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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.**

**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.**

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 nonischemic cardiomyopathy. Independent risk factors include age $\geq$ 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 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 **Co**operative **N**orth **S**candinavian **En**alapril **Su**rvival **S**tudy (CONSENSUS) (30% female), whereas a post hoc analysis did not reveal a survival benefit in females.[31-33] The larger **S**tudies **o**f **L**eft **V**entricular **D**ysfunction (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 | | |
| | HEAAL | Losartan high vs low dose | 30 | 1143 | ≤ 40% | 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 |
| 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 | Spironolactone | 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 | *P* 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 |
| $I_f$ 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–neprilysin inhibitor; ARNI, angiotensin receptor–neprilysin inhibitor; ATLAS, **A**ssessment of **T**reatment with **L**isinopril **a**nd **S**urvival; CHARM, **C**andesartan in **H**eart Failure **A**ssessment of **R**eduction in **M**ortality and Morbidity; CI, confidence interval; CIBIS II, **C**ardiac **I**nsufficiency **Bi**soprolol **S**tudy II; CONSENSUS, **Co**operative **N**orth **S**candinavian **En**alapril **Su**rvival **S**tudy; COPERNICUS, **C**arvedi**l**ol **P**rospective **R**andom**i**zed **Cu**mulative **S**urvival; CV, cardiovascular; DAPA-HF, **D**apagliflozin **a**nd **P**revention of **A**dverse Outcomes in **H**eart **F**ailure; DIG, **D**igitalis **I**nvestigation **G**roup; ED, emergency department; EMPEROR-Reduced, **Emp**agliflozin Outcom**e** **T**rial in Patients With Chr**o**nic Hea**r**t Failure and a **Reduced** Ejection Fraction; EMPHASIS-HF, **E**plerenone in **M**ild **P**atients **H**ospitalization **a**nd **S**urv**i**val **S**tudy in **H**eart **F**ailure; HEAAL, **H**eart Failure **E**ndpoint Evaluation of **A**ngiotensin II **A**ntagonist **L**osartan; HF, heart failure; HR, hazard ratio; LVEF, left ventricular ejection fraction; MERIT-HF, **Me**toprolol CR/XL **R**andomized **I**ntervention **T**rial in Congestive **H**eart **F**ailure; MRA, mineralocorticoid receptor antagonist; PARADIGM-HF, **P**rospective Comparison of **AR**Ni With **A**CEi to **D**etermine **I**mpact on **G**lobal **M**ortality and Morbidity in **H**eart **F**ailure; RALES, **R**andomised **Al**dactone **E**valuation **S**tudy; SENIORS, **S**tudy of the **E**ffects of **N**ebivolol **I**ntervention on **O**utcomes and **R**ehospitalization in **S**eniors With Heart Failure; SGLT-2, sodium-glucose cotransporter 2; SHIFT, **S**ystolic **H**eart Failure Treatment With the $I_f$ Inhibitor Ivabradine **T**rial; SOLVD, **S**tudies **o**f **L**eft **V**entricular **D**ysfunction; Val-HeFT, **Val**sartan **He**art **F**ailure **T**rial; VICTORIA, **Veri**ci**gua**t **G**lo**b**al Study in Subjects With Heart Failure With **R**educed Ejec**t**i**o**n Fr**a**ction.

revealed a trend toward mortality reduction in females, but sex interaction was not tested.[34] Two trials investigating high- vs low-dose lisinopril (**A**ssessment of **T**reatment with **L**isinopril **a**nd **S**urvival [ATLAS] ) and losartan (**H**eart Failure **E**ndpoint Evaluation of **A**ngiotensin II **A**ntagonist **L**osartan [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 **C**andesartan in **H**eart Failure **A**ssessment of **R**eduction in **M**ortality and Morbidity (CHARM) trial and the **Val**sartan **He**art **F**ailure **T**rial (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 **P**erindopril in **E**lderly **P**eople With **C**hronic **H**eart **F**ailure (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 **I**rbesartan in Heart Failure With **Preserve**d 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

**HFrEF.** The large **P**rospective Comparison of **AR**Ni With **A**CEi to **D**etermine **I**mpact on **G**lobal **M**ortality and Morbidity in **H**eart **F**ailure (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 **P**rospective Comparison of **AR**NI with **A**RB Global **O**utcomes in Heart Failure With Preserved Ejectio**n** 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

**HFrEF.** 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 **C**ardiac **I**nsufficiency **Bi**soprolol **S**tudy (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 **Al**dactone **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 **a**nd **S**urv**i**val **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 ≥ 45% in the **T**reatment **o**f **P**reserved **C**ardiac Function Heart Failure With an **A**ldosterone An**t**agonist (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 **a**nd **P**revention of **A**dverse Outcomes 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 **Emp**agliflozin Outcom**e** T**r**ial in Patients With Chr**o**nic Hea**r**t Failure and a **Reduced** Ejection Fraction (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 **Veri**gua**t** Gl**o**bal Study in Subjects With Heart Failure With **R**educed Ejec**t**ion Fr**a**ction (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 **Un**sustained **T**achycardia **T**rial [MUSTT], **M**ulticenter **A**utomatic **D**efibrillator **I**mplantation **T**rial II [MADIT-II], **D**efibrillator **in** **A**cute **M**yocardial **I**nfarction **T**rial [DINAMIT], **Def**ibrillators **i**n **N**on**i**schemic Cardiomyopathy **T**reatment **E**valuation [DEFINITE], and **S**udden **C**ardiac **D**eath in **He**art **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-analysis[70] of MADIT-II, MUSTT, SCD-HEFT, DEFINITE, and **Co**mparison of **M**edical Therapy, **P**acing **an**d Defibrilla**tion** in Heart Failure (COMPANION), ICD implantation was

**Table 2.** Representation of females and mortality benefit for both sexes in primary prevention ICD clinical trials[66]

| 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; DEFIINITE, **Def**ibrillators **i**n **N**on**i**schemic Cardiomyopathy **T**reatment **E**valuation; DINAMIT, **D**efibrillator **in A**cute **M**yocardial **I**nfarction **T**rial; EPG, electrophysiologically guided; HR, hazard ratio; ICD, implantable cardioverter-defibrillator; MADIT-II, **M**ulticenter **A**utomatic **D**efibrillator **I**mplantation **T**rial II; MUSTT, **M**ulticenter **Un**sustained **T**achycardia **T**rial; SCD-HeFT, **S**udden **C**ardiac **D**eath in **He**art **F**ailure **T**rial.

*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, **Ca**rdiac **Re**synchronization—**H**eart **F**ailure; CI, confidence interval; COMPANION, **Co**mparison of **M**edical Therapy, **P**acing **an**d Defibrillat**ion** in Heart Failure; CRT, cardiac resynchronization therapy; CRT-D, CRT with defibrillator; HR, hazard ratio; ICD, implantable cardioverter-defibrillator; MADIT-CRT, **M**ulticenter **A**utomatic **D**efibrillator **I**mplantation **T**rial With **C**ardiac **R**esynchronization **T**herapy; RAFT, **R**esynchronization-Defibrillation for **A**mbulatory Heart **F**ailure **T**rial; REVERSE, **Re**synchronization Re**ve**rses **R**emodeling in **S**ystolic Left V**e**ntricular 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 $\geq$ 150 ms.

A meta-analysis of CRT-D vs ICD trials (**M**ulticenter **A**utomatic **D**efibrillator **I**mplantation **T**rial With **C**ardiac **R**esynchronization **T**herapy [MADIT-CRT], **R**esynchronization-Defibrillation for **A**mbulatory Heart **F**ailure **T**rial [RAFT], and **Re**synchronization Re**ver**ses **R**emodeling in **S**ystolic Left **V**entricular 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 **S**urgical **T**reatment for **I**schemi**c** **H**eart 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 **Inte**ragency **R**egistry for **M**echanically **A**ssisted **C**irculatory **S**upport (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

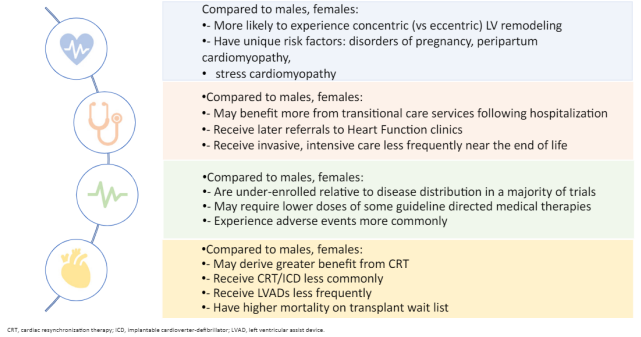


**Figure 1.** Sex differences in heart failure (HF) care. CRT, cardiac resynchronization therapy; GDMT, guideline-directed medical therapy; ICD, implantable cardioverter-defibrillator.

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 CirculatorySupport(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 **A**liskiren **T**rial to **M**inimize **O**utcome**s** in **P**atients With **He**art Failu**re** (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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## References

1. Butrous H, Hummel SL. Heart failure in older adults. Can J Cardiol 2016;32:1140-7.
2. Public Health Agency of Canada: Report from the Canadian Chronic Disease Surveillance System: heart disease in Canada. Available at: https://www.canada.ca/en/public-health/services/publications/diseases-conditions/report-heart-disease-Canada-2018.htm. Accessed May 18, 2020.
3. Eaton CB, Pettinger M, Rossouw J, et al. Risk factors for incident hospitalized heart failure with preserved versus reduced ejection fraction in a multiracial cohort of postmenopausal women. Circ Heart Fail 2016;9(10):e002883.
4. Beale AL, Meyer P, Marwick TH, Lam CSP, Kaye DM. Sex differences in cardiovascular pathophysiology: why women are overrepresented in heart failure with preserved ejection fraction. Circulation 2018;138:198-205.
5. Gori M, Lam CSP, Gupta DK, et al. Sex-specific cardiovascular structure and function in heart failure with preserved ejection fraction. Eur J Heart Fail 2014;16:535-42.
6. Nauta JF, Hummel YM, Tromp J, et al. Concentric vs eccentric remodelling in heart failure with reduced ejection fraction: clinical characteristics, pathophysiology and response to treatment. Eur J Heart Fail 2020;22:1147-55.
7. Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke statistics—2014 update. A report from the American Heart Association. Circulation 2014;129(3):e28-292.
8. Garawi F, Devries K, Thorogood N, Uauy R. Global differences between women and men in the prevalence of obesity: is there an association with gender inequality? Eur J Clin Nutr 2014;68:1101-6.
9. Nieminen MS, Harjola V-P, Hochadel M, et al. Gender related differences in patients presenting with acute heart failure. Results from EuroHeart Failure Survey II. Eur J Heart Fail 2008;10:140-8.
10. Yusuf S, Hawken S, Ounpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet 2004;364(9438):937-52.
11. Daubert MA, Douglas PS. Primary prevention of heart failure in women. JACC Heart Fail 2019;7:181-91.
12. Tuija Männistö, Pauline Mendola, Marja Vääräsmäki, et al. Elevated blood pressure in pregnancy and subsequent chronic disease risk. Circulation 2013;127:681-90.
13. Kao DP, Hsich E, Lindenfeld J. Characteristics, adverse events, and racial differences among delivering mothers with peripartum cardiomyopathy. JACC Heart Fail 2013;1:409-16.
14. Stergiopoulos K, Shiang E, Bench T. Pregnancy in patients with pre-existing cardiomyopathies. J Am Coll Cardiol 2011;58:337-50.
15. Vitale C, Mendelsohn ME, Rosano GMC. Gender differences in the cardiovascular effect of sex hormones. Nat Rev Cardiol 2009;6:532-42.
16. Lam CSP, Arnott C, Beale AL, et al. Sex differences in heart failure. Eur Heart J 2019;40:3859-68c.
17. Soldin OP. Mattison DR Sex differences in pharmacokinetics and pharmacodynamics. Clin Pharmacokinet 2009;48:143-57.
18. Regitz-Zagrosek V, Petrov G, Lehmkuhl E, et al. Heart transplantation in women with dilated cardiomyopathy. Transplantation 2010;89:236-44.
19. Jochmann N, Stangl K, Garbe E, Baumann G, Stangl V. Female-specific aspects in the pharmacotherapy of chronic cardiovascular diseases. Eur Heart J 2005;26:1585-95.
20. Whitelaw S, Sullivan K, Eliya Y, et al. Trial characteristics associated with under-enrollment of females in randomized controlled trials of heart failure with reduced ejection fraction: a systematic review. Eur J Heart Fail 2021;23:15-24.
21. Whitelaw S, Thabane L, Mamas MA, et al. Characteristics of heart failure trials associated with under-representation of women as lead authors. J Am Coll Cardiol 2020;76:1919-30.
22. Andersson C, Vasan RS. Epidemiology of heart failure with preserved ejection fraction. Heart Fail Clin 2014;10:377-88.
23. Lee DS, Gona P, Vasan RS, et al. Relation of disease pathogenesis and risk factors to heart failure with preserved or reduced ejection fraction: insights from the Framingham Heart Study of the National Heart, Lung, and Blood Institute. Circulation 2009;119:3070-7.
24. Fonarow GC, Stough WG, Abraham WT, et al. Characteristics, treatments, and outcomes of patients with preserved systolic function hospitalized for heart failure: a report from the OPTIMIZE-HF registry. J Am Coll Cardiol 2007;50:768-77.
25. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016;37:2129-200.
26. Yancy CW, Fonarow GC, Albert NM, et al. Influence of patient age and sex on delivery of guideline-recommended heart failure care in the outpatient cardiology practice setting: findings from IMPROVE HF. Am Heart J 2009;157:754-62.e2.
27. Tannenbaum C, Norris CM, McMurtry MS. Sex-specific considerations in guidelines generation and application. Can J Cardiol 2019;35:598-605.
28. Asch FM, Miyoshi T, Addetia K, et al. Similarities and differences in left ventricular size and function among races and nationalities: results of the World Alliance Societies of Echocardiography Normal Values Study. J Am Soc Echocardiogr 2019;32. 1396-406.e2.
29. 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;141:338-51.
30. 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(10205):1254-63.
31. Kostis JB, Shelton B, Gosselin G, et al; SOLVD Investigators. Adverse effects of enalapril in the Studies of Left Ventricular Dysfunction (SOLVD). Am Heart J 1996;131:350-5.
32. Shekelle PG, Rich MW, Morton SC, et al. Efficacy of angiotensin-converting enzyme inhibitors and beta-blockers in the management of left ventricular systolic dysfunction according to race, gender, and diabetic status. J Am Coll Cardiol 2003;41:1529-38.
33. CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North

Scandinavian Enalapril Survival Study (CONSENSUS). N Engl J Med 1987;316:1429-35.

34. Investigators SOLVD, Yusuf S, Pitt B, Davis CE, Hood WB, Cohn JN. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med 1991;325:293-302.

35. Packer M, Poole-Wilson PA, Armstrong PW, et al. Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. Circulation 1999;100:2312-8.

36. Konstam MA, Neaton JD, Dickstein K, et al. Effects of high-dose versus low-dose losartan on clinical outcomes in patients with heart failure (HEAAL study): a randomised, double-blind trial. Lancet 2009;374(9704):1840-8.

37. Young JB, Dunlap ME, Pfeffer MA, et al. Mortality and morbidity reduction with candesartan in patients with chronic heart failure and left ventricular systolic dysfunction: results of the CHARM Low—Left Ventricular Ejection Fraction trials. Circulation 2004;110:2618-26.

38. Cohn JN, Tognoni G. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. N Engl J Med 2001;345:1667-75.

39. Cleland JGF, Tendera M, Adamus J, et al. The perindopril in elderly people with chronic heart failure (PEP-CHF) study. Eur Heart J 2006;27:2338-45.

40. Lam CSP, Carson PE, Anand IS, et al. Sex differences in clinical characteristics and outcomes in elderly patients with heart failure and preserved ejection fraction: the Irbesartan in Heart Failure with Preserved Ejection Fraction (I-PRESERVE) trial. Circ Heart Fail 2012;5:571-8.

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

42. Solomon SD, Rizkala AR, Gong J, et al. Angiotensin receptor neprilysin inhibition in heart failure with preserved ejection fraction: rationale and design of the PARAGON-HF trial. JACC Heart Fail 2017;5:471-82.

43. Solomon SD, Vaduganathan M, L Claggett B, et al. Sacubitril/valsartan across the spectrum of ejection fraction in heart failure. Circulation 2020;141:352-61.

44. Tamargo J, Rosano G, Walther T, et al. Gender differences in the effects of cardiovascular drugs. Eur Heart J Cardiovasc Pharmacother 2017;3:163-82.

45. Packer M, Coats AJ, Fowler MB, et al. Effect of carvedilol on survival in severe chronic heart failure. N Engl J Med 2001;344:1651-8.

46. CIBIS Investigators and Committees. A randomized trial of beta-blockade in heart failure. The Cardiac Insufficiency Bisoprolol Study (CIBIS). Circulation 1994;90:1765-73.

47. Simon T, Mary-Krause M, Funck-Brentano C, Jaillon P. Sex differences in the prognosis of congestive heart failure: results from the Cardiac Insufficiency Bisoprolol Study (CIBIS II). Circulation 2001;103:375-80.

48. Zheng SL, Chan FT, Nabeebaccus AA, et al. Drug treatment effects on outcomes in heart failure with preserved ejection fraction: a systematic review and meta-analysis. Heart 2018;104:407-15.

49. Zannad F, McMurray JJV, Krum H, et al. Eplerenone in patients with systolic heart failure and mild symptoms. N Engl J Med 2011;364:11-21.

50. Pitt B, Pfeffer MA, Assmann SF, et al. Spironolactone for heart failure with preserved ejection fraction. N Engl J Med 2014;370:1383-92.

51. Merrill M, Sweitzer N, Lindenfeld J, Kao DP. Sex differences in outcomes and response to spironolactone in HFpEF: a secondary analysis of TOPCAT. JACC Heart Fail 2019;7:228-38.

52. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med 2019;381:1995-2008.

53. Packer M, Anker SD, Butler J, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. N Engl J Med 2020;383:1413-24.

54. Armstrong PW, Pieske B, Anstrom KJ, et al. Vericiguat in patients with heart failure and reduced ejection fraction. N Engl J Med 2020;382:1883-93.

55. Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. N Engl J Med 1997;336:525-33.

56. 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;347:1403-11.

57. Voors AA, Anker SD, Cleland JG, et al. A Systems Biology Study to Tailored Treatment in Chronic Heart Failure: rationale, design, and baseline characteristics of BIOSTAT-CHF. Eur J Heart Fail 2016;18:716-26.

58. Lam CSP, Anand I, Zhang S, et al. Asian Sudden Cardiac Death in Heart Failure (ASIAN-HF) registry. Eur J Heart Fail 2013;15:928-36.

59. Russo AM, Daugherty SL, Masoudi FA, et al. Gender and outcomes after primary prevention implantable cardioverter-defibrillator implantation: Findings from the National Cardiovascular Data Registry (NCDR). Am Heart J 2015;170:330-8.

60. Narasimha D, Curtis AB. Sex differences in utilisation and response to implantable device therapy. Arrhythm Electrophysiol Rev 2015;4:129-35.

61. Buxton AE, Lee KL, Fisher JD, et al. A randomized study of the prevention of sudden death in patients with coronary artery disease. N Engl J Med 1999;341:1882-90.

62. Russo AM, Stamato NJ, Lehmann MH, et al. Influence of gender on arrhythmia characteristics and outcome in the Multicenter Unsustained Tachycardia Trial. J Cardiovascular Electrophysiol 2004;15:993-8.

63. Moss AJ, Zareba W, Hall WJ, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med 2002;346:877-83.

64. Zareba W, Moss AJ, Hall WJ, et al. Clinical course and implantable cardioverter defibrillator therapy in postinfarction women with severe left ventricular dysfunction. J Cardiovasc Electrophysiol 2005;16:1265-70.

65. Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med 2005;352:225-37.

66. Ghanbari H, Dalloul G, Hasan R, et al. Effectiveness of implantable cardioverter-defibrillators for the primary prevention of sudden cardiac death in women with advanced heart failure: a meta-analysis of randomized controlled trials. Arch Intern Med 2009;169:1500-6.

67. Hohnloser SH, Kuck KH, Dorian P, et al. Prophylactic use of an implantable cardioverter-defibrillator after acute myocardial infarction. N Engl J Med 2004;351:2481-8.

68. Kadish A, Dyer A, Daubert JP, et al. Prophylactic defibrillator implantation in patients with nonischemic dilated cardiomyopathy. N Engl J Med 2004;350:2151-8.

69. Albert CM, Quigg R, Saba S, et al. Sex differences in outcome after implantable cardioverter defibrillator implantation in nonischemic cardiomyopathy. Am Heart J 2008;156:367-72.

70. Santangeli P, Pelargonio G, Dello Russo A, et al. Gender differences in clinical outcome and primary prevention defibrillator benefit in patients with severe left ventricular dysfunction: a systematic review and meta-analysis. Heart Rhythm 2010;7:876-82.

71. MacFadden DR, Crystal E, Krahn AD, et al. Sex differences in implantable cardioverter-defibrillator outcomes: findings from a prospective defibrillator database. Ann Intern Med 2012;156:195-203.

72. Udell JA, Juurlink DN, Kopp A, et al. Inequitable distribution of implantable cardioverter defibrillators in Ontario. Int J Technol Assess Health Care 2007;23:354-61.

73. Hess PL, Hernandez AF, Bhatt DL, et al. Sex and race/ethnicity differences in implantable cardioverter-defibrillator counseling and use among patients hospitalized with heart failure: findings from the Get With The Guidelines—Heart Failure program. Circulation 2016;134:517-26.

74. Chatterjee NA, Borgquist R, Chang Y, et al. Increasing sex differences in the use of cardiac resynchronization therapy with or without implantable cardioverter-defibrillator. Eur Heart J 2017;38:1485-94.

75. Cleland JGF, Daubert J-C, Erdmann E, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med 2005;352:1539-49.

76. Saxon LA, Bristow MR, Boehmer J, et al. Predictors of sudden cardiac death and appropriate shock in the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial. Circulation 2006;114:2766-72.

77. Bristow MR, Saxon LA, Boehmer J, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med 2004;350:2140-50.

78. Tang ASL, Wells GA, Talajic M, et al. Cardiac-resynchronization therapy for mild-to-moderate heart failure. N Engl J Med 2010;363:2385-95.

79. Linde C, Abraham WT, Gold MR, et al. Randomized trial of cardiac resynchronization in mildly symptomatic heart failure patients and in asymptomatic patients with left ventricular dysfunction and previous heart failure symptoms. J Am Coll Cardiol 2008;52:1834-43.

80. Randolph TC, Hellkamp AS, Zeitler EP, et al. Utilization of cardiac resynchronization therapy in eligible patients hospitalized for heart failure and its association with patient outcomes. Am Heart J 2017;189:48-58.

81. Varma N, Manne M, Nguyen D, et al. Probability and magnitude of response to cardiac resynchronization therapy according to QRS duration and gender in nonischemic cardiomyopathy and LBBB. Heart Rhythm 2014;11:1139-47.

82. 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;174:1340-8.

83. Sun LY, Tu JV, Bader Eddeen A, Liu PP. Prevalence and long-term survival after coronary artery bypass grafting in women and men with heart failure and preserved versus reduced ejection fraction. J Am Heart Assoc 2018;7(12):e008902.

84. Velazquez EJ, Lee KL, Jones RH, et al. Coronary-artery bypass surgery in patients with ischemic cardiomyopathy. N Engl J Med 2016;374:1511-20.

85. Pina IL, Zheng Q, She L, et al. Sex difference in patients with ischemic heart failure undergoing surgical revascularization: results from the STICH trial (Surgical Treatment for Ischemic Heart Failure). Circulation 2018;137:771-80.

86. Kormos RL, Cowger J, Pagani FD, et al. The Society of Thoracic Surgeons INTERMACS database annual report: evolving indications, outcomes, and scientific partnerships. Ann Thorac Surg 2019;107:341-54.

87. Bogaev RC, Pamboukian SV, Moore SA, et al. Comparison of outcomes in women versus men using a continuous-flow left ventricular assist device as a bridge to transplantation. J Heart Lung Transplant 2011;30:515-22.

88. Birks EJ, McGee ECJ, Aaronson KD, et al. An examination of survival by sex and race in the Heartware Ventricular Assist Device for the Treatment of Advanced Heart Failure (ADVANCE) Bridge to Transplant (BTT) and continued access protocol trials. J Heart Lung Transplant 2015;34:815-24.

89. van Meeteren J, Maltais S, Dunlay SM, et al. A multi-institutional outcome analysis of patients undergoing left ventricular assist device implantation stratified by sex and race. J Heart Lung Transplant 2017;36:64-70.

90. Goldstein DJ, Mehra MR, Naka Y, et al. Impact of age, sex, therapeutic intent, race and severity of advanced heart failure on short-term principal outcomes in the MOMENTUM 3 trial. J Heart Lung Transplant 2018;37:7-14.

91. Hsich EM, Naftel DC, Myers SL, et al. Should women get left ventricular assist device support? Findings from INTERMACS. Circ Heart Fail 2012;5:234-40.

92. Blumer V, Mendirichaga R, Hernandez GA, Zablah G, Chaparro SV. Sex-specific outcome disparities in patients receiving continuous-flow left ventricular assist devices: a systematic review and meta-analysis. ASAIO J 2018;64:440-9.

93. Magnussen C, Bernhardt AM, Ojeda FM, et al. Gender differences and outcomes in left ventricular assist device support: the European Registry for Patients with Mechanical Circulatory Support. J Heart Lung Transplant 2018;37:61-70.

94. McIlvennan CK, Lindenfeld J, Kao DP. Sex differences and in-hospital outcomes in patients undergoing mechanical circulatory support implantation. J Heart Lung Transplant 2017;36:82-90.

95. Hsich EM, Blackstone EH, Thuita L, et al. Sex differences in mortality based on united network for organ sharing status while awaiting heart transplantation. Circ Heart Fail 2017;10(6):e003635.

96. DeFilippis EM, Truby LK, Garan AR, et al. Sex-related differences in use and outcomes of left ventricular assist devices as bridge to transplantation. JACC Heart Fail 2019;7:250-7.

97. Khush KK, Cherikh WS, Chambers DC, et al. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: thirty-sixth adult heart transplantation report—2019; focus theme: donor and recipient size mismatch. J Heart Lung Transplant 2019;38:1056-66.

98. Moayedi Y, Fan CPS, Cherikh WS, et al. Survival outcomes after heart transplantation: does recipient sex matter? Circ Heart Fail 2019;12:e006218.

99. Stolfo D, Uijl A, Vedin O, et al. Sex-based differences in heart failure across the ejection fraction spectrum: phenotyping, and prognostic and therapeutic implications. JACC Heart Fail 2019;7:505-15.

100. Dewan P, Rorth 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.

101. Feldman DE, Huynh T, des Lauriers J, et al. Gender and other disparities in referral to specialized heart failure clinics following emergency department visits. J Womens Health (Larchmt) 2013;22:526-31.

102. Houde S, Feldman DE, Pilote L, et al. Are there sex-related differences in specialized, multidisciplinary congestive heart failure clinics? Can J Cardiol 2007;23:451-5.

103. Abrahamyan L, Sahakyan Y, Wijeysundera HC, Krahn M, Rac VE. Gender differences in utilization of specialized heart failure clinics. J Womens Health (Larchmt) 2018;27:623-9.

104. Van Spall HGC, Lee SF, Xie F, et al. Effect of patient-centered transitional care services in patients hospitalized for heart failure: clinical and sex specific outcomes of the PACT-HF randomized clinical trial. Circulation 2019;140:e965-1011.

105. Van Spall HGC, Hill AD, Fu L, Ross HJ, Fowler RA. Temporal trends and sex differences in intensity of healthcare at the end of life in adults with heart failure. J Am Heart Assoc 2021;10:e018495.