of DCM epidemiology.[6] Men were consistently reported to have a higher incidence of DCM compared with women, but it was not clear if this was due to underdiagnosis in women or a genuine increased risk in men, and whether this applied to genetic and nongenetic forms of DCM. We recently undertook a systematic review, meta-analysis, and population study to evaluate this and found that DCM had a male-to-female ratio of 2:1 across all subtypes, including all-cause DCM, genetic DCM, gene-specific DCM (titin truncated variant [TTNtv] DCM and lamin variant [*LMNA*] DCM), and gene-elusive DCM.[3,7] Using UK Biobank population data,[3] we applied sex-specific imaging diagnostic thresholds and were able to diagnose more females with an imaging label of DCM. This reduced but did not eliminate the male sex bias entirely, demonstrating that the male bias in DCM is due to both underdiagnosis in women (owing to lack of sex-specific diagnostic thresholds) as well as increased susceptibility in men across genetic and nongenetic forms. These findings set the context for further exploration of why biological sex has such diverse effects in DCM.

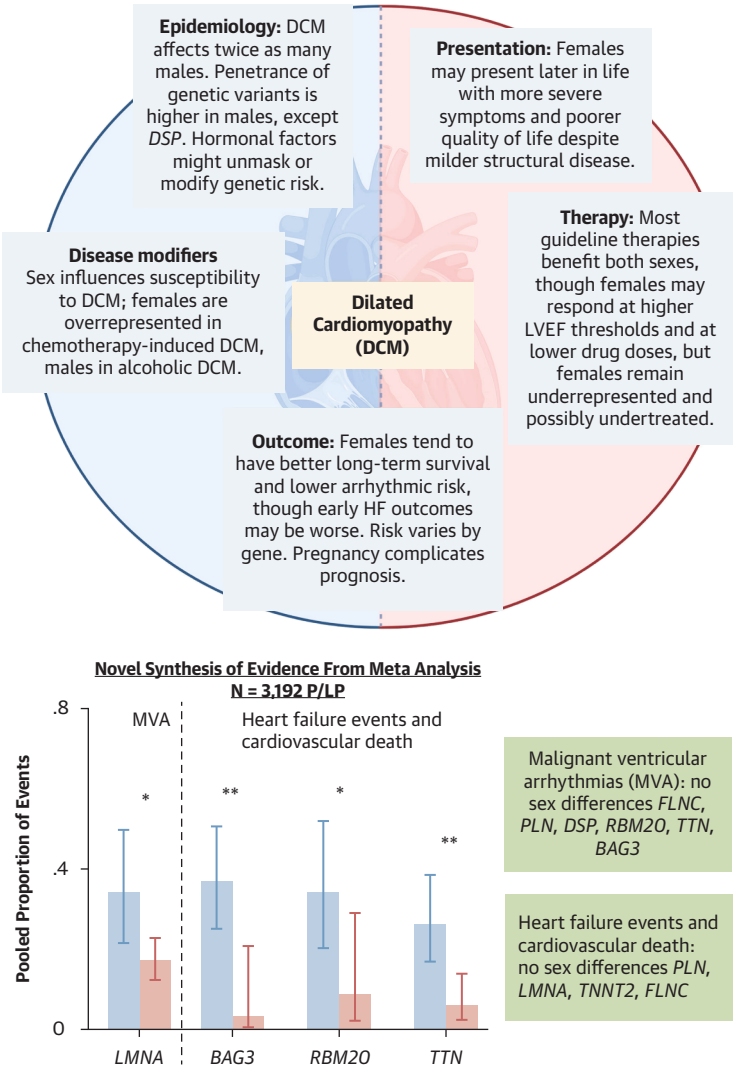
ETIOLOGY

GENETIC FACTORS. DCM is a multifactorial disease influenced by genetic, environmental, and comorbid factors (**Figure 1**). The journey from genotype to phenotype can be modified by traditional and sex-specific risk factors. Genetic risk includes rare monogenic variants, oligogenic interactions, and polygenic susceptibility, but variant presence alone does not ensure disease expression. Traditional risk factors (eg, hypertension, alcohol, infections, pregnancy) and sex-specific influences, such as hormones and immune differences, further modify disease onset and severity. As a result, DCM presentation reflects both genetic architecture and modifiable sex-related variables, as further evaluated in this review.

With approximately one-third of DCM cases attributed to a genetic cause, most often inherited in an autosomal dominant manner, the expression and penetrance of these variants are notably influenced by sex.[8] Although several monogenic subtypes show sex-based differences in penetrance and phenotype, the consistency of these findings across cohorts is variable, and data for many genes remain limited (**Figure 2**).

Our recent unpublished analysis of 3,410 adult and pediatric patients from the international SHaRe registry provides new insights into sex-specific genetic architecture in DCM. Across genotype-positive, gene-elusive, and variant of unknown significance subgroups, men were more frequently affected. However, clear gene-specific sex differences emerged, with TTNtv being significantly less common in women, whereas desmoplakin (*DSP*) variants and grouped sarcomeric variants (including *MYH7* and *TNNT2*) were more prevalent in women. Pediatric-onset cases also showed a male predominance (60%) but were enriched for sarcomeric gene variants. These findings from SHaRe represent the largest sex-stratified genotype analysis to date and underscore the critical importance of incorporating sex into genetic risk interpretation. These findings highlight the combined influence of genetic background and sex on DCM presentation.

CENTRAL ILLUSTRATION **Evaluating Sex Differences in DCM**



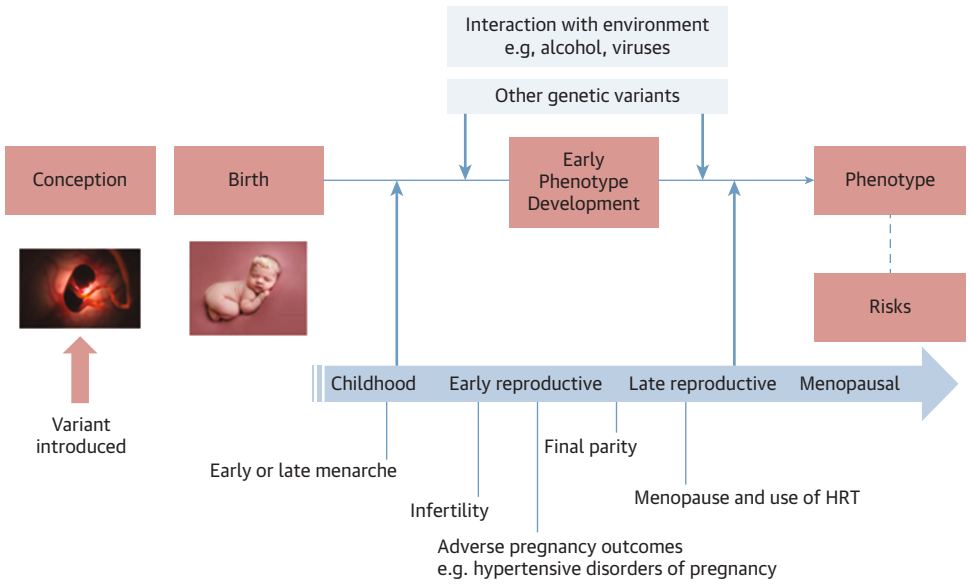
Stroeks SLVM, et al. JACC. 2026;87(6):723–735.

Dilated cardiomyopathy (DCM) appears to be more common in men, but it is not clear if this is due to systematic underdiagnosis in women or whether men are truly at higher risk. Our review explores the impact of sex on the epidemiology, presentation, and outcomes of disease. We summarize the latest research, including a meta-analysis on sex differences in outcome, and identify the gaps and inconsistencies in our current understanding of sex differences in DCM, along with some steps to resolve them.

Previous studies have also reported sex differences in DCM genetics, including a male predominance among carriers of TTNtv, *LMNA*, and RNA-binding motif protein 20 (*RBM20*) variants, and a higher proportion of women with *DSP* DCM (50%-69% in published cohorts).[7,9-13] X-Linked forms of DCM, such as those caused by dystrophin (*DMD*) variants,[14] further illustrate the interplay between sex and inheritance, with male carriers typically exhibiting more severe phenotypes and female carriers presenting with variable and often milder disease manifestations.

POTENTIAL INFLUENCE OF SEX HORMONES AND REPRODUCTIVE FACTORS IN DCM. Sex differences in cardiac pathophysiology and immune responses to cardiac injury contribute to observed disparities in DCM, but the underlying drivers remain unclear. Sex hormones may be important mediators.

FIGURE 1 Impact of Female Reproductive Life Events



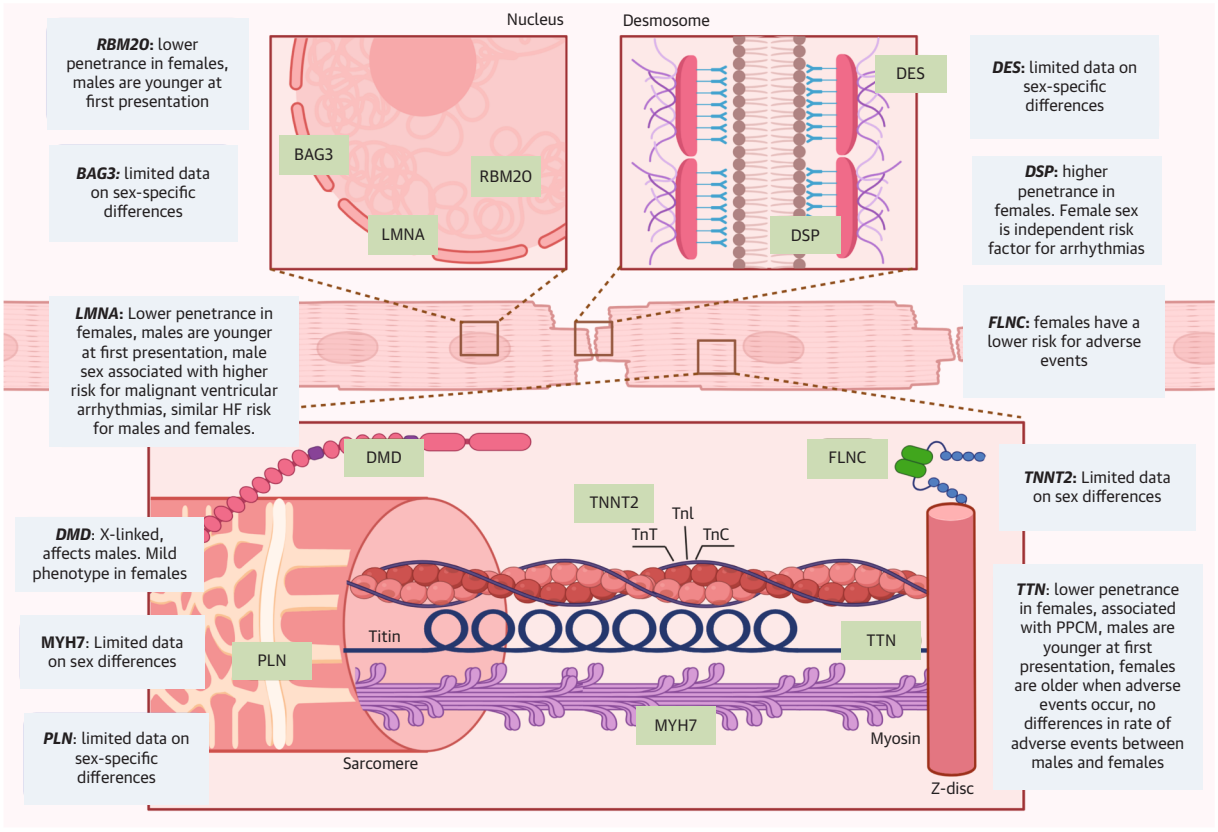
The journey from genotype to phenotype can be modified by traditional and sex-specific risk factors. The clinical presentation and outcome of dilated cardiomyopathy is determined by the coexistence of genetic (rare variant monogenic, oligogenic, and polygenic risk) and acquired factors. Acquired stressors such as pregnancy, toxins, including chemotherapy and alcohol, viruses, and autoimmune diseases have been well characterized. The impact of the reproductive lifespan on the development of dilated cardiomyopathy and modification of outcomes is not yet fully understood.

These hormones influence cardiac function directly by binding to androgen and estrogen receptors on vascular endothelial cells, smooth muscle cells, fibroblasts, and myocytes, and indirectly by modulating immune responses that shape cardiac inflammation, remodeling, and thrombosis in DCM.[15-17]

Testosterone promotes cardiac hypertrophy and inflammation, with studies linking genetically predicted testosterone levels to HF in men.[18] In nonhuman animal models, testosterone increases myocardial inflammation and adverse remodeling, and myocardial fibrosis in men and postmenopausal women is associated with sex hormone status.[19,20] Conversely, estradiol reduces cardiac hypertrophy and fibrosis, prevents cardiomyocyte apoptosis, and protects against oxidative stress-induced damage.[21] Women have higher levels of estrogen receptors, which are cardioprotective when activated by 17β-estradiol.[22] However, the relationship between physiologic hormone levels and cardiac remodeling in DCM remains inconsistent in human studies, suggesting opportunities for further evaluation of sex hormones in DCM pathogenesis.

Hormonal fluctuations also play a significant role in female-specific forms of DCM, such as peripartum cardiomyopathy (PPCM).[23] PPCM occurs in the late stages of pregnancy or postpartum and is more common in women of Black ancestry, with the highest incidences in Africa (1:100-1:1,000 births), Haiti (1:200 births), and Pakistan (1:840 births).[24,25] PPCM is a diagnosis of exclusion, and although pregnancy-related hormonal changes and physiologic stressors contribute to its development, the presence of pathogenic genetic variants, such as TTNtv, may indicate an underlying genetic cardiomyopathy that manifests during the hemodynamic stress of pregnancy.[26,27] Clinical recovery often occurs as hormonal levels return to pre-pregnancy states,[28] highlighting the interplay between genetic predisposition and sex-specific physiologic stressors in this condition. Reproductive risk factors interact with the risk of developing DCM and its complications, although our knowledge in this domain is still evolving (**Figure 1**). Pregnancy complications appear to influence the risk of developing DCM. We have recently shown that hypertensive disorders of pregnancy (HDP), which affect 5% to 10% of pregnancies, are associated with a 2-fold increased risk of developing DCM.[29] DCM develops an average 5 years earlier in those with HDP compared with those with normotensive first

FIGURE 2 **Genotype-Specific Sex Differences in Genetic Dilated Cardiomyopathy (DCM) Patients**



Sex specific genotype-phenotype associations are shown for some key DCM genes. For most genes, the disease appears to be more penetrant in men, with the exception of DSP. LMNA DCM is characterized by a worse phenotype in men. DMD = dystrophin gene associated with Duchenne muscular dystrophy; DSP = desmoplakin; FLNC = filamin C; LMNA = lamin; MYH7 = myosin heavy chain; RBM20 = RNA-binding motif protein 20; TTN = titin; TNNT2 = troponin T2.

pregnancies, and increased maternal age and postpartum hypertension are independently associated with the risk of developing DCM after HDP.

The role of menopause in DCM onset is not well defined. Early menopause has been associated with an increased risk of HF and metabolic issues such as obesity and insulin resistance.[30] Postmenopausal women also show reduced cardiac function, with studies reporting lower left ventricular longitudinal strain compared with premenopausal women of similar age.[31] These findings suggest that hormonal changes during menopause may contribute to sex differences in cardiac health, but they require further evaluation in DCM.

SEX DIFFERENCES IN ENVIRONMENTAL MODIFIERS OF DCM

Inflammation. Cardiac involvement in systemic immune-mediated diseases (SIDs) leading to DCM is common and linked to poor outcomes.[32] Although autoimmune diseases are more prevalent in women, we previously found a male predominance for SID-associated DCM.[33] This was particularly striking in autoinflammatory SID-DCM, where 70% of patients were male. Autoinflammatory diseases include conditions such as sarcoidosis, gout, and inflammatory bowel disease. In the autoimmune SID-DCM group, 52% of patients were male, despite conditions such as systemic lupus and rheumatoid arthritis being more common in women. These findings suggest that women may have protective factors for DCM, warranting further study.

Chemotherapy. Sex differences are notable in chemotherapy-induced DCM, with women disproportionately affected, largely owing to the high prevalence of breast cancer, a condition predominantly treated with cardiotoxic drugs such as anthracyclines.[34] Whether intrinsic biological differences further modulate susceptibility remains

uncertain. Female sex and preexisting cardiac risk factors are recognized contributors to chemotherapy-induced cardiomyopathy.[35] Elevated copeptin, a stable surrogate marker of vasopressin, functions as a prognostic biomarker in HF, with circulating concentrations typically higher in men, although its prognostic significance appears independent of sex.[36] The mechanisms of chemotherapy-induced cardiotoxicity vary by drug and are influenced by factors such as cumulative dose, drug formulation, administration route, and age at treatment.[37] Sex differences in cardiotoxicity across other drugs may be influenced by the role of female hormones in oxidative stress and mitochondrial dysfunction,[38] as well as differences in drug pharmacokinetics.

Alcohol. In alcohol-induced cardiomyopathy, men represent 57%-100% of cases.[39] One study found a 9:1 male-female ratio among admissions for alcohol-induced cardiomyopathy, possibly driven by social factors such as greater cultural acceptance of alcohol use in men.[40] The intersection with genetics is also important. We have previously shown an interaction with TTNtv and moderate alcohol consumption in male-dominated DCM cohorts, leading to a reduction in left ventricular ejection fraction (LVEF), supporting the "second-hit hypothesis," where genetic predisposition combines with environmental stressors such as alcohol to trigger disease.[41]

Sex-based differences in DCM risk after exposure to toxins such as chemotherapy and alcohol remain incompletely understood. Dose and duration of exposure, effects on sex hormone production, and genetic predisposition may all contribute. Limited data are available on the sex-specific effects of other toxins, including immune therapies, recreational drugs such as marijuana and cocaine, and pesticides, highlighting the need for further research in this area.

PRESENTATION

AGE OF DIAGNOSIS. In general, there are not thought to be differences in age of diagnosis between men and women with DCM.[42] However, sex-based differences in age at presentation are more apparent when stratified by genotype. Men with TTNtv appear to present earlier than women,[43] and male carriers of *LMNA* and *RBM20* variants also show earlier disease onset than women (42 vs 54 years for *LMNA*; 29 vs 38 years for *RBM20*).[44,45] It is important to note that social determinants of health, including access to care, socioeconomic status, and potential delays in referral, may also influence these observations of early presentation in men.[46,47] Some of these factors are challenging to quantify and may vary across health care systems, potentially confounding comparisons of age at diagnosis. Taken together, these findings highlight the combined influence of genetic background, sex, and health care–related factors on DCM presentation.

SYMPTOMS AT PRESENTATION AND HEALTH-RELATED QUALITY OF LIFE. The literature on sex differences in symptoms at first presentation of DCM is mixed. Some studies suggest that women present with more severe symptoms and higher NYHA functional class at baseline despite having less severe cardiac dysfunction (higher LVEF) and lower burden of scar, and receiving similar HF pharmacologic therapy compared with men.[6] Furthermore, women exhibited less severe ventricular dysfunction at first presentation than men (28% vs 59%, adjusted for sex-specific volumes).[48] However, other studies report no significant differences in NYHA functional class or LVEF between sexes, a pattern consistent also in patients with late-onset DCM (age >60 years).[49] These findings reveal a discrepancy between symptom severity and clinical measures of heart function in women, which remains unaddressed in clinical care. Symptoms in women may be underrecognized or underreported, contributing to this complexity.[50]

Women with heart failure with reduced ejection fraction (HFrEF) often report worse health-related quality of life than men, despite having similar physician-assessed symptoms and markers of cardiac function.[50,51] The underlying reasons for these differences are not fully understood, because they are not explained solely by HF severity or comorbidities. Coexisting depression and anxiety, which are more prevalent in women, may further contribute to worse quality of life and complicate clinical assessment.[52] Although these findings are derived from HFrEF cohorts, they likely have implications for women with DCM. These observations underscore the importance of incorporating patient-reported outcomes and psychosocial factors when evaluating and managing women with DCM.

BIOMARKERS. Sex differences in DCM also extend to biomarkers, which may influence how DCM is diagnosed and monitored. Women generally have higher natriuretic peptide levels (eg, N-terminal pro-B-type natriuretic peptide [NT-proBNP]) in healthy states, partly influenced by androgens, because testosterone suppression in men increases NT-proBNP.[53] However, in HF, these differences attenuate, with levels similar or lower in women owing to men having more HFrEF, where NT-proBNP levels are higher. Conversely, cardiac injury markers (troponins) and inflammation

biomarkers are typically higher in men, in both healthy individuals and HF patients.[54]

OUTCOME

On average, many studies suggest that women with DCM tend to have better long-term outcomes than men, although this pattern is not uniform across all cohorts or time periods. Women with DCM have significantly lower rates of all-cause mortality, heart transplantation, and ventricular assist device implantation compared with men (22% vs 33% over a 10-year follow-up).[48] Women under 60 years of age had approximately one-half the 5-year mortality rate of men (6.7% vs 13.5%).[6] In addition, women exhibited a 40% lower risk of life-threatening ventricular arrhythmias.[55] However, in the first 2 years after diagnosis, female sex has been associated with worse HF outcomes, despite women presenting with less severe ventricular dilation and higher LVEF than men.[42] Current guidelines, however, do not include sex-specific LVEF thresholds.[56] Women often present with a higher LVEF compared with men, even in health, but this is not accounted for in clinical care, where treatment decisions are often made on sex-agnostic thresholds.[57] Evidence from PARAGON-HF (A Multicenter, Randomized, Double-blind, Parallel Group, Active-controlled Study to Evaluate the Efficacy and Safety of LCZ696 Compared to Valsartan, on Morbidity and Mortality in Heart Failure Patients [NYHA Class II-IV] With Preserved Ejection Fraction; NCT01920711) and TOPCAT (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist; NCT00094302) indicates that female patients may gain greater benefit from therapies such as sacubitril/valsartan and spironolactone at higher LVEFs compared with male patients.[58,59] These data support the concept that adopting sex-specific LVEF cutoffs may more accurately capture the pathophysiology of HF in female patients and improve early identification and management of at-risk female patients. Indeed, we have shown that using sex-specific imaging cutoffs to diagnose DCM can lead to more women being diagnosed with DCM.[3] LVEF is, however, influenced by heart rate, image quality, and other external factors. Therefore, further research is needed to determine whether sex-specific cutoffs can improve clinical decision making. The key remaining challenge is to evaluate whether these cutoffs provide a "net clinical benefit" when evaluated against potential harms from therapy (eg, medication side-effects, inappropriate shocks from implantable cardioverter-defibrillators [ICDs]) and whether the change in treatment thresholds lead to improved outcomes for female and male patients. Broadening treatment decisions beyond single-factor single-threshold approaches (eg, LVEF greater or less than 35%) may enable us to capture the complex interplay between sex, cardiac function, treatment, and outcomes in patients with DCM.

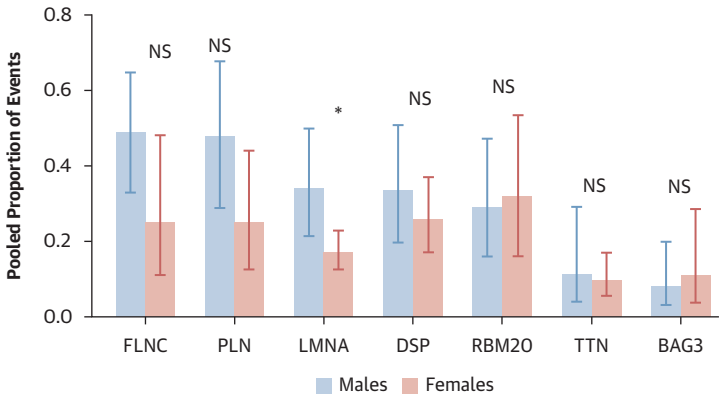
Pregnancy in females with DCM carries significant maternal and fetal risks, with up to one-half experiencing peripartum cardiac events such as HF and arrhythmias, particularly in those with moderate to severe left ventricular dysfunction, NYHA functional class III/IV symptoms, or genetic predispositions such as TTNtv and *LMNA* variants, although data are limited on pregnancy outcomes stratified by genetic DCM.[60,61] These complications are associated with worse long-term survival,[61] and fetal risks include preterm birth, intrauterine growth restriction, and miscarriage.[62,63] Management should involve a multidisciplinary team, with optimization of heart failure therapies, consideration of cardiac devices, and close maternal-fetal monitoring. In severe cases, an elective cesarean section may be necessary to reduce cardiovascular stress during labor.

OUTCOME IN GENETIC DCM. Sex-specific outcomes appear to differ in genetic DCM and are an area of active research. In TTNtv carriers, women experience adverse events later than men (average age 68 vs 56 years), although rates of malignant arrhythmias and all-cause mortality appear to be similar.[64] Women with *LMNA* variants have a 45% lower risk of life-threatening arrhythmias compared with men, making male sex an independent predictor of adverse outcomes in *LMNA* risk stratification.[65] In contrast, women with a *DSP* variant face a higher risk of life-threatening arrhythmias than men in up to 5 years follow-up.[66] Therefore, in *DSP* risk stratification, female sex is currently considered to be an independent predictor, although whether this reflects sex differences in penetrance (increased penetrance in women) or genuine sex differences in prognosis remains to be clarified.[67]

Systematic review and meta-analysis on outcomes stratified by sex and genetic status. Indeed, the overall burden of adverse outcomes stratified by sex and genetic status in DCM has not been established. Therefore, we undertook a systematic review and meta-analysis using a random effects model to assess sex-stratified outcomes in genetic DCM[68] (Supplemental Methods and Results). This section presents a novel synthesis of the literature on sex-stratified outcomes in genetic DCM.

A comprehensive literature search screening 3,723 studies identified 33 studies for inclusion, comprising

FIGURE 3 Combined Male and Female Risk Summary Barplot for the Outcome of Major Ventricular Arrhythmias



This barplot displays the meta-analysis pooled proportions of arrhythmic events (y-axis) in men (blue bars) and women (pink bars) for each gene subgroup (x-axis) ordered by descending male event proportion. The pooled proportions are derived from the meta-analysis results for each sex, which excluded studies with <20 participants per sex. Effect size represents the absolute difference in event proportions between sexes (eg, *LMNA*: 0.34 in men vs 0.17 in women; effect size = 0.17). Error bars indicate 95% CIs. *Statistically significant sex difference ($P < 0.05$), highlighting effect sizes that reflect meaningful differences. Abbreviations as in Figure 2.

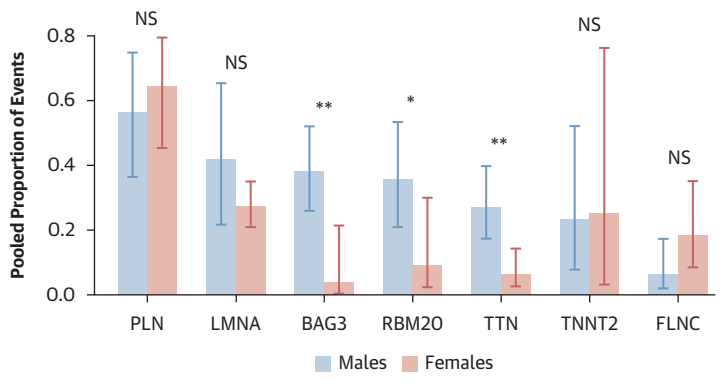
3,192 carriers of pathogenic variants in one of the DCM-associated genes[68] (Supplemental Table 1). Studies with relevant genotype-stratified outcomes were available for only 10 of the 12 DCM-associated genes; relevant data for troponin C1 (*TNNC1*) and desmin (*DES*) variant carriers could not be isolated. The meta-analysis analyzed the pooled proportions of major arrhythmic and HF events, stratified by both gene and sex. Further details are outlined in the Supplemental Methods and Results. Our analysis revealed notable sex-based differences in arrhythmic and heart failure events across genetic subgroups.

Outcome in genetic DCM: major arrhythmic events. Major arrhythmic events (sudden cardiac death and malignant ventricular arrhythmias, defined as sustained ventricular tachycardia associated with hemodynamic compromise or ventricular fibrillation) were significantly more common in men with DCM and *LMNA* variants than in women with DCM and *LMNA* variants (pooled proportion 0.34 male, 0.17 female; $P = 0.01$) (Figure 3). The data are strongest for carriers of *LMNA* and TTNtv variants because they affect more patients with DCM. Arrhythmic events were most common in those with filamin C (*FLNC*) and phospholamban (*PLN*) variants, and they appeared to be more common in male *FLNC* and *PLN* variant carriers than in female carriers, but these differences were not statistically significant, which may reflect the heterogeneity of estimates in the female subgroups due to relatively smaller sample sizes. *DSP* and *RBM20* were associated with high rates of arrhythmic events (>20% pooled event proportion), and this risk appeared to be equal between men and women. *TTN* and *BAG3* variants were associated with the lowest risks of arrhythmic events, and the risks were similar between the sexes.

Outcome in genetic DCM: HF events. Carriers of *PLN* and *LMNA* variants in both sexes were at the highest risk for HF events, including HF hospitalizations, heart transplant, left ventricular assist device, and cardiovascular death. Therefore although *LMNA* cardiomyopathy has a higher risk of arrhythmic complications in men, female carriers have the same elevated risk of HF complications and cardiovascular death as male carriers. Among men, HF complications were common in *BAG3*, *RBM20*, and TTNtv variant carriers (>20% pooled event proportion), and these were also more likely to occur in male patients than in female patients (Figure 4). Interestingly, HF complications were noted to be more frequent in female patients than in male patients with *FLNC* variants, but these differences were not statistically significant, which again may reflect the heterogeneity of estimates in the *FLNC* female subgroups due to relatively smaller sample sizes.

These findings underscore the importance of considering both sex and gene-specific status when assessing risk and tailoring management strategies

FIGURE 4 Combined Male and Female Risk Summary Barplot for the Composite Outcome of Heart Failure Events and Cardiovascular Death



This barplot displays the pooled proportions of the events (y-axis) in men (blue bars) and women (pink bars) for each gene subgroup (x-axis) ordered by descending male event proportion. The pooled proportions are derived from the meta-analysis results for each sex, which excluded studies with <20 participants per sex. Effect size represents the absolute difference in event proportions between sexes. Error bars indicate 95% CIs. Statistically significant sex differences, highlighting effect sizes that reflect meaningful differences: *$P < 0.05$; **$P < 0.01$. Abbreviations as in Figure 2.

for genetic DCM. These findings also highlight the need for sex-stratified reporting of outcome studies in genetic DCM. Further research into sex-specific genetic modifiers and hormonal impacts on gene expression could advance personalized strategies for risk assessment and treatment.

LVEF RECOVERY IN GENETIC DCM AND SEX EFFECTS

Female sex is associated with greater improvement in LVEF, particularly within the first 12 months, as demonstrated in studies of DCM and supported by data from cardiac resynchronization therapy (CRT) in nonischemic cardiomyopathy cohorts.[69] While some studies report similar rates of recovery (often defined as significant and sustained improvement of LVEF, typically involving an increase of at least 10 percentage points or reaching a normal value [≥50%] at follow-up) between sexes, women who achieve recovery tend to have superior long-term outcomes compared with both men and women without recovery.[48]

TREATMENT RESPONSE

Current treatment for DCM primarily follows HF management guidelines, which do not differentiate dosages based on sex. However, the lower body weight, higher fat percentage, and reduced plasma volume of women suggest that standard dosing may not always be optimal for them, potentially increasing their risk of adverse effects, such as angiotensin-converting enzyme inhibitor (ACEI)-related cough, which women experience twice as often as men.[6,70]

Evidence for sex differences in treatment efficacy for DCM is mixed. While typical neurohormonal blockade, such as angiotensin receptor–neprilysin inhibitor, ACEI, and mineralocorticoid receptor antagonist, appears equally effective for men and women, some studies suggest that women achieve greater benefits at higher LVEF levels. For example, the CHARM program, which evaluated candesartan across both ischemic and nonischemic HF, did not demonstrate a statistically significant sex-treatment interaction, yet women had lower risks of fatal and nonfatal outcomes, including cardiovascular and noncardiovascular death as well as HF-related hospitalizations.[71] Importantly, these findings were not explained by cause of HF or baseline LVEF, suggesting that additional biological or clinical factors may contribute to the observed sex differences.[72] In addition, compared with valsartan, sacubitril-valsartan appeared to reduce the risk of HF hospitalization in women more than in men.[58] Sex-specific analyses of digoxin from the DIG trial, however, demonstrated increased mortality in women, although pharmacokinetic studies indicate that when serum digoxin levels remain within the therapeutic range, women derive benefit similarly to men.[73] Other major trials, including DAPA-HF (dapagliflozin, an sodium-glucose cotransporter 2 inhibitor), and EMPEROR-Reduced (empagliflozin, another sodium-glucose cotransporter 2 inhibitor), reported universal benefits without significant sex differences.[74,75] Importantly, women are underrepresented in these trials (21%-40% of participants), raising concerns about the generalizability of findings and highlighting the need for more balanced inclusion in future research.

Notably, large trials with balanced sex representation have provided important insights. For example, in PARADIGM-HF (A Multicenter, Randomized, Double-blind, Parallel Group, Active-controlled Study to Evaluate the Efficacy and Safety of LCZ696 Compared to Enalapril on Morbidity and Mortality in Patients With Chronic Heart Failure and Reduced Ejection Fraction; NCT01035255), which enrolled patients with HFrEF, sacubitril/valsartan was associated with consistent benefit across sexes, with no significant interaction between sex and outcome.[76] The PARAGON-HF study, which primarily focused on heart failure with preserved ejection fraction, but also included patients with heart failure with mid-range ejection fraction (LVEF ≥45%), found that sacubitril/valsartan reduced the risk of HF hospitalizations in women similarly to men.[77] These findings underscore the need for adequately powered sex-specific analyses and for deeper investigation into the biological mechanisms that may underlie differential responses. A clearer understanding of these mechanisms will be essential to optimize treatment strategies for both men and women with HF. Optimizing dosage for females may further improve outcomes. Post hoc analyses from the BIOSTAT-CHF and ASIAN-HF trials revealed that men benefit most from full guideline-recommended doses of ACEI, angiotensin receptor blockers, and beta-blocker, whereas women achieved similar risk reductions at one-half the recommended dose, with no added benefit at higher doses.[78] These findings suggest that tailored dosing for women could provide equivalent long-term outcomes while reducing adverse effects, although further evidence from adequately powered clinical trials are needed to support guideline changes.

While baseline therapy may appear similar between men and women in some cohorts, recent real-

world data reveal substantial sex disparities in guideline-directed medical therapy (GDMT) utilization.[79] In a national U.S. cohort of >60,000 newly diagnosed HFrEF patients, women were less likely than men to receive any GDMT or achieve optimal therapy within the first year after diagnosis, with a 23% lower probability of attaining guideline-recommended treatment targets.[80] Similarly, an analysis of >2,000 patients with incident HFrEF found that female patients were more often prescribed only single-agent therapy, highlighting persistent undertreatment.[81] Contributing factors include differences in comorbidity burden, underreferral to cardiology or HF specialists, and potential physician bias or therapeutic inertia. Although meta-analytic data confirm that the efficacy of HFrEF therapies is largely similar between sexes,[82] these real-world findings indicate that female patients might be systematically undertreated. This disparity underscores the urgent need for targeted implementation strategies to ensure equitable care and maximize therapeutic benefit for women with HFrEF.

Device-based therapies are a cornerstone of HF management, yet sex-specific responses and utilization patterns warrant careful consideration. Data from the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy; NCT00180271) trial, which evaluated cardiac resynchronization therapy with defibrillator (CRT-D), indicate more favorable outcomes in women than in men, suggesting potential sex-specific benefits of device therapy.[83] A meta-analysis of patient-level data from multiple CRT-D trials demonstrated that women with left bundle branch block experienced a mortality benefit at shorter QRS durations (≥130 ms) compared with men (≥150 ms), despite primarily having mild HF.[84] However, these sex-specific differences are not implemented in current guidelines. Importantly, female patients remain less likely than men to receive CRT-D in practice, highlighting a persistent sex gap in device utilization. In SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial; NCT00000609), ICD therapy reduced mortality in patients with HFrEF.[85] Female patients made up only 23% of participants, limiting the ability to detect sex-specific differences, although available data suggest that benefits were broadly similar between men and women. In SCD-HeFT, prespecified subgroup analyses did not show a greater benefit of ICD therapy in women, with hazard ratios numerically more favorable in men.[86] These findings suggest that ICDs reduce mortality in HFrEF in both sexes, but the trial was not powered to evaluate sex-specific effects. More broadly, the consistent underrepresentation of women in ICD trials makes it challenging to draw firm conclusions regarding sex differences in treatment response.[87] Contemporary analyses support similar overall efficacy of ICDs in male and female patients, although emerging data indicate that the mode of death may differ by sex, being more similar in nonischemic cardiomyopathy and higher cardiac deaths in men with ischemic cardiomyopathy.[88] These results underscore the need to consider sex-specific thresholds when evaluating patients for CRT-D and ICDs, as well as adequately powered sex-specific analyses and the broader potential of pooled trial data to inform guideline development and optimize outcomes for female patients.

Sex differences in the utilization and outcomes of advanced HF therapies, including left ventricular assist devices (LVADs) and heart transplantation, are increasingly recognized. Female patients remain underrepresented among LVAD recipients, comprising only about 20% of patients, and are less likely than men to undergo heart transplantation after implantation.[89] After implantation, female patients experience higher mortality and more adverse events, including rehospitalization, bleeding, stroke, and device complications. Younger female patients (<50 years) are particularly affected, whereas outcomes are similar in those ≥65 years old.[89] Structural factors, such as delayed referral, lower access to specialized centers, and social determinants of health, further contribute to these disparities.[90] These findings highlight the need for strategies to ensure equitable access and outcomes for female patients requiring advanced HF therapies.

MAJOR GAPS IN OUR UNDERSTANDING OF SEX DIFFERENCES IN DCM

FEMALE-SPECIFIC RISK FACTORS FOR DCM. There are observed sex-based differences in the prevalence and onset of DCM, which might be partially explained by genetic and environmental disease modifiers. Although we have gained insight into some of these factors, such as chemotherapy and alcohol consumption, sex-specific risk factors remain largely unknown. These risk factors might include hormonal fluctuations such as hormonal contraception, pregnancy-related factors such as preeclampsia, peripartum cardiomyopathy, lactation, repeated hemodynamic stress, and menopause. The impact of female-specific risk factors on DCM onset and progression is poorly understood and not currently incorporated into DCM management. Younger menarche age, premature menopause, and infertility

are associated with HF risk, but their specific impact on DCM remains unclear.[91] Menopause is a known period of accelerated coronary risk,[92] yet its influence on DCM development is undefined. A comprehensive evaluation of reproductive risk factors represents an opportunity to identify individuals at risk for DCM and refine risk calculators for adverse outcomes, enabling better disease management and reducing the burden of DCM in women.

We have recently evaluated sex differences in the underlying genetic architecture of DCM. There appears to be a male predominance for most of the common genetic causes of DCM, with the exception of *DSP* DCM, which has a female predominance and an earlier disease onset in women.[93] Understanding the genetic and environmental drivers for why *DSP* variants appear to be more penetrant in women may help us gain insights into the sex specificity of DCM.

SEX DIFFERENCES IN RISK STRATIFICATION. Women with DCM often exhibit a "milder-looking" phenotype, with less hypertrophy, less fibrosis, and better cardiac function than men. However, despite this, women have a 2-fold higher risk of adverse outcomes, such as cardiovascular death and HF, compared with men.[94] Current risk stratification for DCM, including recommendations for ICDs, relies on a sex-agnostic threshold of LVEF <35%. This approach may undertreat women by failing to account for sex-specific differences in disease progression and outcomes.

Efforts to refine risk stratification are beginning to address these gaps. For example, sex has been integrated into the *LMNA* DCM risk prediction model, which estimates the likelihood of life-threatening arrhythmias in *LMNA* variant carriers.[65] Similarly, risk prediction tools have been developed for *DSP*, *FLNC*, and *PLN* DCM,[67,94,95] enhancing individualized risk assessment by incorporating genotype-specific features and clinical variables. The incorporation of sex in such models underscores its relevance in predicting outcomes and guiding interventions in genetic forms of DCM.

CONCLUSIONS

Sex differences in DCM are observed in aspects of prevalence, age at onset, clinical presentation, risk factors, and outcomes, although the strength and consistency of these differences vary across domains. Despite significant strides in understanding DCM pathophysiology, current clinical care and risk stratification remain largely sex neutral, potentially overlooking critical differences that influence disease progression and prognosis. Emerging evidence underscores the role of genetic, environmental, and reproductive factors in shaping sex-specific risks, but much remains unknown. Advancing DCM care requires prioritizing sex-specific research that will not only enhance outcomes for women but also provide more holistic and equitable care for all DCM patients.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Hirst has received funding from the UKRI (UK) (MR/T040750/1). Dr Tayal has received funding from the Medical Research Council (UK) (MR/W023830/1); and has received fees for educational content from Chiesi Medical. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Upasana Tayal, National Heart and Lung Institute, Imperial College London, Sydney Street, London SW3 6NP, United Kingdom. E-mail: u.tayal14@imperial.ac.uk.

REFERENCES

1. Hershberger RE, Hedges DJ, Morales A. Dilated cardiomyopathy: the complexity of a diverse genetic architecture. *Nat Rev Cardiol*. 2013;10:531–547.

2. Heymans S, Lakdawala NK, Tschöpe C, Klingel K. Dilated cardiomyopathy: causes, mechanisms, and current and future treatment approaches. *Lancet*. 2023;402:998–1011.

3. Bergan N, Prachee I, Curran L, et al. Systematic review, meta-analysis, and population study to determine the biologic sex ratio in dilated cardiomyopathy. *Circulation*. 2025;151:442–459.

4. Myers MC, Berge A, Zhong Y, et al. Prevalence and incidence of dilated cardiomyopathy in the United States and Western Europe: a systematic review. *Cardiol Res*. 2025;16:295–305.

5. Bozkurt B, Colvin M, Cook J, et al. Current diagnostic and treatment strategies for specific dilated cardiomyopathies: a scientific statement from the American Heart Association. *Circulation*. 2016;134:e579–e646.

6. Halliday BP, Gulati A, Ali A, et al. Sex- and age-based differences in the natural history and outcome of dilated cardiomyopathy. *Eur J Heart Fail*. 2018;20:1392–1400.

7. Jain A, Norton N, Bruno KA, Cooper LT Jr, Atwal PS, Fairweather D. Sex differences, genetic and environmental influences on dilated cardiomyopathy. *J Clin Med*. 2021;10.

8. Bourfiss M, van Vugt M, Alasiri AI, et al. Prevalence and disease expression of pathogenic and likely pathogenic variants associated with inherited cardiomyopathies in the general population. *Circ Genom Precis Med*. 2022;15:e003704.

9. Akhtar MM, Lorenzini M, Cicerchia M, et al. Clinical phenotypes and prognosis of dilated cardiomyopathy caused by truncating variants in the TTN gene. *Circ Heart Fail*. 2020;13:e006832.

10. Tayal U, Newsome S, Buchan R, et al. Phenotype and clinical outcomes of titin cardiomyopathy. *J Am Coll Cardiol*. 2017;70:2264–2274.

11. Kayvanpour E, Sedaghat-Hamedani F, Amr A, et al. Genotype-phenotype associations in dilated cardiomyopathy: meta-analysis on more than 8000 individuals. *Clin Res Cardiol*. 2017;106:127–139.

12. Smith ED, Lakdawala NK, Papoutsidakis N, et al. Desmoplakin cardiomyopathy, a fibrotic and inflammatory form of cardiomyopathy distinct from typical dilated or arrhythmogenic right ventricular cardiomyopathy. *Circulation*. 2020;141:1872–1884.

13. Wang W, Murray B, Tichnell C, et al. Clinical characteristics and risk stratification of desmoplakin cardiomyopathy. *Europace*. 2022;24:268–277.

14. Johnson R, Otway R, Chin E, et al. DMD-associated dilated cardiomyopathy: genotypes, phenotypes, and phenocopies. *Circ Genom Precis Med*. 2023;16:421–430.

15. Vitale C, Mendelsohn ME, Rosano GM. Gender differences in the cardiovascular effect of sex hormones. *Nat Rev Cardiol*. 2009;6:532–542.

16. Watts K, Richardson WJ. Effects of sex and 17β-estradiol on cardiac fibroblast morphology and signaling activities in vitro. *Cells*. 2021;10.

17. Adu-Amankwaah J, Bushi A, Tan R, et al. Estradiol mitigates stress-induced cardiac injury and inflammation by downregulating ADAM17 via the GPER-1/PI3K signaling pathway. *Cell Mol Life Sci*. 2023;80:246.

18. Diaconu R, Donoiu I, Mirea O, Bălşeanu TA. Testosterone, cardiomyopathies, and heart failure: a narrative review. *Asian J Androl*. 2021;23:348–356.

19. Cavasin MA, Tao ZY, Yu AL, Yang XP. Testosterone enhances early cardiac remodeling after myocardial infarction, causing rupture and degrading cardiac function. *Am J Physiol Heart Circ Physiol*. 2006;290:H2043–H2050.

20. Chehab O, Shabani M, Varadarajan V, et al. Endogenous sex hormone levels and myocardial fibrosis in men and postmenopausal women. *JACC Adv*. 2023;2:100320.

21. Xiang D, Liu Y, Zhou S, Zhou E, Wang Y. Protective effects of estrogen on cardiovascular disease mediated by oxidative stress. *Oxid Med Cell Longev*. 2021;2021:5523516.

22. Iorga A, Cunningham CM, Moazeni S, Ruffenach G, Umar S, Eghbali M. The protective role of estrogen and estrogen receptors in cardiovascular disease and the controversial use of estrogen therapy. *Biol Sex Differ*. 2017;8:33.

23. Pearson GD, Veille JC, Rahimtoola S, et al. Peripartum cardiomyopathy: National Heart, Lung, and Blood Institute and Office of Rare Diseases (National Institutes of Health) workshop recommendations and review. *JAMA*. 2000;283:1183–1188.

24. Brar SS, Khan SS, Sandhu GK, et al. Incidence, mortality, and racial differences in peripartum cardiomyopathy. *Am J Cardiol*. 2007;100:302–304.

25. Sliwa K, Fett J, Elkayam U. Peripartum cardiomyopathy. *Lancet*. 2006;368:687–693.

26. Goli R, Li J, Brandimarto J, et al. Genetic and phenotypic landscape of peripartum cardiomyopathy. *Circulation*. 2021;143:1852–1862.

27. Ware JS, Li J, Mazaika E, et al. Shared genetic predisposition in peripartum and dilated cardiomyopathies. *N Engl J Med*. 2016;374:233–241.

28. Moulig V, Pfeffer TJ, Ricke-Hoch M, et al. Long-term follow-up in peripartum cardiomyopathy patients with contemporary treatment: low mortality, high cardiac recovery, but significant cardiovascular co-morbidities. *Eur J Heart Fail*. 2019;21:1534–1542.

29. Tayal U, Kallis C, Massen GM, Rossberg N, Graul EL, Quint JK. Hypertensive disorders of pregnancy and long-term risk of dilated cardiomyopathy. *JAMA Cardiol*. 2025;10:498–502.

30. Ebong IA, Watson KE, Goff DC Jr, et al. Age at menopause and incident heart failure: the Multi-Ethnic Study of Atherosclerosis. *Menopause*. 2014;21:585–591.

31. Keskin Kurt R, Nacar AB, Güler A, et al. Menopausal cardiomyopathy: does it really exist? A case-control deformation imaging study. *J Obstet Gynaecol Res*. 2014;40:1748–1753.

32. Comarmond C, Pagnoux C, Khellaf M, et al. Eosinophilic granulomatosis with polyangiitis (Churg-Strauss): clinical characteristics and long-term followup of the 383 patients enrolled in the French Vasculitis Study Group cohort. *Arthritis Rheum*. 2013;65:270–281.

33. Stroeks S, Henkens M, Dominguez F, et al. Genetic landscape of patients with dilated cardiomyopathy and a systemic immune-mediated disease. *JACC Heart Fail*. 2025;13:133–145.

34. Liu C, Chen H, Guo S, et al. Anti-breast cancer-induced cardiomyopathy: mechanisms and future directions. *Biomed Pharmacother*. 2023;166:115373.

35. Diaz ANR, Hurtado GP, Manzano AAA, et al. Sex differences in the development of anthracycline-associated heart failure. *J Card Fail*. 2024;30:907–914.

36. Sun H, Sun T, Ma B, et al. Prediction of all-cause mortality with copeptin in cardiocerebrovascular patients: a meta-analysis of prospective studies. *Peptides*. 2015;69:9–18.

37. Oeffinger KC, Mertens AC, Sklar CA, et al. Chronic health conditions in adult survivors of childhood cancer. *N Engl J Med*. 2006;355:1572–1582.

38. Varga ZV, Ferdinandy P, Liaudet L, Pacher P. Drug-induced mitochondrial dysfunction and cardiotoxicity. *Am J Physiol Heart Circ Physiol*. 2015;309:H1453–H1467.

39. Domínguez F, Adler E, García-Pavía P. Alcoholic cardiomyopathy: an update. *Eur Heart J*. 2024;45:2294–2305.

40. Ram P, Lo KB, Shah M, Patel B, Rangaswami J, Figueredo VM. National trends in hospitalizations and outcomes in patients with alcoholic cardiomyopathy. *Cli Cardiol*. 2018;41:1423–1429.

41. Ware JS, Amor-Salamanca A, Tayal U, et al. Genetic etiology for alcohol-induced cardiac toxicity. *J Am Coll Cardiol*. 2018;71:2293–2302.

42. Owen R, Buchan R, Frenneaux M, et al. Sex differences in the clinical presentation and natural history of dilated cardiomyopathy. *JACC Heart Fail*. 2024;12:352–363.

43. Franaszczyk M, Chmielewski P, Truszkowska G, et al. Titin truncating variants in dilated cardiomyopathy—prevalence and genotype-phenotype correlations. *PLoS One*. 2017;12:e0169007.

44. Ollila L, Nikus K, Holmström M, et al. Clinical disease presentation and ECG characteristics of LMNA mutation carriers. *Open Heart*. 2017;4:e000474.

45. Hey TM, Rasmussen TB, Madsen T, et al. Pathogenic RBM20-variants are associated with a severe disease expression in male patients with dilated cardiomyopathy. *Circ Heart Fail*. 2019;12:e005700.

46. Johnson HM, Gorre CE, Friedrich-Karnik A, Gulati M. Addressing the bias in cardiovascular care: missed & delayed diagnosis of cardiovascular disease in women. *Am J Prev Cardiol*. 2021;8:100299.

47. Bairey Merz CN, Andersen H, Sprague E, et al. Knowledge, attitudes, and beliefs regarding cardiovascular disease in women: the Women's Heart Alliance. *J Am Coll Cardiol*. 2017;70:123–132.

48. Cannatà A, Fabris E, Merlo M, et al. Sex differences in the long-term prognosis of dilated cardiomyopathy. *Can J Cardiol*. 2020;36:37–44.

49. Cannatà A, Merlo M, Dal Ferro M, et al. Association of titin variations with late-onset dilated cardiomyopathy. *JAMA Cardiol*. 2022;7:371–377.

50. Dewan P, Rørth R, Jhund PS, et al. Differential impact of heart failure with reduced ejection fraction on men and women. *J Am Coll Cardiol*. 2019;73:29–40.

51. Ravera A, Santema BT, Sama IE, et al. Quality of life in men and women with heart failure: association with outcome, and comparison between the Kansas City Cardiomyopathy Questionnaire and the EuroQol 5 dimensions questionnaire. *Eur J Heart Fail*. 2021;23:567–577.

52. Lesman-Leegte I, Jaarsma T, Coyne JC, Hillege HL, van Veldhuisen DJ, Sanderman R. Quality of life and depressive symptoms in the elderly: a comparison between patients with heart failure and age- and gender-matched community controls. *J Card Fail*. 2009;15:17–23.

53. Lam CS, Cheng S, Choong K, et al. Influence of sex and hormone status on circulating natriuretic peptides. *J Am Coll Cardiol*. 2011;58:618–626.

54. de Bakker M, Anand A, Shipley M, et al. Sex differences in cardiac troponin trajectories over the life course. *Circulation*. 2023;147:1798–1808.

55. Saxena S, Goldenberg I, McNitt S, et al. Sex differences in the risk of first and recurrent ventricular tachyarrhythmias among patients receiving an implantable cardioverter-defibrillator for primary prevention. *JAMA Netw Open*. 2022;5:e2217153.

56. Chung ES, Katra RP, Ghio S, et al. Cardiac resynchronization therapy may benefit patients with left ventricular ejection fraction >35%: a PROSPECT trial substudy. *Eur J Heart Fail*. 2010;12:581–587.

57. Chung AK, Das SR, Leonard D, et al. Women have higher left ventricular ejection fractions than men independent of differences in left ventricular volume. *Circulation*. 2006;113:1597–1604.

58. McMurray JJV, Jackson AM, Lam CSP, et al. Effects of sacubitril-valsartan versus valsartan in women compared with men with heart failure and preserved ejection fraction: insights from PARAGON-HF. *Circulation*. 2020;141:338–351.

59. Merrill M, Sweitzer NK, Lindenfeld J, Kao DP. Sex differences in outcomes and responses to spironolactone in heart failure with preserved

ejection fraction: a secondary analysis of TOPCAT trial. *JACC Heart Fail*. 2019;7:228–238.

60. Grewal J, Siu SC, Ross HJ, et al. Pregnancy outcomes in women with dilated cardiomyopathy. *J Am Coll Cardiol*. 2009;55:45–52.

61. Yokouchi-Konishi T, Kamiya CA, Shionoiri T, et al. Pregnancy outcomes in women with dilated cardiomyopathy: peripartum cardiovascular events predict post delivery prognosis. *J Cardiol*. 2021;77:217–223.

62. Restrepo-Córdoba MA, Chmielewski P, Truszkowska G, et al. Pregnancy in women with dilated cardiomyopathy genetic variants. *Rev Esp Cardiol (Engl Ed)*. 2025;78:2–9.

63. Siu SC, Colman JM, Sorensen S, et al. Adverse neonatal and cardiac outcomes are more common in pregnant women with cardiac disease. *Circulation*. 2002;105:2179–2184.

64. Herman DS, Lam L, Taylor MR, et al. Truncations of titin causing dilated cardiomyopathy. *N Engl J Med*. 2012;366:619–628.

65. Wahbi K, Ben Yaou R, Gandjbakhch E, et al. Development and validation of a new risk prediction score for life-threatening ventricular tachyarrhythmias in laminopathies. *Circulation*. 2019;140:293–302.

66. Gasperetti A, Carrick R, Protonotarios A, et al. Long-term arrhythmic follow-up and risk stratification of patients with desmoplakin-associated arrhythmogenic right ventricular cardiomyopathy. *JACC Adv*. 2024;3:100832.

67. Carrick RT, Gasperetti A, Protonotarios A, et al. A novel tool for arrhythmic risk stratification in desmoplakin gene variant carriers. *Eur Heart J*. 2024;45:2968–2979.

68. Jordan E, Peterson L, Ai T, et al. Evidence-based assessment of genes in dilated cardiomyopathy. *Circulation*. 2021;144:7–19.

69. Verdonschot JAJ, Hazebroek MR, Wang P, et al. Clinical phenotype and genotype associations with improvement in left ventricular function in dilated cardiomyopathy. *Circ Heart Fail*. 2018;11:e005220.

70. Alharbi FF, Kholod AAV, Souverein PC, et al. The impact of age and sex on the reporting of cough and angioedema with renin-angiotensin system inhibitors: a case/noncase study in VigiBase. *Fundam Clin Pharmacol*. 2017;31:676–684.

71. O'Meara E, Clayton T, McEntegart MB, et al. Sex differences in clinical characteristics and prognosis in a broad spectrum of patients with heart failure: results of the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) program. *Circulation*. 2007;115:3111–3120.

72. Ghani A, Delnoy P, Adiyaman A, et al. Predictors and long-term outcome of super-responders to cardiac resynchronization therapy. *Clin Cardiol*. 2017;40:292–299.

73. Rathore SS, Wang Y, Krumholz HM. Sex-based differences in the effect of digoxin for the treatment of heart failure. *N Engl J Med*. 2002;347:1403–1411.

74. McMurray JJ, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med*. 2014;371:993–1004.

75. Køber L, Thune JJ, Nielsen JC, et al. Defibrillator implantation in patients with nonischemic systolic heart failure. *N Engl J Med*. 2016;375:1221–1230.

76. Chimura M, Butt JH, Matsumoto S, et al. Comprehensive analysis of the effects of sacubitril/valsartan according to sex among patients with heart failure and reduced ejection fraction in PARADIGM-HF. *J Am Heart Assoc*. 2025;14:e038249.

77. Solomon SD, McMurray JJV, Anand IS, et al. Angiotensin-neprilysin inhibition in heart failure with preserved ejection fraction. *N Engl J Med*. 2019;381:1609–1620.

78. Santema BT, Ouwerkerk W, Tromp J, et al. Identifying optimal doses of heart failure medications in men compared with women: a prospective, observational, cohort study. *Lancet*. 2019;394:1254–1263.

79. Breathett K, Yee E, Pool N, et al. Association of gender and race with allocation of advanced heart failure therapies. *JAMA Network Open*. 2020;3. e2011044-e2011044.

80. Sumarsono A, Xie L, Keshvani N, et al. Sex disparities in longitudinal use and intensification of guideline-directed medical therapy among patients with newly diagnosed heart failure with reduced ejection fraction. *Circulation*. 2024;149:510–520.

81. Rasmusson K, Dong L, Butschek R, et al. Underutilization and sex disparities in real world heart failure guideline directed therapy prescription rates over time in a large health system. *J Card Fail*. 2025;31:294–295.

82. Wang N, Evans J, Sawant S, Sindone J, Lal S. Sex-specific differences in the efficacy of heart failure therapies: a meta-analysis of 84,818 patients. *Heart Fail Rev*. 2023;28:949–959.

83. Tompkins CM, Kutyifa V, Arshad A, et al. Sex differences in device therapies for ventricular arrhythmias or death in the Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy (MADIT-CRT) trial. *J Cardiovasc Electrophysiol*. 2015;26:862–871.

84. Zusterzeel R, Selzman KA, Sanders WE, et al. Cardiac resynchronization therapy in women: US Food and Drug Administration meta-analysis of patient-level data. *JAMA Intern Med*. 2014;174:1340–1348.

85. Russo AM, Poole JE, Mark DB, et al. Primary prevention with defibrillator therapy in women: results from the Sudden Cardiac Death in Heart Failure Trial. *J Cardiovasc Electrophysiol*. 2008;19:720–724.

86. Poole Jeanne E, Olshansky B, Mark Daniel B, et al. Long-term outcomes of implantable cardioverter-defibrillator therapy in the SCD-HeFT. *J Am Coll Cardiol*. 2020;76:405–415.

87. Han JK, Russo AM. Underrepresentation of women in implantable cardioverter defibrillator trials. *Am Heart J Plus*. 2022;14:100120.

88. Tompkins CM, Zareba W, Greenberg H, et al. Differences in mode of death between men and women receiving implantable cardioverter-defibrillators or cardiac resynchronization therapy in the MADIT trials. *Heart Rhythm*. 2023;20:39–45.

89. Ramu B, Cogswell R, Ravichandran AK, et al. Clinical outcomes with a fully magnetically levitated left ventricular assist device among women and men. *JACC Heart Fail*. 2023;11:1692–1704.

90. Mazimba S. Toward equitable utilization of durable left ventricular assist device therapy in advanced heart failure—raising the veil of health disparities. *J Card Surg*. 2022;37:3595–3597.

91. Lakshman R, Forouhi NG, Sharp SJ, et al. Early age at menarche associated with cardiovascular disease and mortality. *J Clin Endocrinol Metab*. 2009;94:4953–4960.

92. Atsma F, Bartelink ML, Grobbee DE, van der Schouw YT. Postmenopausal status and early menopause as independent risk factors for cardiovascular disease: a meta-analysis. *Menopause*. 2006;13:265–279.

93. Mangino M, McGurk KA, Theotokis P, et al. Sex differences in the genetic causes of dilated cardiomyopathy. *J Am Coll Cardiol*. 2025;86:400–403.

94. Gigli M, Stolfo D, Barbati G, Sinagra G, Mestroni L, Filamin C, Registry Consortium. Arrhythmic risk stratification of filamin C truncating variants carriers. *Eur Heart J*. 2023;44(Suppl 2):ehad655.643.

95. Verstraelen TE, van Lint FHM, Bosman LP, et al. Prediction of ventricular arrhythmia in phospholamban p.Arg14del mutation carriers—reaching the frontiers of individual risk prediction. *Eur Heart J*. 2021;42:2842–2850.

KEY WORDS DCM, female, heart, male, sex-specific

APPENDIX For supplemental material, please see the online version of this paper.



Go to https://www.acc.org/jacc-journals-cme to take the CME/MOC quiz for this paper.