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Review

Sex-Specific Differences in Heart Failure: Pathophysiology, Risk Factors, Management, and Outcomes

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ABSTRACT

Heart failure (HF) is a leading cause of hospitalisation, morbidity, and mortality in Canada. There are sex-specific differences in the etiology, epidemiology, comorbidities, treatment response, and treatment adverse effects that have implications on outcomes in HF. Sex-specific analyses of some HF trials indicate that optimal doses of drug therapies and benefit of device therapies may differ between male and female patients, but the trials were not designed to test sex differences. The under-representation of female participants in HF randomised controlled trials (RCTs) is a major limitation in assessing

RÉSUMÉ

L'insuffisance cardiaque (IC) est l'une des principales causes d'hospitalisation, de morbidité et de mortalité au Canada. Il existe des différences entre les sexes sur les plans de l'étiologie, de l'épidémiologie, des affections concomitantes, de la réponse au traitement et des effets indésirables des traitements, qui ont toutes des répercussions sur les résultats de l'IC. Les analyses des résultats de certains essais sur l'IC selon le sexe des participants révèlent qu'il existe des différences entre les doses optimales des pharmacothérapies et les bienfaits des dispositifs thérapeutiques chez les

Heart failure (HF) affects 600,000 Canadians and is a leading cause of hospitalisation, morbidity, and mortality in older adults.^{1,2} In this review, we outline the differences in etiology, epidemiology, comorbidities, treatment response, and treatment adverse effects that have implications on the clinical care and disease trajectory of HF.

Pathophysiology and Risk Factors

There are sex-specific differences in HF risk factors and pathophysiology. While traditional cardiovascular (CV) risk

factors are present in both sexes, hypertension and diabetes are predominant risk factors for HF in females.³ Females have higher systolic and diastolic left ventricular (LV) stiffness than males, which increases to a greater extent with age.^{4,5} Possible explanations include a postmenopausal reduction in estrogen and nitric oxide, factors that regulate blood pressure and arterial tone.⁴ In addition, LV remodelling differs between the sexes, with females more likely to develop concentric remodelling and HF with preserved ejection fraction (HFpEF); and males more likely to develop eccentric remodelling and HF with reduced ejection fraction (HFrEF).⁶ This may contribute to sex differences in treatment efficacy among those with HF; the renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system appear to be important in the pathophysiology of eccentric remodelling, and less so in concentric remodelling, so RAAS inhibitors and β -blockers may attenuate remodelling in HFrEF more than in HFpEF.⁶

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the sex-specific efficacy and safety of treatments. To ensure that female patients receive safe and effective HF therapies, RCTs should include participants proportionate to the sex-specific distribution of disease. This review outlines the sex-specific differences in HF phenotype and treatment response, and highlights disparities in services and gaps in knowledge that merit further investigation.

Physical inactivity, obesity, and smoking are important lifestyle risk factors for incident HF. In the National Health Interview Survey, age-adjusted physical inactivity is higher among females than males.⁷ Obesity, a risk factor for incident HFpEF, is more prevalent in females.⁸ In a survey of 151 countries, the prevalence of obesity was higher among females compared with males in 87% of the countries.⁸ Among patients with acute heart failure, the odds of smoking among females is less than a third those of males.⁹

HF risk factors related to pregnancy include gestational diabetes and preeclampsia. Gestational diabetes increases the risk of type 2 diabetes and myocardial infarction,¹⁰ and preeclampsia increases the risk of hypertension, coronary artery disease, stroke, and HF up to 40 years later.^{11,12}

Peripartum cardiomyopathy can lead to chronic non-ischemic cardiomyopathy. Independent risk factors include age ≥ 30 years, African-American race, hypertension, anemia, substance abuse, asthma, multiple gestations, and preeclampsia/eclampsia.¹³ In addition, preexisting cardiomyopathies can be unmasked in pregnancy during the second trimester owing to decompensation from increased circulating blood volume and other physiologic changes.¹⁴

Stress cardiomyopathy is also more common in females, hypothesised to be related to sympathetic drive and microvascular dysfunction.¹⁵ Emotional stress has a greater impact on females than males in terms of CV events and the rates of takotsubo cardiomyopathy have a female-to-male ratio of 9:1.¹⁶

Under-representation of Females as Participants in HF Randomised Controlled Trials: A Limitation in Sex-Specific Analysis

Sex-related differences in physiology, pharmacokinetics, and pharmacodynamics may contribute to differences in response to HF drugs.¹⁷⁻¹⁹ However, the under-representation of females as participants in HF randomised controlled trials (RCTs) is a major limitation in analyzing the sex-specific efficacy and safety of treatments, which appear to vary between males and females. In a contemporary systematic review of RCTs published in high-impact journals, females represented only a fourth of 183,097 participants in RCTs of HFrEF.²⁰ Females were underenrolled relative to sex distribution of HF in more than 70% of the RCTs, with no significant change over time.²⁰ Underenrollment was associated with sex-specific eligibility criteria and the gender of the trial leaders.²¹ Females also have

hommes et les femmes, mais les essais ne sont pas conçus pour évaluer les différences entre les sexes. La sous-représentation des femmes au sein des essais contrôlés avec répartition aléatoire sur l'IC constitue une limite importante pour l'évaluation de l'efficacité et de l'innocuité des traitements selon le sexe. Afin que les patientes atteintes d'IC puissent recevoir des traitements sûrs et efficaces, les participants aux essais contrôlés avec répartition aléatoire doivent être représentatifs de la distribution des cas d'IC selon le sexe dans la population. Nous décrivons brièvement les différents phénotypes de l'IC et les différentes réponses au traitement chez les hommes et les femmes, et nous soulignons les disparités en matière de services ainsi que les lacunes dans les connaissances qui mériteraient d'être étudiées plus en profondeur.

been underenrolled in RCTs of HFpEF.²²⁻²⁴ These gaps merit closing so that adequate balance and statistical power is achieved for meaningful sex analysis.

Pharmacologic Therapies

Because sex-based differences have been under-recognised and females have been under-represented in RCTs, the current sex-neutral HF guidelines are largely based on data reflecting response to therapies in males.^{25,26} The call for improving evidence-based pharmacologic therapies in males and females with HF has resulted in an increasing number of studies with predefined sex-specific subgroup analyses and reporting of sex-specific data in post hoc analyses (Table 1). Tannenbaum et al. describe a framework for generating sex-specific guidelines which involves assessing the relevance of sex-differences in disease, appraising the evidence, and incorporating these differences into guideline recommendations.²⁷

Current left ventricular ejection fraction (LVEF) thresholds defining HFrEF, HF with midrange ejection fraction (HFmEF), and HFpEF may be inadequate to distinguish those who respond to specific therapies. LVEF is a continuum, and arbitrarily established thresholds for clinical trial recruitment do not necessarily reflect the bounds of treatment efficacy. Furthermore, the threshold for normal LVEF may be higher in females than in males,²⁸ which may explain the sex-LVEF interaction that is evident with some treatments.²⁹

Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers

HFrEF. The evidence for sex-differences in the efficacy of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) in HF is limited. Overall, they appear to benefit both males and females, but most of the studies were not adequately powered to test for sex differences and sex interaction was not typically provided. In addition, there is some evidence that females may benefit from therapies even at submaximal doses.³⁰ A survival benefit of enalapril was observed among males in the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) (30% female), whereas a post hoc analysis did not reveal a survival benefit in females.³¹⁻³³ The larger Studies of Left Ventricular Dysfunction (SOLVD) trial investigating enalapril in symptomatic patients with HFrEF included 505 (20%) females and

Table 1. Overview of sex-specific characteristics and outcomes of randomised controlled clinical drug trials in patients with heart failure with reduced ejection fraction

Drug class	Study	Drug	% females	No. of females	LVEF	Primary end point	Sex-specific outcome	P value for sex interaction
ACEI	CONSENSUS	Enalapril	30	74	≤ 35%	Death	Significant benefit in males, not in females	Not provided
	SOLVD-Treatment	Enalapril	20	505	≤ 35%	Death	Significant benefit in males, trend toward benefit in females	Not provided
	ATLAS	Lisinopril high vs low dose	20	648	≤ 30%	Death	Trend toward higher doses more beneficial in males, lower doses more beneficial in females	Not provided
ARB	Val-HeFT	Valsartan	20	1,003	< 40%	Death or HF hospitalisation/ED presentation	Significant benefit in males, trend toward benefit in females	Not provided
	CHARM-Added	Candesartan	21	542	≤ 40%	CV death or HF hospitalisation	CHARM low-LVEF trials combined: no sex difference in primary end point	0.95
	CHARM-Alternative	Candesartan	32	646	≤ 40%	CV death or HF hospitalisation	HR 0.86 (95% CI 0.77-0.96) in males (high dose better), HR 1.02 (95% CI 0.85-1.23) in females	0.10
	HEAAL	Losartan high vs low dose	30	1143	≤ 40%	Death or HF hospitalisation		
ARNI	PARADIGM-HF	Sacubitril/valsartan	22	1832	≤ 40%	CV death or HF hospitalisation	Significant benefit in males and females	0.63
β-Blocker	US Carvedilol HF	Carvedilol	23	256	≤ 35%	Death	HR 0.41 (95% CI 0.22-0.80) in males, HR 0.23 (95% CI 0.07-0.69) in females	Not provided
	CIBIS II	Bisoprolol	19	515	≤ 35%	Death	Significant benefit in males and females	Not provided
	MERIT-HF	Metoprolol	23	898	≤ 40%	Death or all-cause hospitalisation	Significant benefit in males, not in females	Not provided
	COPERNICUS	Carvedilol	20	465	< 25%	Death	Significant benefit in males, trend toward benefit in females	Not provided
	SENIORS	Nebivolol	37	785	≤ 35% or HF hospitalisation in the previous year	Death or CV hospital admission	HR 0.93 (95% CI 0.78-1.11) in males, HR 0.72 (95% CI 0.55-0.93) in females	0.11
MRA	RALES	Spirolonactone	27	446	≤ 35%	Death	Significant benefit in males and females	Not provided
	EMPHASIS-HF	Eplerenone	22	610	≤ 35%	Death or HF hospitalisation	Significant benefit in males and females	0.36
SGLT-2 inhibitor	DAPA-HF	Dapagliflozin	23	1109	≤ 40%	CV death or worsening HF (hospitalisation or urgent HF visit with intravenous therapy)	HR 0.73 (95% CI 0.63-0.85) in males, HR 0.79 (95% CI 0.59-1.06) in females	Not provided
	EMPEROR-Reduced	Empagliflozin	24	893	≤ 40%	CV death or HF hospitalisation	HR 0.80 (95% CI 0.68-0.93) in males, HR 0.59 (95% CI 0.44-0.80) in females	Not provided
Soluble guanylate cyclase stimulator	VICTORIA	Vericiguat	24	1208	< 45%	CV death or HF hospitalisation	HR 0.90 (95% CI 0.81-1.00) in males, HR 0.88 (95% CI 0.73-1.08) in females	Not provided

Table 1. Continued.

Drug class	Study	Drug	% females	No. of females	LVEF	Primary end point	Sex-specific outcome	<i>P</i> value for sex interaction
Digitalis	DIG	Digoxin	22	1519	< 45%	Death	Rate of death 5.8% higher in females on digoxin compared with males on digoxin	0.034
<i>I</i> ₁ inhibitor	SHIFT	Ivabradine	24	1535	≤ 35%	CV death or HF hospitalisation	HR 0.84 (95% CI 0.76-0.94) in males, HR 0.74 (95% CI 0.60-0.91) in females	0.26

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; ATLAS, Assessment of Treatment with Lisinopril and Survival; CHARM, Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity; CI, confidence interval; CIBIS II, Cardiac Insufficiency Bisoprolol Study II; CONSENSUS, Cooperative North Scandinavian Enalapril Survival Study; COPERNICUS, Carvedilol Prospective Randomized Cumulative Survival; CV, cardiovascular; DAPA-HF, Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure; DIG, Digitalis Investigation Group; ED, emergency department; EMPEROR-Reduced, Empagliflozin Outcome Trial in Patients With Chronic Heart Failure and a Reduced Ejection Fraction; EMPHASIS-HF, Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure; HEAAL, Heart Failure Endpoint Evaluation of Angiotensin II Antagonist Losartan; HF, heart failure; HR, hazard ratio; LVEF, left ventricular ejection fraction; MERIT-HF, Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure; MRA, mineralocorticoid receptor antagonist; PARADIGM-HF, Prospective Comparison of ARNi With ACEi to Determine Impact on Global Mortality and Morbidity in Heart Failure; RALES, Randomised Aldactone Evaluation Study; SENIORS, Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors With Heart Failure; SGLT-2, sodium-glucose cotransporter 2; SHIFT, Systolic Heart Failure Treatment With the *I*₁ Inhibitor Ivabradine Trial; SOLVD, Studies of Left Ventricular Dysfunction; Val-HeFT, Valsartan Heart Failure Trial; VICTORIA, Vericiguat Global Study in Subjects With Heart Failure With Reduced Ejection Fraction.

revealed a trend toward mortality reduction in females, but sex interaction was not tested.³⁴ Two trials investigating high- vs low-dose lisinopril (Assessment of Treatment with Lisinopril and Survival [ATLAS]) and losartan (Heart Failure Endpoint Evaluation of Angiotensin II Antagonist Losartan [HEAAL]) in chronic HF revealed that males might benefit more from the higher dose levels, whereas lower doses may be effective in females.^{35,36} This observation warrants further analysis in HF RCTs to ensure that our guideline-directed medical therapy doses are sex-specific.

The Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM) trial and the Valsartan Heart Failure Trial (Val-HeFT) showed no significant sex difference in the reduction of CV death or HF hospitalisation, with no sex interaction demonstrated in CHARM and no sex interaction testing performed in Val-HeFT.^{37,38}

HFpEF. ARBs may have a greater treatment effect in females than males with HFpEF. In the Perindopril in Elderly People With Chronic Heart Failure (PEP-CHF) RCT of patients with LVEF > 40%,³⁹ perindopril did not reduce the primary outcome (all-cause mortality and unplanned HF hospitalisation) overall, and no sex analysis was reported. In the Irbesartan in Heart Failure With Preserved Ejection Fraction (I-PRESERVE) trial of irbesartan vs placebo in patients with LVEF ≥ 45% (61% female), females had a lower rate of all-cause mortality or first CV hospitalisation than did males in subgroup analysis (adjusted hazard ratio [HR] females vs males 0.81, 95% confidence interval [CI] 0.72-0.92; *P* = 0.001).⁴⁰ Given that females represented a higher proportion of the total study participants in I-PRESERVE, we can be more confident in this treatment effect.

Angiotensin receptor neprilysin inhibitors

HFrfEF. The large Prospective Comparison of ARNi With ACEi to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial investigated the effects of sacubitril-valsartan vs enalapril (22% female) on CV mortality or HF hospitalisation.⁴¹ The significant effect on the composite end point in favour of sacubitril-valsartan was similar in males and females, with no significant sex interaction (*P* = 0.63).⁴¹

HFmEF and HFpEF. The Prospective Comparison of ARNI with ARB Global Outcomes in Heart Failure With Preserved Ejection Fraction (PARAGON-HF) trial of sacubitril-valsartan vs valsartan in patients with LVEF ≥ 45%, had a neutral effect on the composite outcome of HF hospitalisations or CV death, but prespecified subgroup analysis revealed a significant treatment effect in females (relative risk [RR] 0.73, 95% CI 0.59-0.90) but not in males (RR 1.03, 95% CI 0.85-1.25).^{29,42} There was a significant sex interaction (*P* = 0.017).^{29,42} Furthermore, there was a sex-LVEF interaction, in which females with HFpEF appeared responsive to treatment with ARNIs at higher LVEF ranges than males.⁴³

β-Blockers

HFrfEF. There is no evidence of a sex-specific difference in response to β-blockers, but the trials were not powered for these analyses.^{16,32,44} In the US Carvedilol HF trial, a significant mortality benefit was found in both males (RR 0.44, 95% CI 0.24-0.82) and females (RR 0.32, 95% CI 0.11-0.93).^{32,45} This was consistent with the Cardiac Insufficiency Bisoprolol Study (CIBIS) II, in which both males (RR 0.71,

95% CI 0.58-0.87) and females (RR 0.52, 95% CI 0.30-0.89) experienced a reduction in mortality with the use of bisoprolol.^{32,46,47}

HFmEF/HFpEF. There are limited high-quality data to inform the use of β -blockers in HFmEF and HFpEF. In a meta-analysis of 25 RCTs of patients with HFpEF, β -blockers reduced the risk of all-cause mortality compared with control (RR 0.78, 95% CI 0.65-0.94; $P = 0.008$), but this included patients with LVEF $> 40\%$ and no sex-specific subgroup analysis was undertaken.⁴⁸

Mineralocorticoid receptor antagonists

HFREF. This class of drugs improves outcomes in both males and females. The **R**andomized **A**ldactone **E**valuation **S**tudy (RALES) of spironolactone vs placebo in patients with severe HF (New York Heart Association [NYHA] functional class III or IV), showed a reduction in the risk of all-cause death in both males and females.⁴⁹ The **E**plerenone in **M**ild **P**atients **H**ospitalization and **S**urvival **S**tudy in **H**eart **F**ailure (EMPHASIS-HF) found no sex-treatment difference in the effect of eplerenone on the composite outcome of CV death or HF hospitalisation (interaction $P = 0.36$).⁴⁹

HFmEF/HFpEF. Females may be more responsive to treatment with spironolactone than males in the setting of HFmEF and HFpEF. Among those with LVEF $\geq 45\%$ in the **T**reatment of **P**reserved **C**ardiac **F**unction **H**eart **F**ailure **W**ith an **A**ldosterone **A**ntagonist (TOPCAT) trial, spironolactone did not reduce the incidence of CV death or HF hospitalisation; however, in an exploratory subgroup analysis, a sex-treatment interaction was noted ($P = 0.02$), with a reduction in the risk of death in females (HR 0.66, 95% CI 0.48-0.90) but not in males (HR 1.06, 95% CI 0.81-1.39).^{50,51}

Sodium-glucose cotransporter-2 inhibitors

HFREF. This class appears to confer benefit in both males and females, although sex interaction was not reported in the trials. The **D**apagliflozin and **P**revention of **A**dverse **O**utcomes in **H**eart **F**ailure (DAPA-HF) showed a large reduction of composite CV death or worsening HF in males (HR 0.73, 95% CI 0.63-0.85) but no difference in females (HR 0.79, 95% CI 0.59-1.06; P value for interaction not provided).⁵² The **E**mpagliflozin **O**utcome **T**rial in **P**atients **W**ith **C**hronic **H**eart **F**ailure and a **R**educed **E**jection **F**raction (EMPEROR-Reduced) trial revealed a larger treatment benefit with empagliflozin vs placebo for the composite of CV death or HF hospitalisation in females (HR 0.59, 95% CI 0.44-0.80) than in males (HR 0.80, 95% CI 0.68-0.93, P value for sex interaction not provided).⁵³

Soluble guanylate cyclase stimulators

HFREF. The soluble guanylate cyclase stimulator vericiguat has been studied in the contemporary **V**ericiguat **G**lobal **S**tudy in **S**ubjects **W**ith **H**eart **F**ailure **W**ith **R**educed **E**jection **F**raction (VICTORIA) trial, in which 1208 (24%) females

were enrolled.⁵⁴ A prespecified subgroup analysis showed similar beneficial effects of vericiguat in males (HR 0.90, 95% CI 0.81-1.00) and females (HR 0.88, 95% CI 0.73-1.08) compared with placebo.⁵⁴

Digitalis

HFREF. The use of digoxin was recommended after the **D**igitalis **I**nvestigation **G**roup (DIG) trial showed a reduction of HF-related and overall risk of hospitalisations.⁵⁵ However, a post hoc subgroup analysis revealed that females treated with digoxin had a 5.8-fold higher absolute risk of all-cause death compared with males (interaction $P = 0.034$), which raised concerns about using digoxin therapy in females.⁵⁶ Despite this signal of possible harm, there are no sex-specific recommendations about digoxin in HF guidelines, and additional trials will need to be conducted to assess safety in female patients.

Optimal doses

The optimal doses of guideline-recommended HF therapies may differ in males and females.³⁰ In a large prospective European cohort study, females with HFREF had 30% lower risk of death or HF hospitalisation at only 50% of the recommended doses of ACE inhibitors/ARBs and β -blockers, with no further risk decrease at higher doses,^{30,57} whereas males had the lowest risk of the composite end point on recommended target doses. These results were validated in a large prospective observational HF study from Asia, which showed similar sex differences in optimal dose levels.^{30,58} Physiologic sex differences in body weight and height, body fat percentage and distribution, and renal and hepatic drug metabolism and clearance may contribute to higher plasma concentrations of drugs in females. This might partly explain the findings of higher efficacy of drugs at lower doses in females than in males.

Devices

Implantable cardioverter-defibrillators

Females have been under-represented in implantable cardioverter-defibrillator (ICD) trials,^{20,59,60} constituting 10% to 23% of participants,⁶¹⁻⁶⁹ and the sex-specific efficacy of ICDs in primary prevention is unclear. In a meta-analysis of 5 trials (**M**ulticenter **U**nsustained **T**achycardia **T**rial [MUSTT], **M**ulticenter **A**utomatic **D**efibrillator **I**mplantation **T**rial II [MADIT-II], **D**efibrillator **i**n **A**cute **M**yocardial **I**nfarction **T**rial [DINAMIT], **D**efibrillators **i**n **N**onschemic **C**ardiomyopathy **T**reatment **E**valuation [DEFINITE], and **S**udden **C**ardiac **D**eath in **H**eart **F**ailure **T**rial [SCD-HeFT]),⁶⁵ there was no ICD-sex interaction on the outcome of mortality (Table 2).⁶⁶ While a statistically significant decrease in mortality was seen in males with HFREF in primary-prevention ICD vs medical therapy (HR 0.78, 95% CI 0.70-0.87), there was no significant decrease for females (HR 1.01, 95% CI 0.76-1.33).⁶⁶ In a meta-analysis⁷⁰ of MADIT-II, MUSTT, SCD-HEFT, DEFINITE, and **C**omparison of **M**edical **T**herapy, **P**acing and **D**efibrillation in **H**eart **F**ailure (COMPANION), ICD implantation was

Table 2. Representation of females and mortality benefit for both sexes in primary prevention ICD clinical trials⁶⁶

Trials	Percentage female patients	Study arms	Mortality
MUSTT	10%	Medical therapy plus EPG therapy vs standard medical therapy*	Females: HR 1.64, 95% CI 0.92-2.92; Males: HR 0.83, 95% CI 0.71-0.97
MADIT-II	16%	ICD vs medical therapy	Females: HR 0.57, 95% CI 0.28-1.18; Males: HR 0.66, 95% CI 0.48-0.91
SCD-HeFT	23%	ICD vs placebo	Females: HR 0.96, 95% CI 0.58-1.61; Males: HR 0.73, 95% CI 0.57-0.93
DEFINITE	29%	ICD vs pharmacologic therapy alone	Females: HR 1.14, 95% CI 0.50-2.64; Males: HR 0.49, 95% CI 0.27-0.89
DINAMIT	24%	ICD vs pharmacologic therapy alone	Females: HR 1.00, 95% CI 0.49-2.04; Males: HR 1.14, 95% CI 0.77-1.69

CI, confidence interval; DEFINITE, **Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation**; DINAMIT, **Defibrillator in Acute Myocardial Infarction Trial**; EPG, electrophysiologically guided; HR, hazard ratio; ICD, implantable cardioverter-defibrillator; MADIT-II, **Multicenter Automatic Defibrillator Implantation Trial II**; MUSTT, **Multicenter Unsustained Tachycardia Trial**; SCD-HeFT, **Sudden Cardiac Death in Heart Failure Trial**.
* Included either an antiarrhythmic medication or an ICD. This was not a primary ICD randomised controlled trial.

associated with a 33% mortality reduction in males compared with placebo (HR 0.67, 95% CI 0.58-0.78), whereas in females the effect was smaller and nonsignificant (HR 0.78, 95% CI 0.57-1.05), possibly owing to the sample size and imbalance in subgroups (22% females). Furthermore, females had fewer appropriate ICD interventions than males (HR 0.63, 95% CI 0.49-0.82), suggesting a smaller contribution of ventricular arrhythmias and sudden cardiac death to all-cause mortality.⁷⁰

In a multivariable model of 6021 patients who underwent ICD implantation,⁷¹ females had nearly twice the odds of major complications $\leq$ 45 days and 1 year after implantation than males. Females were 31% less likely to receive an appropriate ICD shock and 27% less likely to receive appropriate antitachycardia pacing than males. However, there was no significant difference in mortality or inappropriate shocks, and no interaction between sex and ICD type for appropriate or inappropriate shocks/therapy.⁷¹

Females who have an indication for an ICD have lower implantation rates and are less likely to be counselled regarding implants than males, and the reasons for this require

further investigation.^{72,73} Among patients who were counselled, there were no sex differences in implantation of ICDs.⁷³ Based on pooled evidence, it appears that females may derive less benefit from ICDs than males, but the studies are heterogeneous preventing definitive conclusions. Further studies are needed to determine sex differences in arrhythmia risk and effect of ICD therapy.

Cardiac resynchronisation therapy

A lower proportion of females than males receive cardiac resynchronisation therapy (CRT). In a cross-sectional study of the National Inpatient Sample database of 311,009 patients with CRT implantation, males were more likely than females to undergo CRT with defibrillator (CRT-D) implantation (88.6% vs 80.1%; $P < 0.001$).⁷⁴ The major CRT trials and the effects of sex on mortality alone or in combination with other outcomes are included in **Table 3**.^{63,75-79}

Females may derive greater benefit from CRT than males. Data from Get With The Guidelines—Heart Failure (GWTG-HF) database and the Centers for Medicare and Medicaid

Table 3. Representation of female patients in trials of CRT or CRT-D therapy

Trials	Percentage female patients	Study arms	Outcome
MADIT-CRT	25%	CRT-D vs ICD	Risk of death or HF: Females: HR 0.37, 95% CI 0.22-0.61; Males: HR 0.76, 95% CI 0.59-0.97; $P = 0.01$ for sex interaction
RAFT	17%	CRT-D vs ICD	Risk of death or HF admission: Females: HR 0.52, 95% CI 0.35-0.85; Males: HR 0.82, 95% CI 0.7-0.95
REVERSE	21%	CRT-ON vs CRT-OFF	Composite outcome of death, HF morbidity, and hospitalisation: Females: HR 0.75, 95% CI 0.26-2.19; Males: HR 0.69, 95% CI 0.43-1.11
CARE-HF	27%	CRT vs pharmacologic therapy alone	Risk of death or cardiac hospitalisation: Females: HR 0.64, 95% CI 0.42-0.97; Males: HR 0.62, 95% CI 0.49-0.79
COMPANION	33%	CRT-D, CRT, or pharmacologic therapy	Risk of death: Females: HR 0.58, 95% CI 0.25-1.13; Males: HR 0.63, 95% CI 0.4-0.9

CARE-HF, **Cardiac Resynchronization—Heart Failure**; CI, confidence interval; COMPANION, **Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure**; CRT, cardiac resynchronization therapy; CRT-D, CRT with defibrillator; HR, hazard ratio; ICD, implantable cardioverter-defibrillator; MADIT-CRT, **Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy**; RAFT, **Resynchronization-Defibrillation for Ambulatory Heart Failure Trial**; REVERSE, **Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction**.

Services (CMS) demonstrated that females had a slightly greater mortality reduction with CRT (HR 0.53, 95% CI 0.45-0.63) than did males (HR 0.69, 95% CI 0.62-0.77), and there was a significant sex-treatment interaction ($P = 0.043$).⁸⁰ However, from analysis of this data set, females were less likely to receive device counselling than males, which may be a factor in sex-related differences in CRT implantation despite the greater benefit.⁸⁰ Similarly, in a retrospective study of NYHA functional class III/IV patients (49.5% female) with left bundle branch block (LBBB) and nonischemic cardiomyopathy, a greater proportion of females than males had a treatment response to CRT (84% and 58%, respectively).⁸¹ Response rate remained high in females regardless of QRS duration, whereas males benefited more with QRS ≥ 150 ms.

A meta-analysis of CRT-D vs ICD trials (Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy [MADIT-CRT], Resynchronization-Defibrillation for Ambulatory Heart Failure Trial [RAFT], and Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction [REVERSE]), with 4076 patients, demonstrated a reduction in HF or death (absolute CRT-D–ICD difference 23%, HR 0.24, 95% CI 0.11-0.53) and death (absolute difference 9%, HR 0.24, 95% CI 0.06-0.89) in females with an LBBB QRS of 130-149 ms, while at QRS > 150 ms CRT-D benefited both sexes.⁸² Although current guidelines are the same for females and males, there may be a role for sex-specific indications for CRT-D based on QRS duration.

Revascularisation for Ischemic Cardiomyopathy

In a retrospective cohort of 40,083 Canadian patients (20.6% females) undergoing coronary artery bypass grafting (CABG) from 2008 to 2015, 18.9% of the patients had HF. Females had more HF hospitalisations in the year before CABG and a longer interval between HF onset and CABG,

suggesting later surgical referral than males. In the first year following CABG, females had higher rates of repeated revascularisation, myocardial infarction, stroke, dialysis, HF admission, and admission to long-term care.⁸³ It is possible that earlier diagnosis and referral for CABG may attenuate some of the postoperative morbidity and mortality among females.

The Surgical Treatment for Ischemic Heart Failure (STICH) study, which randomised 1212 patients (12% female) with coronary artery disease and LVEF $< 35\%$ to CABG plus medical therapy vs medical therapy alone, demonstrated favourable surgical outcomes among the females.⁸⁴ At 10 years, female patients had significantly lower all-cause mortality (adjusted HR 0.67, 95% CI 0.52-0.86; $P = 0.002$) and CV mortality (adjusted HR 0.65, 95% CI 0.48-0.89; $P = 0.006$) than male patients, highlighting that female sex should not be a deterrent for surgical referral.⁸⁵

Mechanical circulatory support: long-term left ventricular assist device

The Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) 2019 annual report showed that 78.8% of the 18,539 patients with continuous-flow left ventricular assist devices (LVADs) from 2008 to 2017 were male.⁸⁶ However, there were no sex-based differences in mortality after LVAD implantation.⁸⁷⁻⁹² An analysis of the INTERMACS database from 2006 to 2010 did not demonstrate significant sex differences for pulsatile or continuous-flow devices in adjusted models.⁹¹ However, other studies demonstrated higher rates of early/long-term mortality in females,^{93,94} emphasising the need for more sex-specific analysis.

There are sex-specific differences in adverse events after LVAD implantation. A study of the INTERMACS database showed that females had a shorter time to first neurologic

Figure 1. Sex differences in heart failure (HF) care. CRT, cardiac resynchronization therapy; ICD, implantable cardioverter-defibrillator; LVAD, left ventricular assist device.

event than males (transient ischemic attack or hemorrhagic/ischemic stroke) regardless of type of LVAD implanted.⁹¹ There were no differences in time to first infection, bleed, or device malfunction between sexes. Furthermore, the type of device, pulsatile or continuous flow, did not show an interaction with sex.⁹¹

Females are referred to HF specialists for LVAD implantation later in the disease course than males. In analysis of 966 patients (15.6% female) of the European Registry for Patients with Mechanical Circulatory Support (EUROMACS), females presented more often in INTERMACS level 1 or 2 than males,⁹³ suggesting that they are transferred in a more critical condition.

Heart Transplantation

There are sex differences in mortality on the transplant waiting list. In a multivariable analysis of waiting list patients from 2004 to 2015, females had a significant increased risk of death in United Network for Organ Sharing (UNOS) status 1A (HR 1.14, 95% CI 1.01-1.29) and status IB (HR 1.17, 95% CI 1.05-1.30) compared with males.⁹⁵ Some risk factors for death while on the waiting list that interacted with sex included serum albumin, age, peak oxygen consumption, cardiac index, pulmonary arterial pressure, and pulmonary capillary wedge pressure.⁹⁵ Using the UNOS database, 13,305 bridge-to-transplant LVAD patients (20.8% female) with continuous-flow devices were included in a propensity-matched cohort. Females were less likely to receive a heart transplant (62.3% vs 76%; $P < 0.001$) and more commonly delisted for worsening clinical status. Furthermore, 9.2% of females and 5.1% of males ($P < 0.001$) died on the waiting list, most commonly because of cerebrovascular and CV causes.⁹⁶

The recent International Society for Heart and Lung Transplantation guidelines reported that females constituted 25.6% of recipients from 2010 to 2018. Similar to other therapies, females were less likely to receive a transplant despite significantly higher post-transplantation survival than males (median survival 12.2 vs 11.4 years), which may be partly due to less cardiac allograft vasculopathy.⁹⁷ Compared with males, females were more likely to be younger and less likely to have comorbidities including diabetes, hypertension, peripheral vascular disease, smoking history, and previous CV surgery, though more likely to have a malignancy history.⁹⁸ Further studies are needed to determine the reasons for this disparity including referral pattern and post-transplantation adverse event differences between sexes.

Health Care Services

There are sex disparities in the referral patterns to HF clinics. In the Swedish Heart Failure Registry population, which includes 42,987 patients with a range of LVEF, females were older, less likely to receive specialised care, and less likely to be referred to an HF nurse-led clinic compared with males.⁹⁹ In an analysis of the PARADIGM-HF and Aliskiren Trial to Minimize Outcomes in Patients With Heart Failure (ATMOSPHERE) trials, females were less likely to be enrolled in a disease management program or prescribed an exercise regimen than were males.¹⁰⁰ In a prospective study

examining referrals to HF clinics in Québec, males were twice as likely as females to be referred at 6 months after an emergency room visit for HF.¹⁰¹ In a retrospective study of 765 patients newly referred to HF clinics in Montréal, Québec (27.1% female), females were more symptomatic with a higher NYHA functional class, indicating possible delays in referrals compared with males.¹⁰² In a retrospective review of 9 HF clinics in Ontario (35.5% female), there were no sex differences in the number of echocardiographic assessments or medical therapies, but females were less likely to be referred to electrophysiologists.¹⁰³

The sex differences in referral for, use of, and response to health care services extend through hospitalisations and to end of life (Fig. 1). In a pragmatic RCT of transitional care services offered in the hospital, home, and heart function clinics, there was a sex-treatment interaction ($P = 0.03$) with a reduction in composite all-cause death, hospitalisation, or emergency visit in females vs males (HR 0.84, 95% CI 0.69 to 1.00; $P = 0.05$).¹⁰⁴ In a retrospective cohort study of 396,024 adults who died from HF in Ontario, there were several sex-based differences in end-of-life care.¹⁰⁵ Females had fewer hospitalisations, critical care admissions, and invasive procedure in the last 6 months of life than did males and lower odds of dying in a hospital setting after adjusting for factors such as age, preceding presentation to emergency, receipt of community palliative care services, and hospital bed capacity.¹⁰⁴ The reasons for differences in health care services warrant further investigation.

Conclusion

Despite some sex-specific differences in HF pathophysiology, risk factors, and treatment response, guideline recommendations are the same for males and females. Little information is available on the optimal dose of HF drug therapies in males and females. In most RCTs that reported sex-specific subgroup analyses, males and females seemed to benefit equally from drug and device interventions. Some studies showed important sex differences that have not translated to sex-specific treatment recommendations. There is some evidence that females with HF are referred for health care services less frequently than males.

To ensure that females receive safe and effective HF therapies, RCTs should include participants proportionate to the sex-specific distribution of the disease. Until data from appropriately designed and adequately powered trials demonstrate sex differences in efficacy, females should be offered the same interventions as males, with attention to the adverse effects associated with some therapies in observational datasets.

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