THE ROLE OF SEX IN HEART FAILURE AND TRANSPLANTATION

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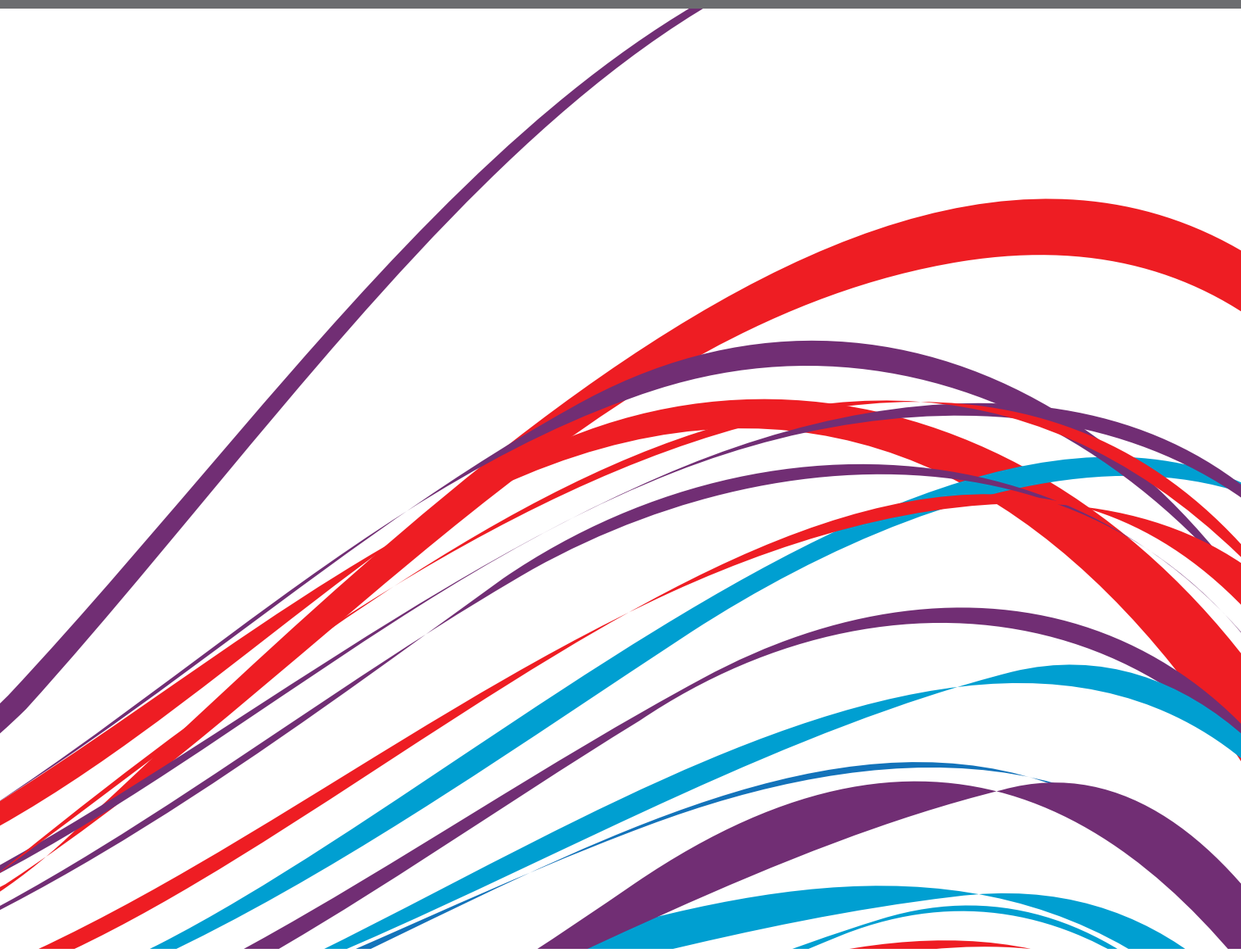

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THE ROLE OF SEX IN HEART FAILURE AND TRANSPLANTATION

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EDITORIAL
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Editorial: The Role of Sex in Heart Failure and Transplantation

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Keywords: heart failure, heart transplantation, sex, prognosis, gender

Editorial on the Research Topic

The Role of Sex in Heart Failure and Transplantation

The epidemic of heart failure (HF) is increasing, mainly due to population aging. As women tend to develop HF at an older age compared to men (1), the prevalence of HF will probably grow at a higher speed in females than in males. Sex-related differences in HF have been described and include epidemiology, etiology, diagnosis, treatment, and prognosis. Unfortunately, women are underrepresented in HF trials and the source of most of these differences is unclear. Women have a better age-adjusted prognosis but survival gains were less in women over the last two decades (2). In addition, women experience worse quality of life during and after HF hospitalization (3). This Research Topic aims to focus on sex-related factors in HF and transplantation.

In this special volume, Postigo and Martínez-Sellés showed that women with HF are more likely to be older, hypertensive, present valvular heart disease, and non-ischemic cardiomyopathy than men. They depicted relevant sex-related differences, including biological mechanisms for HF, age, etiology, precipitating factors, comorbidities, left ventricular ejection fraction, treatment effects, and prognosis. Women have greater clinical severity of HF, with more symptoms and worse functional class, and receive less guideline-proven therapies than men. In spite of both facts, females with HF have better prognosis than males. The authors showed how the reasons for this survival advantage are probably multifactorial but prior pregnancies seem to play a role. López-Vilella et al. describe how female sex confers different prognosis in patients with HF. In 1,291 patients discharged after HF exacerbation, the authors found a trend to better survival in females with reduced ejection fraction than in males. Yet, women presented more readmissions than men, in accordance with the previously described greater clinical severity in females.

Cediel et al. described sex-related differences in HF biomarkers. Kinetics of biological circulating biomarkers are different in women and men but most clinicians do not take sex into account when they assess them. Women tend to exhibit higher levels of natriuretic peptides and galectin-3 and lower levels of cardiac troponins and soluble ST2 than man. Many biological factors explain these differences, including body composition, fat distribution, or menopausal status.

Farrero et al. focused on the impact of HF therapies in women. Current HF guidelines recommend drug up-titration to the same target doses in both men and women, but some factors may impair achieving this goal in women, among them, more common adverse drug reactions and lack of evidence regarding the optimal drug dose. Women are less likely than men to receive a cardiac device in clinical practice, although they show better response to cardiac resynchronization therapy. Females also receive advanced HF therapies less frequently. Technological advances in mechanical circulatory support, with smaller devices, will likely increase their implantation in

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women. Tokodi et al., used a machine learning approach in a registry of 2,191 patients treated with cardiac resynchronization therapy. The authors were able to create models that predicted all-cause mortality. Interestingly, sex-specific patterns of predictors were identified, and hemoglobin was less important in females compared to males. Chibber and Baranchuk revised sex-related differences in catheter ablation for HF patients with atrial fibrillation. These differences include the referral of fewer women for catheter ablation, older age of women at ablation, and higher risk of post-ablation recurrence of atrial fibrillation.

García-Cosío et al. focused on sex influence in advanced HF therapies and outcome following heart transplantation. The authors described how women account for a minority of patients on the waiting list for heart transplantation or other advanced HF therapies. However, long-term results of heart transplants are equal for both men and women. Ayesta described the influence of sex-mismatch on prognosis after heart transplantation. In most studies, donor/recipient sex-mismatch has been associated with poor prognosis, especially in male recipients of female hearts. This is probably related to physiological sex-related differences, differences in complications rates after heart transplantation (rejection, cardiovascular allograft vasculopathy, and primary graft failure), size mismatch, and recipient pulmonary hypertension. The author concluded that, when allocating a graft, sex-mismatch should be considered.

Finally, Sobanski et al. described sex-related differences in palliative care for HF patients. Women live longer, and after a husband or partner's death, they suffer from a stronger sense of loneliness, are more dependent on institutionalized care and have more unaddressed needs than men. As the prevalence of comorbidities [like diabetes (4) or chronic pain syndromes] grows with age, women suffer from a higher number of symptoms (such as pain and breathlessness) than men. Sex-specific differences have been described in symptom pathophysiology, distribution and the required management needed for their successful alleviation.

This Research Topic highlights the importance of studying sex differences in HF and provide insight on factors that may contribute to future studies regarding the role of sex in cardiovascular physiology and HF pathophysiology. Further data may help to improve the diagnosis and management of HF in women and men.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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REVIEW
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Sex-Related Differences in Catheter Ablation for Patients With Atrial Fibrillation and Heart Failure

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The coexistence of atrial fibrillation and heart failure significantly increases the risk of all-cause mortality and heart failure hospitalizations. Sex-related differences in all patients undergoing atrial fibrillation catheter ablation include the referral of fewer women for catheter ablation (15–25%), older age of women at ablation, and higher risk of post-ablation recurrence of atrial fibrillation. We searched the existing literature for sex-related differences in patients undergoing atrial fibrillation catheter ablation with a focus on heart failure. Randomized controlled trials assessing atrial fibrillation catheter ablation in patients with heart failure have demonstrated a significant reduction in all-cause mortality and heart failure hospitalizations. Within the eight existing randomized controlled trials on heart failure with reduced ejection fraction, women composed a small proportion of the study population. Only two studies (CASTLE-AF and AATAC-HF) specifically assessed the effect of gender on outcome and showed no difference in post-ablation outcomes. Registry data-based studies assessing sex-related differences in atrial fibrillation catheter ablation in heart failure reveal that women are half as likely as men to undergo ablation. Conflicting data exist on the interaction of gender and heart failure as they may affect peri-ablation and post-ablation long-term outcomes such as atrial fibrillation recurrence or heart failure hospitalizations. In conclusion, existing studies provide insight into the gender-based differences in patients undergoing catheter ablation for atrial fibrillation as it pertains to heart failure. Further prospective studies with higher proportions of female participants are required to accurately determine gender-based differences in this population.

Keywords: atrial fibrillation, heart failure, catheter ablation, sex-related differences, gender differences

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INTRODUCTION

In patients with clinically overt heart failure (HF), atrial fibrillation (AF) affects ∼15–30% of patients (1). Concomitant occurrence of AF and HF significantly increases the risk of all-cause mortality, HF hospitalizations, and thromboembolism (1–3). Existing randomized controlled trials evaluating the effect of catheter ablation (CA) on outcomes in patients with AF and heart failure with reduced ejection fraction (HFrEF) have demonstrated a significant reduction in all-cause mortality and HF hospitalizations (4–11). The largest randomized controlled trial—CASTLE-AF (4)—demonstrated significant improvement in left ventricular ejection fraction (LVEF), all-cause mortality, and HF hospitalization with AF-CA in patients with LVEF ≤35% as compared to the oral rate or rhythm control (4). It is not clear if and how the results of the trials of AF-CA in HF

are applicable to women in particular. In the general AF population, epidemiologic studies have demonstrated that women are more likely to have adverse events from anti-arrhythmic drugs, higher stroke risk, more disabling strokes, and higher cardiovascular mortality compared with men (2, 12–15). Yet, generally, women with AF are less likely to undergo CA (15–17). Proposed reasons for this include more procedural difficulty due to non-pulmonary vein triggers and atrial fibrosis, older age and presence of more underlying comorbidities. Women may have up to a 2.3–fold increased risk of procedural complications, including tamponade, vascular site complications and longer post-procedural hospitalization (17–20). The aim of this non-systematic review is to amalgamate the knowledge on gender differences in patients undergoing AF-CA with a focus on HF.

METHODS AND MATERIALS

A non-systematic review of the existing literature on sex-related differences in CA for AF in HF has been conducted. We searched PUBMED, EMBASE, and MEDLINE looking for the most relevant existing literature on this topic. MESH terms included: atrial fibrillation, catheter ablation, gender/sex differences, heart failure, and their combinations. Studies that were not in humans or in English were not considered for this review. Studies combining arrhythmias where atrial fibrillation data could not be separately assessed were also eliminated. The papers obtained by the search were reviewed by the two authors for their relevance to the topic. Disagreements were solved by consensus.

RESULTS

AF-CA in *HFrEF*: Gender Effect

Eight randomized controlled trials assess the effect of AF-CA in patients with HFrEF. The female population in these studies ranges from 4 to 27%. **Table 1** summarizes the eight randomized controlled trials, including the ratio of men to women in these trials (4–11). Two trials assess the gender effect on outcomes. The AATAC trial (8) comparing AF-CA with amiodarone in patients with LVEF ≤40% demonstrated significantly less recurrence of AF (recurrence free in CA 70 vs. 34% in amiodarone group; $p < 0.001$), reduced hospitalization (CA 31% vs. amiodarone 57%; $p < 0.001$), and reduced mortality (CA 8% vs. amiodarone 18%; $p = 0.037$). Gender did not affect AF recurrence, but women only composed 25% of the study population (8). In CASTLE-AF (4)—the largest randomized controlled trial in patients with AF and LVEF ≤35%—patients were randomized to CA or medical therapy (rate or rhythm control) with follow-up over 37.8 months. AF-CA demonstrated significantly greater maintenance of sinus rhythm (CA 63.1% vs. control 21.7%; $p < 0.001$), improvement in LVEF (CA 8% increase vs. control 0.2% increase; $p = 0.005$), and reduction in the composite outcome of all-cause mortality and HF hospitalization (CA 28.5% vs. control 44.6%; $p = 0.006$). Subgroup analysis to determine the effect of gender did not demonstrate a statistically significant difference in the primary outcome of death or hospitalization for HF (female HR 0.93 vs. men HR 0.58; $p = 0.36$). However, there is a trend toward men benefiting more from ablation while women appeared to have no significant benefit. The interpretation of this analysis is limited by the low proportion of women in both treatment arms (13% CA vs. 16% medical therapy) (4). The most recent trial in the AF and HFrEF population—AMICA (11)—did not demonstrate improvement in LVEF or symptoms with CA. Notably, women made up only 10% of the study population, and no gender-based differences in outcomes were assessed (11).

AF-CA in *HFpEF*: Gender Effect

In patients with HF with preserved ejection fraction (HFpEF), only retrospective studies have assessed the effect of AF-CA. The most recent retrospective analysis of 85 patients with HFpEF (EF > 50%) and previous hospitalization with AF and HF, showed that AF-CA reduced HF hospitalization compared to pharmacotherapy (rate or rhythm control) over 2 years of follow-up. This cohort included only 35% women and gender based effects on outcomes were not assessed (21). In another 2018 retrospective study of 230 patients with AF and HF who underwent AF-CA, patients were subdivided into HFpEF (58.8%) and HFrEF (42.2%). CA showed similar effectiveness in both groups. Interestingly, women were 31.3% of the study population and were significantly more likely to have HFpEF (42.1%) as opposed to HFrEF (16.5%) but outcomes were not analyzed for gender effect (22).

AF-CA in HF: Gender Effect in Registry Data

Given the limited gender-based data available in trials focusing on AF-CA and HF, studies based on registry datasets provide more insight into gender-related differences. In a Quebec cohort of 101,931 patients with AF and HF only 432 had undergone AF-CA. While 51.4% of the AF and HF cohort was female, only 25.6% of the CA population was female. In the general AF-HF cohort, women were older and had less frequent comorbidities, ICDs, CRTs, and use of medications, while men were younger and had less hypertension, valvular disease, and prior stroke. In the cohort of patients that underwent CA, there were no significant gender differences in age or comorbidities. Adjusting for advanced age and multiple comorbidities, women were approximately half as likely to undergo CA (23). In a 2018 retrospective cohort analysis of 54,645 patients with AF or atrial flutter and HF, 6,443 patients underwent left atrial CA. Of this cohort, 37.5% were female, who were significantly older than men (women 69 years old vs. men 62.7 years old; $p < 0.001$) and had significantly more comorbidities ($p < 0.001$). Women had significantly longer length of hospital stay (women 6 days vs. men 4.6 days; $p < 0.001$), vascular access complications (2.7 vs. 0.7%; $p < 0.001$) and cardiac tamponade (1.5 vs. 0.5%; $p < 0.001$) (24). In another cohort of 10,966 patients who underwent AF-CA, compared with those patients without HF, patients with HF were more likely to be women (41 vs. 37.3%; $p = 0.002$). While the study demonstrated a significant reduction in all-cause hospitalization up to 4 months post CA in the HF and non-HF groups, the effect was more pronounced in the HF group. Outcomes were not stratified according to gender (25).

TABLE 1 | Summary of randomized controlled trials on atrial fibrillation catheter ablation in patients with heart failure with reduced ejection fraction.

Trial (year of publication)	*N*	Gender M:F ratio	Inclusion criteria	Treatment arm	Primary end point	FU (months)	Prominent findings
PABA-CHF (2008) (5)	81	74:7	Paroxysmal or persistent AF, NYHA II–III, and LVEF ≤40%	PVI (±additional ablation) vs. CRT plus AV node ablation	Composite of LVEF (echo), 6MWD or MLWHF score	6	88% AF-free survival in ablation arm (71% off AAD); significant increase in LVEF (+8 vs. −1%), functional capacity, QOL
MacDonald et al. (2011) (6)	41	32:9	Persistent AF, NYHA II–IV, and LVEF <35%	PVI (±additional ablation) vs. pharmacological rate control	LVEF change (MRI)	6	50% AF-free survival in ablation arm (50% off AAD); non-significant increase in LVEF (significant if SR: +10 vs. +1%), functional capacity, QOL
ARC-HF (2013) (10)	52	45:7	Persistent AF, NYHA II–IV, and LVEF ≤35%	PVI (±additional ablation) vs. pharmacologic rate control	Change in peak oxygen consumption	12	88% AF-free survival in ablation arm (84% off AAD); significant improvement in peak VO2, QOL, BNP; non-significant increase in LVEF (+11 vs. +5%), 6MWD
CAMTAF (2014) (7)	50	48:2	Persistent AF, NYHA II–IV, and LVEF <50%	PVI (±additional ablation) vs. pharmacologic rate control	LVEF change (echo)	6	81% AF-free survival in ablation arm (81% off AAD); significant improvement in LVEF (+8 vs. −3%), functional capacity, QOL, BNP
AATAC-AF (2016) (8)	203	151:52	Persistent AF, NYHA II–III, LVEF ≤40%, and DC-ICD/CRT-D	PVI (±additional ablation) vs. amiodarone	AF-free survival	24	70% AF-free survival in ablation arm vs. 34% in amiodarone arm; significant improvement in LVEF (+8 vs. +6%), mortality (8 vs. 18%), hospitalization (31 vs. 57%), QOL
CAMERA-MRI (2017) (9)	68	60:6	Persistent AF, NYHA II–IV, LVEF ≤45%, and idiopathic cardiomyopathy	PVI + posterior box isolation vs. pharmacologic rate control	LVEF change (MRI)	6	75% AF-free survival in ablation arm (56% off AAD); significant improvement in LVEF (+18 vs. +14%), LVEF normalization ≥50% (58 vs. 9%); LGE-predicted LVEF improvement, normalization
CASTLE-AF (2018) (4)	363	311:52	Paroxysmal or persistent AF, NYHA II–IV, LVEF ≤35%, and DC-ICD/ CRT-D with remote monitoring	PVI (±additional ablation) vs. pharmacologic rate (70%) or rhythm control (30%)	Composite of HF hospital-ization or all-cause mortality	60	63 vs. 22% in SR at 5 years; significant improvement in LVEF (+8 vs. 0%), all-cause mortality or HF hospitalization (28 vs. 44%), all-cause mortality (13 vs. 25%), cardiovascular mortality (11 vs. 22%), HF hospitalization (21 vs. 36%)
AMICA (2019) (11)	140	126:14	Persistent AF, LVEF ≤35%, ICD/CRT-D	PVCI vs. optimal medical therapy (rate, rhythm or AV nodal ablation)	LVEF increase	12	73.5 vs. 50% in SR at 1 year; no significant increase in LVEF (8.8 vs. 7.3%), NT-proBNP, 6MWT, QOL

AF-CA General Population

Greater Female Baseline Prevalence of HF

Broadening assessment to registry data in the general AF-CA population, recent studies provide further insight. In a cohort of 1,060 patients with AF-CA under the age of 60, 21% were females. Women were significantly older than men (women 50.8 years old vs. men 49.5 years old) and were more likely to have HF ($p = 0.017$), specifically, diastolic dysfunction ($p < 0.01$). Women showed significantly greater AF recurrence (39% for women vs. 27% for men; $p < 0.001$), but the interaction of gender and HF was not assessed (26). Using the FIRE and ICE study database, 750 patients with symptomatic paroxysmal AF refractory to anti-arrhythmic drugs underwent CA. The cohort included 39% women, who were older (age 64 years old for women vs. 57 years old for men), and had more HF at baseline. Women had significantly more AF recurrence, specifically a 37% increased risk of arrhythmia recurrence. However, a history of HF did not further affect this gender-based difference (27). In another cohort of 54,597 patients with AF-CA, 37.7% were female. Women were older, had significantly more comorbidities, specifically a greater prevalence of HF than men (women 17% vs. men 15.7%; $p < 0.0001$). Importantly, it identified a significantly higher 30-day post-ablation readmission rate for women than men (13.4 vs. 9.4%; $p < 0.0001$), with HF being the second leading

cause of readmission accounting for 13% of all readmissions. However, a history of HF did not further influence the gender based difference in all-cause readmission (28).

No Baseline Gender Difference in HF Prevalence

In a Chinese cohort of 1,410 patients who underwent AF-CA, 31.9% were women who were older and had more paroxysmal AF. There was no significant gender difference in the baseline prevalence of HF (women 5% vs. men 5.3%; $p = 0.75$). While the study did not show any gender-related differences with respect to in-hospital complications or early or late recurrence of AF, women with AF recurrence were more likely to have had a previous history of HF (recurrence CHF 10.1% vs. no recurrence CHF 3.6%; $p < 0.01$) (29). In a prospective, multicenter, observational study of 5,010 consecutive patients undergoing AF-CA, women constituted 27.3% of the study population, were significantly older, and had a lower prevalence of non-paroxysmal AF. At baseline, there was no difference between men and women in HF prevalence (women 14% vs. men 12.9%). Women experienced significantly higher 3-year AF recurrence. Peri-procedurally, there was no significant gender-based difference in HF decompensation (women 0.37% vs. men 0.33%; $p = 0.85$). However, the 3-year incidence of HF hospitalizations tended to be higher in women (2.2% for women vs. 1.5% for men; $p = 0.066$). After adjusting for confounders, being female was an independent predictor for HF hospitalization (adjusted HR 2.17; $p = 0.0014$) (30).

In a meta-analysis of randomized controlled trials and large prospective observational studies to compare sex-related differences in patients undergoing cryoballoon vs. radiofrequency ablation, no effect of HF or LV systolic dysfunction (LVEF < 45%) was identified in either gender on peri-procedural complications, procedural/fluoroscopy time, or the combined outcome of arrhythmia recurrence, reablation, or reinitiation of medications up to 3 years of follow-up (31). Furthermore, 674 patients undergoing AF-CA from the AXAFA-AFNET 5 study, made consisted of 33% women, who were significantly older and more often had paroxysmal AF but were not otherwise more comorbid than men. At baseline, there were no gender-based differences in HF prevalence, but there was a trend toward women having more symptomatic NYHA II-III CHF (28.2% for women vs. 21.5% for men; $p = 0.07$). While there was no sex-related difference in maintenance of sinus rhythm, the effect of HF or HF as an outcome was not reported (32). Another systematic review and meta-analysis of observational studies included 151,370 patients undergoing AF-CA, of which 34% were women. Baseline characteristics and results were divided into two outcomes: freedom from AF/atrial tachycardia (AT) recurrence and complications (stroke/TIA, all-cause mortality). For the demographic of freedom from AF/AT recurrence, there were no baseline differences in the prevalence of HF and women were found to have a lower rate of freedom from AF/AT recurrence. In the demographic of complications, women had significantly less HF at baseline (23.8% for women vs. 25.5% for men; $p = 0.0014$) and demonstrated a trend toward an increased risk of stroke/TIA and all-cause mortality compared with men. Women were also more likely to experience pericardial effusion/tamponade, major bleeding, and pacemaker implantation. The exact interaction of gender and HF on these outcomes was not evaluated, although LVEF was not found to have an effect on freedom from AF/AT or stroke/TIA incidence in either gender (33).

DISCUSSION

In our review, we report that women are significantly underrepresented in trials assessing the effect of AF-CA in HF. Women with AF and HF undergoing CA are older with different comorbidities than men such as stroke or valvular heart disease. Within the limited available information, discrepancy exists on the interaction of gender and HF for AF-CA with respect to peri- and post-ablation outcomes.

Women are more likely to have AF and HF but are half as likely to undergo CA despite adjusting for age and comorbidities. Moreover, women are underrepresented compared to men in both randomized controlled trials and registry based cohort studies of patients with AF and HF (23, 25). This finding is also evident in many general AF-CA registry-based studies where there is no gender-based difference in the prevalence of HF, suggesting that despite the fact that women have more AF and HF, they are not equally being referred for CA (29–33). This gender discrepancy has been demonstrated in the general AF population undergoing CA where <30% of the CA population is female (15–17). Only two of the existing eight randomized trials of AF-CA in HFrEF assess for the effect of gender on outcomes. While gender did not have an effect on outcomes in either trial, the validity of the analysis is limited by the poor representation of women in both trials (4, 8). The limited number of women in these HFrEF trials may be explained by the finding from existing literature that men have a higher incidence of HFrEF and women with AF are more likely to have HFpEF (22, 34). However, even the few small trials of AF-CA in HFpEF include significantly fewer women than men and do not stratify outcomes for gender effect (21, 22).

While women with AF and HF are generally older than men, among those patients who undergo AF-CA there may not be an age difference between men and women. This suggests that apart from gender alone, older age may be another deterring factor in referring women with AF and HF for CA. This can possibly be mitigated by earlier referral of women for AF-CA, especially as previous studies have demonstrated that women are referred later for CA (35). Interestingly women with AF and HF are more likely to have valvular disease and prior stroke yet these differences are often not reflected in the population undergoing CA (23). Valvular heart disease particularly may be a factor that limits the efficacy of catheter ablation, which may again prevent women from being referred for CA (36). When women undergoing AF-CA in HF are older and more comorbid than men, women have a significantly greater length of post-procedural hospital stay, vascular access complications, and cardiac tamponade (24). Some discrepancy does exist with respect to peri-procedural complications, with some data suggesting no effect of HF or LV dysfunction on peri-procedural complications for either gender,

nor any gender difference in peri-procedural HF occurrence (30, 31). In the general AF population undergoing CA, some studies have found women to have higher peri-procedural complications (17–20, 33). Anatomical differences, such as smaller heart size in women, may be factors that affect catheter manipulation in the heart chambers (35). Such an emerging finding may be another factor contributing to women being referred less often for AF-CA.

In the general AF-CA cohorts, there is a significant discrepancy in the effect of gender and HF on the efficacy of AF-CA. In some cohorts where women are older and more likely to have HF at baseline, women have significantly more AF recurrence post CA. However, the independent effect of a history of HF on this gender difference could not be consistently established, as some chorts even demonstrated no gender-based difference in AF recurrence in the general AF-CA cohort (26–29, 31, 33). Conflicting data also exist with respect to post-ablation readmission outcomes. In one cohort where women have a higher HF prevalence, women demonstrate a greater rehospitalization rate for up to 30 days post CA, with HF accounting for 13% of all readmissions (28). Meanwhile, another cohort study where women were more likely to have HF at baseline demonstrated lower post-ablation all-cause hospitalizations up to 4 months post CA (25). Furthermore, a cohort study with no gender-based difference in baseline prevalence of HF demonstrated significantly higher HF hospitalizations for up to 3 years post-CA in women (30). From these studies it is difficult to ascertain the direct interaction of gender and HF on the efficacy and outcomes of AF-CA.

CONCLUSION

We report that in patients with AF and HF, women are significantly underrepresented in randomized controlled trials and cohort studies assessing the effects of AF-CA. Independent of other factors, female sex and older age were both factors that limited the inclusion of women with HF in studies assessing the efficacy of AF-CA. Conflicting evidence exists on the interaction of HF and gender with respect to outcomes at the time of and after AF-CA. Going forward, trials on AF-CA in HF should work toward including more female participants and at least assessing for the effect of gender on outcomes as there may be significant gender-based differences. Future research should also attempt to explicitly determine the factors that lead to the disparities between men and women from referral for AF-CA in HF to degree of benefit or harm from the ablation.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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REVIEW
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Sex Influence on Heart Failure Prognosis

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Heart failure (HF) affects 1–2% of the population in developed countries and ∼50% of patients living with it are women. Compared to men, women are more likely to be older and suffer hypertension, valvular heart disease, and non-ischemic cardiomyopathy. Since the number of women included in prospective HF studies has been low, much information regarding HF in women has been inferred from clinical trials observations in men and data obtained from registries. Several relevant sex-related differences in HF patients have been described, including biological mechanisms, age, etiology, precipitating factors, comorbidities, left ventricular ejection fraction, treatment effects, and prognosis. Women have greater clinical severity of HF, with more symptoms and worse functional class. However, females with HF have better prognosis compared to males. This survival advantage is particularly impressive given that women are less likely to receive guideline-proven therapies for HF than men. The reasons for this better prognosis are unknown but prior pregnancies may play a role. In this review article we aim to describe sex-related differences in HF and how these differences might explain why women with HF can expect to survive longer than men.

Keywords: heart failure, sex, women, gender, prognosis

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INTRODUCTION

Heart failure (HF) is an increasing global problem, with a current worldwide prevalence of more than 64 million cases, which means roughly 8.5 per 1,000 inhabitants (1). Although ∼50% of patients with HF are women, sex-related differences within HF are poorly recognized, and understood. According to recent evidence, such differences may include biological mechanisms, epidemiology, pathogenesis, treatment response, quality of care, and prognosis.

The prevalence of HF increases with age, but this is particularly true in women, with a higher prevalence of HF in elderly women than in their male counterparts (2). While men more frequently suffer from HF as a consequence of ischemic heart disease (3–7), women with HF present with more frequent comorbidities such as hypertension, obesity and diabetes Besides, women with HF have higher left ventricular ejection fraction (LVEF) than men (8, 9). In fact, in acute decompensated HF, women tend to have preserved left ventricular systolic function almost twice as often as men (3, 10). HF management also has several sex-related differences, with women being less frequently studied for their underlying HF-etiology and their LVEF less often assessed than in men. In addition, women are less frequently treated with evidence-based drugs, even after adjustment for age, comorbidities, and LVEF (11, 12).

This review article focuses on the influence of sex in HF prognosis. Women are known to have a better prognosis than men in other cardiovascular conditions, including hypertension, aortic stenosis, and hypertrophic cardiomyopathy. Moreover, they typically adapt to those conditions with less chamber dilation, wall thinning, and better contractility than men (13). However, there are some exceptions where males do not fare worse than females such as Tako-tsubo syndrome or cardiac toxicity in alcoholic cardiomyopathy (14, 15).

BIOLOGICAL DIFFERENCES

It is widely known that male and female hearts and cardiovascular systems are different both at baseline and in response to insults (16). Women have smaller hearts, with lower end-diastolic pressures, and higher right ventricular ejection fraction, in spite of having similar LVEF (17). During exercise, women have greater increase in their end-diastolic volume as a compensation for their lower increase of LVEF compared to men. Over the years, women experience less deterioration in their contractile function (18).

When considering the causes for these differences, estrogens are obvious candidates. It has been demonstrated that cardiovascular risk increases when estrogen production ceases, being a strong argument in favor of their protective role. Moreover, the presence of estrogenic and androgenic receptors in cardiac tissue, which could influence the function of contractile proteins, has been proven. Furthermore, endogenous estrogens have been shown to be relatively protective from apoptosis and cell death in response to acute coronary ischemia, making women have greater myocardial salvage after successful reperfusion, smaller infarct sizes, less adverse cardiac remodeling, and higher preservation of left ventricular function (19–21).

Being an exclusive cause of female HF, peripartum cardiomyopathy is worth mentioning as an exception to favorable female hormonal influence. Several mechanisms such as myocarditis, autoimmune processes, and hemodynamic stress of pregnancy, all of them triggered by the hormonal context, have been studied as potential causes of this condition. As in other causes of HF in women, delayed diagnosis is not uncommon and is associated with more adverse outcomes. Worse prognosis is also related to the decrease of LVEF, the degree of left ventricular dilatation, obesity, and black race (22). Nevertheless, given its small prevalence, many questions remain about peripartum cardiomyopathy global prognosis compared to any other cause of HF (23).

Despite hormones playing a leading role, a single factor is unlikely to justify every difference found (24). This has led to the study of genetic predictors for cardiovascular disease, and for HF in particular, with no relevant findings to date For instance, women's Health Genome Study followed more than 19,000 women prospectively during a median of 12 years, showing no incremental capability to predict cardiovascular disease risk (25).

On the other hand, there is a tendency to think that the main cause of the prognostic benefit of women with HF is their higher frequency of diastolic HF. However, there is strong evidence against this thought. Although it is true that women have higher LVEF and therefore mid-range and systolic HF are less common in women than in men, several data have confirmed that women with HF have better survival than men irrespective of LVEF (5, 26). Female sex has also been proven to be an independent predictor of lower mortality in patients with HF with preserved ejection fraction (6). In addition, studies that included patients with systolic dysfunction showed that women live longer than men, even after adjustment for ischemic etiology and even when only patients with advanced systolic dysfuntion (LVEF $<$ 20%) were considered (12, 27). In fact, LVEF seems to have less prognostic influence in women than in men (27, 28).

In absence of other clear causes, sex related differences in HF prognosis have been associated with three additional mechanisms (**Figure 1**):

- Differences in etiology, prevalence of comorbidities, triggers, predisposing or precipitating factors.
- Treatments received and treatments effects.
- Previous pregnancies.

Differences in Etiology and Comorbidities

The etiology of HF varies depending on sex, age, and race. Since many patients suffer from different conditions that might cause it, HF is often multifactorial. Ischemic heart disease, hypertension, valvular heart disease, and idiopathic dilated cardiomyopathy are the most frequent etiologies of HF, with different distribution according to sex (**Table 1**).

Hypertension

Hypertension is an important precursor of HF in general population. Global prevalence of hypertension is higher in women that in men, with this difference being more pronounced in the elderly (29). Multiple hypotheses try to explain this higher prevalence of hypertension in women, being the role of female sex hormones a known important contributing factor. While women are premenopausal, estrogens activate nitric oxide causing vasodilatation and reducing vascular stiffness (30). Moreover, ovarian hormones reduce plasma renin and angiotensin-converting enzyme activity (31). With the onset of menopause, the drop in estrogens levels is associated with an increased rigidity of the arterial wall due to collagen accumulation and elastin fragmentation, which leads to a two-fold greater risk of hypertension (29).

Regarding premenopausal women, oral contraceptive use could explain a certain trend to higher blood pressure, being associated with an increase in around 7–8 mmHg from baseline and almost double risk of hypertension compared with never-users (32, 33). Importantly, hypertensive women are more likely to develop left ventricular hypertrophy, diastolic dysfunction, and HF compared with men (3, 34). Levy and collaborators showed that the adjusted risk for HF development was about 2-fold in hypertensive men but 3-fold in hypertensive women compared to normotensive patients (35). Interestingly, they showed that hypertension could be causing 39% HF cases in men and 59% in women.

FIGURE 1 | Determining factors of the differences in female heart failure syndrome.

Ischemic Heart Disease

Ischemic heart disease is more common in men than in women (2). Even in the setting of acute coronary syndrome, women have less atherosclerotic burden and less plaque rupture than men (36, 37). Also in patients with chronic coronary artery disease, men have greater amount of coronary lesions, whereas women more frequently suffer from chest pain without obstructive coronary artery disease, which has been attributed to endothelial and microvascular dysfunction (38). Along with hypertension, ischemic heart disease is responsible for the largest proportion of the newly diagnosed cases of HF, being associated with a 52% of cases in the Framingham Heart Study (39). Importantly, ischemic heart disease is main cause of HF for men, whereas it plays a smaller role in the etiology of HF for women (3, 5, 40). However, large registries and clinical trials have shown that, in patients with coronary artery disease, women have higher risk of HF than men (41, 42). In the Pexelizumab in Conjunction With Angioplasty in Acute Myocardial Infarction (APEX-AMI) trial (42) female sex was an independent predictor of HF and cardiogenic shock. This difference in the risk of HF after a myocardial infarction persists not only throughout hospitalization but also during long-term follow-up (43). On the other hand, sex-bias has been identified in the diagnosis and treatment of ischemic heart disease. According to the Euro Heart Survey of Stable Angina (44, 45), women were less likely to undergo exercise electrocardiogram and coronary angiography than men. Women with ischemic heart disease were also less likely to be revascularized, and received antiplatelet treatment and statins less frequently, with a poorer control of cardiovascular risk factors including blood pressure and LDL-cholesterol. Interestingly, sex-related differences in HF prognosis are less marked in patients with ischemic etiology, and women survival benefit is lower in this context (7). Furthermore, men suffering from ischemic heart disease who bear an implantable cardioverter defibrillator suffered more ventricular arrhythmias and received more device therapies than women (46–48). This suggests that different degrees of susceptibility to arrhythmia triggering may explain differences in sudden cardiac death rates (49, 50).

TABLE 1 | Differences in heart failure etiologies.

Male	Female
Ischemic heart disease	Hypertension
Dilated cardiomyopathy	Valvular heart disease
Hypertrophic cardiomyopathy	Atrial fibrillation
Arrhythmogenic cardiomyopathy	

Non-ischemic Dilated Cardiomyopathy

In recent years, there has been a broad advance in our knowledge of the genetic causes that justify the appearance of dilated cardiomyopathy, being most of the implicated genes autosomal dominant in transmission (51). Despite this common pattern, the hypothesis that sex may affect the penetrance of disease genes could explain why men have a slightly greater prevalence of dilated cardiomyopathy than women (52). Regarding prognosis, myocardial recovery is more common in women than in men, as is transplant-free survival (53). Several examples of female-protection have been described, as in the case of mutations in genes encoding for the sarcomere protein titin, found in ∼25% of familial dilated cardiomyopathy cases, with male carriers suffering adverse events up to 10 years earlier than females (54). Whether these differences are caused by variances in factors such as penetrance, expressivity, modifier genes, or environmental factors, remain unknown (53).

Atrial Fibrillation

Women with atrial fibrillation (AF) have larger left atrial volume index and lower emptying fraction than men (55). While AF increases the risk of HF in women, this association has not been clearly established for men (56). In addition, in females AF is associated with greater risk for adverse clinical outcomes, particularly HF hospitalization (57).

Other Cardiomyopathies

See **Table 2**.

TABLE 2 | Sex-related differences in heart failure etiology and its implication in prognosis.

Other causes		Males	Females	References
Valvular heart disease	Mitral regurgitation	Equal prevalence	Frequent underdiagnosis and delayed valvular interventions. Less mitral valve repair, worse outcomes associated with replacement. Higher probability of recurrent HF after surgery. Similar outcomes after Mitraclip.	(58–60)
	Aortic stenosis	Equal prevalence and similar prognostic implications for both sexes. More frequently referred for surgery.	Higher prevalence of paradoxical low flow- low gradient stenosis. More frequent concomitant significant mitral disease. Similar survival rates after surgery. Lower all-cause mortality after TAVR.	(61–64)
	Tricuspid regurgitation		Higher prevalence. Similar results in isolated surgery, but poorer perioperative outcomes when combined with coronary artery bypass surgery.	(65, 66)
Other cardiomyopathies	Hypertrophic cardiomyopathy	Higher prevalence (2:1 predominance in males). More hypertrophy and fibrosis. More ventricular arrhythmias	Worse symptoms Higher all-cause mortality	(67, 68)
	Arrhythmogenic cardiomyopathy	Higher prevalence (approximate ratio of 3:1). Higher mortality rate and sudden cardiac death.		(69, 70)
	Restrictive cardiomyopathy	Male predominance in mutant and Wild-type transthyretin amyloid. More frequent Cardiac involvement in sarcoidosis.	Higher occurrence of endomyicardial fibrosis, but better survival. No sex differences for hyper-eosinophilic syndrome, scleroderma or carcinoid heart disease.	(52, 71)

TAVR, transcatheter aortic valve replacement.

Differences in Treatment Administration and Response

Women have been historically underrepresented in HF clinical trials and, to a lesser amount, in registries. Moreover, many data come from *post-hoc* analyses and registries, with their inherent bias (26). This has limited our understanding of the efficacy of HF treatment in women (72). Moreover, it has been shown that women are less likely to receive guideline-proven HF therapies than men, and more frequently receive suboptimal doses (11, 40). However, adherence to HF treatments is higher in women than in men (73, 74).

Drugs to Treat HF With Reduced Ejection Fraction

Women with HF and reduced ejection fraction receive significantly less furosemide than men, both at admission and during hospitalizations (12, 75). Regarding angiotensin-converting enzyme (ACE) inhibitors, the benefit for women may not be as great as for men, with particular doubts concerning its value in women with still asymptomatic LV systolic dysfunction (76, 77). However, this is probably related with limited power due to the low representation of women in studies (78). Conversely, the effect of angiotensin receptor blockers (ARB) seems to be similar in both sexes (79). Sacubitril/valsartan has a similar tolerability in men and women with more frequent functional class improvement and greater reduction in the risk of HF hospitalization in women than in men (80, 81). The data regarding hydralazine and isosorbide dinitrate in females are extremely scarce, being particularly surprising given that this combination is frequently used to treat HF during pregnancy, when ACE inhibitors and ARBs are contraindicated. Besides, spironolactone and eplerenone improve survival in symptomatic systolic HF in men and women (82–84) (**Figure 2**).

On the other hand, betablockers improve outcomes in women, even though the main benefits in most studies were related to the reduction in hospitalizations (85–87). At any rate, meta-analyses data have confirmed that the effect of betablockers in mortality reduction is similar in both sexes (76). Less than 25% of patients in ivabradine trials were women. Despite the limited evidence, there is no reason to think that their main benefit, the reduction in hospital admissions, is different in men and women (88). In contrast, a previous study yielded worrying results regarding digoxin use in women due to its possible association with an increased risk of death. Digoxin use and dosage should, therefore, be very cautious in women (89). Finally, sodium glucose co-transporter 2 (SGLT2) inhibitors have demonstrated benefits in terms of cardiovascular mortality and especially in lowering the risk of HF hospitalization (90) and the benefit seems to be similar in women and men (91).

Devices

Women are less often considered eligible for implantable cardioverter defibrillator (ICD) implantation, and even after adjustment for potential confounders, women are 40% less likely to receive ICD therapy than men (92–94). This is not justified

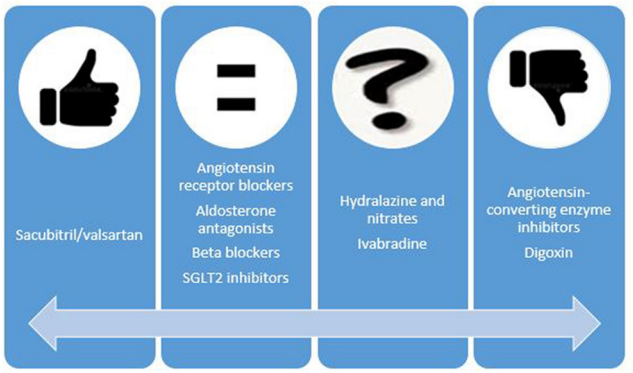

FIGURE 2 | Possible sex-related differences in the benefit of heart failure drugs. Thumb up means data that suggest higher benefit in women than in men. Thumb down means the opposite.

by a lower efficacy in this subgroup, since previous studies have shown similar ICD effectiveness in both sexes (48).

Regarding resynchronization therapy (CRT), women are, once again, significantly less likely to undergo CRT implant compared to men despite its demonstrated greater benefit (95). Among patients enrolled in the Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT) trial, women treated with CRT experienced greater reductions in the combined endpoint of HF or death and had more reverse cardiac remodeling (96). Similar findings were found in the Multicenter InSync Randomized Clinical Evaluation (MIRACLE) study, with woman having less occurrence of HF or death than men (97).

Ventricular Assist Devices

Left ventricular assist devices (LVAD) are mainly used in men, with only 21–33% being implanted in women (98). There was an initial concern that women had increased mortality and risk of bleeding or neurologic events compared with men (99, 100). However, recent evidence has shown no significant sex-related differences in terms of infections, bleeding, or device malfunction (26, 101, 102). Moreover, survival with LVAD has improved for both women and men with no differences in mortality (98, 103). The main persistent limitation is the female higher risk of neurologic events (101), even though some authors have blamed the differences in axial vs. centrifugal continuous flow and the dissimilarities in anticoagulation treatment as potential explanations for these differences. In fact, the latest models such as HeartMate 3 have no sex-related difference in stroke risk (104).

Heart Transplantation

Heart transplantation provides the best opportunity of quality and quantity of life for eligible patients with advanced HF (105). However, women are significantly less frequently transplanted, being approximately a quarter of total transplants (106). This has a multifactorial explanation, but age is likely an important factor since older age decreases eligibility for heart transplantation (98). Women also have a higher likelihood to be sensitized with antibodies, although few women are not referred to transplant for this reason (107). Among patients in heart transplant waitlist, women have worse prognosis, probably because only those with more severe forms reach that list, but also due to the lower rates of mechanical circulatory support despite similar INTERMACS status. That could also explain why this higher mortality risk only applies for women listed high priority, whereas those listed as low priority have similar or even better prognosis than men (108). Survival after heart transplantation is better in women with a median survival of 11.5 years as opposed to 10.5 years for men (105). Conversely, they admit worse quality of life and worse functional class, with more frequent depression not only early but also later after transplantation (109). Regarding long-term associated diseases, men recipients suffer significantly more frequent post-transplant malignancy (110), which is not only related to sex-specific cancers, as this risk remains after exclusion of prostate, breast and cervical cancer (111). On the other hand, although some previous evidences have suggested that women have higher risk of antibody-mediated rejection, which is supposed to subsequently increase their risk of cardiac allograft vasculopathy, in fact coronary vasculopathy is also less frequent in women, being an important difference to bear in mind during follow-up (112, 113).

Finally, it is worth mentioning that sex is an important fact when it comes to deciding the recipient for a particular donor, as some studies have highlighted the prognostic importance of donor/recipient sex-mismatch (114). Particularly, male recipients have been found to have a worse prognosis after a sex mismatch transplant, whereas women seem to do similarly when they receive a male allograft. Although some anatomical, physiological, and immunological facts have been suggested, the reasons for this interaction remain unknown (115).

Pregnancies

Women's bodies experience a non-pathological period of strong changes for the anatomy and physiology of the heart: pregnancy. This carries a huge increase in ventricular volumes, cardiac output and ventricular hypertrophy as well as a significant decrease in vascular resistance due to vasodilatation and the interposition of a low resistance circuit such as the placenta (116). This cardiovascular remodeling, as well as the ability to adapt volume overcharge, have been suggested to be a sort of training for the heart, which could represent a benefit in terms of preventing HF or improving its global prognosis if it occurs. Furthermore, persisting fetal male cells have been found in the hearts of women with previous pregnancies. This microchimerism has been hypothesized to be beneficial for the mother's heart, and even lead to a better tolerance to the graft in case of transplant (117). Although more studies are required to quantify the benefits of previous pregnancies in HF outcomes, a previous series including 756 females with HF found an association between the number of previous gestations and better 1-year survival (HR 0.878, 95% CI: 0.773–0.997, $P = 0.045$) (118)

DISCUSSION

As a result of all previous explained differences, HF syndrome seems to have several distinctive features in women. They have greater clinical severity of HF, evidenced by worse functional class and higher prevalence of symptoms and signs, with more frequent edemas, murmurs, rales, jugular venous distension and gallop (5, 53, 119). They also tend to have more comorbidities such as anemia, iron deficiency, renal disease and thyroid abnormalities, while frailty sex-differences have not been extensively analyzed in HF patients (120). As a consequence, women with HF have significantly lower global quality of life and higher ratings for anxiety and worse social activity (121, 122). Previous articles that have studied the differences in quality of life in HF defined social health as the sum of social function, social life satisfaction, and intimacy (120). Riedinger et al., using the Functional Status Questionnaire, found that women had worse general life satisfaction and social health than men (121). We could speculate that as women usually have more social activities than men, including visiting relatives and participating in community activities, when they reduce these activities due to HF-related symptoms they might have a worse social life satisfaction. Besides, they are also more likely to suffer from depression than men (123).

Whether this greater severity translates into differences in HF hospitalizations was classically controversial, but nowadays most studies agree that after adjustment for relevant covariates, women with HF are less prone to cardiovascular or all-causehospitalizations than men (5). Thereby, male sex is an independent risk factor for all-cause admissions after HF diagnosis (124). Particularly, recent evidences shows that women have a 13% lower adjusted risk of HF hospitalization, with this risk being also lower in women with low LVEF (38). However, once admitted for HF, women tend to have an increased length of stay, although this does not affect to in-hospital mortality, which is comparable among both sexes (125). A large multicenter registry confirmed that despite differences in baseline characteristics, women and men with both reduced and preserved LVEF have similar in-hospital mortality and risk factors predicting death (126).

Survival after the onset of HF has been improving in both sexes in recent decades (127). Regarding sex-differences in mortality, in the vast majority of trials and registries women with HF have better age-adjusted survival rate than men (5, 40, 118, 128). They have a lower risk of death irrespective of cause of HF and of comorbidities (7, 40). This benefit is more apparent when the etiology is unrelated to ischemia, as women with HF related to non-ischemic diseases have significantly better survival than men with or without coronary artery disease as their main cause of HF. (7, 129). Furthermore, LVEF has lower prognostic influence in women than in men (28, 130).

On the other hand, women with HF included in the CHARM (Candesartan in Heart Failure: Assessment of Reduction in Mortality and morbidity) program had lower adjusted risk not only of cardiovascular death but also of non-cardiovascular death. Particularly for the first group, that risk was lower for the two main cardiovascular types of death related to HF, pump failure and sudden death (38). Other studies have also shown that male sex is in fact one of the main predictors for sudden cardiac death (131). Notwithstanding, given that the reduction of mortality is comparable for both, it is not possible to clarify if the benefit is mainly due to electrical stability or the pump function itself. More studies regarding this sex differences in mortality and its causes are needed.

CONCLUSIONS

HF represents a major global health issue with important sex-related differences in several aspects that include epidemiology, natural history, clinical manifestations, effects of therapy, and prognosis. Women are underrepresented in clinical studies. Women peculiarities also include genetics, comorbidities, hormones, and pregnancy. Compared to men, women are more likely to be older and suffer hypertension, valvular heart disease, and non-ischemic cardiomyopathy. Women have greater clinical severity of HF, with more symptoms and worse functional class. However, females with HF have better prognosis compared to males. This survival advantage is particularly impressive given that women are less likely to receive guideline-proven therapies for HF than men.

Future Perspectives

Understanding the underlying sex-related differences within HF may improve the management of HF by presenting more targeted options for personalized medicine.

AUTHOR CONTRIBUTIONS

AP: conceptualization, writing—original draft, and writing—review & editing. MM-S: conceptualization, investigation, resources, writing—review & editing, supervision, and project administration. All authors contributed to the article and approved the submitted version.

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REVIEW
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Gender-Related Differences in Heart Failure Biomarkers

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Important differences in comorbidities and clinical characteristics exist between women and men with heart failure (HF). In particular, differences in the kinetics of biological circulating biomarkers—a critical component of cardiovascular care—are highly relevant. Most circulating HF biomarkers are assessed daily by clinicians without taking sex into account, despite the multiple gender-related differences observed in plasma concentrations. Even in health, compared to men, women tend to exhibit higher levels of natriuretic peptides and galectin-3 and lower levels of cardiac troponins and the cardiac stress marker, soluble ST2. Many biological factors can provide a reliable explanation for these differences, like body composition, fat distribution, or menopausal status. Notwithstanding, these sex-specific differences in biomarker levels do not reflect different pathobiological mechanisms in HF between women and men, and they do not necessarily imply a need to use different diagnostic cut-off levels in clinical practice. To date, the sex-specific prognostic value of HF biomarkers for risk stratification is an unresolved issue that future research must elucidate. This review outlines current evidence regarding gender-related differences in circulating biomarkers widely used in HF, the pathophysiological mechanisms underlying these differences, and their clinical relevance.

Keywords: biomarker, heart failure, gender, troponin, natriuretic peptide, ST2, Galectine-3

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INTRODUCTION

Heart failure (HF) is a major health care issue in both sexes; it is associated with significant morbidity, mortality, and health care costs (1). Several differences between women and men have been observed in HF, including the epidemiology, etiology, pathogenesis, risk factors, and prognosis (2). The incidence of HF also differs between men and women, depending on the study population analyzed (3, 4). For example, women had a lower risk of incident HF than men, in middle-aged to older individuals, but women had a higher HF risk than men in the oldest age groups (5). Men tended to be at higher risk of developing HF with reduced ejection fraction (HFrEF), and conversely, women were more likely to develop HF with preserved ejection fraction (HFpEF) (6). This distinction might be attributable to the predisposition of women to develop coronary microvascular dysfunction/endothelial inflammation and the predisposition in men to develop macrovascular coronary artery disease and myocardial infarction (7). These sex-related differences in HF phenotypes and underlying pathophysiology are also reflected in HF biomarker dissimilarities.

In 2007, the National Academy of Clinical Chemistry and the International Federation of Clinical Chemistry recommended the development of sex-specific reference ranges for cardiac biomarkers used routinely in clinical practice (8). Consequently, over the years, sex-driven differences in both reference and cut-off values have been described for several biomarkers in cardiovascular disease (9). However, most of these cardiovascular biomarkers are used day-to-day by clinicians without taking sex into account. It is hypothesized that the lack of sex-specific thresholds for cardiac biomarkers might contribute to under-diagnosing HF in women, which could potentially result in worse outcomes (10).

Improving HF care requires consideration of all gender-related differences. Moreover, improving our understanding of gender-specific differences in HF biomarkers might enrich our understanding of physiological differences between men and women with HF. Taking these points into consideration, this review covers the four most important and frequent HF biomarkers available in daily clinical practice, with a focus on differences between women and men (**Figure 1**).

CARDIAC TROPONIN

Currently, assays are available for detecting cardiac troponin (cTn) with high clinical sensitivity and high specificity for myocardial tissue. Moreover, many assays are capable of early cTn detection, when necrosis is minimal or even in the absence of cell necrosis by different mechanisms (increased myocyte turnover or increased cell wall permeability among others). Due to these features, cTn has become the standard biomarker for myocardial damage and the preferred biomarker for diagnosing acute myocardial infarction. In addition, individuals in the HF population frequently have increased concentrations of high-sensitivity cTn (hs-cTn). In up to 93% of patients with acute HF and up to 74% of patients with stable chronic HF, hs-cTn concentrations are above the 99th percentile of the reference value (11). However, several studies and critical reviews have examined sex-related differences in cTn levels that might affect diagnostic and prognostic performance.

Variations in cTn Concentrations According to Gender

Marked variations in cTn concentrations have been detected between women and men, with higher values commonly found in men (12, 13). This difference has also been evident in patients with HF (14, 15). Consequently, when interpreting cTn results, sex-related peculiarities in the pathobiology of cardiac disease must be considered. Men tend to have a greater cardiac mass and a higher incidence of subclinical coronary artery disease than women (16, 17). Women tend to show less severity in atherosclerosis, left ventricular hypertrophy, and cardiomyocyte apoptosis than men (18, 19). In addition, HFrEF (from ischemic and non-ischemic etiologies) occurs more frequently in men than in women, and HFpEF is more prevalent among women than among men (6, 20). The possibility of an indirect hormonal influence should also be considered, in light of cardioprotective effects of estrogens, which suppress cardiomyocyte apoptosis, and the potentially harmful effects of testosterone, which induces hypertrophy and apoptosis in cardiomyocytes (21–23). Obesity was also independently associated with a positive, linear increase in the likelihood of high hs-cTn levels, as shown in a recent population-based study of subjects without cardiovascular disease at baseline. In that study, individuals with severe obesity and high hs-cTn levels had a >9-fold higher risk of incident HF compared to individuals with normal weight and undetectable hs-cTn levels (24). All these variations could contribute to sex-related differences in serum cTn concentrations and had allowed the thoroughly study of sex-tailored cut-off values of hs-cTn in the setting fundamentally of ACS, where sex-specific cut-off points might improve sensitivity for diagnosis of myocardial infarction in women (25). Diagnostic performance of hs-cTn for HF is however limited. In the general population, the application of dichotomous cut-off values of hs-cTn, lower in women than men: 4.7 vs. 7.0 pg/ml, respectively, for hs-cTnI as studied by Zeller et al., allowed substantial reclassification information for prediction of cardiovascular disease, including HF, being considered an independent predictor of cardiovascular events (26).

Prognostic Utility of cTn in HF

In the HF spectrum, the diagnostic utility of cTn is limited; however, its prognostic value is highly relevant. Studies by Parikh et al. (27) and by de Boer et al. (28) demonstrated that cTn levels could predict incident HF in different community-based cohorts. Recently, a meta-analysis that pooled data from 16 prospective studies and included nearly 67,000 subjects demonstrated a strong association between cTn and the development of incident HF, and this association was found in both men and women (29). Robust evidence from a meta-analysis based on individual patient data from 10 studies and 11 cohorts (30) also suggested that cTn could become an affordable biomarker for risk stratification in patients with HF, due to the similarity of its prognostic value between men and women. However, data are inconsistent as to whether the prognostic value of cTn differs with sex. Current evidence has indicated that the 99th percentile cutoff values were higher in males than in females (26, 31). However, despite the widespread use of cTn in clinical practice, all available assays lack sex-specific reference values.

NATRIURETIC PEPTIDES

Natriuretic peptides are a group of neurohormones that play a central role in the regulation of electrolytes and water balance through their diuretic and natriuretic effects (32). In humans, mainly three forms of natriuretic peptides are found: A-type natriuretic peptide (ANP), B-type type natriuretic peptide (BNP), and C-type natriuretic peptide (CNP). CNP is primarily produced in vascular endothelial cells; ANP and BNP are mostly found in the myocardium. Natriuretic peptides are released by the myocardium in response to stretch and hypoxic stimuli (33). The majority of clinical evidence on natriuretic peptides in the setting of HF is related to BNP and the amino terminal of the proBNP molecule (NT-proBNP). Therefore, this review focuses

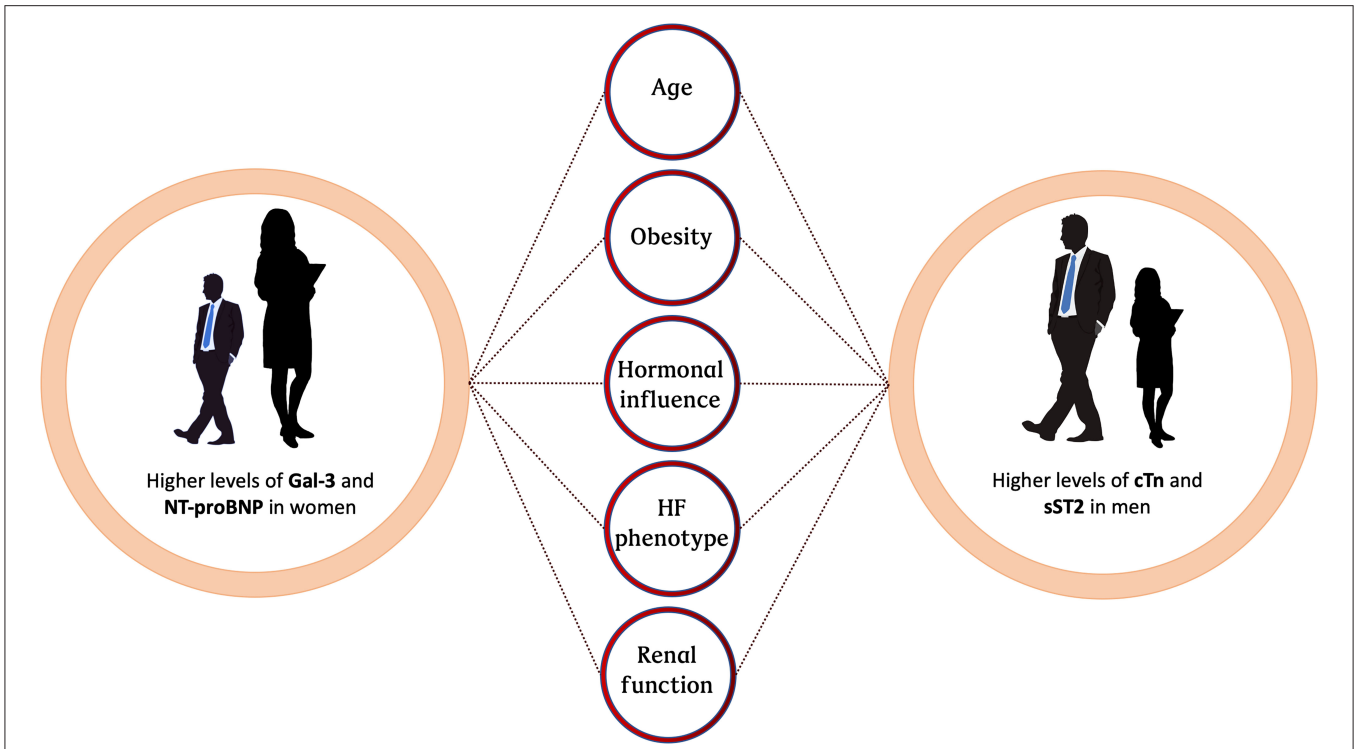

FIGURE 1 | Schematic of factors contributing to sex-related differences in HF biomarkers. HF, heart failure; Gal-3, Galectine 3; NT-proBNP, N-terminal pro-B-type natriuretic peptide; cTn, cardiac troponin; sST2, soluble interleukin-like receptor-like-1.

on NT-proBNP, because it is the best choice for a diagnostic and prognostic biomarker in HF, according to the 2016 European Society of Cardiology HF clinical guidelines (34).

The most extensive evidence on the value of BNP-related *in vitro* diagnostic tests was published in the early 2000s. Comparative studies that measured concentrations of the active BNP hormone vs. NT-proBNP generally demonstrated diagnostic equivalency for differentiating HF from other causes of shortness of breath. The proBNP molecule contains 108 amino acids. The first 76 amino acids are biologically inactive, and amino acids 77–108 constitute the biologically active component of the molecule, BNP.

Currently, NT-proBNP is a well-established, powerful biomarker for the diagnosis and prognosis of HF (35–37). It is also a useful biomarker for risk stratification in other several cardiovascular disorders (38, 39). Strong clinical evidence has revealed that several factors influence NT-proBNP levels. Elevated concentrations were observed in patients with various cardiovascular disorders and in patients with renal dysfunction (40, 41). A previous study, which included 7,770 individuals from the Framingham Heart Study and the Malmö Diet and Cancer study, reported that obesity was associated with 6–20% lower NT-proBNP levels, compared to normal-weight status, and insulin resistance was associated with 10–30% lower levels of NT-proBNP, compared to insulin sensitive status (42). Age and sex are also important in modifying circulating levels of natriuretic peptides. Most studies found that at baseline NT-proBNP levels were lower in males than in females (**Figure 2**) and, in both genders, increases were correlated with age (44).

Sex Differences in NT-proBNP Levels

Although sex-specific differences in NT-proBNP levels have been documented, the precise mechanism that gives rise to higher NT-proBNP levels in women than in men is not well-established in healthy subjects. Several possible explanations have been explored. One reasonable pathobiological explanation involves the effects of sex hormones. Strong clinical evidence has shown that testosterone could lower cardiac natriuretic peptide levels, probably by upregulating neprilysin activity; this effect might explain why NT-proBNP levels are lower in men than in women (45, 46). Other studies showed that estrogen increased cardiac natriuretic peptide gene expression and its release, which might explain the elevated cardiac natriuretic peptides levels in women compared to men. However, other reports suggested that estrogen also increased neprilysin activity (43, 47). In postmenopausal women, hormone replacement therapy administered for 3 months resulted in elevations in ANP and BNP concentrations (48). Some research however hypothesized that free testosterone could increase lean mass and may directly decrease natriuretic peptide synthesis. This last statement goes beyond the notion that estrogens are primarily responsible for gender differences in natriuretic peptides considering

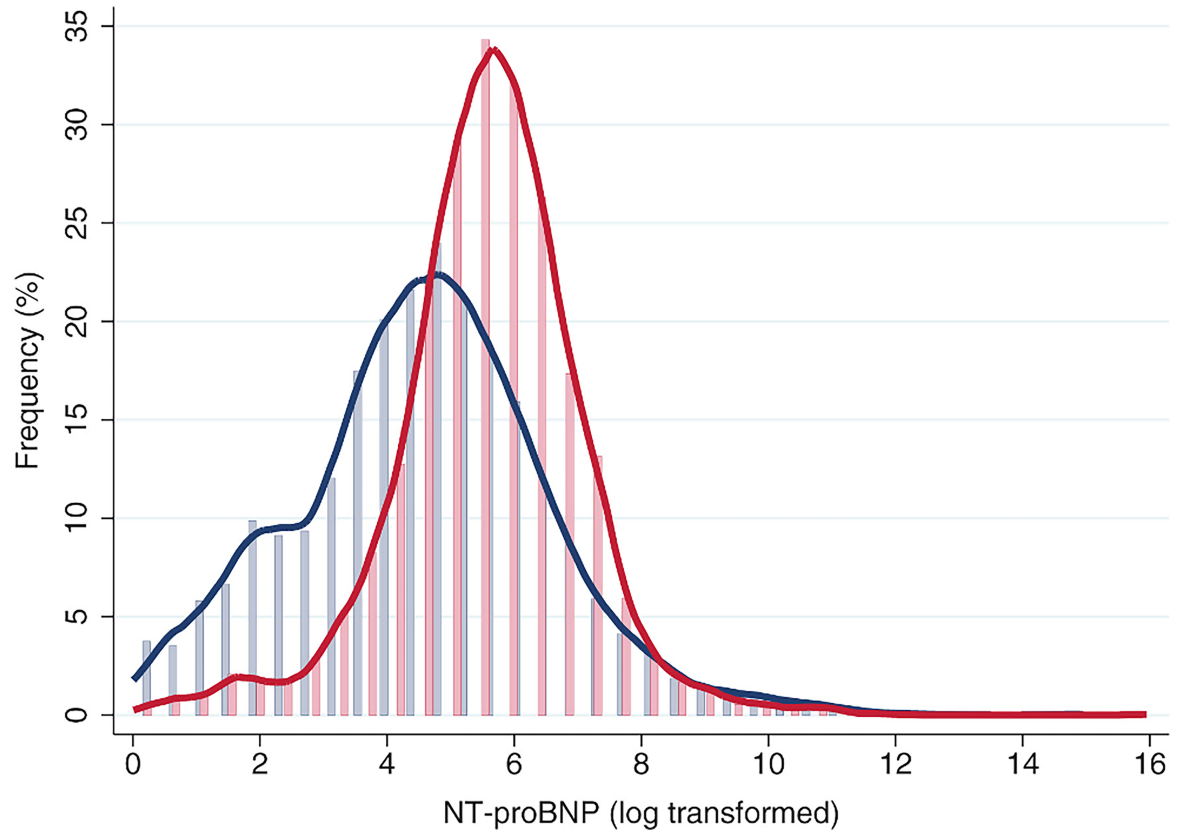

FIGURE 2 | Distribution of N-terminal pro-B-type natriuretic peptide (NT-proBNP) in both sexes. Reproduced with permission from Suthahar et al. (43).

that exogenous estrogen increased the sex hormone-binding globulin with a subsequent lower free testosterone (49). Of note, the profoundly different anthropometric characteristics and fat distributions found in males and females might also play a role in natriuretic hormone levels. Recent evidence from a general population study found that the relationship between NT-proBNP and obesity had a significant sex-associated component. The inverse association between NT-proBNP and obesity was more pronounced among females than among males. Furthermore, among females, but not males, individuals with abdominal (visceral) obesity had lower NT-proBNP levels than individuals with peripheral (subcutaneous) obesity (50). Some studies propose at a molecular level a higher clearance of BNP in obesity due to increased expression of natriuretic peptide receptor on adipose tissue, which binds BNP and leads to its internalization and degradation (51) A reduced release of natriuretic peptides from myocardial tissue in obese individuals have also been pustuled as an alternative hypothesis (52) Therefore, a combination of increased degradation and decreased release may contribute to relative deficiency of natriuretic peptides in obesity.

However, these sex-related dissimilarities observed in the general population appeared to be less pronounced in HF and other disease populations associated with upregulated NT-proBNP levels. Some studies have reported the opposite findings, noting that natriuretic peptide levels were similar or lower in women compared to men (53, 54). However, this change in tendency should be interpreted cautiously, because over the past decade, one of the most robust findings across numerous HF studies was that the gender distribution varied according to the HF phenotype. Among individuals with HF, women significantly outnumber men, and the gender ratio is ∼2:1 in HFpEF (6, 20). Numerous reports have shown that natriuretic peptide levels are much lower in patients with HFpEF than in patients with HFrEF (35, 55, 56). Consequently, when studies analyze the convoluted relationship between sex, ejection fraction, and BNP levels in the setting of HF, the results show that women tend to have higher BNP levels than men (57, 58). However, despite the gender-related differences in the levels of natriuretic peptides, the performance of these peptides for diagnosing HF and their prognostic utility are similar in both sexes, and sex specific cut-off points are not usually recommended. At this point, it should also be noted that there is a lack of coincidences between molecular mechanisms that affect HF progression and gender particularities in the context of biomarker levels' variability (**Figure 3**).

Prediction of HF Incidence

NT-proBNP levels have shown clinical relevance in predicting the incidence of HF in the general population. High levels were associated with a high risk of HF (59–61), which suggested

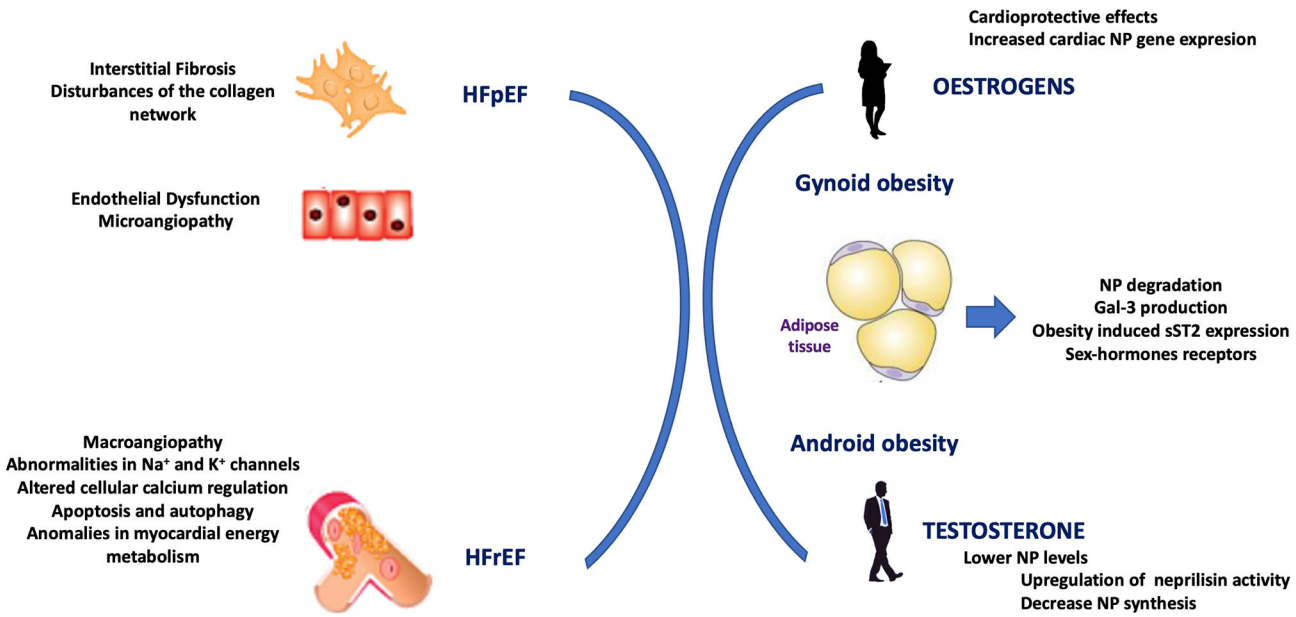

FIGURE 3 | Representation of a lack of coincidences between mechanisms that affect heart failure progression and gender particularities in the context of biomarker levels' variability. HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; NP, natriuretic peptide; Gal-3, Galectine 3; sST2, soluble interleukin-like receptor-like-1.

that elevated baseline levels might reflect subclinical cardiac dysfunction that could subsequently manifest as overt HF. Recent studies have explored sex-specific differences in using NT-proBNP to evaluate cardiac functional competence. Evidence from two community-based studies (44, 61) showed that the optimal cut-off point for detecting moderate to severe left ventricular disfunction was higher in women than in men. The discriminatory ability of the biomarker was similar in both sexes, but the strength of the association might be different between men and women. Indeed, a recent meta-analysis of prospective studies (62) found that NT-proBNP was more strongly associated with incident HF in men than in women. In the near future, the use of natriuretic peptides to assess risk in asymptomatic adults is expected to become translated from clinical studies to routine clinical practice.

SOLUBLE INTERLEUKIN-1 RECEPTOR-LIKE 1 (ST2)

ST2 is a member of the interleukin-1 receptor family. ST2 exists in both membrane-bound (ST2L) and soluble (sST2) forms. Interleukin-33 (IL-33) is the functional ligand for ST2L, and in the heart, the IL-33/ST2L interaction mitigates cellular responses to mechanical stress. This function is thought to be mediated by the inhibition of apoptosis and cell death (63). Loss of IL-33/ST2L signaling results in unchecked remodeling in the ventricular myocardium, which leads to myocyte hypertrophy, fibrosis, and a decline in left ventricular function (64). In contrast, sST2 acts as a "decoy" receptor for IL-33; thus, sST2 inhibits the cardioprotective effects mediated by the IL-33/ST2L interaction, which indirectly promotes myocardial damage (65). With the development of a highly sensitive ELISA method for measuring sST2 (66), in the last decade, clinical evidence has highlighted the biological and clinical importance of plasma sST2 concentrations. Currently, sST2 is considered a strong, independent prognostic biomarker in patients with myocardial infarction and HF (67, 68).

Clinical data has suggested that sex has a potentially important effect on sST2 concentrations. Women exhibited lower sST2 levels than age-matched men (69). In a large population-based study of ambulatory individuals, women had lower sST2 levels than men, but among older women, an age-associated rise in sST2 concentrations was observed. However, even among older adults, men had higher sST2 levels than women (69). These differences, which seem to be evident beginning in late adolescence (70), were present both in patients with cardiovascular disease and in healthy subjects. Currently, the mechanism underlying these differences has not been elucidated. The hypothesis that sex hormones might be responsible for differences in sST2 levels has not been adequately proven, and current evidence remains controversial. Some studies have supported this hypothesis by showing that elevated testosterone levels were linked to elevated ST2 concentrations, and conversely, exogenous estrogen therapy was linked to lower sST2 levels. In contrast, another study did not find any significant correlation between sex hormones and sST2

levels (69, 71). Obesity is also an important factor to consider in this setting, because sex hormones are produced by adipose tissue, and gender-related differences have been shown in the association between obesity and metabolic diseases. A recent study by Zhao et al. revealed, in an animal model, that obesity induced sST2 expression and secretion in adipocytes (72). A deep physiological understanding of the reasons and clinical relevance of gender-specific differences in sST2 concentrations requires future research.

Due to the prognostic value of ST2 (73–75) and its ability to predict incident HF (76), it has become part of the risk stratification strategy in HF clinical practice guidelines (77). A cut-off point of 35 ng/ml ST2 has been universally adopted as a good indicator of prognosis in both sexes; thus, to date, sex-specific cut-off points have not been needed for risk predictions.

GALECTIN-3

Galectin-3 (Gal-3), a unique member of the chimera-type galectins, is involved in a large number of disease processes. It is widely expressed in human tissues, including epithelial, endothelial, and immune cells (78). Gal-3 plays a role in both acute and chronic inflammation, and its effects on cell function include the activation of fibroblasts and macrophages, which lead to fibrosis in various organs, including the heart (79). As a biomarker, Gal-3 has been associated with cardiac function (80); several studies have demonstrated significantly higher Gal-3 levels in patients with HF, particularly those with HFpEF, compared to controls (80). Nevertheless, this biomarker is not predominantly produced in the heart; non-cardiac sources appear to be responsible for high Gal-3 levels in patients with HF (81).

Recent data from population-based studies (82–84) have indicated that plasma Gal-3 levels were slightly higher in women than in men. The physiological explanation for this gender-specific difference is not fully understood, but differences in fat mass might play a role, considering that, for the same body mass index, women typically have 10% more body fat than men (85). Indeed, prior studies have observed an association between total body fat and Gal-3 levels (86). Although the sex-specific prognostic value of Gal-3 in HF remains unknown, baseline Gal-3 concentrations were associated with adverse outcomes during follow-up in patients with acute and chronic HF (87–89). However, the prognostic value of Gal-3 in the setting of chronic HF remains controversial; other biomarkers, such as NT-proBNP or sST2, have frequently exhibited superior predictive value (90). Moreover, other studies have shown that the predictive value of Gal-3 in HF was less pronounced when the analysis was adjusted for renal function (87).

In the Framingham Heart Study, an analysis of more than 3,000 participants showed that elevated Gal-3 concentrations were associated with increases in the risk of new-onset HF (HR 1.28 per 1 standard deviation increase in the log-Gal-3 concentration). This association was clearly attenuated after adjusting for kidney function (82). This "renal implication" highlights the paramount relevance of cardio-renal interactions in the setting of HF, and it suggests that HF might involve a common profibrotic process in the heart and kidneys.

LESS COMMON BIOMARKERS IN CLINICAL PRACTICE

In the last decade there has been an intensified interest in additional biomarkers as an objective alternative for diagnosis, prognosis or personalized treatment in HF. Among them is the growth differentiation factor-15 (GDF-15), a member of the transforming growth factor-?? cytokine superfamily with anti-apoptotic, anti-hypertrophic, and anti-inflammatory properties. GDF-15 is weakly expressed in tissues under normal conditions. Although its pathobiology is not fully understood, it is strongly induced by macrophages in response to inflammation and tissue injury. It appears to be only moderately expressed in the heart (81). Despite GDF-15 have been identified as an inflammatory biomarker with prognostic value in several conditions, particularly in cardiovascular diseases (91, 92), with strong association with incident HF (93), sex differences in plasma levels of this biomarker have not been clearly established (94, 95). It has been showed that testosterone together with estradiol significantly decreased GDF-15 levels through an androgren receptor/estrogen receptor-mediated pathway (96). Osteopontin, a glycoprotein expressed in various cell types, including cardiomyocytes and fibroblasts has also gained interest as a prognostic marker in HF. It had been found to be significantly elevated in patients with systolic HF (97). Its cardiac expression promotes myocardial fibrosis and increases left ventricular stiffness (98). It appears that plasma osteopontin levels are higher in men than in women as evidence in the study by Arnlöv et al. (99), however there are lacking evidence in the literature of sex differences in osteopontin expression, and this requires further investigation.

CONCLUSIONS AND PERSPECTIVES

Most circulating HF biomarkers are used daily by clinicians without taking sex into account. Nevertheless, multiple gender-related differences have been observed in the plasma concentrations of several biomarkers. In the healthy population, women tend to exhibit higher levels of natriuretic peptides and Gal-3 and lower levels of cTn and sST2, compared to men. Plausible biological explanations for these sex-related differences have been postulated, like differences in body composition, fat distribution, or sex hormones. Nonetheless, several clinical studies have shown that these differences were attenuated in patients with HF, despite the fact that distinct gender distributions have been extensively described for different HF phenotypes. Moreover, these sex-related differences do not necessarily translate into a need to use different cut-off

points for men and women, either for HF diagnosis or HF prognosis, in clinical practice. Future research should explore the clinical value of considering possible sex-related differences in specific HF biomarkers, in both diagnostic and prognostic settings, with the aim of improving HF management and patient care.

AUTHOR CONTRIBUTIONS

GC drafted the manuscript with support from AB-G. All the authors contributed to manuscript revision and read and approved the submitted version.

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REVIEW
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Palliative Care for People Living With Heart Disease—Does Sex Make a Difference?

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The distribution of individual heart disease differs among women and men and, parallel to this, among particular age groups. Women are usually affected by cardiovascular disease at an older age than men, and as the prevalence of comorbidities (like diabetes or chronic pain syndromes) grows with age, women suffer from a higher number of symptoms (such as pain and breathlessness) than men. Women live longer, and after a husband or partner's death, they suffer from a stronger sense of loneliness, are more dependent on institutionalized care and have more unaddressed needs than men. Heart failure (HF) is a common end-stage pathway of many cardiovascular diseases and causes substantial symptom burden and suffering despite optimal cardiologic treatment. Modern, personalized medicine makes every effort, including close cooperation between disciplines, to alleviate them as efficiently as possible. Palliative Care (PC) interventions include symptom management, psychosocial and spiritual support. In complex situations they are provided by a specialized multiprofessional team, but usually the application of PC principles by the healthcare team responsible for the person is sufficient. PC should be involved in usual care to improve the quality of life of patients and their relatives as soon as appropriate needs emerge. Even at less advanced stages of disease, PC is an additional layer of support added to disease modifying management, not only at the end-of-life. The relatively scarce data suggest sex-specific differences in symptom pathophysiology, distribution and the requisite management needed for their successful alleviation. This paper summarizes the sex-related differences in PC needs and in the wide range of interventions (from medical treatment to spiritual support) that can be considered to optimally address them.

Keywords: palliative care, symptom control and palliative care, sex related differences, heart disease, breathlessness, spiritual care, holistic care

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INTRODUCTION

Heart failure (HF) is a global epidemic, having a complex epidemiology and an estimated prevalence of almost 38 million individuals globally (1, 2). It is a common end-pathway of many cardiovascular diseases. HF causes a substantial burden for the numerous individuals affected and their relatives, even under optimal cardiological care, it is also the leading cause of mortality

in many populations. As HF is a polyetiological syndrome, differences in the distribution of specific HF types between women and men in different age groups mirror the prevalence of underlying diseases in individual ethnic and geographical populations. The quite universal clinical syndrome evoked by heart dysfunction, especially in advanced stages, consists of breathlessness, exercise intolerance, tendency to hypervolemia and tissue hypoperfusion in the end stages. This can be complicated by features of individual underlying disease (like angina in people with HF of ischemic etiology, neuropathy in those affected by the wild type of amyloidosis, or hemoptysis in the case of pulmonary arterial hypertension), age related problems (i.e., frailty syndrome or dementia) and/or concomitant disease (i.e., degenerative arthrosis, peripheral vascular disease, diabetic neuropathy) (3). Two other symptoms commonly seen in people affected by HF are depression and fatigue. They often coexist, with a complex etiology and influence the perception of other symptoms such as pain or breathlessness (4). The majority of people living with HF experience daily a number of symptoms limiting their functioning, quality of life (QoL) and negatively affecting their life-expectancy (5). Optimal cardiological care could be improved by the concomitant provision of palliative care (PC).

DEFINITION OF PALLIATIVE CARE

PC has evolved in recent decades to become a discipline caring for people living with serious diseases whose' health status does not respond fully to the disease specific treatment. They typically have health related symptoms, problems and needs that can, if complex, be addressed by a multidisciplinary team (consisting at least of medical and nursing staff, psychologists, social workers, physiotherapist, occupational therapists, chaplains) with the goal of improving QoL, even whilst the underlying disease is progressing or entering the terminal phase (6). Unfortunately PC is misconceived as being synonymous with end of life or hospice care and falsely understood as an approach dedicated to those dying from cancer. In fact, if the recommended care pattern is implemented in a timely fashion alongside specialist (e.g., cardiological) care, it can benefit many people living with advanced diseases, including HF, by decreasing the burden caused by the symptoms (such as pain, breathlessness, fatigue, depression), improving QoL and spiritual well-being (6–14). Studies investigating the influence of PC in a population affected with HF are scarce and show a modest improvement in QoL when PC has been added to standard cardiologic care (9, 11, 15, 16). The sex related differences on the efficacy of PC interventions for people living with HF has been investigated by only one single center study. The study population of just 150 people (71 women, and 79 men) was randomized in a 1: 1 proportion to usual care and usual care plus PC. Improvement in the QoL scores with PC interventions have been proven with men only, despite women experiencing a greater symptom burden (17). Just changing the perception of PC from a discipline providing end of life care to one focused on improving QoL could be enough to improve access to PC (18). PC added to optimal cardiac care, rather than replacing it, is still underused despite being recommended by both palliative and cardiological societies. A recent analysis of a large US database with a national in-patient sample has shown that from 2002 to 2017 on average only 4.1% of people who had been discharged after acute HF hospitalization had a PC encounter. There has been, however, some improvement over the last 15 years (from 0.4% in 2002 to 6.2% in 2017), but even recently only 6.5% of women and 5.9% of men encounter PC, predominantly when they are suffering from a terminal condition (19). The median time from first specialist PC consultation to death between 2006 and 2011 was only 21 days in a single center study (20). Qualitative/narrative study showed that HF patients and their relatives who received PC concurrently to cardiac care, whilst being in III or IV NYHA (New York Heart Association) class, wished they had received PC interventions earlier in their care, particularly at the time of diagnosis of advanced HF. In contrast, the clinicians representing primary care and cardiology interviewed reported concerns about the overly early implementation of concurrent PC (21).

The management of both physical and psychological symptoms, support in decision-making, coordinating care, social assistance, and spiritual support all are elements of PC. To make optimal medical decisions, the integration of the patients' personal values with their knowledge and understanding about disease progression and the possibility of both improvement and deterioration/death should be ensured. Such an individual approach, based on sensitive in-depth communication, could support or prevent invasive interventions and hospitalizations. Some interventions may not correspond with personal values and wishes, or be perceived as too burdensome (22). Such advance care planning reduces readmissions and costs and increases the satisfaction with the care received (16, 23). The involvement of PC should be triggered by needs rather than the risk of deterioration or death. Unfortunately, the second pattern still dominates, postponing PC provision to the moment of active dying or even preventing it completely (6, 8). PC can be provided in the form of primary (called generic) PC to most people living with HF by health care professionals with a knowledge of PC principles, or in form of specialist PC delivered by clinicians with special training, possessing knowledge, skills, and competencies to address difficult to treat symptoms, existential distress or more complicated problems (24).

THE EPIDEMIOLOGIC DIFFERENCE BETWEEN WOMEN AND MEN AFFECTED BY HF

Men prone to macrovascular coronary artery disease and myocardial infarction are at almost twice the risk of HF with reduced ejection fraction (HFrEF) and are usually younger at the time they are affected by HF than women. Women are more susceptible to microvascular dysfunction/endothelial inflammation, thus are at higher risk of HF with preserved ejection fraction (HFpEF) and are usually older at the time of diagnosis (25–27). Among people affected by HFpEF, men suffer from greater limitations in terms of functional capacity,

have more comorbidities and higher cardiac mortality (death caused by refractory HF and sudden cardiac death); women die more often of infections and cancer, but the all-cause mortality is similar between both genders (28). Post-partum cardiomyopathy only affects women up to 6 months after delivery and Takotsubo cardiomyopathy or pulmonary arterial hypertension predominantly affects women (the ratio between women and men is 9:1 for Takotsubo cardiomyopathy) (26, 27). Women with advanced HF are older than men, they are less likely to be married or to be in a domestic partnership, more often widowed, and are more likely to be dependent on institutional support (17, 27, 29).

QUALITY OF LIFE OF PEOPLE LIVING WITH HEART FAILURE

There are many concepts concerning the definition and components of QoL and numerous instruments for assessing it. Some tool, like the disease-specific Minnesota Living with Heart Failure questionnaire, or generic ones such as the Medical Outcomes Study SF-36—used commonly to assess QoL of people living with HF—focus on the negative impact of health on pre-specified items and thus reflect disease advancement rather than patients' self-reported QoL (30–32). Such instruments for assessing symptoms/disease related limitations in daily living and distress used for measuring health-related QoL (HRQoL), show the constant deterioration of QoL in parallel to disease status (33). Over 80% of people living with HF report physical symptoms such as dyspnoea, fatigue, oedema, sleeping difficulties, and chest pain, all negatively impacting QoL (33, 34). Emotional status and depression can significantly diminish QoL, exaggerate the experiencing of symptom burden, and be aggravated by physical symptoms (35).

QoL is, however, more complex than described above and reflects the multidimensional impact of a clinical condition and its treatment on a person's daily life. It is a subjective experience encompassing emotional status, social functioning, and symptom burden and merely reflects their objective clinical, or physiological status. In other words, QoL can be defined in a more comprehensive way as the ability to maintain happiness, engage in fulfilling relationships and perform physical and social activities. Many people living with even advanced HF can perceive their QoL as good, despite suffering from symptoms and experiencing limitations in physical and social functioning (31).

PC goes beyond limiting symptom burden and addresses more comprehensive dimensions of human life including psychosocial, existential, spiritual problems as well as providing support for family and informal carers. There are gender related differences in QoL in people suffering from HFrEF: women with HFrEF have worse HRQoL compared to men assessed by the Kansas City Cardiomyopathy Questionnaire (KCCQ, a disease-specific instrument); and EuroQoL 5 dimensions (EQ-5D, a generic instrument). Women report higher symptom frequency, symptom burden, physical limitations and social limitations, as well as lower QoL. These differences do not appear to be mediated by clinical or biological factors (such as age, body mass index, systolic blood pressure) classically associated with HRQoL nor with HF severity (17, 27, 36–38).

SYMPTOM BURDEN

Symptoms affecting people living with advanced HF surprisingly do not differ substantially from symptoms reported by people living with advanced cancer who receive PC (39–41). There are only a few significant differences in patients with HF: they suffer more often from dyspnea that is higher in intensity, report reduced appetite almost as frequently, albeit less intensely, and have almost as much pain but which is slightly less severe in comparison to patients with advanced cancer (40). Women experience a greater symptom burden and suffer more frequently from depression than men, despite similar or even less advanced HF (17, 27, 37). Using a comprehensive and reliable questionnaire (i.e., Memorial Symptom Assessment Scale for HF—MSAS-HF), people living with HF report about 13.6 symptoms on average, despite optimal medical management of HF (42, 43). Each of those symptoms should not be considered individually. Some symptoms are seen in clusters (breathlessness, anxiety, and depression termed a distress cluster; fatigue, drowsiness, nausea, and reduced appetite—referred to as a decondition cluster; pain, and a sense of generalized discomfort—known as a discomfort cluster), with relatively small to moderate correlations between clusters, suggesting the existence of a common pathway or interdependence for symptoms grouped in one cluster (44).

Symptom burden and distribution differ between females and males. Women affected by HF report a higher symptom burden for pain other than chest pain, dry mouth, swelling of the arms and legs, sweats, feeling nervous, fatigue, nausea and vomiting (43, 45). Men suffering from HF report a higher burden with sexual problems (they were, however, more often married than women, which might clarify why they were more likely to report this issue as a problem) (43). A review of patient records indicates that there are substantial differences in how health care professionals perceive symptom burden in women and men—females had to report a higher level of distress than males in order to get their symptoms acknowledged, documented and managed (46, 47).

Some studies have shown an association between depression, fatigue, pain, and breathlessness (4, 48–50). The relationship between depression and physical symptoms is bidirectional—people suffering from depression perceive more intense physical symptoms and conversely people affected by physical symptoms are more prone to suffer for depression (51–53). The top-down (predictions, anticipation, modulation) and bottom-up (afferent signaling) theory, stress the role of the integration of both centrally and peripherally originating signaling in processes of stimulus initiation, transmission and processing in symptom perception. This clarifies the crosstalk between emotional status, memory, and meaning with the sensitivity of peripheral receptors (54).

Symptoms in people living with HF do not correlate with objective measures such as left ventricular ejection fraction

(LVEF), right heart catheterisation parameters, serum creatinine, hemoglobin, amino-terminal pro-B type natriuretic peptide (NT-proBNP) concentrations and only poorly with peak oxygen uptake (55–60). However, one study reports the severity of HF symptoms relates to decreased ventricular compliance in women, but not in men and to the dilatation of the left ventricle, but only in men. Larger left ventricle size is associated with better physical symptoms for women and worse physical symptoms for men (60). All this suggests that there is no simple link between the degree of heart or circulation system dysfunction and symptoms.

THE ELEMENTS OF PC INTERVENTIONS

A fundamental for PC is symptom management (61). Patients living with serious disease, including those with HF, identify symptom management as a top priority, particularly at the end of life (62). Despite this, only a minority of people living with advanced HF receive management and care focused on symptom alleviation (62). The three most common symptoms affecting people living with HF are pain (prevalence over 80%) shortness of breath (prevalence 65–75%) and a lack of energy (79–76%) (42, 43, 63). The last two symptoms are perceived as a hallmark of HF and are commonly used for the classification of HF advancement (according to NYHA) but unfortunately, they do not trigger interventions aimed at alleviating them, even if they are severe. The gap between frequency of documented symptoms and interventions prescribed to alleviate them can be as high as 60% (64). The upper mentioned three most frequent symptoms (non-cardiac pain, breathlessness and lack of energy) are also the most severe and most distressing symptoms (43).

Symptom Management in People Living With HF

Pain

Pain, the most commonly reported symptom by those living with advanced HF, affects up to 84% of those affected by heart failure (29, 65). Its frequency increases along with the severity of HF (up to 89% of people in IV HYHA class) (63). Pain, other than chest pain (reported as well, as non-cardiac pain), predominates and affects up to 77% of people living with HF (43). It is only rarely perceived by health care professionals and identified as a target to address. That is why it is underreported and undertreated (39, 40, 50, 63, 66). Pain is not only one of the factors limiting QoL, but it also negatively influences HF pathophysiology (66). Uncontrolled pain stimulates the sympathetic nervous system and activates the renin-angiotensin-aldosterone system, all of which lead to increases in the haemodynamic workload, sodium and water retention and finally to HF decompensation and a higher risk of rehospitalisation (66, 67). Untreated pain additionally increases the use of non-steroidal anti-inflammatory pain killers (NSAID), including those contraindicated in HF, worsens self-monitoring and self-management (risk factor of HF decompensation and hospitalization) (66, 67) and increases the risk of depression (a factor limiting QoL and increasing the risk of HF related hospitalization and mortality in people with HF) (48, 68–70).

Successful and safe pain management in people living with HF is more challenging than in people without HF, but can decrease mortality in people with cardiovascular disease (71–73). The best-known framework for treating pain is known as the WHO analgesic ladder. It aids in decision making over the choice of painkillers. Non-opioids are recommended for mild pain (step I), weak opioids for moderate pain (step II) and strong opioids for severe pain (step III), always with the addition of adjuvants, if appropriate. Unfortunately, most non-opioids, particularly NSAIDs carry the risk of worsening HF, renal function and atherothrombotic events, and are contraindicated in people with cardiovascular disease, including HF (10, 74–77). Two non-opioid pain killers seem to be free of those side effects, namely paracetamol and metamizole. Both lack an anti-inflammatory effect and cause other potentially serious side effects (hepatotoxicity and bone marrow suppression, respectively). Weak opioids (step II of the WHO analgesic ladder), tramadol and codeine, are prescribed with decreasing frequency, due to their variable pharmacokinetics and the risk of tachycardia and hyponatremia, and tramadol additionally due to risk of orthostatic hypotension and falls in people over 65 years (78, 79). Strong opioids (step III of the WHO analgesic ladder) are recommended for treatment of moderate to severe pain. A small dose of strong opioids (up to 30 mg of morphine or 20 mg of oxycodone) has recently been proposed as step II on the analgesic ladder (80). [For details on treating pain in people living with HF, see the recent EAPC expert position statement (6)].

For those reasons, the most commonly recommended measures to treat pain in people living with HF are topical interventions, non-pharmacological techniques and prescribing strong opioids (81). The last, especially if not properly used, bear potential serious side effects, including addiction and the risk of opioid related death (82). Surprisingly, there is a lack of evidence demonstrating the superiority of opioids over other analgesics in treating chronic non-cancer pain (83). Two strong opioids, buprenorphine and methadone, may prolong the QTc and thus are not recommended in people with borderline prolongation of QTc (450–500 ms) and are considered as contraindicated if QTc exceeds 500 ms (79). Additionally, the safety of strong opioids in patients with advanced HF has not been extensively studied, but some research suggests that they represent a source of potential harm, specifically to this population. One retrospective study has shown increased risk of ICU admissions, the need for ventilators, prolonged hospitalization and higher mortality in people with acute HF who have been exposed to opioids (84). A cohort study revealed that using opioids was associated with increased risk of coronary heart disease and cardiovascular death among females but not males (85). Opioids might increase the risk of atrial fibrillation—individuals with an opioid prescription develop this arrhythmia 34% more often than those without it (86, 87). Recent studies suggest that morphine increases 4.37-fold the risk of developing AF in women with breast cancer, but this is abolished by antioestrogen treatment with tamoxifen. The risk of AF is especially high in current morphine users of all ages with a low Carlson Comorbidity Index score, and rises along with the duration of morphine use (88). The tamoxifen protective effect may be related to the specific pharmacologic effect of the drug

or be an indirect consequence of estrogen deprivation. This is in line with the hypothesized detrimental effects of opioids on cardiovascular risk in women described above.

The prevalence of symptoms, including pain, depends on biological/chromosomal (sex related differences) and socio-cultural (gender related) factors. Studies, if they have even considered the differences in the experiencing of pain between women and men at all, analyzed only biological sex. Socio-cultural factors' impact on symptoms in HF have not yet been investigated. There are social and cultural influences on pain experience in humans, and thus men and women experience pain in a way that conforms to gender expectations. For this reason, gender has an impact on pain reporting—it is socially accepted that women tend to report more pain than men and have a lower tolerance for pain (89). Few studies have explored the role of biological sex as it pertains to the safety of prescribing of opioids in patients with chronic pain. There are several reasons why opioids might be prescribed differently to men and women, including differences in pain perception (90). It is hypothesized that the sex dependent biological factors influence differences in the perception of chronic pain, that they are related to substantial differences in the functioning of the immune system, and that they play a crucial role in chronic pain syndrome. Based predominantly on animal studies, it seems that the immune system (inflammation in the spinal cord around pain transmitting pathways) functions differently in females and males. Females predominantly utilize T-cells while microglia in the spinal cord in males mediates the modification of chronic pain (89). Whether this observation has a clinical implication with respect to different perceptions of pain and the varying degree of effectiveness of pain killers is currently unclear (89). Previous research suggests that women are more likely to be prescribed opioids, but men tend to receive more potent agents (91–94). Long-term opioid use was substantially higher among older women than it was among younger women or men in any age group (93). A cohort study spanning 13 years using the healthcare records of 32,499 individuals aged 15–64 who commenced chronic opioid therapy for non-cancer pain showed that men are at a higher risk than women of escalation to high-dose opioid therapy and death from opioid-related causes (82). This can be a consequence of more attention being paid to pain reporting by men and more intense efforts to alleviate it. Older women have a lower risk of opioid misuse but may be more vulnerable to the adverse medical effects of opioids such as sedation, falls, constipation, respiratory depression, dysphoria, accidental overdose, and medication interactions (95). Women are at a greater risk of undertreatment of pain, although the use of both prescription and non-prescription analgesics is significantly higher among women than men (90).

Despite many doubts regarding the safety of pain management in people living with HF, optimal pain alleviation has to be achieved since uncontrolled pain increases the risk of HF related hospitalization and cardiovascular mortality (66, 73).

Breathlessness

Dyspnoea is a hallmark symptom in advanced HF. It is defined as the subjective, multidimensional experience of breathing discomfort (96). Breathlessness, if unrelieved and severe, can be devastating to a person's QoL and is associated with poor survival rates (97). The perception of breathlessness is driven by a mismatch between demand for ventilation (sensed by chemo- and metabo-receptors) and actual ventilation (sensed by pulmonary stretch receptors, pulmonary C-fibers, chest wall joint and skin receptors, and skeletal muscle ergoreceptors) (98). Breathlessness, especially in its chronic form, does not correspond with any sign that can be objectively seen in clinical examination or any parameters that can be tested (such as breath rate, saturation, echocardiographic data, pulmonary wedge pressure or blood tests) (6). The language of breathlessness (how a person describes it) is complex and indicates its complex pathophysiology (99). Breathlessness can vary respective character, intensity, unpleasantness, emotional and behavioral significance. It is classified as acute, chronic (having usual fluctuations with regard to the above-mentioned features) with usually superimposed episodes of exacerbations (they can be triggered, by predictable or unpredictable, factors or non-triggered). Those episodes of breathlessness go beyond the usual fluctuations (100). The most commonly seen triggered, predictable episodes are usually provoked by physical activity, with breathlessness accompanying exercise with gradual onset, sometimes becoming very intense—in healthy people with heavy exertion (perceived as normal breathlessness, mostly not unpleasant), but in people with HF, especially if this is advanced, it is precipitated by moderate or slight exercise (perceived as unpleasant) (101). This kind of breathlessness is a universal feature of HF (even if optimally treated) and relates to the skeletal myopathy that is present in the HF syndrome of any etiology. As HF progresses, the episodes of breathlessness can be seen at rest—typically after taking up a supine position, sometimes with wheezing and coughing (asthma cardiale) or bending forwards (102, 103). Breathlessness is so ubiquitous in people living with HF that it has become the basis for the most commonly used classification of HF according to NYHA (104). Breathlessness, is also common in many other conditions like infectious, lung, renal, metabolic, hematologic, neuro-muscular or even psychiatric disease, and so more than one pathology can often evoke it in one person. Before considering the symptomatic (i.e., palliative) management of breathlessness, its etiology and the possibility of specific treatment have to be actively sought.

In women more often than in men with heart disease, breathlessness can be equivalent to anginal pain (105). In people affected by HF, blocking neurohormonal activation, optimizing afterload, heart rate and volaemia are the principles of breathlessness management. Even in end-stage-disease using vasodilators/neurohormonal antagonists, heart rate controlling interventions and drugs as well as diuretics improves dyspnoea. It has been shown that the continuation of these drugs, sometimes in modified doses, improves the QoL, even in advanced HF (106–108). If the cause of breathlessness cannot be treated specifically, and if the breathlessness is severe or disabling (corresponding with III or IV NYHA class), symptomatic treatment should be considered as mandatory, unfortunately it often remains untreated. Acute breathlessness is perceived as an alarming symptom for both patients and health care professionals. It is 1 of

the 10 leading causes of all emergency room visits (5%), 20% of those delivered by ambulance and causes 25% of hospitalisations (109, 110). Chronic breathlessness, affecting the everyday lives of almost 9% of the general population, remains "invisible" i.e., unnoticed as indication for symptomatic treatment, even if the people suffering from it are unable to walk more than 100 m or to leave home (111, 112). This invisibility of breathlessness affects health care professionals (as patients examined at rest do not demonstrate breathlessness, even if the exercise threshold for inducing dyspnoea is very low) but surprisingly the patients themselves as well (due to the omnipresence of breathlessness in their life). Finally, given the lack of established, effective standards in breathlessness alleviation, healthcare professionals do not ask about symptoms that they feel unable to alleviate (111). The treatment gap in the case of dyspnoea can be as high as over 70% in hospitalized patients with acute HF (113). 42% of patients hospitalized for decompensated HF report no improvement in dyspnoea 1 week after discharge in comparison to admission (114).

Many people living with HF suffer from breathlessness, or its resulting limitation in daily activity, despite optimal cardiologic treatment. Similar conclusions come from studies in people with chronic respiratory disease, in those optimizing the treatment of the underlying disease has an inconsistent impact on the symptoms. All this suggest that even optimal disease specific treatment cannot be only intervention to ameliorate breathlessness; symptomatic interventions are needed (98). Non-pharmacological (physiotherapy, breathing-relaxation training, cognitive, behavioral strategies, walking-aids, hand-hold ventilators) and pharmacological management should be considered (6, 115, 116). There are a plethora of non-pharmacological approaches to ameliorate breathlessness, without evidence to guide the individualization of therapy (98). Multi-modal, non-pharmacological approaches that work concurrently at multiple points within the brain, respiratory and skeletal system offer the most successful amelioration of breathlessness (117–119). Without proper support, people suffering from breathlessness reduce their activity and thus become increasingly deconditioned, in turn worsening breathlessness. This mechanism could in part explain the progression of breathlessness severity, despite the fact that the underlying disease remains stable (98, 120). A recently developed clinical model, the "Breathing Thinking Functioning" (BTF), stresses the importance of the cognitive and behavioral reactions responsible for the worsening perception of dyspnoea in people with chronic obstructive pulmonary disease (**Figure 1**). Parallel interventions affecting all domains should be provided to improve the alleviation of breathlessness (**Table 1**). Oxygen can be tried, but improvement is to be expected mainly in hypoxemic patients (121). The basis for pharmacological treatment are low-dose opioids, usually morphine titrated up to 30 mg orally/day in divided, appropriately to formulation, doses (or oxycodone in equivalent doses), but their efficacy and safety in people living with HF is still not well-established [for more details, see the recent EAPC expert position statement (6)]. Some studies even suggest that harm can be caused by using opioids for this indication in people with acute heart failure (84). Benzodiazepines are widely used, but do not improve breathlessness and cause serious side effects, including sedation, increased risk of death, falls and pneumonia, and for those reasons, except for uncommon situations when anxiety plays really a crucial role (usual in case of acute breathlessness, especially with panic attacks), they should be considered as contraindicated (122–126).

Breathlessness affects women more often than men. In the general population, the prevalence of chronic breathlessness is almost twice as frequent in women in comparison to men (odds ratio, OR 1.9, $p < 0.001$) (112). A similar trend has been reported in those affected by HF, however the magnitude of the difference is smaller; for dyspnoea at exertion OR 1.2, $p < 0.001$ and for rest dyspnoea OR 1.19, $p = 0.01$ (25).

Depression

Depression is up to four times more frequent in people living with HF (21.5%) than in the general population (2.6 in males and 7% in females) (70). Significant differences in the prevalence of depression exist between those who are hospitalized and outpatients with HF (13–77% vs. 13–48%, in different studies) (68, 70, 127–129). The meta-analysis indicates the prevalence of depression among different groups. Its prevalence rises with HF severity (11% in I NYHA class, 42% in IV NYHA class) and is an important factor limiting QoL, increasing the risk of hospitalisations, emergency room visits and death (48, 68–70). Some studies reported that anxiety, depression and psychological distress are more frequent in females than in males (64 vs. 44%), with 37% of women vs. 24% of men with advanced HF suffering from current depression (17, 27, 47, 69, 130). Patients with higher levels of depression had a higher total symptom burden (43). Based on this observation, it has been hypothesized that the effective management of depression could be one measure to improve the general symptom burden in people living with HF. Intensity of anxiety, depression, and psychological distress seems to be higher in female patients when they are accompanied by decreased social functioning, limits in pursuing hobbies, increased dependency or a disturbed body image. Depression in patients older than 51 years after myocardial is almost twice as frequent in women than in men (15–19% vs. 9–14%) (131). Tricyclic antidepressants are contraindicated in people living with HF, due to their negative inotropic and proarrhythmic properties. Sertraline does not cause an additional risk for this population, and venlafaxine can even reduce the risk of HF in the general geriatric population, so both are considered drugs of choice in HF (132, 133). Selective serotonin inhibitors can precipitate however syndrome of inappropriate antidiuretic hormone secretion and as consequence hyponatremia, especially in older women. For this reason caution is needed and monitoring of natrium in serum, already several days after starting this drugs is required (134).

Spiritual Care and the Whole Person Care Approach

A mandatory mission of PC in modern medicine is to remind everybody of the potential to find new realistic hopes, to develop his/her creativity and to grow as a person, even in the most

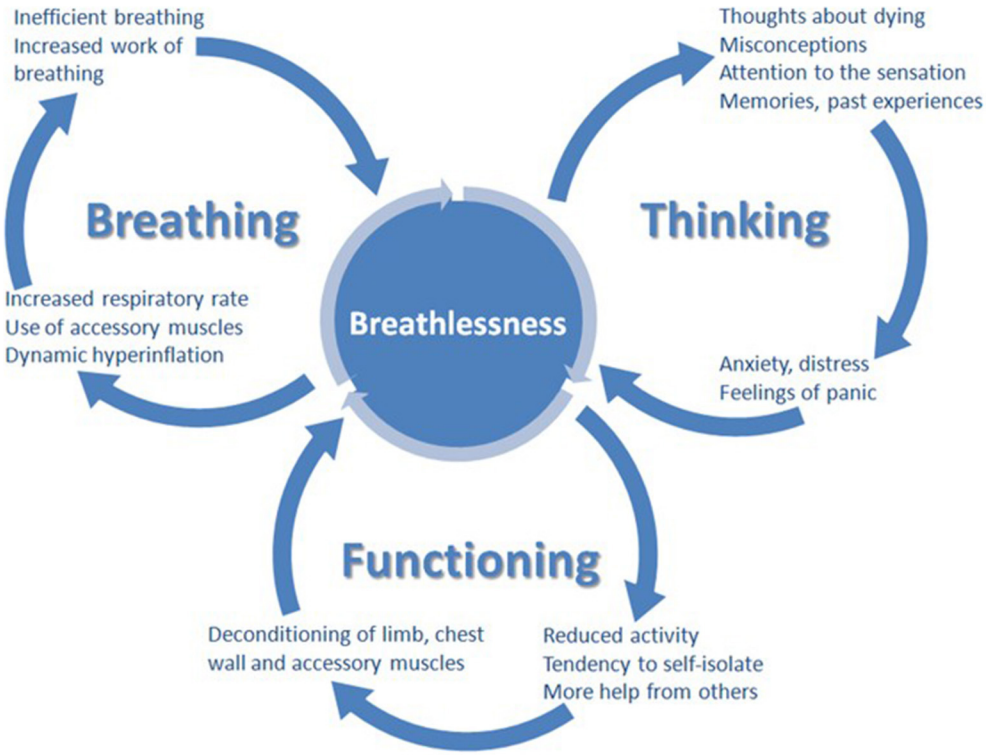

FIGURE 1 | The breathing, thinking, functioning clinical model (98).

TABLE 1 | The categorization of symptom management approaches according to breathing, thinking, functioning domain (98).

Breathing	Thinking	Functioning
Breathing techniques	Cognitive behavioral therapy	Pulmonary rehabilitation
Handheld fan	Relaxation techniques	Activity promotion
Airway clearance techniques	Mindfulness	Walking aids
Inspiratory muscle training	Acupuncture	Pacing
Chest wall vibration		Neuromuscular electrical stimulation
Non-invasive ventilation		

difficult situations such as dealing with his/her own imminent dying/death. One of the dimensions of growing significance, especially as a disease is progressing, is a person's spirituality, which explains why spiritual care has to be an integral element of PC (6). Spirituality is the way a person seeks and expresses the meaning and purpose of their own life, and the way they experience their connectedness to the moment, to themselves, to others, to nature and to the significant or sacred and goes far beyond religiosity (135). According to EAPC, spirituality is multidimensional and consists of existential challenges, value based considerations and attitudes and religious considerations and foundations (136). The "whole person care" concept extends the goals for medicine as a whole in the twenty-first century, not only PC. This shifts the focus from just curing (treating a disease) to healing (treating the patient as a person). The process of healing is defined as becoming psychologically and spiritually more integrated and whole, enabling a person to become more completely her- or himself and more fully alive (137). To empower this phenomenon, the recognition of the central place of spirituality in a persons' life and the importance of the relationship between the clinician and patient are needed (135, 138, 139). Thus spiritual care is understood as an integral part of PC and, along with the whole person care approach, has started to be recognized as the optimal model of caring (6).

The evidence shows the positive impact of spirituality on treatment efficacy, prognosis, mortality and better coping of the patient and his/her relation to clinicians. Spiritual peace better predicts the mortality of people with HF than comorbidity and functional status (140). Higher level of religiosity/spirituality or greater spiritual well-being is associated with less depression, (141) lower anxiety (142) and better resilience (143). Quality of religious coping, seeking spiritual support and help from God is associated with less distress among patients undergoing cardiac surgery (144). Spirituality has also been shown to be related to self-management and lifestyle changes in people with heart disease (145). Praying positively affected QoL and the

psychological status of patients who have undergone a pacemaker implantation (146) and self-care of elderly patients with HF (147). The provision of spiritual-religious interventions has also led to the improvement of life satisfaction and depression rate among elderly patients with HF (148). The trajectories of social and psychological well-being track the physical decline observed at the end-of-life of people with HF, however spiritual distress reveals independent background fluctuations (149). Spiritual well-being remains stable for up to 30 months during observations among advanced HF patients and is lower for those with more symptom distress (150). However, if a gradual decrease is observed, it may reflect a progressive loss of identity and growing dependence (151). Religious beliefs, love, hope and trust help to increase spiritual well-being even at the very end of life. Importantly, people who felt valued by their clinicians were more able to find a sense of their own worth and meaning (149). Such a healing relation and basic spiritual care begins from the therapeutic presence of the clinician (being on hand, i.e., "here and now"), from the enhancement of the patient's dignity and his or her need to be respected as an unique human being, from asking about spiritual needs of the patient and cooperation with a chaplain and other people involved in spiritual care. EAPC recommends that clinicians caring for people should respectfully inquire about the patients' spiritual needs and, if they wish, make time to address them as they would with physical concerns (6).

Are there sex related differences in the spiritual needs of the patient and modes of spiritual care? Any comparison of spirituality/religiosity among men and women appears to be complicated. Evidence from a meta-analytic sample representing nearly 126,000 participants suggest that the relation between spirituality/religiousness and health differs between men and women and that researchers should separately estimate those two models (152). One partial explanation proposed for this phenomenon was differences in the psychosocial resources that men and women receive from religious involvement, with women being more religious and living longer, thus may have stronger network connections and benefit more from them compared to men when elderly. As an example, both men and women attending services at least once a week (compared with those who attend less frequently or never) have between a 1.1 and 5.1 years longer total life expectancy and between 1.0 and 4.3 years longer activities of daily living, disability-free life expectancy (153). However, these differences in total, disability-free, and disabled live expectancy across religion groups tended to be larger for women than men, which may be partially related to the influence of social support and network integration. Some studies suggest gender related differences in images of God or in the ways of applying religious coping strategies and in the use of positive and negative religious coping (154–156). Another study revealed while men and women suffering from serious or life-limited illness endorsed an overall similar level psycho-social-spiritual healing, women were shown to have greater enjoyment of mind-body practices, including prayers, gratitude, compassion and a desire to be more positive than men (157). Evidence they may experience introspective and reflective processes of healing in a different way may have some practical implications in choosing specific therapeutic interventions. Very few studies explore this topic specifically among people with HF. One of the few is a longitudinal observation of more than 180 elderly people with heart disease assessing whether gender and the existence of cardiac health problems affected older adults' spiritual and religious involvement after 12 months (158). While women in poor cardiac health turned toward prayer and devotion, older men with cardiac problems engaged in more religious doubt and questioning which seemed to be a new coping strategy for them. The study suggests that spiritual interventions directed to help elderly men with heart disease should recognize the likelihood of a patient's religious doubt and existential questioning. Nevertheless, two main conclusions related to the potential sex differences in spiritual care among people with HF can be made: 1/ there is no typical pattern of spiritual needs for men or women, thus spiritual needs assessment and support should always be tailored individually; 2/ spiritual history and screening for spiritual needs should be done for each PC patients, not as a once-only activity, but as a process of caring and developing healing relations. And this is in agreement with the recent EAPC white paper recommendations regarding how one should educate clinicians on spiritual care for patients receiving PC (136).

Care for Carers

HF is one of most common chronic diseases leading to disability and a need for long-term care. Home based assistance is becoming a mandatory strategy to support and care for those in this condition. In Europe, the number of informal caregivers range from 10 to 25% of the total population, yet they provide 80% of all long-term care.

PC acknowledges caring for unformal carers, their well-being and ability to care for their ill loved ones as one of its tasks. Unrelieved symptoms not only burden patients but their caring relatives as well. A higher severity of breathlessness corelates with worse carer psychological health, indicating not only the need for optimal symptom management but also for support for the informal caregivers, especially in the case of severe dyspnoea (159). The relatively sparse studies on sex related differences in caring suggests that women, including those who are elderly and fragile, provide the majority of family caregiving for older adults. The higher proportion of women is linked to the societal expectation that they should provide care at the end-of-life for family members. They experienced a greater degree of mental and physical strain, higher levels of distress and burden as well as worse QoL than males. Women's psychological distress was associated with the health condition of their partner, whereas men's psychological distress was found to only be associated with their own health condition. Unfortunately, the burden of informal caregivers remains mostly unrecognized and the need for support is usually uncovered. Health care professionals should provide assistance and support more sensitively for older females caring for their relatives (160–162). Many relatives feel burned out from the length of time they have spent being a caregiver (21). These observations suggest that providing institutionalized care at the end of life should be considered even if family care in the community is theoretically possible. The aim of this would be to give support to mostly older women caring for their loved ones to prevent physical and psychosocial burden.

TABLE 2 | Differences between women and men in relation to PC for people living with HF.

As a person suffering for HF	Women compared to men
Age and concomitant diseases	More likely to be older and to have a history of hypertension and diabetes mellitus.
Characteristics of HF	More common HFpEF
In case of HFrEF	Severity of symptoms depends on lowered ventricular compliance and not on dilatation of LV (inversely in men)
Cause of death	More common non-cardiovascular deaths
Symptoms:	
Pain other than chest pain, dry mouth, swelling of the arms and legs, sweats, feeling nervous, fatigue, nausea and vomiting	Higher symptom related burden
Self-reported breathlessness at rest and with exertion	Significantly higher rate
Comorbid depression and anxiety	Higher rate
Depression treated with medication	Higher prevalence
Pain management	Greater risk of undertreatment of pain in spite of higher use of prescription and non-prescription analgesics
Opioid use	Potentially higher risk for atrial fibrillation related to opioid use Lower risk of escalation to high dose and death from opioid-related causes Lower risk for opioid misuse (for older women) but more vulnerability to adverse medical effects of opioids
Quality of Life measured by Kansas City Cardiomyopathy Questionnaire (KCCQ)	Significantly lower, despite similar physician assigned NYHA class
Psychosocial needs/aspects	More poorly cope with the disease More likely to be widowed or alone Increased reliance on family as caregivers and more likely dependence on institution
Spiritual needs	More often religion deeply important
Impact of PC interventions on quality of life	Not observed (compared to the significant effect in men)
As a patient	**Sex-related aspects of doctor-patient communication**
Perceiving of symptom burden	Female patient has to report higher level of distress in order to get their symptoms acknowledged, documented and managed
As informal caregiver of a person with advanced HF	**Women compared to Men**
Burden and quality of life	Greater degree of mental and physical strain, higher level of distress and burden Worse QoL
Social expectations	More often related to the role of women as caregivers for family member at the end-of-life
Psychological distress	More related to spouses' health condition (more distress in healthy wives of patients than healthy husbands of patients)

The differences between women and men in relation to PC for people living with HF have been summarized in **Table 2**.

CONCLUSIONS

People living with HF are confronted with suffering caused by physical, emotional, existential and spiritual problems despite optimal cardiologic care, usually during the long journey of living with this syndrome, and not only at the end-of-life. Symptom management requires close cooperation between cardiology and other disciplines including PC. Implementing PC for all those with health-related needs as soon as they emerge could improve their QoL. PC is underused and offered to the minority of people living with HF in the very last moments of their life. Putting suffering in the center of care requires clinicians to attend to the individual experiences of persons' illness, to address its physical, psychological, spiritual and social burdens, and to support the patient in the journey to real healing by careful listening and witnessing. However, this very individual approach should not be the reason for ignoring the impact of different factors such as sex on how those individuals usually or more often experience illness, how they react to treatment, or cope with the suffering. Data suggest that PC interventions need to be more specific to women vs. men. This specificity may involve sex related symptoms prevalence and intensity, efficacy of symptom management, response to pharmacotherapy, identifying comorbidity and additional symptoms related to it, specific social challenges such as widower status or loneliness, up to different spiritual coping and needs. The differences between both sexes really matter in the way people perceive their life, its quality and the support they receive, and they should be acknowledged when providing medical care.

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All authors contributed to designing the scope of the paper, have written parts of the text, reviewed, and adjusted the whole manuscript.

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Sex-Specific Patterns of Mortality Predictors Among Patients Undergoing Cardiac Resynchronization Therapy: A Machine Learning Approach

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Background: The relative importance of variables explaining sex-related differences in outcomes is scarcely explored in patients undergoing cardiac resynchronization therapy (CRT). We sought to implement and evaluate machine learning (ML) algorithms for the prediction of 1- and 3-year all-cause mortality in CRT patients. We also aimed to assess the sex-specific differences in predictors of mortality utilizing ML.

Methods: Using a retrospective registry of 2,191 CRT patients, ML models were implemented in 6 partially overlapping patient subsets (all patients, females, or males with 1- or 3-year follow-up). Each cohort was randomly split into training (80%) and test sets (20%). After hyperparameter tuning in the training sets, the best performing algorithm was evaluated in the test sets. Model discrimination was quantified using the area under the receiver-operating characteristic curves (AUC). The most important predictors were identified using the permutation feature importances method.

Results: Conditional inference random forest exhibited the best performance with AUCs of 0.728 (0.645–0.802) and 0.732 (0.681–0.784) for the prediction of 1- and 3-year mortality, respectively. Etiology of heart failure, NYHA class, left ventricular ejection fraction, and QRS morphology had higher predictive power, whereas hemoglobin was less important in females compared to males. The importance of atrial fibrillation and age increased, while the importance of serum creatinine decreased from 1- to 3-year follow-up in both sexes.

Conclusions: Using ML techniques in combination with easily obtainable clinical features, our models effectively predicted 1- and 3-year all-cause mortality in CRT patients. Sex-specific patterns of predictors were identified, showing a dynamic variation over time.

Keywords: heart failure, cardiac resynchronization therapy, sex differences, machine learning, mortality prediction

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INTRODUCTION

Despite the comparable overall lifetime risk of heart failure (HF) between sexes (1, 2), there are notable differences between males and females with HF across the entire spectrum of ejection fraction (EF) (3). In HF patients with reduced EF (HFrEF), several studies have highlighted sex-related differences that involve multiple aspects of the syndrome, such as epidemiology, pathophysiology, phenotyping, and prognosis (4). Nevertheless, females are under-represented in HFrEF trials questioning their generalizability and leaving significant gaps in knowledge (4, 5).

While women with HFrEF have better survival and lower hospitalization rates, they have a greater burden of symptoms and more impaired health-related quality of life than men (6). Although sex disparities are also remarkable in the accessibility to HF device therapy, including cardiac resynchronization therapy (CRT) (7–9), women are more likely to respond favorably and derive a greater survival benefit from CRT implantation (10–13). Nonetheless, the sex-related differences in both short- and long-term outcomes and the varying importance of different predictors are still scarcely explored in this patient population (14). One conceivable explanation could be the failure of the applied statistical methods to harness the potential prognostic value of complex interactions between several weaker, often unexpected risk factors and the outcome. However, this limitation might be circumvented by advanced data analytic techniques (15).

To improve predictive modeling and elucidate novel determinants of a specific outcome, machine learning (ML) has been increasingly utilized in cardiovascular research (16–20). ML represents a collection of algorithms that autonomously acquire knowledge by identifying patterns from complex, multi-dimensional datasets. ML models can account for interactions between myriads of predictors and their non-linear associations with the outcome; therefore, their utilization could potentially lead to improved explanatory models (21).

In the current study, we sought to implement and evaluate ML algorithms for the prediction of 1- and 3-year all-cause mortality among patients undergoing CRT implantation. We also aimed to explore the sex-specific differences and similarities in the predictors of mortality using advanced ML-based approaches.

METHODS

Study Population and Protocol

We identified 2,412 patients with chronic HFrEF (NYHA functional class II-IV) who underwent successful CRT implantation at the Heart and Vascular Center of Semmelweis University (Budapest, Hungary) between September 2000 and September 2018. For each patient, pre-implant clinical characteristics (demographics, medical history, physical status, vitals, currently applied medical therapy, ECG-, echocardiographic- and laboratory parameters) and procedural parameters [type of the implanted device, left ventricular (LV) lead position] were collected retrospectively from paper-based or electronic medical records and entered to our structured database.

The study protocol complies with the Declaration of Helsinki, and it was approved by the Regional and Institutional Committee of Science and Research Ethics (Approval No. 161/2019).

Study Outcomes

Follow-up data [status (dead or alive), date of death] was obtained for all patients by querying the National Health Insurance Database of Hungary in September 2019. Accordingly, all patients included in our database were followed for at least 1 year or died within 1 year. In the entire study population, 2,116 patients also had 3-year outcome data available. The primary endpoint of our study was all-cause mortality.

Feature Selection and Data Pre-processing

The data analysis pipeline, including feature selection, data pre-processing, and ML model development and evaluation is illustrated in **Figure 1**.

Feature selection included two consecutive steps. First, any feature with ≥40% missing data was removed. Second, collinear variables (Spearman correlation coefficient ≥ 0.3 or $\leq$-0.3) were also excluded as variables containing redundant information might bias the further steps of the analysis (**Supplementary Figure 1**). The final set of input features comprised 30 pre-implant and procedural variables: baseline demographics and clinical characteristics ($n = 10$), comorbidities ($n = 6$), ECG- ($n = 1$), laboratory parameters ($n = 3$), and currently applied medications ($n = 10$). The list of candidate variables and the feature selection process are presented in **Table 1**.

Patients with more than 30% of missing values were excluded from further analyses. Missing values were imputed using Multiple Imputation by Chained Equations (MICE). As the range of different continuous features varied widely, Z-score transformation was applied after imputation to eliminate the possibility of model bias caused by the differing magnitude of the numerical values.

ML Model Development and Evaluation

We developed ML models to predict two separate outcomes: (1) 1-year all-cause mortality, and (2) 3-year all-cause mortality in the entire cohort, in males and females separately (a total of 6 separate binary classification tasks). To quantify a model's discriminatory power, receiver operating characteristic curve analysis was performed, and the area under the curve (AUC) was calculated. Model development included trials of several binary classifiers such as logistic regression, support vector machines, k-nearest neighbors classifier, gradient boosting classifier, traditional random forest (TRF), conditional inference random forest (CIRF), and multi-layer perceptron.

As the first step of model derivation, 20% of the given patient subset (all, males or females) was randomly selected as the holdout (*test cohort*). This split was performed in a stratified manner to ensure that the original ratio of outcomes is preserved in the training and test cohorts. Hyperparameter tuning was performed with stratified 10-fold cross-validation in the remaining data (80%, *training cohort*). The algorithm (with fine-tuned hyperparameters) exhibiting the highest AUC was

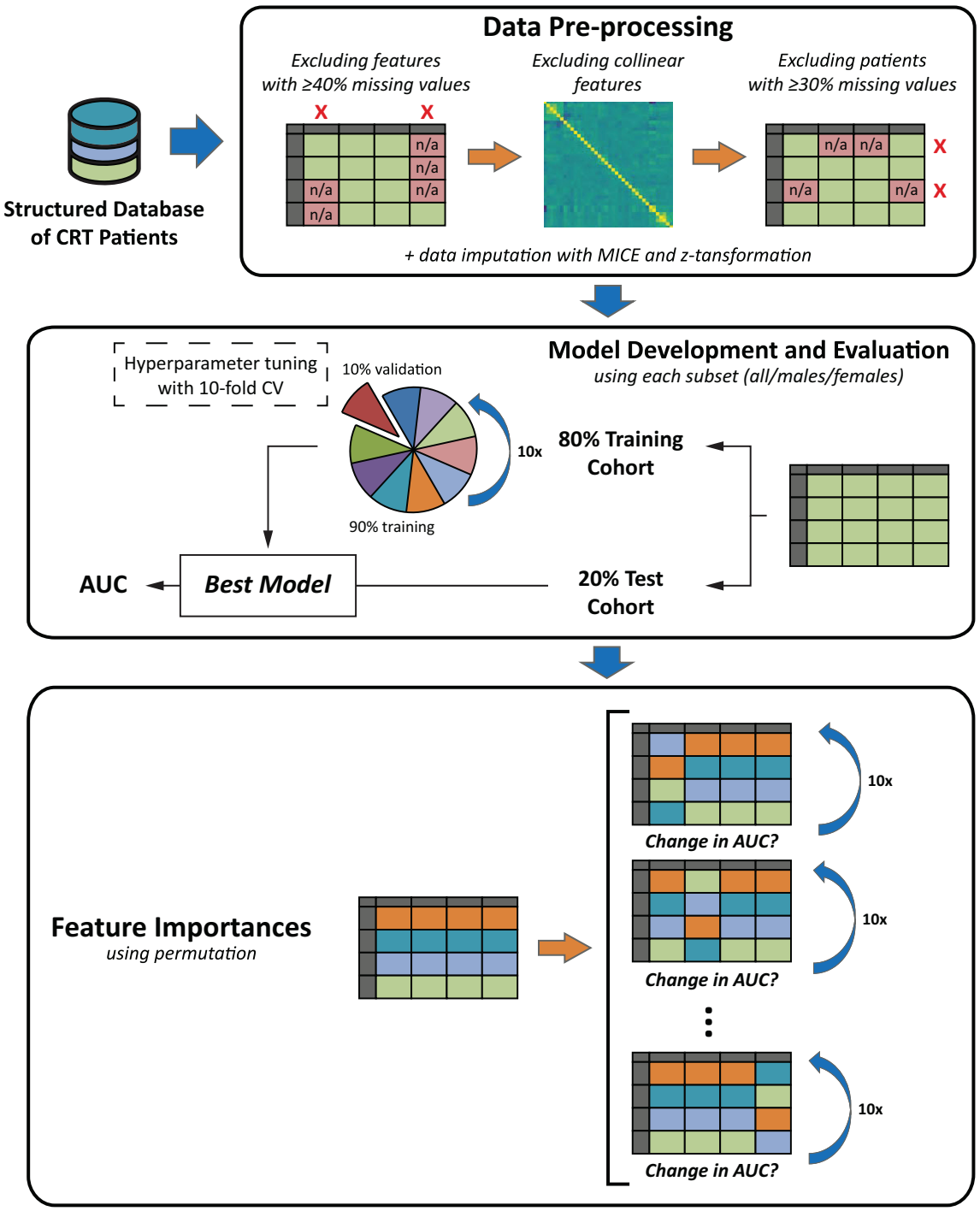

FIGURE 1 | The schematic outline of the data analysis pipeline. The data analysis pipeline included three major steps: (1) data pre-processing, (2) machine learning model development and evaluation, and (3) the calculation of feature importances. During *data pre-processing*, feature selection was performed, patients with a high proportion of missing data were excluded, missing values were imputed using MICE, and z-transformation was performed. Then, *machine learning models* were implemented in the 6 partially overlapping subsets of patients (in all patients, females, or males of the 1- and 3-year cohorts). Before model training, each patient subset was split into training and test cohorts (80:20 ratio). Hyperparameter tuning was performed with 10-fold CV in each training cohort. Models' discriminatory power was estimated using the area under the receiver-operating characteristic curves. Each of the 6 models was retrained in the given training cohort, and its performance was evaluated in the corresponding test cohort. Finally, to identify the most important predictors of mortality in each subset, permutation *feature importances* were computed from each of the 6 final models. See text for further details. AUC, area under the receiver operating characteristic curve; CRT, cardiac resynchronization therapy; CV, cross-validation; MICE, Multiple Imputation by Chained Equations.

TABLE 1 | Steps of feature selection and the list of clinical features included in the machine learning models.

	Demographics and clinical characteristics	Comorbidities	ECG	Laboratory parameters	Medications
Included in the ML models	Age at CRT implantation Sex Body mass index NYHA functional class HF duration >18 months Etiology of heart failure LVEF LV end-diastolic diameter Type of implanted device LV lead position	Hypertension Diabetes mellitus Type of AF COPD Smoking status Valvular heart disease	QRS morphology	Hemoglobin Serum sodium Serum creatinine	ACE-I/ARB Beta-blockers CCB Loop diuretics Thiazide diuretics MRA Digitalis Amiodarone Statin Allopurinol
Excluded due to collinearity	Height Weight	History of MI History of CABG and/or PCI		Serum urea GFR	Oral anticoagulants
Excluded due to ≥40% missing values	Systolic blood pressure Diastolic blood pressure Heart rate LV end-diastolic volume LV end-systolic volume		QRS duration PR interval	Lymphocyte Total cholesterol Serum uric acid NT-proBNP	

Feature selection included two consecutive steps. First, features missing in more than 40% of patients were excluded. Then, collinear variables (Spearman correlation coefficient ≥0.3 or ≤-0.3) were also eliminated as highly correlated variables might bias the further steps of the analysis. The final set of features included 30 clinical variables: age at CRT implantation, sex, body mass index, New York Heart Association functional class, heart failure duration >18 months, etiology of heart failure (ischemic or non-ischemic), left ventricular ejection fraction and end-diastolic diameter assessed with two-dimensional echocardiography, type of the implanted device (CRT-P or CRT-D), left ventricular lead position (anterior, lateral or posterior), hypertension, diabetes mellitus, type of atrial fibrillation (paroxysmal, persistent or permanent), chronic obstructive pulmonary disease, smoking status, valvular heart disease (moderate to severe aortic valve disease, moderate to severe mitral valve disease, severe tricuspid regurgitation), QRS morphology (non-LBBB or LBBB), hemoglobin concentration, serum sodium and creatinine, medical treatment with angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers, beta-blockers, calcium channel blockers, loop diuretics, thiazide diuretics, mineralocorticoid receptor antagonists, digitalis, amiodarone, statins, and allopurinol.

ACE-I, angiotensin-converting enzyme inhibitors; AF, atrial fibrillation; ARB, angiotensin II receptor blockers; CABG, coronary artery bypass grafting; CCB, calcium channel blocker; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; ECG, electrocardiogram; EF, ejection fraction; GFR, glomerular filtration rate; HF, heart failure; LV, left ventricular; MI, myocardial infarction; ML, machine learning; NYHA, New York Heart Association; NT-proBNP, N-terminal pro-brain natriuretic peptide; MRA, mineralocorticoid receptor antagonists; PCI, percutaneous coronary intervention.

then retrained in the entire training cohort, and its performance was evaluated in the test cohort in a statistically independent way. Finally, calibration of the ML models was assessed in the test cohort using Brier score (ranging from 0 to 1, with 0 representing the best possible calibration), which is defined as the mean squared difference between the observed outcomes and the predicted probabilities.

Feature Importances

To determine the major predictors of 1- and 3-year all-cause mortality in each patient subset, permutation feature importances were computed from each of the 6 final models. Briefly, the importance of an input feature is measured by calculating the increase in the model's prediction error after permuting its values while keeping other features the same as before. In the current study, permutation was performed 10 times for each feature. A feature is considered important if shuffling its values decreases the model's discriminatory power (AUC) as the model relies heavily on that feature for the prediction. On the other hand, a feature is unimportant if shuffling its values leaves the AUC unchanged because, in this case, the model ignores the feature while predicting the outcome. After calculating the importance of each feature, we divided it by the AUC measured in the dataset before shuffling any of its features to enable the comparison of feature importances between different models.

RESULTS

Baseline Clinical Characteristics and All-Cause Mortality

The final 1- and 3-year cohorts included 2,191 (74.7% males, 56.7% CRT-D) and 1,900 patients (75.0% males, 54.1% CRT-D), respectively (**Figure 2**). In the 1-year cohort, 50.4% of the patients had ischemic etiology of HF, 57.8% had NYHA functional class III/IV, and the median left ventricular EF (LVEF) was 28 (24–32) %. In the 3-year cohort, ischemic etiology was reported in 51.5% of the patients, 61.0% presented with NYHA functional class III/IV, and the median LVEF was 28 (24–32) %. The baseline clinical characteristics of the patients are summarized in **Tables 2**, **3**.

In the 1-year cohort, 203 (12.4%) men and 49 (8.8%) women died during the 1-year follow-up period. Univariable Cox regression analysis revealed a significantly lower risk of all-cause mortality in women compared to men [Hazard Ratio (HR): 0.698, 95% Confidence Interval (CI): 0.511–0.954; $p = 0.024$]; however, after adjusting for age, etiology of HF, QRS morphology, type of implanted device, and type of atrial fibrillation (AF, history of or current), we could not observe a significant difference between sexes (HR: 0.803, 95% CI: 0.581–1.110; $p = 0.183$) (**Figure 3A**).

As observed in the 1-year cohort, males exhibited significantly higher mortality rates compared to females in the 3-year cohort

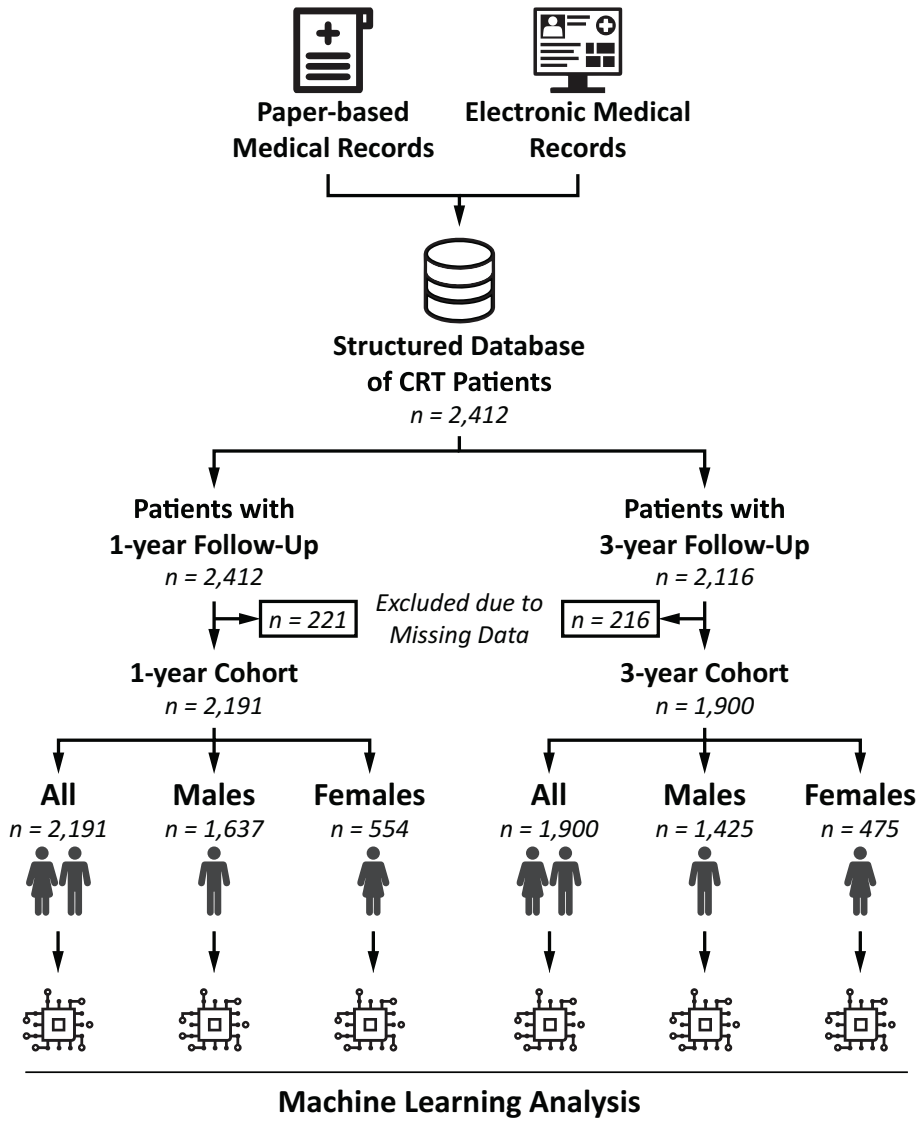

FIGURE 2 | Flowchart illustrating the steps of patient selection. For each patient who underwent successful CRT implantation at our center, pre-implantation clinical characteristics and procedural parameters were collected retrospectively from paper-based or electronic medical records and entered to our structured database. After excluding patients with ≥30% missing values, machine learning models were implemented to predict 1- and 3-year all-cause mortality in the entire cohort, in males and females separately (altogether 6 separate binary classification tasks). CRT, cardiac resynchronization therapy.

as well [502 (35.2%) vs. 113 (23.8%); $p < 0.001$]. The univariable Cox regression analysis also confirmed this finding as it showed a significantly lower risk of all-cause mortality in females compared to males (HR: 0.625, 95% CI: 0.510–0.767; $p < 0.001$) (**Figure 3B**). Moreover, this difference remained significant even after adjusting for the previously listed covariates (HR: 0.686, 95% CI: 0.555–0.848; $p < 0.001$).

Patients with ischemic etiology had a significantly increased risk of death in both sexes; however, this difference was more pronounced in females compared to males in the 1- and 3-year cohorts as well (**Supplementary Figure 2**).

ML for the Prediction of All-Cause Mortality

Among the evaluated ML classifiers, CIRF exhibited the best performance for discrimination between survival/all-cause death with an AUC of 0.717 (95% CI: 0.676–0.758) and 0.739 (95% CI: 0.715–0.762) in the 1- and 3-year training cohorts, respectively (**Supplementary Tables 5, 6**). When evaluating the models' discriminatory power in the test cohorts, we observed an AUC of 0.728 (95% CI: 0.645–0.802) and 0.732 (95% CI: 0.681–0.784) for the prediction of 1- and 3-year mortality, respectively. Models were also trained and tested separately in the female and male subsets of the 1- and 3-year cohorts. The AUCs ranged

TABLE 2 | Clinical characteristics of the 1-year cohort.

	All patients ($n = 2,191$)	Males ($n = 1,637$)	Females ($n = 554$)	*p*-value
Demographics, vitals, and key electrophysiological characteristics				
Age, years*	68 (61–74)	68 (60–74)	69 (63–75)	<0.001
Weight, kg (1,423)	80 (70–91)	84 (75–95)	70 (60–80)	<0.001
Height, cm (1,413)	172 (165–177)	175 (170–179)	162 (157–167)	<0.001
BMI, kg/m^2 (1,413)*	27.4 (24.5–30.7)	27.6 (24.8–30.8)	26.7 (23.4–30.5)	<0.001
SBP, mmHg (807)	125 (111–136)	125 (111–136)	124 (110–136)	0.403
DBP, mmHg (807)	73 (65–80)	74 (65–80)	71 (64–80)	0.089
NYHA III/IV (1,803)*	1,043 (57.8)	781 (57.9)	262 (57.7)	0.945
CRT-D*	1,239 (56.5)	1,005 (61.4)	234 (42.2)	<0.001
QRS duration, ms (754)	160 (140–180)	160 (140–180)	160 (140–170)	0.068
QRS morphology, LBBB*	1,572 (71.7)	1,127 (68.8)	445 (80.3)	<0.001
LV lead position (1,890)*				
Anterior	84 (4.4)	62 (4.4)	22 (4.7)	
Lateral	1,227 (64.9)	932 (65.7)	295 (62.5)	
Posterior	579 (30.6)	424 (25.9)	155 (32.8)	0.442
Medical history				
Ischemic etiology of HF*	1,104 (50.4)	902 (55.1)	202 (36.5)	<0.001
History of MI	868 (39.6)	713 (43.6)	155 (28.0)	<0.001
HF duration >18 months*	680 (31.0)	519 (31.7)	161 (29.1)	0.245
History of or current AF*				
No AF	1,394 (63.6)	998 (61.0)	396 (71.5)	
Paroxysmal	342 (15.6)	257 (15.7)	85 (15.3)	
Persistent	59 (2.7)	51 (3.1)	8 (1.4)	
Permanent	396 (18.1)	331 (20.2)	65 (11.7)	<0.001
Valvular heart disease*	135 (6.2)	99 (6.0)	36 (6.5)	0.780
Hypertension*	1,618 (73.8)	1,216 (74.3)	402 (72.6)	0.459
Diabetes mellitus*	813 (37.1)	624 (38.1)	189 (34.1)	0.092
COPD*	325 (14.8)	239 (14.6)	86 (15.5)	0.597
Current smoker*	131 (6.0)	103 (6.3)	28 (5.1)	0.288
Laboratory parameters				
Hemoglobin, g/L (1,440)*	136 (123–148)	139 (126–150)	130 (120–140)	<0.001
Serum sodium, mmol/L (1,374)*	138 (136–141)	138 (136–140)	139 (136–141)	0.019
Total cholesterol, mmol/L (956)	4.1 (3.4–5.1)	4.0 (3.3–4.9)	4.7 (3.6–5.5)	<0.001
Serum creatinine, μmol/L (1,473)*	101 (82–131)	105 (87–134)	86 (71–112)	<0.001
Urea, mmol/L (1,445)	8.3 (6.4–11.7)	8.6 (6.6–11.8)	7.5 (6.0–10.9)	<0.001
Uric acid, μmol/L (766)	405 (322–492)	412 (330–494)	383 (307–474)	0.020
NT-proBNP, pg/mL (309)	2,640 (1,262–3,699)	2,490 (1,367–3,473)	2,680 (1,250–3,710)	0.938
Echocardiographic parameters				
LV ejection fraction, % (1,610)*	28 (24–32)	28 (23–32)	28 (25–33)	0.046
LVEDD, mL (1,610)*	64 (58–70)	65 (59–71)	61 (55–66)	<0.001
Medications				
ACE-I/ARB*	2,014 (91.9)	1,509 (92.2)	505 (91.2)	0.499
Beta-blocker*	1,951 (89.0)	1,457 (89.0)	494 (89.2)	0.914
Ca-channel blocker*	127 (5.8)	99 (6.0)	28 (5.1)	0.387
Loop diuretics*	1,757 (80.2)	1,315 (80.3)	442 (79.8)	0.780
Thiazide diuretics*	516 (23.6)	402 (24.6)	114 (20.6)	0.056
MRA*	1,497 (68.3)	1,115 (68.1)	382 (69.0)	0.713
Digitalis*	464 (21.2)	359 (21.9)	105 (19.0)	0.138
Amiodarone*	593 (27.1)	466 (28.5)	127 (22.9)	0.011
Statin*	1,314 (60.0)	995 (60.8)	319 (57.6)	0.184

(Continued)

TABLE 2 | Continued

	All patients ($n = 2,191$)	Males ($n = 1,637$)	Females ($n = 554$)	*p*-value
Allopurinol*	591 (27.0)	475 (29.0)	116 (20.9)	<0.001
Oral anticoagulants	729 (33.3)	598 (36.5)	131 (23.6)	<0.001
Outcome				
1-year all-cause mortality	252 (11.5)	203 (12.4)	49 (8.8)	0.028

**Features included in the machine learning models.*

The value (in parenthesis) after a feature's name indicates the number of patients with available data. If there is no value reported, the given feature was available for all patients. Continuous variables are presented as median (interquartile range), categorical variables as n (%). The comparison between males and females was performed using unpaired Student's t-test or Mann-Whitney U test for continuous variables, Chi-squared or Fisher's exact test for categorical variables, as appropriate.

ACE-I, angiotensin-converting enzyme inhibitors; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CRT-D, cardiac resynchronization therapy defibrillator; DBP, diastolic blood pressure; DM, diabetes mellitus; HF, heart failure; LBBB, left bundle branch block; LVEDD, left ventricular end-diastolic diameter; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association functional class; SBP, systolic blood pressure.

from 0.712 to 0.748 in the training sets and from 0.681 to 0.798 in the test sets suggesting a modest variability in the models' predictive capabilities across the different subsets of patients (**Supplementary Tables 7, 8**).

After sorting the patients in ascending order based on the predicted probability of death and plotting the distribution of probability values, the accumulation of patients who died during the given follow-up period could be observed in the higher risk regions of the plots (**Supplementary Figure 3**). These findings suggest that our models can perform risk stratification effectively.

The Brier score—measuring the accuracy of the probabilistic predictions—for the 1- and 3-year models were 0.197 and 0.201, indicating a sufficiently good calibration of our models. **Supplementary Table 9** summarizes the Brier scores for the remainder of the CIRF models.

Most Important Predictors of Mortality as Assessed Using ML

Leading predictors of all-cause mortality are illustrated in **Figure 4**, and the comprehensive list of feature importances is provided as **Supplementary Tables 10, 11**.

Top Predictors of Mortality in the 1- and 3-Year Cohorts

In the overall study population (including both sexes), the most important predictor of 1-year mortality was serum sodium, which was followed by serum creatinine, hemoglobin concentration, age, and etiology of HF (**Figure 4**). These features were also found among the strongest predictors of 3-year mortality, however, in different order of importance (serum sodium, age at implantation, hemoglobin concentration, serum creatinine, and etiology). Digitalis and type of AF were found to show the most prominent change in their importance from 1 to 3 years (both $p < 0.001$).

Sex-Specific Patterns of Mortality Predictors at 1-Year Follow-Up

We observed several sex-specific differences during the subgroup analysis. In males, the top predictors of 1-year mortality were hemoglobin concentration, serum sodium, serum creatinine, LBBB morphology, and age, whereas, in females, the most important predictors were serum sodium, etiology, LVEF, age, and serum creatinine (**Figure 4**).

The comparison of predictors by sex at 1-year revealed that etiology ($p < 0.001$), LVEF ($p < 0.001$), and treatment with amiodarone ($p < 0.01$) were at least twice as important in females as in males. Moreover, age at implantation and NYHA functional class were also significantly more predictive for 1-year mortality in women compared to men (both $p < 0.001$). Whereas, in males, hemoglobin concentration, type of the implanted device, treatment with allopurinol had significantly higher predictive power than in females (all $p < 0.001$).

Sex-Specific Patterns of Mortality Predictors at 3-Year Follow-Up

In males, the strongest determinants of 3-year mortality were serum sodium, hemoglobin concentration, age at implantation, serum creatinine, and allopurinol, whereas, in females, these features were serum sodium, age at implantation, type of AF, NYHA functional class, and etiology in decreasing order (**Figure 4**).

Regarding females, NYHA functional class, etiology, LVEF, and type of AF exhibited significantly higher predictive power than in men (all $p < 0.001$). In males, features with at least a 2-fold higher importance were loop diuretics ($p < 0.001$), hemoglobin concentration ($p = 0.021$), allopurinol ($p < 0.001$), diabetes ($p < 0.001$), LV lead position ($p < 0.001$) and LBBB morphology ($p < 0.001$).

Longitudinal Changes in the Sex-Specific Patterns of Mortality Predictors

We also identified features with the most prominent changes in importance from 1 to 3 years of follow-up.

Among males, the most prominent increase of feature importance occurred in LV lead position, NYHA class, age, type of AF, hypertension, and digitalis (all $p < 0.001$). The importance of serum creatinine declined significantly ($p = 0.026$).

In females, we observed the greatest increase in the importance of NYHA functional class ($p < 0.001$), type of AF ($p < 0.001$), hypertension ($p < 0.001$), and age at implantation

TABLE 3 | Clinical characteristics of the 3-year cohort.

	All patients ($n = 1,900$)	Males ($n = 1,425$)	Females ($n = 475$)	*p*-value
Demographics, vitals, and key electrophysiological characteristics				
Age, years*	68 (61–74)	68 (60–74)	69 (63–75)	<0.001
Weight, kg (1,280)	80 (70–90)	84 (75–95)	70 (60–80)	<0.001
Height, cm (1,270)	172 (165–177)	175 (170–179)	161 (157–167)	<0.001
BMI, kg/m^2 (1,270)*	27.3 (24.3–30.5)	27.5 (24.7–30.5)	26.5 (23.3–30.5)	<0.001
SBP, mmHg (660)	123 (110–136)	124 (111–136)	122 (110–135)	0.463
DBP, mmHg (660)	72 (65–80)	72 (65–80)	71 (64–80)	0.292
NYHA III/IV (1,568)*	956 (61.0)	719 (61.0)	237 (60.9)	0.984
CRT-D*	1,027 (54.1)	839 (58.9)	188 (39.6)	<0.001
QRS duration, ms (718)	160 (140–180)	160 (142–180)	160 (140–170)	0.035
QRS morphology, LBBB*	1,385 (72.9)	1,000 (70.2)	385 (81.1)	<0.001
LV lead position (1,630)*				
Anterior	75 (4.6)	54 (4.4)	21 (5.2)	
Lateral	1,072 (65.8)	814 (66.3)	258 (64.0)	
Posterior	483 (29.6)	359 (29.3)	124 (30.8)	0.633
Medical history				
Ischemic etiology*	979 (51.5)	802 (56.3)	177 (37.3)	<0.001
History of MI	793 (41.7)	655 (46.0)	138 (29.1)	<0.001
HF duration >18 months*	616 (32.4)	477 (33.5)	139 (29.3)	0.090
History of or current AF*				
No AF	1,181 (62.2)	850 (59.6)	331 (69.7)	
Paroxysmal	306 (16.1)	227 (15.9)	79 (16.6)	
Persistent	49 (2.6)	43 (3.0)	6 (1.3)	
Permanent	364 (19.2)	305 (21.4)	59 (12.4)	<0.001
Valvular heart disease*	131 (6.9)	97 (6.8)	34 (7.2)	0.875
Hypertension*	1,417 (74.6)	1,067 (74.9)	350 (73.7)	0.648
Diabetes mellitus*	704 (37.1)	542 (38.0)	162 (34.1)	0.125
COPD*	288 (15.2)	213 (14.9)	75 (15.8)	0.658
Current smoker*	110 (5.8)	89 (6.2)	21 (4.4)	0.140
Laboratory parameters				
Hemoglobin, g/L (1,254)*	136 (123–148)	139 (125–150)	131 (120–140)	<0.001
Serum sodium, mmol/L (1,180)*	138 (136–141)	138 (136–140)	139 (136–141)	0.020
Total cholesterol, mmol/L (827)	4.1 (3.4–5.1)	4 (3.3–4.9)	4.7 (3.6–5.5)	<0.001
Serum creatinine, μmol/L (1,278)*	102 (82–132)	106 (87–135)	87 (71–113)	<0.001
Urea, mmol/L (1,254)	8.5 (6.4–11.7)	8.8 (6.6–12.0)	7.7 (6.1–10.9)	<0.001
Uric acid, μmol/L (655)	406 (323–494)	409 (329–495)	386 (313–479)	0.082
NT-proBNP, pg/mL (237)	2,758 (1,398–3,570)	2,610 (1,496–3,376)	2,804 (1,290–3,616)	0.931
Echocardiographic parameters				
LV ejection fraction, % (1,378)*	28 (24–32)	28 (23–32)	28 (25–32)	0.185
LVEDD, mL (1,378)*	64 (58–70)	65 (59–71)	61 (56–67)	<0.001
Medications				
ACE-I/ARB*	1,731 (91.1)	1,303 (91.4)	428 (90.1)	0.429
Beta-blocker*	1,691 (89.0)	1,264 (88.7)	427 (89.9)	0.472
Ca-channel blocker*	106 (5.6)	81 (5.7)	25 (5.3)	0.729
Loop diuretics*	1,526 (80.3)	1,153 (80.9)	373 (78.5)	0.257
Thiazide diuretics*	456 (24.0)	354 (24.8)	102 (21.5)	0.137
MRA*	1,270 (66.8)	953 (66.9)	317 (66.7)	0.955
Digitalis*	442 (23.3)	341 (23.9)	101 (21.3)	0.234
Amiodarone*	528 (27.8)	415 (29.1)	113 (23.8)	0.025
Statin*	1,134 (59.7)	862 (60.5)	272 (57.3)	0.214

(Continued)

TABLE 3 | Continued

	All patients (n = 1,900)	Males (n = 1,425)	Females (n = 475)	p-value
Allopurinol*	521 (27.4)	422 (29.6)	99 (20.8)	<0.001
Oral anticoagulants	627 (33.0)	510 (35.8)	117 (24.6)	<0.001
Outcome				
3-year all-cause mortality	615 (32.4)	502 (35.2)	113 (23.8)	<0.001

**Features included in the machine learning models.*

The value (in parenthesis) after a feature's name indicates the number of patients with available data. If there is no value reported, the given feature was available for all patients. Continuous variables are presented as median (interquartile range), categorical variables as n (%). The comparison between males and females was performed using unpaired Student's t-test or Mann-Whitney U test for continuous variables, Chi-squared or Fisher's exact test for categorical variables, as appropriate.

ACE-I, angiotensin-converting enzyme inhibitors; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CRT-D, cardiac resynchronization therapy defibrillator; DBP, diastolic blood pressure; DM, diabetes mellitus; HF, heart failure; LBBB, left bundle branch block; LVEDD, left ventricular end-diastolic diameter; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association functional class; SBP, systolic blood pressure.

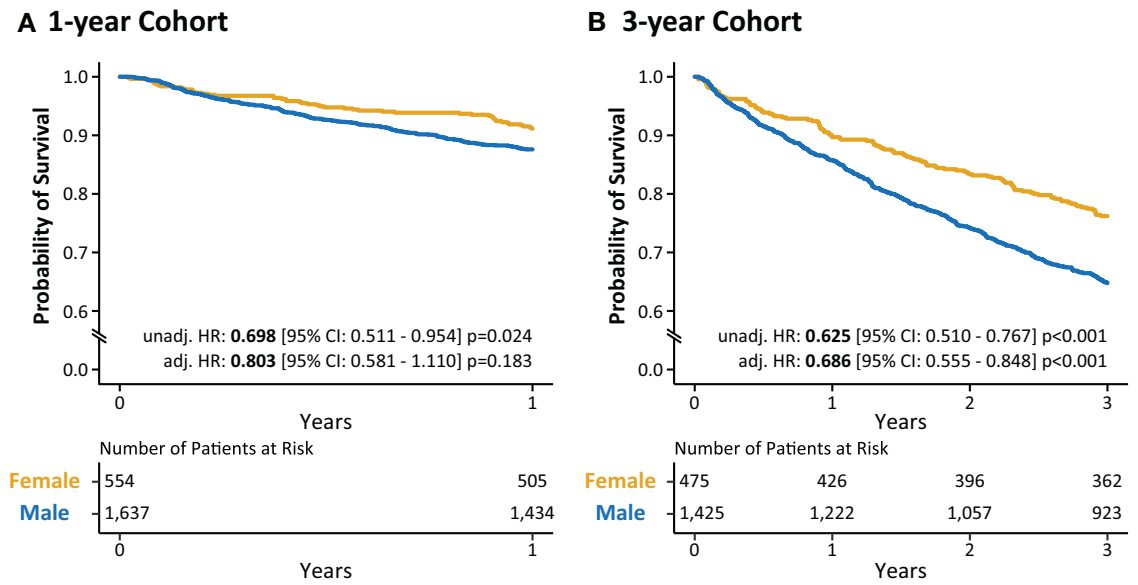

FIGURE 3 | Kaplan-Meier curves for males and females in the 1- **(A)** and 3-year **(B)** cohorts. Kaplan-Meier curve analysis illustrates the difference in the survival of male and female CRT patients during 1- and 3-year follow-up. Cox proportional hazards models were used to compute hazard ratios with 95% confidence intervals. Hazard ratios were adjusted for age (at implantation), QRS morphology, etiology of heart failure, the type of the implanted device, and the type of atrial fibrillation. CI, confidence interval; CRT, cardiac resynchronization therapy; HR, hazard ratio.

($p < 0.014$). Among the top 10 predictors, the most considerable decrease from 1- to 3-year in feature importance was noted in the following factors: serum creatinine, LV end-diastolic diameter, QRS morphology, and amiodarone (all $p < 0.001$).

In-depth Analysis of the Associations Between Top Predictors and Outcomes

The association between the most important predictors and the predicted outcome is visually presented in **Figures 5**, **6**. Older age, higher serum levels of creatinine, lower values of LVEF, serum sodium, hemoglobin concentration, ischemic etiology, non-LBBB morphology, higher NYHA classes, and the history of or current paroxysmal, persistent or permanent AF were associated with a higher predicted probability of 1- and 3-year all-cause mortality. Males exhibited higher values of predicted probability of all-cause death in all examined features compared to females. However, as ML models capture complex, high-level interactions among a multitude of variables, it is challenging to determine the effect of a single feature on the predicted probability of mortality, and the results of univariable analyses should be interpreted with caution.

DISCUSSION

Using data from a single-center cohort of HF patients undergoing CRT implantation, we developed and evaluated ML-based algorithms for the prediction of 1- and 3-year all-cause mortality. The resulting CIRF models demonstrated good discriminatory

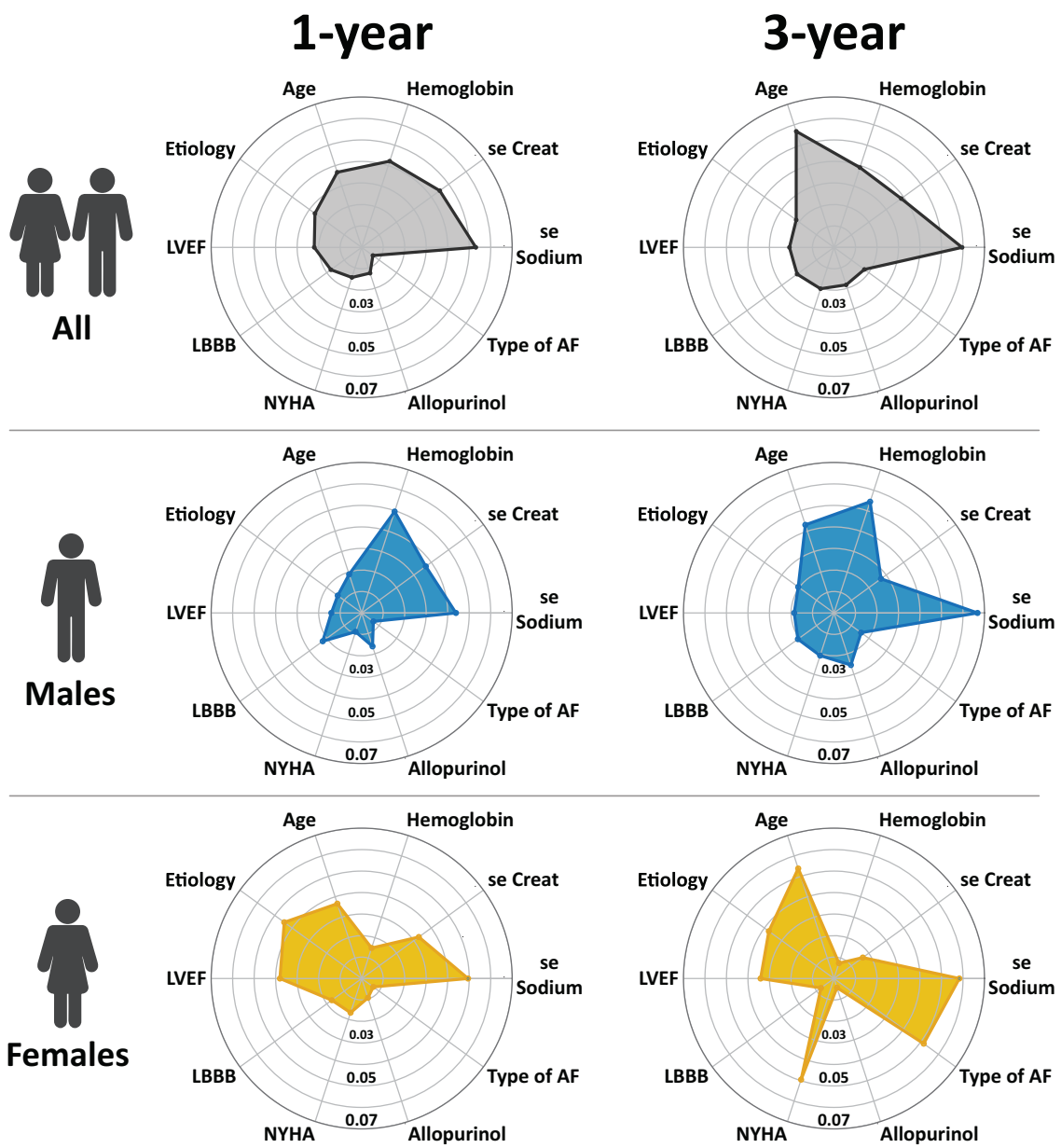

FIGURE 4 | The most important predictors of 1- and 3-year all-cause mortality in patients undergoing CRT implantation. The importance of each feature was quantified with the permutation feature importances method, which measures the importance of a feature by calculating the mean decrease in the model's performance (area under the receiver-operating characteristic curve) after permuting its values 10 times (see text for further details). To keep the data comparable between the different models, we identified the top 5 predictors in each model and took the union of these features; then, we plotted the results on radar charts. AF, atrial fibrillation; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

power in assessing the risk of mortality with an AUC over 0.700 at 1- and 3-year follow-up. Moreover, ML performed substantially well across patient subsets containing exclusively males or females (AUCs ranging from 0.681 to 0.798). Serum sodium, creatinine, hemoglobin, age, and HF etiology were among the most important determinants of short- and mid-term mortality; however, their relative importance varied over time. As expected, female sex was associated with significantly better survival rates in our cohort as well. Sex-specific patterns were also identified in the predictors of mortality. The role of HF etiology (ischemic or non-ischemic), NYHA functional class, and LVEF were more pronounced in females, whereas hemoglobin concentration, QRS morphology, and treatment with allopurinol were notably more predictive for all-cause mortality in males.

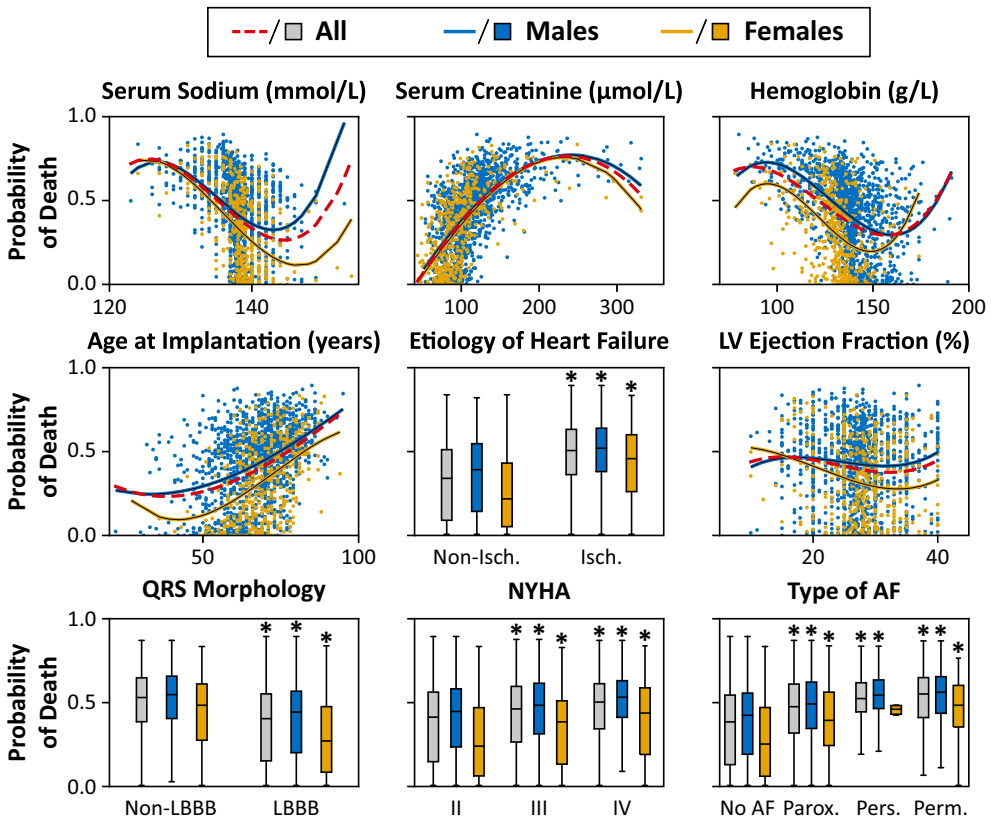

FIGURE 5 | Effect of the most important features on the predicted probability of 1-year all-cause mortality in the training cohorts. The probability of death was calculated for each patient in the training cohort with 10-fold cross-validation. The predicted probability is plotted for each patient, and second-order polynomial trendlines are fitted to their values. *$p < 0.05$ vs. non-ischemic/non-LBBB morphology/NYHA class II/no AF, unpaired Student's *t*-test or Mann-Whitney *U* test. Abbreviations as in **Figure 4**.

Risk Stratification of HF Patients Using ML

The personalized prediction of prognosis is fundamental to patient-centered care, both in optimizing treatment strategies and informing patients as part of shared decision making. For this purpose, an abundance of prediction models has been developed; however, most of them had achieved only modest success, particularly when they were applied in HF populations other than those from which the scores were derived (22, 23). The unsatisfactory results of previous HF risk scores are likely due to multiple causes, including the fact that most of them were created using conventional statistical methods that failed to capture high-dimensional interactions among predictors that bear relevant prognostic information.

In contrast to traditional statistics, ML was explicitly designed to reveal and harness these correlations. Several studies have proved that these advanced data analytic approaches can leverage the complex, higher-level interplay between predictors and outcomes to achieve better discrimination. ML can improve the care of HF patients in various ways, e.g., by augmenting the prediction of readmission after HF hospitalization or by predicting the risk of mortality (16, 17, 19). In HF patients undergoing CRT implantation, our research group has previously confirmed the superiority of ML over pre-existing risk scores (24), and similar results have been reported by others as well (25, 26). Underpinning these findings, we were able to predict the 1- and 3-year mortality of CRT patients with good discrimination and excellent calibration, even in subsets of patients divided by sex. In light of the promising results of our single-center study, we will endeavor to validate our models in external cohorts in a multi-centric manner.

In our analysis, CIRF exhibited the best discriminative ability for predicting both 1- and 3-year mortality. To understand the outstanding performance of tree-based approaches such as CIRF in outcome prediction, an important difference between conventional regression models and tree-based methods should be highlighted. The former favors variables that have a uniform effect across the entire patient population, whereas the latter can uncover variables that might act differently in different patient subgroups. This is essential for personalized prognostication as in an individual patient, the discriminatory power of a given feature may be significantly enhanced or overshadowed by others. Due to this attribute, tree-based methods such as TRF and CIRF are extremely suitable for application as clinical decision-making tools (27).

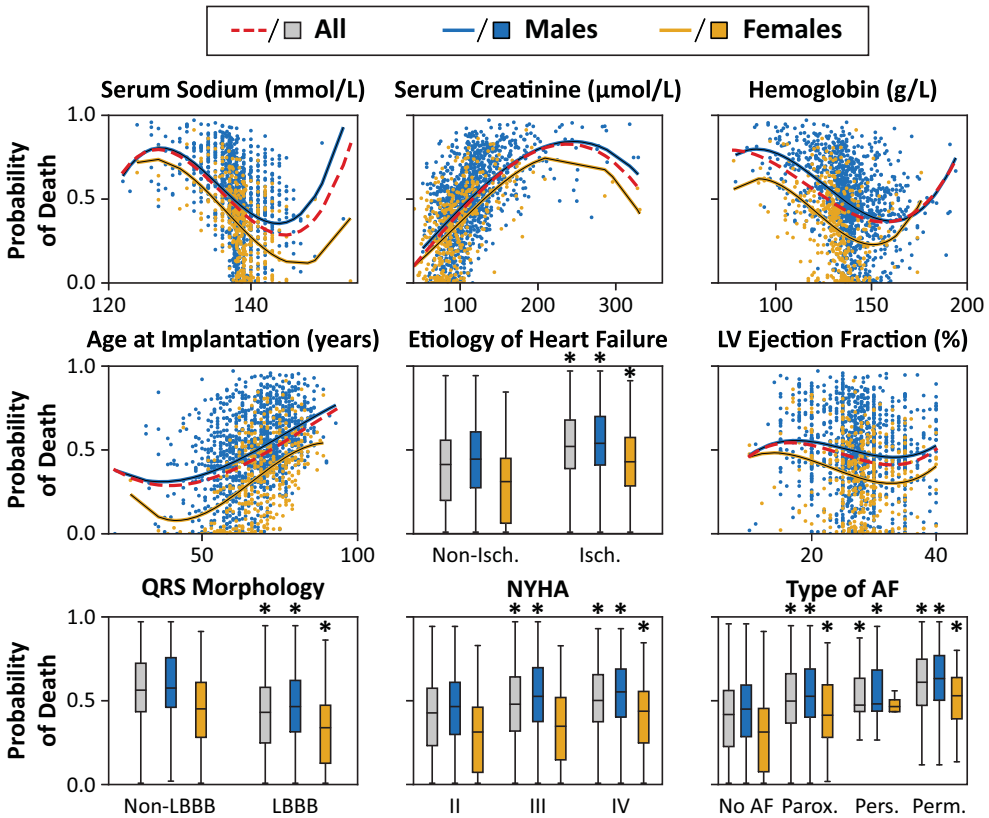

FIGURE 6 | Effect of the most important features on the predicted probability of 3-year all-cause mortality in the training cohorts. The probability of death was calculated for each patient in the training cohort with 10-fold cross-validation. The predicted probabilities are plotted for each patient, and second-order polynomial trendlines are fitted to their values. *$p < 0.05$ vs. non-ischemic/non-LBBB morphology/ NYHA class II/no AF, unpaired Student's *t*-test or Mann-Whitney *U* test. Abbreviations as in **Figure 4**.

Sex-Specific Differences in Outcomes Following CRT Implantation

Sex is increasingly recognized as an important modulator of outcomes in CRT patients, and several studies such as the MADIT-CRT (10), the RAFT (28), or the MASCOT (29) trials have suggested a greater CRT benefit in women. Despite the expanding knowledge about sex-related differences in HFrEF, the reason women benefit more than men from CRT remains unclear (14). Numerous plausible explanations have been proposed, such as the dissimilarities between sexes in the frequency of ischemic cardiomyopathy (30), AF, and comorbidities (9), or the sex-related differences in body height, LV size, and QRS duration (31, 32). In addition, the impact of sex hormones on the pathophysiology of HF or the sex-specific characteristics of pharmacodynamics and pharmacokinetics are also considerable factors (4, 33).

The sex-specific effects of QRS prolongation and morphology on outcomes have been intensively investigated in CRT patients (30, 31, 34–37). Thus, the findings of these studies have prompted calls for sex-specific guideline recommendations regarding the selection of CRT recipients. As women have shorter QRS durations than men in the absence of any conduction delay, they are more likely to exhibit a true LBBB compared to men at shorter QRS duration (38, 39). It has also been reported that among patients with LBBB and non-ischemic etiology, women have electrical dyssynchrony more frequently compared to men at any given QRS duration, and consequently, they would exhibit a better response to CRT (35). According to the study conducted by Beela et al., the interaction between HF etiology and mechanical dyssynchrony seems to represent another important aspect: due to the lower rate of ischemic etiology and the lower extent of scarred myocardium, women have more frequently uncomplicated patterns of LBBB-like mechanical dyssynchrony which is better amendable by CRT (30).

The beneficial effects of CRT also depend on device programming and the percentage of effective biventricular pacing. Notably, that latter significantly varies by sex, and therefore, sex-specific CRT programming has attracted increased attention (40). According to the results of the SMART-AV trial, the optimization of atrioventricular delay intervals is associated with improved outcomes in women but not in men (41), which might be attributable to the inherent sex-related differences in atrial geometry and PR intervals. A higher percentage of biventricular pacing has also been reported in women (29, 41, 42),

most probably due to the lower rate of atrial fibrillation compared to men (43, 44). This could also contribute to the observed differences in mortality between sexes as even a small increment in the biventricular pacing rate may improve outcomes (45).

Although there are still many open questions, it is clear that multiple intercorrelated factors contribute to this phenomenon. Therefore, during the search for answers, ML-based approaches may come in handy, as they are particularly helpful in uncovering hidden patterns in large datasets by simultaneously interpreting predictors even in the presence of complex, non-linear interactions.

Sex-Specific Patterns in Mortality Predictors

Given the sex-related differences in the anatomy and physiology of the cardiovascular system, encountering dissimilarities in the importance of prognostic predictors between males and females is to be expected in CRT patients. Nevertheless, there is only a limited number of publications dedicated to the thorough exploration of this topic. To the best of our knowledge, our study is the first that evaluated the sex-related differences and similarities in mortality predictors of CRT patients using ML. In our analysis, we observed significant variations in the importance of several predictors such as HF etiology, NYHA functional class, LVEF, and AF between sexes, to name a few.

Utilizing the tools of conventional statistics, the sex-specific prognostic value of HF etiology has been previously investigated in large cohorts of HFrEF patients. In the MAGGIC meta-analysis, the ischemic etiology appeared to attenuate the protective effect of female sex on prognosis (46). In addition, ischemic cardiomyopathy and the extent of myocardial scar were found to be significant predictors of mortality in females but not in males among CRT patients (30). In line with this evidence, the paramount importance of HF etiology in women was proved in our study as well.

When analyzing the interaction between sex and different covariates in the prediction of survival after CRT implantation, Beela et al. reported that NYHA class was a significant predictor in males only (30). Moreover, among HFrEF patients, NYHA class had a more prominent prognostic value in men than in women (3). Contrary to these findings, a stronger association of NYHA functional class with outcomes was observed in females in our current analysis and the BEST trial as well (47).

Another well-established prognostic factor is LVEF, whose interaction with sex in the prediction of all-cause death has been demonstrated in CRT patients (30). Complementing these findings and the results of the BEST trial (47), we have also demonstrated that LVEF is a stronger predictor of prognosis in women than in men.

In HFrEF patients, most studies agree on the prognostic value of AF; however, there is some inconsistency regarding its exact role as some investigations attribute more prognostic impact to AF in females (47), whereas others observed comparable predictive power in males and females (3, 30). Our results support the former as we found AF to have a more prominent effect on outcomes in females.

According to our analysis, the prognostic relevance of hyponatremia and renal function should also be emphasized in CRT patients. Our results are in accordance with the findings of Zusterzeel et al., who reported that despite being significant determinants in both sexes, serum creatinine and hyponatremia appeared to be stronger predictors in women than in men (34).

Lately, the interplay between sex and diabetes in HFrEF patients has attracted increased attention among researchers. Confirming the findings of the MAGGIC (46), the recently published analysis of the ASIAN-HF registry demonstrated that diabetes is coupled with a greater risk of adverse outcomes in women than in men (48). In contrast, diabetes was associated with a higher risk of all-cause death or HF hospitalization in males in the Swedish HF Registry (3), and it was proven to be a significant predictor only in men in the BEST trial (47). Interestingly, in our study, diabetes was not ranked among the top five predictors in any of the analyzed patient subsets, and we detected inter-sex differences in its importance only at 3-year follow-up.

Some of our findings coincide with those of previous studies, whereas some others may not. These apparent discrepancies might be partly attributable to the fact that most studies applied Cox proportional hazards regression, whereas we utilized an entirely different methodology that captures other aspects of associations between risk factors and outcomes. Although the exact reasons behind these contradicting results should be clarified in further investigations, our findings underscore the necessity of sex-specific approaches in the management of HFrEF patients.

Limitations

Despite the highlighted advantages, there are a few limitations to be acknowledged. First, our study represents results from a single center. As we were aware of this limitation, we performed hyperparameter tuning with 10-fold cross-validation in the training cohorts, and we also tested our models in statistically independent test cohorts to enhance generalizability. Nonetheless, as the next step, the robustness of our models should be tested in external populations as well. Second, the utilized database bears the inherent limitations of retrospective data collection, such as the higher proportion of missing data (compared to prospective trials) and the heterogeneity partly attributable to the changes in guideline recommendations over the years. However, the use of such real-world data holds the potential for better generalizability. Third, our models use baseline (pre-implant and procedural) variables without incorporating the time-varying values of these parameters. Although a dynamic model integrating values of the same parameter from multiple time points may be superior, in the present study, we aimed to predict 1- and 3-year mortality using clinical data that could be acquired at device implantation. Finally, there may remain additional domains of variables (e.g., imaging data, novel biomarkers, genetics, or quality of life questionnaires) that could further improve the predictive capability of our models. Future work should explore the addition of such features to enhance the models proposed in the present study.

CONCLUSIONS

Using advanced ML techniques in combination with easily obtainable clinical features, our models effectively predicted 1- and 3-year all-cause mortality in patients undergoing CRT implantation. ML also exhibited good discriminative ability in patient subsets containing males or females exclusively. Moreover, sex-specific patterns of mortality predictors were identified, which also changed over time. These models lay the foundation stone for future testing of their clinical utility as decision support tools to optimize candidate selection and to improve the prognostication of CRT patients.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Regional and Institutional Committee of Science and Research Ethics (Approval No. 161/2019). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR'S NOTE

A part of the results was presented at the Ph.D. Scientific Days (2020) of the Semmelweis University and at the annual scientific congress of the European Society of Cardiology (ESC Congress 2020—The Digital Experience).

AUTHOR CONTRIBUTIONS

MT participated in the conceptualization and designing of the study, implemented the machine learning models and analyzed the data, interpreted the results, and was a major contributor to writing the manuscript. AB was a major contributor to data collection, participated in the interpretation of results, reviewed the literature, and thoroughly reviewed the manuscript. EM participated in data collection, helped in reviewing the literature, and reviewed the manuscript. AKov participated in the conceptualization and designing of the study and critically reviewed the manuscript. ZT made a major contribution to the conceptualization of the study, supervised the machine learning model development, and participated in the interpretation of the results. AS and MC participated in the machine learning model development and helped in the interpretation of the results. BL participated in the interpretation of results, helped in the literature review, and critically reviewed the manuscript. WS contributed to data collection and critically reviewed the manuscript. AKos made a major contribution to the conceptualization of the study and supervised data collection and study execution. BM provided the institutional background of the research, supervised the study execution, and thoroughly reviewed the manuscript. All authors read and approved the final version of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2021.611055/full#supplementary-material

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Influence of Gender in Advanced Heart Failure Therapies and Outcome Following Transplantation

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Biological differences between males and females change the course of different diseases and affect therapeutic measures' responses. Heart failure is not an exception to these differences. Women account for a minority of patients on the waiting list for heart transplantation or other advanced heart failure therapies. The reason for this under-representation is unknown. Men have a worse cardiovascular risk profile and suffer more often from ischemic heart disease. Conversely, transplanted women are younger and more frequently have non-ischemic cardiac disorders. Women's poorer survival on the waiting list for heart transplantation has been previously described, but this trend has been corrected in recent years. The use of ventricular assist devices in women is progressively increasing, with comparable results than in men. The indication rate for a heart transplant in women (number of women on the waiting list for millions of habitants) has remained unchanged over the past 25 years. Long-term results of heart transplants are equal for both men and women. We have analyzed the data of a national registry of heart transplant patients to look for possible future directions for a more in-depth study of sex differences in this area. We have analyzed 1-year outcomes of heart transplant recipients. We found similar results in men and women and no sex-related interactions with any of the factors related to survival or differences in death causes between men and women. We should keep trying to approach sex differences in prospective studies to confirm if they deserve a different approach, which is not supported by current evidence.

Keywords: gender, female, heart transplantation, outcome, women, advanced heart failure, ventricular assist device

INTRODUCTION

There is a growing interest in sex-related differences in several clinical scenarios. Men and women differ in body composition and physiology; they present differences in pharmacokinetics and pharmacodynamics; and they may also respond differently to cardiovascular drugs. Women are underrepresented in most clinical trials, and real-life data have shown that they are less often treated with evidence-based therapies and experience adverse drug reactions more often (1). The reason for these differences between men and women is beyond the scope of the present study. Still, a better knowledge of these sex-related differences may be helpful to improve patient care.

Most heart failure (HF) patients are female. Women have a different clinical profile than men (2); they develop end-stage HF at an older age, have a higher prevalence of HF with preserved ejection fraction and a lower prevalence of ischemic heart disease (IHD) (3–5). HF prognosis seems to be better in women with a lower rate of premature death than men (4). Moreover, in HF with reduced ejection fraction, women seem to have a better response to treatment, with a more favorable reverse remodeling regardless of the cause and severity of the left ventricle systolic dysfunction (5). In the field of advanced HF, the underrepresentation of women among heart transplant (HT) or ventricular assist devices (VAD) recipients has been attributed to selection and referral bias and potentially poorer outcomes for these therapies. However, whether the described better outcomes in women with HF may also explain this under-representation in advanced heart failure stages has not been explored.

The majority of the studies in the field of heart transplantation (HT) are focused on donor-recipient mismatch (6–8). However, sex-related differences in patients on the waiting list for an HT or ventricular assist device and long term survival after an HT have been addressed recently. We aim to review those topics and look for sex-related differences in 1-year outcomes after an HT in an extensive nationwide registry to elucidate possible gaps that may need further investigation in the future.

MATERIALS AND METHODS

Data Source

The Spanish Heart Transplant Registry is a prospective database promoted by the Heart Failure Working Group of the Spanish Society of Cardiology, containing detailed clinical information about all HT procedures performed in our country from 1984 to the present. The registry is updated yearly with data supplied by all transplant centers in the country (9). The Ethics Committees of all participating centers have approved the Spanish Heart Transplantation Registry for investigational purposes.

For the present study, we included all patients aged ≥18 years who underwent an HT in Spain from January 1, 2005 to December 31, 2019. Vital status at the end of follow-up and cause of death (when applicable) was known for all participants. The cause of death was locally adjudicated in each participating center. We excluded recipients of a second HT and multiorgan recipients.

Abbreviations: DCM, Dilated cardiomyopathy; HF, Heart Failure; HT, Heart transplant; IHD, ischemic heart disease; VAD, Ventricular assist device.

Missing Data

Missing data (**Supplementary Table 1**) were handled by multiple imputations using the wholly conditional specification method, generating 10 imputed datasets using all applicable adjustment variables and the outcome variable as predictors. The average of the 10 imputed data sets was used for analysis. For imputation, categorical and continuous variables were modeled using logistic regression and linear regression, respectively.

Statistical Analysis

Quantitative variables were summarized as median (interquartile range), and the Mann-Whitney *U*-test assessed between-sex differences. Categorical variables were summarized as percentages, with Chi-squared or Fisher's exact tests, as appropriate, for between-sex comparisons.

The primary outcome was 1-year all-cause mortality or re-transplantation. The associations between baseline population characteristics and outcome were fitted by the use of Cox proportional hazards regression. Multivariable adjustment included the recipient's sex and those variables with a significance level <0.10 in the univariable analysis. To further explore possible differences between men and women, additional multivariable models were considered to include the interaction between the recipient sex and each variable that reached statistical significance in the final multivariable analysis.

All statistical tests were 2-sided, and a p-value <0.05 was considered significant. All analyses were performed using the SPSS 25.0 (SPSS Inc., Chicago, IL).

RESULTS

A total of 3,616 HT procedures were performed in 16 HT centers during the study period. We identified 869 female recipients (24%). Sex-stratified baseline characteristics of the study population are shown in **Table 1**.

Women were significantly younger, and had a lower body mass index and predicted heart mass than men. They also presented with history of neoplastic disease more often.

Men had a poorer cardiovascular risk profile assessed as a higher prevalence of hypertension and diabetes, and triple the prevalence of peripheral artery disease. They also had two times the prevalence of chronic obstructive pulmonary disease. Men had undergone previous cardiac surgery more frequently than women.

HT indication was mainly due to IHD in men. Conversely, in women, HT's leading cause was dilated cardiomyopathy (DCM), followed by other etiologies (valvular heart disease, congenital heart disease, hypertrophic cardiomyopathy, restrictive cardiomyopathy, and myocarditis).

Urgent HT and mechanical circulatory support (VAD and intra-aortic balloon pump) were more frequent in men. Abnormal bilirubin levels and active infection at the moment of HT were also more frequent in men.

TABLE 1 | Characteristics of the study cohort stratified by gender.

	Female ($n = 869$)	Male ($n = 2,747$)	P-value
Recipient			
Age (years)	54.0 (43.0, 61.0)	57.0 (49.0, 63.0)	<0.001
Etiology (%)			<0.001
Dilated	38.7	36.4	
Ischemic	22.8	45.0	
Others	38.6	18.6	
Predicted heart mass (*g*)	126.8 (118.1, 138.2)	176.0 (164.5, 189.2)	<0.001
Body mass index (Kg/m^2)	24.0 (21.3, 27.6)	25.5 (23.4, 28.2)	<0.001
Diabetes (%)	12.1	23.3	<0.001
Hypertension (%)	23.2	38.9	<0.001
COPD (%)	6.1	12.2	< 0.001
Peripheral vascular disease (%)	2.6	7.8	<0.001
Pretransplant malignancy (%)	8.5	4.1	<0.001
GFR (ml/min/1.73 m^2)	71.1 (51.4, 95.0)	71.3 (52.8, 94.5)	0.64
GFR < 45 mL/min/1.73 m^2	17.6	15.0	0.08
CMV serology positive	82.3	80.0	0.15
Bilirubin >2 mg/dL	15.3	18.9	0.02
Pulmonary vascular resistance (WU)	2.0 (1.3, 2.9)	2.0 (1.3, 2.8)	0.42
Pre-transplant cardiac surgery (%)	25.3	29.2	0.03
Pre-transplant infection (%)	10.4	14.8	0.001
Pre-transplant mechanical ventilation (%)	15.5	14.4	0.44
Pre-transplant circulatory support (%)			0.002
None	71.1	65.6	
IABP	11.1	13.0	
ECMO	8.1	7.3	
VAD	9.7	14.1	
Recipient location (%)			0.08
Home	56.0	52.5	
Hospital ward	11.4	10.7	
Intensive care unit	32.6	36.8	
Surgical procedure			
Urgent transplant (%)	33.8	37.9	0.03
Cold ischemic time (min)	210.0 (153.3, 240.0)	205.0 (155.0, 245.0)	0.94
Surgical technique (bicaval) (%)	61.0	64.3	0.08
Transplant era			0.34
2005–2009	31.4	33.7	
2010–2014	30.1	30.3	
2015–2019	38.4	36.0	
Donor			
Age (years)	45.0 (34.0, 53.0)	44.0 (32.0, 52.0)	0.11
Gender (female)	57.3	28.7	<0.001
Predicted heart mass (g)	139.3 (129.0, 152.0)	184.0 (169.5, 199.0)	<0.001
Body mass index (Kg/m^2)	24.4 (22.5, 26.7)	26.0 (24.0, 28.4)	<0.001
CMV serology positive	74.4	72.3	0.25
Cause of death (%)			0.02
Trauma	24.2	29.0	
CVD	49.3	46.7	
Other	26.6	24.3	
Donor/recipient interaction			
Donor/recipient gender mismatch (%)	42.7	28.7	<0.001

(Continued)

TABLE 1 | Continued

	Female ($n = 869$)	Male ($n = 2,747$)	*P-value*
Donor/recipient predicted heart mass ratio	1.09 (1.00, 1.12)	1.03 (0.96, 1.13)	<0.001
Donor/recipient CMV serology mismatch (%)	34.9	36.2	0.81
Donor/recipient BMI ratio	1.00 (0.89, 1.16)	1.01 (0.91, 1.14)	0.31

COPD, Chronic Obstructive Pulmonary Disease; GFR, Glomerular Filtration Rate; CMV, cytomegalovirus; WU, wood units; IABP, Intraaortic balloon pump; ECMO, extracorporeal membrane oxygenator; VAD, ventricular assist device; CVD, cerebrovascular disease.

Although women received grafts from female donors who had a lower body mass index and predicted heart mass more often, donor/recipient sex mismatch was more frequent. Consequently, donor/recipient predicted heart mass ratio was higher.

Median follow-up was 1.01 years (interquartile range 0.71–1.01). Results of the univariate and multivariate Cox regression analysis are summarized in **Table 2**. Variables related to impaired survival included recipient age, higher body mass index, diabetes mellitus, bilirubin of >2 mg/dl, pre-HT infection, previous cardiac surgery, need for mechanical ventilation at the moment of HT, mechanical circulatory support at the time of HT, recipient location in the Intensive Care Unit, urgent transplant, cold ischemic time, female donor and donor/recipient sex mismatch, and donor/recipient body mass index ratio. Higher glomerular filtration rate, bicaval surgical technique, and HT in the recent period (2015–2019) were related to a better outcome. After multivariate analysis, body mass index and diabetes of the recipient lost statistical significance as did any type of mechanical circulatory support at the time of HT, recipient location at the time of HT, urgent status, female donor, and donor-recipient body mass index.

In the final model, variables independently related to reduced survival were recipient age, history of previous cardiac surgery, bilirubin of >2 mg/dl, pre-HT infection, need for mechanical ventilation at the moment of HT, cold ischemic time, and donor/recipient sex mismatch. Higher glomerular filtration rate, bicaval surgical technique, and HT in the recent period (2015–2019) were independently associated with a better prognosis.

Women and men had a similar 1-year survival (women 76.4 vs. 78.6% men $p = 0.34$) by adjusted Kaplan-Meier analysis (**Figure 1**). We did not find any differences in the cause of death between men and women (**Figure 2**).

We did not find any interaction between sex and variables independently related to survival in the multivariate analysis (**Table 3**).

DISCUSSION

Advanced heart failure affects 1–10% of the overall HF population and implies a severe decline in patients' quality of life and survival. The Heart Failure Association of the European Society of Cardiology has recently updated diagnostic criteria. It focuses on patient referral to advanced HF centers and a proper transition of patients to palliative care (10). Although there are interesting HF registries to gather information about HF patients' clinical parameters and characteristics and their therapies, the advanced heart failure population is somehow challenging to study and scarcely described in the literature. Gender differences in HF patients have been previously described, but their clinical implications remain unclear. A better knowledge of the sex-related differences appears as a potential field of improvement in the diagnosis, treatment, and likely prognosis of HF patients. The more significant publications addressing sex differences in advanced HF patients (waiting-list, HT, and VAD) are summarized in **Table 4**.

Previous studies with a small sample of patients showed a worse survival rate for women on the waiting list for HT (19). Several analyses of the Scientific Registry of Transplant Recipients of the United States of America have assessed the same topic. Hsich et al. in 2014 analyzed sex differences in patients listed for HT in 10 years (2000–2010) stratified by severity of illness (1A, high risk; 1B, intermediate risk; and 2, low-risk ambulatory patients) and adjusted by baseline characteristics. Women accounted for 25% of the study population, and they had a higher mortality rate than men in urgent status (1A) but a lower mortality rate than men in an elective ambulatory setting (status 2). No differences were observed in the intermediate-risk status 1B (11). Women were younger and had a non-ischemic cardiomyopathy more often, and men had a worse cardiovascular risk profile, and IHD was the leading cause for HF. The same authors tried to confirm these sex differences in a more recent period (2004–2015) and attempted to identify factors associated with waiting-list mortality and transplantation timing. Although similar differences in mortality were observed between 2004 and 2008 (higher mortality in woman in status 1A and 1B and lower in status 2), in the most recent years, some of them were solved, and women had a similar survival in urgent status (1A) and elective status (2). They also identified many sex interactions for death and HT that varied with prioritization on the waiting list that should be addressed as a new field to understand these differences between men and women (12). Improvements in the risk of death or deterioration in women waiting for HT have also been observed in other studies (20).

There is also available information about sex-related differences in VAD therapy. As expected, baseline characteristics and underlying comorbidities and etiologies differed between men and women as it has been described for studies of patients on the HT waiting list. An analysis of the European Registry for Patients with Mechanical Circulatory Support showed that

TABLE 2 | Uni- and multivariate Cox regression analysis of 1-y survival.

	Univariate			Multivariate		
	HR	**CI (95%)**	***P*-value**	**HR**	**CI (95%)**	***P*-value**
Recipient						
Female gender	1.11	0.94–1.30	0.21	1.15	0.97–1.36	0.10
Age (years)	1.01	1.01–1.02	<0.001	1.01	1.00–1.02	0.005
Predicted heart mass (g)	1.00	1.00–1.00	0.59			
Body mass index (Kg/m^2)	1.02	1.00–1.04	0.02	1.01	0.97–1.03	0.68
Etiology						
Dilated	1					
Ischemic	1.11	0.94–1.30	0.22			
Other	1.16	0.97–1.40	0.11			
Diabetes	1.18	1.00–1.40	0.05	1.11	0.93–1.33	0.23
Hypertension	1.13	0.98–1.32	0.10			
COPD	1.09	0.87–1.36	0.48			
PVD	1.20	0.92–1.56	0.18			
GFR (mL/min/1.73 m^2)	0.99	0.99–0.99	<0.001	0.99	0.99–1.00	<0.001
CMV serology positive	1.10	0.92–1.33	0.29			
Bilirubin >2 mg/dL	1.49	1.25–1.78	<0.001	1.35	1.13–1.61	0.001
PVR (Wood U.)	1.05	1.00–1.11	0.08	1.02	0.97–1.08	0.42
Pre-transplant infection	1.60	1.34–1.92	<0.001	1.34	1.10–1.63	0.004
Pre-transplant cardiac surgery	1.32	1.14–1.53	<0.001	1.22	1.04–1.43	0.02
Mechanical ventilation	2.00	1.70–2.37	<0.001	1.64	1.32–2.05	<0.001
Pre-transplant circulatory support						
None	1			1		
IABP	1.45	1.18–1.77	<0.001	1.10	0.88–1.37	0.41
ECMO	1.69	1.34–2.15	<0.001	1.20	0.89–1.63	0.23
VAD	1.39	1.14–1.71	0.001	1.21	0.94–1.57	0.15
Recipient location[a]						
Home	1					
Hospital ward	1.15	0.90–1.46	0.27			
Intensive care unit	1.57	1.35–1.82	<0.001			
Pre-transplant malignancy (%)	1.19	0.89–1.61	0.24			
Surgical procedure						
Urgent transplant	1.51	1.31–1.74	<0.001			
Cold ischemic time (min)	1.00	1.00–1.00	<0.001	1.00	1.00–1.00	<0.001
Surgical technique (bicaval) (%)	0.78	0.68–0.90	0.001	0.85	0.73–0.99	0.03
Transplant era						
2005–2009	1			1		
2010–2014	0.90	0.76–1.07	0.24	0.91	0.77–1.09	0.30
2015–2019	0.72	0.61–0.86	<0.001	0.70	0.58–0.85	<0.001
Donor						
Age (years)	1.00	1.00–1.01	0.22			
Gender female[a]	1.20	1.07–1.34	0.001			
Predicted heart mass (g)	1.00	1.00–1.00	0.33			
Body mass index (Kg/m^2)	0.99	0.98–1.01	0.50			
Cause of death						
Trauma	1					
CVD	0.95	0.81–1.13	0.56			
Other	1.00	0.83–1.21	0.99			
CMV serology positive	0.88	0.75–1.04	0.12			
Donor/recipient interaction						

(Continued)

TABLE 2 | Continued

	Univariate			Multivariate		
	HR	**CI (95%)**	***P*-value**	**HR**	**CI (95%)**	***P*-value**
Donor/recipient gender mismatch	1.16	1.00–1.34	0.049	1.22	1.05–1.42	0.01
Recipient/Donor CMV mismatch						
No	1					
Donor (−)/recipient (+)	1.14	0.96–1.37	0.14			
Donor (+)/recipient (−)	0.91	0.73–1.15	0.43			
Donor/recipient predicted heart mass ratio	0.92	0.55–1.54	0.75			
Donor/recipient body mass index ratio	0.65	0.45–0.95	0.02	0.80	0.50–1.28	0.35

HR, Hazard ratio; CI, Confidence interval; COPD, Chronic obstructive pulmonary disease; CVD, cerebrovascular disease; ECMO, extracorporeal membrane oxygenator; GFR, glomerular filtration rate; IABP, intra-aortic balloon pump; PVD, peripheral vascular disease; PVR, pulmonary vascular resistance; VAD, ventricular assist device.

[a] *Urgent transplant, recipient location, and donor sex were not included in the multivariate model due to collinearity with Pre-transplant Circulatory Support and recipient and donor sex.*

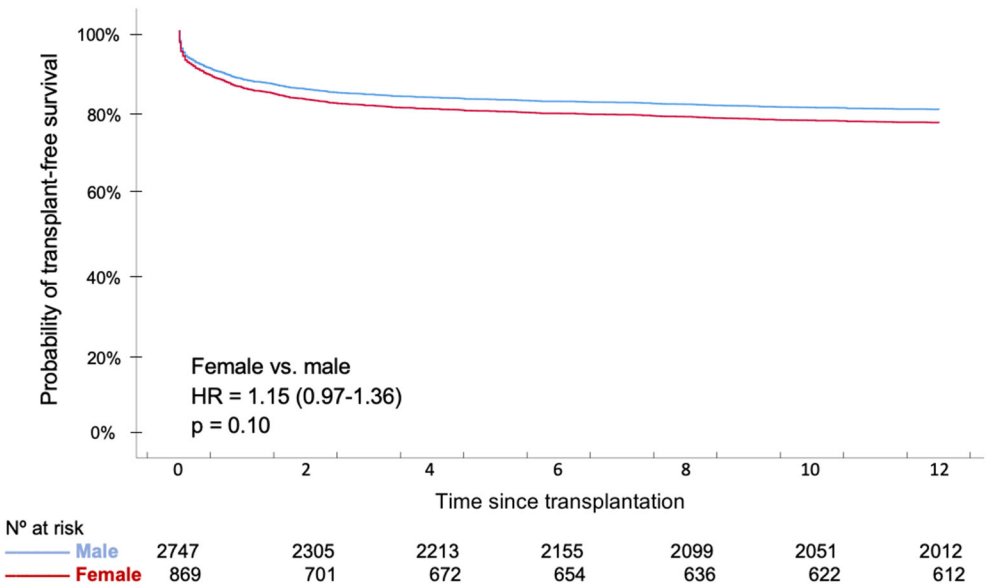

FIGURE 1 | Adjusted 1-year survival curves according to recipient sex.

only 15% of patients receiving a VAD were women. HT rates were similar for men and women. However, women were at a more advanced stage at the moment of implantation, presented a higher rate of significant bleeding, arrhythmias, and right ventricular failure, and had a worse prognosis than men (13). Two studies in the United States of America also showed a lower use of VAD in women, although slightly higher than in the European Registry (21–23%). This higher percentage of women undergoing a VAD implantation might be explained by the inclusion of patients listed in a more recent time-lapse. Increasing use of VAD therapy in women throughout the observation period is described. Both American registries represent conflicting results on survival. The former is focused on in-hospital survival and showed similar survival for men and women (15). The latter evaluated more extended follow-up periods and described lower HT rates and a lower survival in women (14). In both registries, women presented with a more severe HF, but a similar adverse event rate. Those differences in outcomes may reflect different follow-up times and, thus, different rates of adverse events in men and women after perioperative period.

Several factors might play a role in sex-related differences in HT outcomes: the higher frequency of anti-HLA antibodies detection in women, differences in predicted heart mass as a critical factor in donor-recipient matching, and variability in clinical presentation men and women (21, 22). The New Heart study was the first one to address this topic. They found a similar survival for HT in women, who represented 28% of the analyzed population. Conversely, women were younger and developed graft rejection and needed hospitalization more often than men (16). An analysis of the International Society of Heart and Lung Transplantation Registry, in which 23.7% of included patients were women, also showed similar survival rates after adjusting by recipient and donor risk scores but suggested a higher mortality

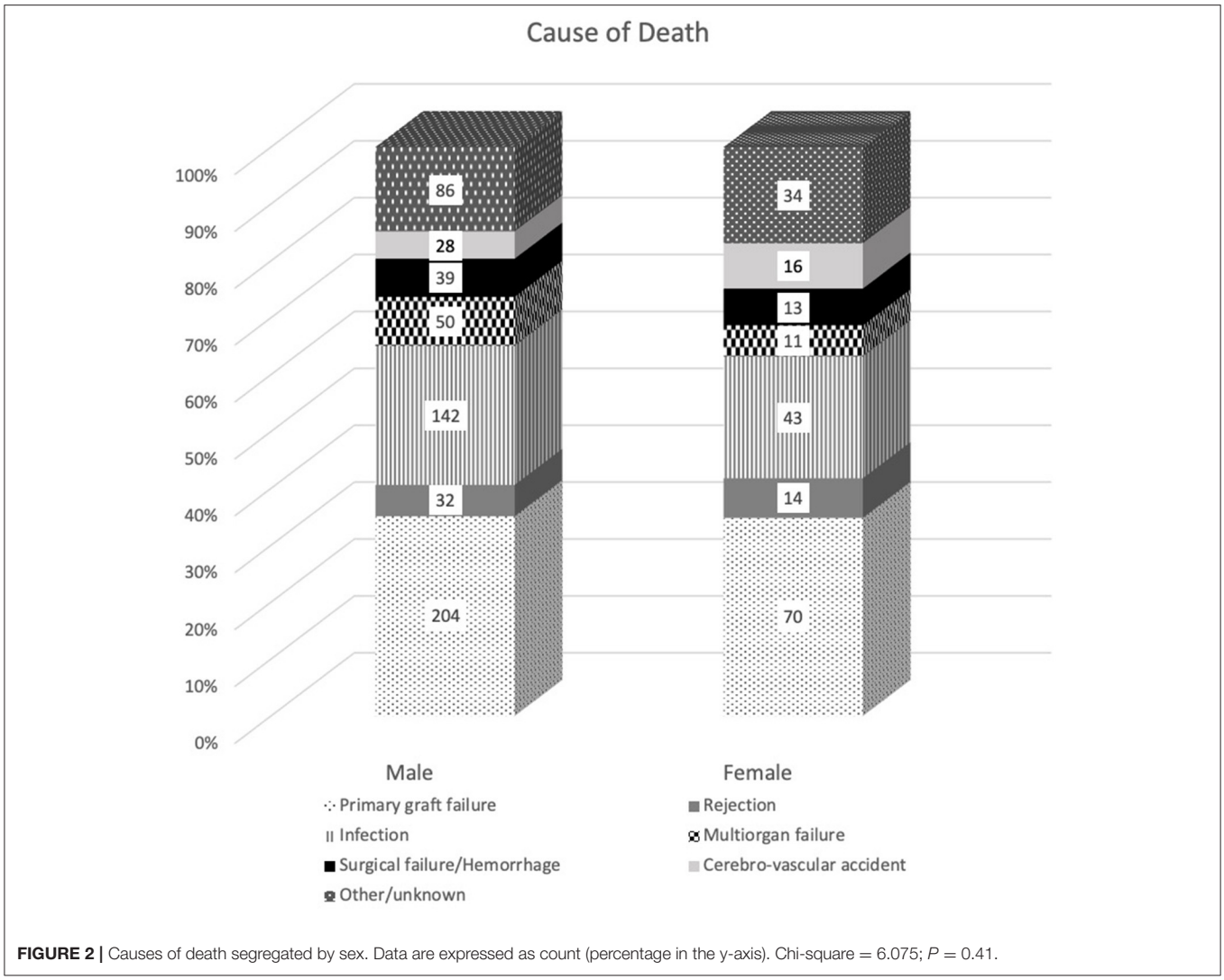

FIGURE 2 | Causes of death segregated by sex. Data are expressed as count (percentage in the y-axis). Chi-square = 6.075; $P = 0.41$.

TABLE 3 | Analysis of interactions between recipient gender and significant variables in multivariate analysis.

Variable	Recipient female gender			Interaction recipient sex * variable		
	HR	CI (95%)	*P*-value	HR	CI (95%)	*P*-value
Recipient age	0.83	0.36–1.90	0.66	1.01	0.99–1.02	0.46
GFR (mL/min/1.73 m^2)	1.01	0.64–1.60	0.95	1.00	0.99–1.01	0.64
Bilirubin >2 mg/dL	1.08	0.89–1.30	0.43	1.21	0.81–1.79	0.35
Pre-transplant infection	1.07	0.89–1.28	0.49	1.34	0.89–2.04	0.17
Pre-transplant cardiac surgery	1.08	0.88–1.31	0.47	1.14	0.81–1.61	0.46
Mechanical ventilation	1.11	0.92–1.34	0.30	1.06	0.73–1.54	0.76
Bicaval surgical technique	1.22	0.95–1.55	0.12	0.87	0.62–1.20	0.39
Cold ischemic time	0.81	0.46–1.44	0.47	1.00	1.00–1.00	0.24
Transplant era	1.04	0.79–1.37	0.76			
2010–2014				1.20	0.81–1.77	0.37
2015–2019				1.05	0.70–1.56	0.81
Donor/Recipient gender mismatch	1.11	0.89–1.38	0.35	1.03	0.74–1.43	0.88

GFR, glomerular filtration rate.

TABLE 4 | Summary of recent publications addressing gender differences in patients on the waiting for a heart transplant, receiving a long term ventricular assist device, or heart transplant recipients.

Publication	Population	Period	Analysis	Conclusions
Hsich et al. (11)	28852 PWL 24% women (SRTR)	2000–2010	Propensity Score Long term survival	Women higher risk in urgent status Similar results in intermediate status in men and women Men higher risk in elective status
Hsich et al. (12)	33069 PWL 25% women (SRTR)	2004–2015	3 year survival Random survival forest	Higher risk in urgent and intermediate status in women, similar in recent period Higher risk in elective status in men Multiple interactions between sex in different status
Magnussen et al. (13)	966 VAD (75% BTT) 15% women (EUROMACS)	2011–2014	1–2-year survival	Similar HT rates Women worse survival Women sicker at implant Women higher major bleeding, arrhythmias, and RV failure
DeFilippis et al. (14)	13305 VAD 20.8% women (UNOS)	2008–2018	Propensity Score 1-2-year survival	Increase in VAD use among decade (lower in women) Women sicker at implant, similar complications Women lower HT rate and survival
Ahmed et al. (15)	3511 VAD 23.3% women (NIS)	2009–2014	Propensity Score In hospital survival	Similar survival Similar complications VAD in females have doubled lately
Hickey et al. (16)	345 HT 28% women NEW HEART study	2011–2015	1-year survival	Similar survival Women younger Women more rejection episodes and hospitalizations
Moayedi et al. (17)	34198 HT 23.7% women (ISHLTR)	2004–2014	Propensity Score Adjusted IMPACT / DRI Long-term survival	Similar survival Lowest survival in undersized donors Women higher mortality in regular sized donors
García-Cosío et al. (18)	6740 HT 20.6% women (SHTR)	1997–2017	Temporal trends Transplant rate pmh Long term survival	Similar survival Similar HT pmh in women among 25 years (lower in men) Women died due to rejection and primary graft failure Men died due to malignancies
Current series	3616 HT 24% women (SHTR)	2005–2019	1-year survival	Similar survival

PWL, Patients on the waiting list; SRTR, USA Scientific Registry of Transplant Recipients; VAD, long term ventricular assist device; BTT, bridge to transplantation; EUROMACS, European Registry for Patients with Mechanical Circulatory Support; HT, Heart transplant; RV, right ventricle; UNOS, United Network for Organ Sharing; NIS, USA National Inpatient Database; ISHLTR, International Society of Heart and Lung Transplantation Registry; IMPACT, Index for Mortality Prediction After Cardiac Transplantation score; DRI, Donor Risk Index; SHTR, Spanish Heart Transplant Registry; Pmh, per million habitants.

rate to women who received a graft of a regular-sized donor (17). Our previous work analyzing the Spanish Heart Transplant Registry results over the last 25 years showed a similar survival and similar HT rate in women per million habitants. Causes of death differed between men, mainly due to neoplastic diseases, and women, mainly due to primary graft failure and rejection (18). All the described studies show a comparable pattern of baseline characteristics and underlying heart disease.

Our study aims to describe sex-related differences in 1-year outcomes after an HT in a contemporary cohort. Given that previous studies showed sex-related differences in higher-risk recipients, we sought to analyze 1-year HT results as they may be affected considerably by perioperative factors like the patient's clinical situation on the waiting list or the etiology of HF.

We did not find differences in the recipient's location (outpatient or hospitalized) at the time of HT. The need for circulatory support at the moment of HT was more frequent in men (mainly VAD), but it was not associated with different outcomes. VADs were used in a low percentage of HT candidates in our cohort. Given that VAD therapy may have different results in men and women, we cannot extrapolate our results to other populations with a higher VAD use. Urgent HT was more frequent in men, but it was not associated with higher mortality after multivariate analysis. We cannot determine whether this difference is influenced by a higher delisting rate of women due to clinical deterioration before HT or different use of therapies that determine urgent status in our country (i.e., intra-aortic balloon pump until 2015, extracorporeal membrane oxygenator, or VAD).

To conclude, despite sex-related differences in the clinical profile and the donor-recipient matching, 1-year outcomes are comparable. We did not find differences in the cause of death, and we did not find any interactions between sex and factors significantly associated with differences in survival.

LIMITATIONS

Our analysis of 1-year outcomes after HT has some limitations that must be acknowledged. The main limitation is the lack of information about patients included on the waiting list for HT

since the patient's follow-up begins at HT. Thus, we do not have any data about those patients who are included on the waiting list and are delisted or died before HT. Another limitation is the low rate of VAD implantation in our cohort that prevents us from extrapolating these results to other populations. Furthermore, the retrospective nature of a registry analysis also constitutes a significant limitation.

CONCLUSION

Women are under-represented in the waiting list for an HT or a VAD. Although clinical profile and HF etiology differ between men and women, overall survival and complications are similar. It is desirable to study sex-related differences to understand if we should adjust clinical protocols in advanced HF patients by sex.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MG-C, JD, and FG-V have contributed to the conception and design of the work. MG-C and FG-V have contributed to the analysis and interpretation of the work's data and drafting. BM, RL-V, EB-C, MG, MM-S, JM, DR, JG-C, SM, FP-V, GR, AP, LdlF, and IG have contributed in revising the article critically. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2021.630113/full#supplementary-material

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The Female Sex Confers Different Prognosis in Heart Failure: Same Mortality but More Readmissions

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Introduction: Heart failure (HF) is a major cause of morbimortality both in men and women. Differences between sex in etiopathogenesis, response to treatment, and quality of care have been found in patients with HF. Females are usually under-represented in clinical trials and there is no solid evidence demonstrating the influence of sex in the prognostic of chronic HF. The primary objective of this study was to analyse the differences in mortality and probability of hospital readmission between males and females with HF. The secondary objective was to compare mortality and probability of hospital readmission by ejection fraction (reduced vs. preserved).

Methods: Patients with decompensated HF that were consecutively admitted to a Cardiology Service of a tertiary hospital for 4 years were recruited. *De novo* HF, death during hospitalization, programmed admissions and those patients with moderate left ventricular ejection fraction (LVEF) (40–50%) were discarded. Finally, 1,291 patients were included. Clinical profiles, clinical history, functional status, treatment at admission, first blood analysis performed, readmissions and mortality at follow-up were analyzed and compared. All patients underwent an echocardiographic study at admission. HF with reduced ejection fraction (HFrEF) was considered when left ventricular ejection fraction (LVEF) was <40%, whilst HF with preserved ejection fraction (HFpEF) was considered when LVEF was ≥50%.

Results: 716 participants were male (55%). Basal characteristics showed differences in some outcomes. No differences were found in probability of survival among patients with decompensated HF by sex and ejection fraction ($p = 0.25$), whereas there was a clear tend to a major survival in females with HFrEF ($p < 0.1$). Females presented more readmissions when compared to males, independently from the LVEF (females = 33.5% vs. males = 26.8%; $p = 0.009$). Adjusted multivariate analysis showed no association between sex and mortality (HR = 0.97, IC 95% = 0.73–1.30, $p = 0.86$), although there was association between female sex and probability of readmission (OR = 1.37, IC 95% = 1.04–1.82, $p = 0.02$).

Conclusions: Sex does not influence mid-term mortality in patients admitted for decompensated HF. Nevertheless, probability of readmission is higher in females independently from LVEF. Thus, it should be considered whether healthcare may be different depending on sex, and a more personalized and frequent care may be recommended in females.

Keywords: heart failure, sex, gender, mortality, morbidity, readmissions, left ventricular ejection fraction

INTRODUCTION

Heart failure (HF) is a major cause of morbimortality both in males and females (1). The incidence is higher in males, although in elders the prevalence is higher in females, due to the fact that females usually have a higher survival rate after the onset of the disease, and as age advances prevalence increases when comparing to males (2–4). Therefore, the total number of patients with HF the in general population is similar in both sexes, or even higher in females (5). In addition, there are also differences by sex in etiopathogenesis of HF, response to treatment and quality of care (5). On the one hand, HF is presented in most cases as a chronic disease with a high rate of comorbidities, some related to sex (6). On the other hand, it should be taken into account that in general females are under-represented in clinical trials and therefore in clinical guidelines (7). It is known that women receive lower average drug doses, show more adverse effects (8) and undergo less frequently therapies related to advanced HF, such as heart transplantation and ventricular assistance (9). Moreover, care process, resource use, and quality of care in patients with HF may be different depending on sex (10).

However, a small number of studies have analyzed evolution and prognosis by sex and by type of HF in detail. No solid evidence about influence of sex on prognosis of HF has been reported, thus it is still a matter of controverse discussion.

The primary objective of this study was to analyse the differences in mortality and probability of hospital readmission between males and females with HF. The secondary objective was to compare mortality and probability of hospital readmission by ejection fraction (reduced vs. preserved).

METHOD

Patients with decompensated HF that were consecutively admitted to a Cardiology Service of a tertiary hospital for 4 years were recruited. This is an ambispective study. *De novo* HF, death during hospitalization, programmed admissions for studies o for therapeutic interventions and those patients with moderate left ventricular ejection fraction (LVEF) (40–50%) were discarded (**Figure 1**). We decided not to include patients with de novo HF in order to homogenize the sample, so that all patients included in the study are patients with decompensated chronic HF. On the other hand, patients with intermediate ejection fraction were excluded due to their intermediate characteristics between reduced and preserved ejection fraction, and taking into account that it is a less well defined group, in order to make two clear groups of patients. The objective was to select exclusively patients with chronic HF with defined ejection fraction and acute decompensation. Finally, 1,291 patients were included. Clinical profiles, clinical history, functional status, treatment at admission, first blood analysis performed, readmissions and mortality at follow-up were analyzed and compared by sex. All patients underwent an echocardiographic study at admission to assess left ventricular ejection fraction (LVEF). HF with reduced ejection fraction (HFrEF) was considered when LVEF was <40%, whilst HF with preserved ejection fraction (HFpEF) was considered when LVEF was ≥50% (1). The study was approved by the authors' Hospital Research Ethics Committee and all procedures were conducted according to the Declaration of Helsinki. Continuous variables are presented as mean ± SD. Categorical variables are presented as proportions. Univariate comparison was performed using Pearson chi-squared test and t-Student test. Multivariate

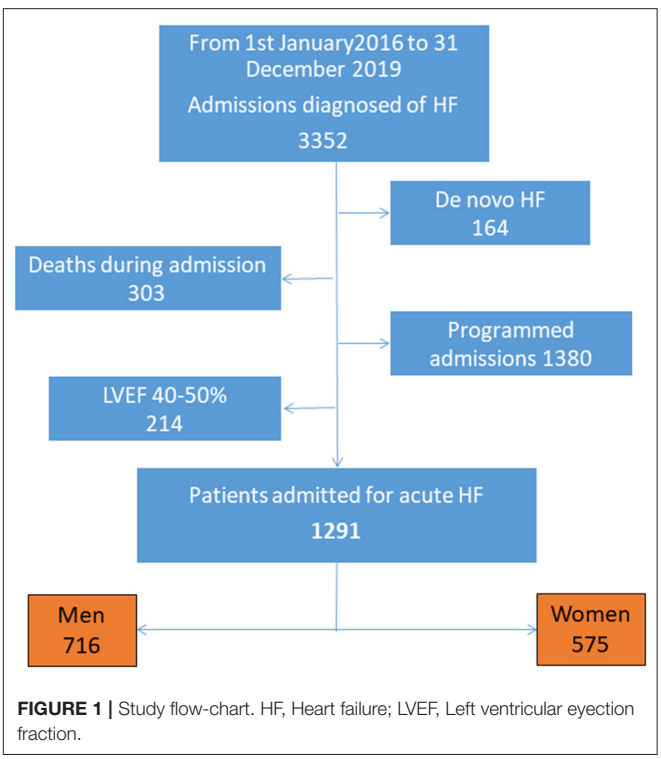

FIGURE 1 | Study flow-chart. HF, Heart failure; LVEF, Left ventricular eyection fraction.

Abbreviations: HF, Heart failure; HFrEF, Heart failure HF with reduced ejection fraction; HFpEF, Heart failure HF with preserved ejection fraction; LVEF, Left ventricular ejection fraction.

TABLE 1 | Basal characteristics.

	Women 575	Men 716	*p*
Age (years)	75 ± 12	72 ± 12	0.0001
Previous admissions, *n* (%)	259 (45%)	315 (44%)	0.7
Days admitted at hospital	8.3 ± 6.4	8.7 ± 6.1	0.3
Underlying heart disease, *n* (%)			
Ischemic heart disease	149 (26%)	315 (44%)	0.0001
Non-ischemic cardiomyopathy	52 (9%)	158 (22%)	0.0001
Valve disease	190 (33%)	129 (18%)	0.0001
Congenital heart disease	23 (4%)	7 (1%)	0.0001
Hypertension	132 (23%)	93 (13%)	0.0001
Others	29 (5%)	14 (2%)	0.004
Previous heart surgery, *n* (%)	115 (20%)	158 (22%)	0.4
Hypertension, *n* (%)	460 (80%)	544 (76%)	0.08
Dyslipidemia, *n* (%)	270 (47%)	390 (54%)	0.007
Diabetes mellitus, *n* (%)	253 (44%)	337 (47%)	0.3
Smoker*, *n* (%)	75 (13%)	365 (51%)	0.0001
Alcohol#, *n* (%)	6 (1%)	64 (9%)	0.0001
Coronary disease	155 (27%)	322 (45%)	0.0001
COPD, *n* (%)	58 (10%)	229 (32%)	0.0001
Obesity (BMI > 30), *n* (%)	63 (11%)	100 (14%)	0.1
Hypothyroidism, *n* (%)	86 (15%)	50 (7%)	0.0001
Atrial fibrilation, *n* (%)	374 (65%)	387 (54%)	0.0001
NYHA previous to admission, *n* (%)			
I	12 (2%)	57 (8%)	0.0001
II	396 (69%)	466 (65%)	0.2
III	155 (27%)	179 (25%)	0.4
IV	12 (2%)	14 (2%)	0.9
SBP (mmHg)	137 ± 25	134 ± 24	0.03
DBP (mmHg)	77 ± 27	78 ± 15	0.4
Heart rate (bpm)	82 ± 21	81 ± 19	0.4
CRT, *n* (%)	12 (2%)	50 (7%)	0.0001
ICD, *n* (%)	17 (3%)	100 (14%)	0.0001
LVEF ≥ 50%	374 (65%)	251 (35%)	0.0001
LVEF < 40%	201 (35%)	465 (65%)	0.0001
Drugs, *n* (%)			
Antiplatelets	173 (30%)	308 (43%)	0.0001
Anticoagulant	242 (42%)	272 (38%)	0.1
ACEI/ARB/ARNI	391 (68%)	559 (78%)	0.0001
Beta-blockers	345 (60%)	422 (59%)	0.7
Ivabradine	17 (3%)	50 (7%)	0.001
Diuretics	437 (76%)	437 (61%)	0.0001
MRA	184 (32%)	243 (34%)	0.5
Thiazides	75 (13%)	107 (15%)	0.3
Tolvaptan	23 (4%)	14 (2%)	0.03
Nitrates	35 (6%)	86 (12%)	0.0001
Acetazolamide	12 (2%)	14 (2%)	0.9
Digoxin	46 (8%)	43 (6%)	0.2
Antidiabetics (no iSGLT2)	115 (20%)	236 (33%)	0.0001
SGLTi2	12 (2%)	100 (14%)	0.0001
Potassium supplements	115 (20%)	86 (12%)	0.0001
Blood analysis			
Creatinine	1.3 ± 1.1	1.5 ± 1.0	0.001
Sodium	137 ± 4.8	138 ± 4.4	0.2
Potassium	4.4 ± 0.7	4.4 ± 0.6	0.05
NT-ProBNP	8247 ± 6876	8805 ± 7810	0.2
CA125	117 ± 126	119 ± 136	0.2
Troponine T	140 ± 122	176 ± 101	0.0001
Hemoglobin	11.9 ± 1.8	12.4 ± 2.2	0.0001
Uric acid	8.0 ± 2.5	8.2 ± 2.4	0.1

**Current smoker < 10 years.*

#Alcoholism < 1 year.

ACEI, Angiotensin-converting enzyme inhibitor; ARB, Angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease; CRT, Cardiac resynchronization therapy; DBP, Diastolic blood pressure; ICD, implantable cardioverter defibrillator; iSGLT2, sodium–glucose cotransporter 2 inhibitor; LVEF, Left ventricular ejection fraction; SBP, Sistolic blood pressure.

comparison was performed using Cox regression (survival) and binary logistic regression (readmissions) with death and readmission as dependent variables. Independent variables were those with a significance > 0.05 in the univariate analysis using the intro method. Significance was set at $p < 0.05$. Data were analyzed using SPSS (version 27) and Stata (version 16, number 501606323439).

RESULTS

Clinical Characteristics

Univariate analysis showed significant differences when comparing the clinical profile by sex. Differences were conditioned by the different prevalence of underlying heart disease. Therefore, ischemic heart disease was the etiology that most frequently caused HF in men, while in women it was valve disease and hypertension. This fact determines differences in the history of cardiovascular risk factors, percentage of implantation of devices and treatment administered (**Table 1**).

Analysis of Global Morbimortality

No differences were found in probability of survival among patients admitted for decompensated HF, independently from sex. The curves were superimposable (**Figure 2**). There were differences in readmission rates at follow-up between males and females (**Figure 3**).

Analysis of Morbimortality by Ejection Fraction

No differences were found in probability of survival when comparing gender by ejection fraction. Nevertheless, there is an evident trend toward a higher probability of survival in women with decompensated HF and reduced LVEF (**Figure 4**). There were differences in readmission rate depending on ejection

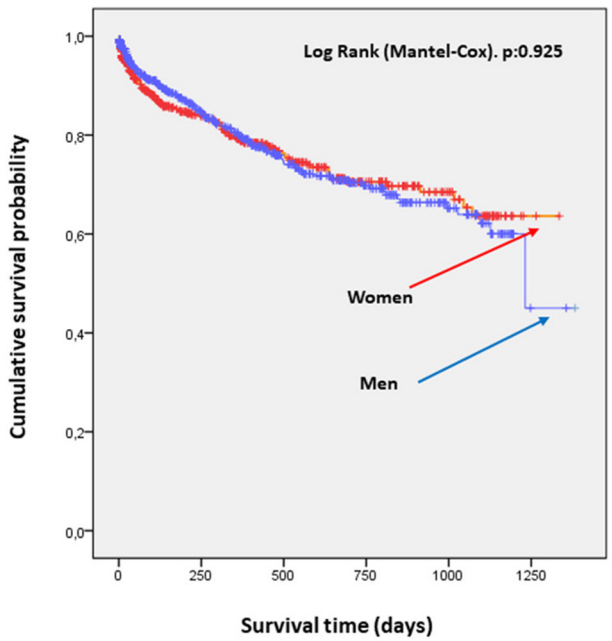

FIGURE 2 | Survival curves by sex. No significant differences were found in probability of survival in patients admitted for decompensated HF by sex.

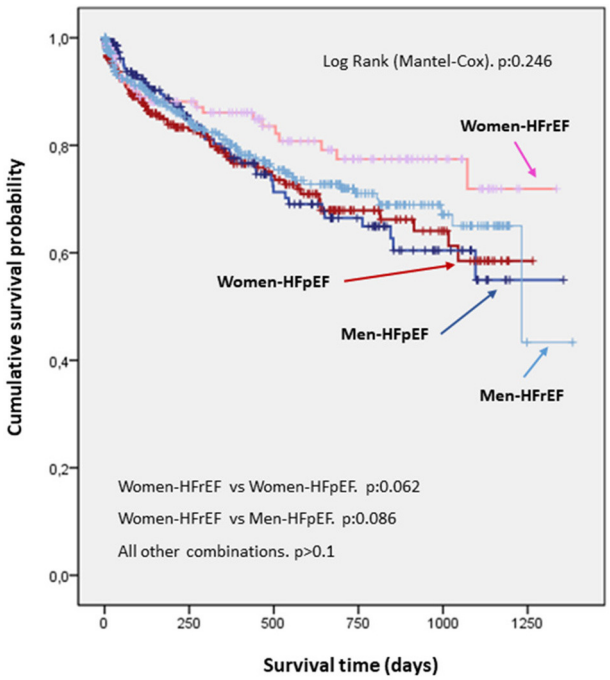

FIGURE 3 | Survival curve by sex and by left ventricular ejection fraction. No differences were observed in probability of survival by sex and by LVEF. Nevertheless, there was a trend for women with HFrEF to have a better prognosis. HFrEF, Heart failure with reduced ejection fraction; HFpEF, Heart failure with preserved ejection fraction.

fraction. Thus, women are more frequently readmitted than men, independently from presenting HFrEF or HFpEF (**Figure 3**).

Multivariate Analysis

Adjusted multivariate analysis showed no association between sex and mortality. Age and creatinine were related to mortality (**Table 2**). Adjusted probability of readmission was independently associated to sex and age. LVEF did not show sufficient statistical power to achieve a statistically significant result.

DISCUSSION

Influence of sex in morbimortality of patients with HF has been subject of debate in the last decade (11, 12). There is an unmet need to assess whether sex differences in comorbidities related to HF require specific management strategies. Differences by sex in clinical profile and LVEF mean that comparison analysis do not allow to extract a sufficiently reliable idea. Therefore, great divergences on the influence of sex on morbimortality of HF are observed in the scientific literature. This study aimed at analyzing whether there were differences by sex in morbimortality in admitted patients with decompensated HF, as well as at follow-up, and whether LVEF was a predictive variable of death or readmissions. Sex does not influence mortality. However, women present a probability of readmission 37% higher with respect to men. On the other hand, it has been stated that LVEF is not independently associated to probability of death nor readmission in patients with decompensated HF.

Basal characteristics of both groups showed differences in the clinical profile of both men and women. In our study, women are older than men, as observed in previous literature, since women tend to develop HF at an older age than men (11, 13–16). Ischemic heart disease is the etiology that most frequently causes HF in men, while in women it is valve disease and hypertension (13, 14, 17, 18). This fact conditions the differences in associated comorbidity and in the history of cardiovascular risk factors: dyslipidemia, smoking, history of alcohol consumption and chronic obstructive pulmonary disease were more frequent in men, in accordance with previous studies (14, 19, 20), whilst othe comorbidities related to HFpEF such as atrial fibrillation and hypothyroidism were more frequent in women. Nevertheless, in our study no greater presence of obesity in females was found, as shown in previous literature (19–22). HFpEF is more frequent in women and represents at least half of the cases of HF in women (13, 17). No differences were found in functional status (NYHA New York Heart Association) II to IV, however, a lower percentage of asymptomatic women was observed in our sample (NYHA I) (14). On the other hand, the percentage of patients with pharmacological treatment for HF is higher in men. Adherence to guidelines in diagnosis treatment of HF is less strict in women than in men, which leads to often insufficient pharmacological treatment with prognostic-modifying drugs for the disease (23, 24). It should be taken into account that this difference could be partially explained by the higher frequency of ischemic heart disease in men, as

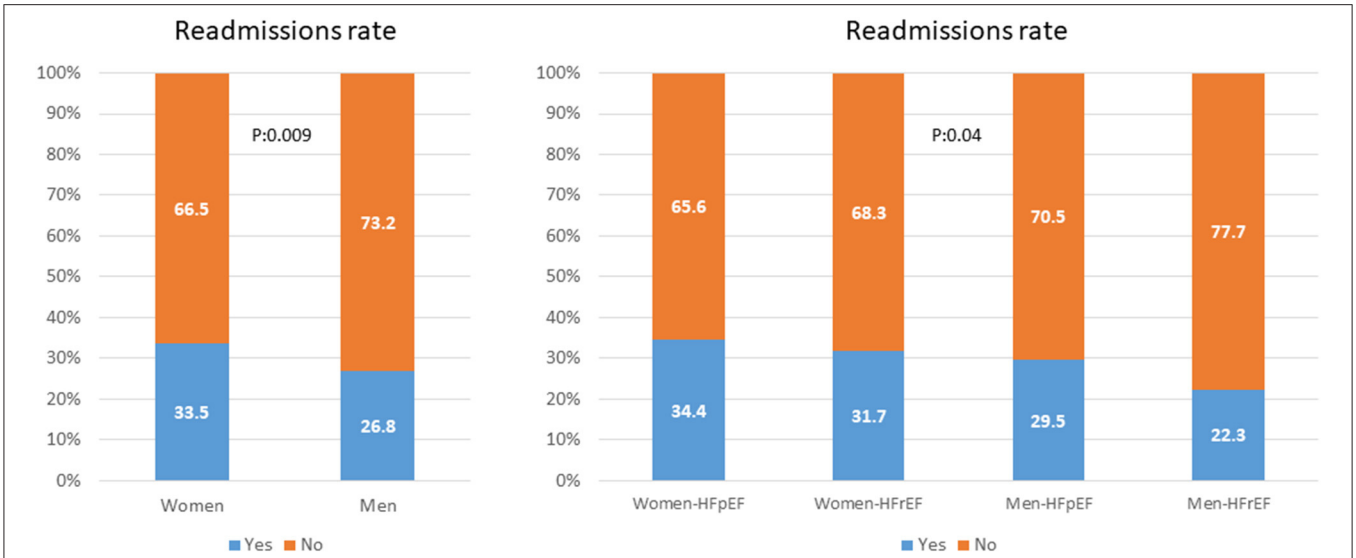

FIGURE 4 | Left: readmission rate between men and women. Right: readmission rate between men and women by LVEF. HFrEF, Heart failure with reduced ejection fraction; HFpEF, Heart failure with preserved ejection fraction.

well as a higher prevalence of HFrEF in men (25). The use of diuretics is more frequent in women, most likely because they are used in the symptomatic control of HF, and it is known that women usually have more severe symptoms than men (5). Women tend to have lower left ventricle end-diastolic volumes at similar left ventricle end-diastolic pressures compared to men. This fact suggests that diastolic dysfunction is an explanation for the paradox of women having more frequent HF symptoms despite frequently preserved left ventricle systolic function (5). Thus, when comparing to men, women have higher rates of dyspnea on exertion, difficulty exercising, and congestion (26–28). Women are less frequently carriers of devices related to HF, both implantable cardioverter defibrillator and cardiac resynchronization therapy (9), despite the fact that some studies have observed that women are more likely to respond favorably to cardiac resynchronization therapy than men (29–31).

One of the most questioned aspects of HF is whether women have a better prognosis than men. Our results support the hypothesis that the survival rate is similar in both sexes, since no significant differences were found in the probability of survival between patients admitted for decompensated HF. Likewise, the adjusted multivariate analysis showed that there is no association between sex and survival, whilst age and creatinine were the only variables associated with mortality. These findings coincide with those obtained in other Spanish registries. In the BADAPIC study (Database of Patients with Heart Failure) (14), carried out mainly in Spanish Departments of Cardiology, similar mortality rates were found in both sexes. Conde-Martel et al. (21) reported, in Departments of Internal Medicine, age-adjusted 1-year mortality rates of 28 and 25% in hospitalized men and women with HF, respectively. In the Olmsted population study, 5-year mortality rates of 59 and 49% were found in outpatient men and women (32, 33). On the other hand, other studies have shown higher survival in women with HF compared to men, however, the effect on sex survival varies according to the characteristics of the cohort. In the I-PRESERVE study (34) in hospitalized patients with preserved LVEF, women had a 20% lower risk of death from cardiovascular and non-cardiovascular events. The MAGGIC meta-analysis (35), with information of 41,949 patients, also showed higher survival for women, suggesting that a lower prevalence of ischemic heart disease, arrhythmias, and sympathetic activation, and better LVEF are protective factors (22, 24).

In our study, no difference was found in the probability of survival when sex was compared by LVEF. However, there was an evident trend toward a higher probability of survival in women with decompensated HF and reduced LVEF. This finding, not described in the previous literature, could be due to the clinical profile of the included women, since in general women with HFpEF associate a greater comorbidity, which frequently determines the prognosis.

TABLE 2 | Multivariate analysis by sex.

	HR	IC95%	*p*
Mortality			
Sex	0.97	0.73–1.30	0,86
Age	1.02	1.01–1.03	0.001
Creatinine	1.32	1.17–1.49	0.0001
	OR	**IC95%**	***p***
Readmission for HF			
Sex (woman vs. man)	1.37	1.04–1.82	0.02
Age	1.01	1.00–1.02	0.05
LVEF	0.98	0.75–1.29	0.9

Adjusted- analysis to all significant variables in the univariate analysis.
LVEF, Left ventricular ejection fraction.

It should be noted that readmissions are a growing concern worldwide, since greatly increase the morbidity and mortality of patients and increase the health expenditure of all health systems globally (36). Current patterns of hospital readmission are often associated with organizational factors, such as length of stay, clinical factors, such as age and comorbidities, and factors such as quality of care during admission (37–39). Some authors have focused on sex differences in HF (11, 40–42), although to our best knowledge no study has examined sex differences in relation to readmission rates. Our study has shown significant differences in readmission rate at follow-up between women and men, as well as in the readmission rate depending on LVEF: women are readmitted more frequently than men, independently from having HFpEF or HFrEF. Similarly, the adjusted multivariate analysis confirmed that the adjusted readmission probability was independently associated to gender: the female sex multiplies the readmission probability by 1.37 with respect to men. These data are in line with the trend shown in previous studies (14, 43–46) that observed although the mortality of women and men with HF is similar, the readmission rate for HF is higher in women in specialized HF clinics. These results may be associated with previously described differences in pharmacological treatment. A meta-analysis found more articles reporting that men with HF had significantly higher readmission rates compared to women (47). The effect of sex on readmission may depend on the length of follow-up, with a longer duration of follow-up favoring higher readmission rates among men. Thus, Hoang-Kim et al. (47) reported that the readmission rate for men was higher when the duration of follow-up was >1 year. In contrast, women were more likely to experience higher readmission rates than men when the time to event was <1 year. Consequently, possibly future studies should consider different time horizons in their designs.

One of the most important limitations of previous studies is the lack of data regarding LVEF, data that have been included in this analysis, given the differences by sex in the prevalence of HFrEF vs. HFpEF. Differentiating the LVEF allows us to analyze the effect of this relevant clinical variable in the evaluation of sex differences in the treatment and prognosis of HF.

The limitations of this study are those related to the patient databases However, this database is filled prospectively during the admission of the patient, so clinical data have a very high reliability. In addition, echocardiographic studies are performed at each admission so that HF classification does not have a temporal cadence with admission. On the other hand, the clinical impact of this work is high as it is a study with a large number of patients that demonstrates equality of sexes in terms of mortality, but with a greater number of readmissions in women during follow-up, independently from the type of HF.

CONCLUSIONS

Sex does not influence mid-term mortality in patients admitted for decompensated HF. Nevertheless, probability of readmission is higher in females independently from LVEF. Thus, it should be considered whether health strategies may be different depending on sex, and a more personalized and frequent healthcare may be recommended in females.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Instituto de Investigación Sanitaria La Fe. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

RL-V: data collection, data analysis, writing results, writing the manuscript, translation, and revision of the final manuscript. EM-S: data collection, translation and revision of the final manuscript. RL: data collection and writing the manuscript and revision of the final manuscript. IS-L, VD, and LM: writing the manuscript and revision of the final manuscript. LA: data analysis, writing results, writing the manuscript and translation and revision of the final manuscript. All authors contributed to the article and approved the submitted version.

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Influence of Sex-Mismatch on Prognosis After Heart Transplantation

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The influence of donor and recipient sex on prognosis after heart transplantation has been analyzed in single, multi-center studies, and international registries. In most of them, sex-mismatch was identified as a risk factor for the worst prognosis, especially in men recipients of female heart. This could be attributed to physiological differences between women and men, differences in complications rates after heart transplantation (rejection, cardiovascular allograft vasculopathy, and primary graft failure), and pulmonary hypertension of the recipient. Confounding variables as age, urgent transplantation, and size-mismatch should also be considered. When allocating a graft, sex-mismatch should be considered but its influence in long-term survival should be further explored.

Keywords: sex-mismatch, transplantation, prognosis, size-mismatch, rejection

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INTRODUCTION

Heart failure (HF) is a clinical syndrome appearing in the final pathway of heart disease. It affects 1–2% of the adult population and it increases with age. The development of symptoms leads to morbidity, mortality, and poor quality of life. It has a poor prognosis, and heart transplantation (HT) is the treatment of choice in selected patients (1). When allocating a graft, donor, and recipient characteristics should be considered (2). Among them, the influence of donor/recipient sex-mismatch on prognosis has been broadly discussed. In this manuscript, we will address this issue and will try to figure out the mechanisms underlying this relationship.

STATE OF THE ART: DONOR/RECIPIENT SEX-MISMATCH INFLUENCE ON HEART TRANSPLANTATION PROGNOSIS

Influence on Early and Long-Term Survival

Initially, donor, and recipient sex influence on mortality were analyzed separately (3–9). After heterogeneous results, the influence of donor/recipient sex-mismatch was analyzed. In 1998 two studies found an influence on early mortality (10) and worst annual survival (11), due to lower survival in the female donor to male recipient (F/M) group, attributed to size-mismatch. Later, several studies confirmed this relation. In 2011, a single-center study with 857 patients did not show worse survival of F/M group compared to male donor to female recipient (M/F) group, although a trend in early mortality was suggested and better survival in recipients without mismatched heart was shown (12). Other studies reported significantly worst survival of F/M group in early stages after HT (13–15), while other authors related sex-mismatch with mortality regardless of the recipient sex (10, 16–18). However, in Bello et al. (16) sex matched pairing conferred a survival benefict, and M/F combination had worst survival. On the contrary, others failed to relate sex-mismatch with poorer prognosis (19–24). In this sense, De Santo et al. (19) found no differences in one and three-year cumulative survival between sex-mismatch and sex-match patients in a cohort with 99 patients.

Jalowiec et al. (20) found in a multicentric analysis of 347 patients no significant differences in early survival (30-days and 1-year survival) between sex-mismatch and sex-matched patients. Tsao et al. (21) and Yamani et al. (22) also did not find differences in survival between 4 groups created according to donor/recipient sex. In 2014, Correia et al. published the results of the analysis of 200 male recipients in a Portuguese center. They did not find higher mortality in sex-mismatch group than in sex-matched group. The authors reported selection bias, as recipients of mismatched hearts had lower pulmonary gradient and lower systolic pulmonary pressure (24). The results of the Spanish Heart Transplantation Registry published in 2014 included 4,625 patients and found an influence of sex-mismatch on early mortality only in male recipients and mainly in those with pulmonary gradient >13mmHg (25).

The results of the analysis of large registries, expected to be more accurate and reliable, also reported heterogeneous results (26–32). In 2002, Zeier et al. (29) found higher mortality of F/M group analyzing the Collaborative Transplant Study database. The United Network for Organ Sharing (UNOS) database analysis published in 2009 (28) compared 4 groups, based on the combination of donor and recipient sex, and showed a lower survival at 5 years in the F/M group and greater survival in the male to male (M/M) group. A later analysis of this same database (31) found that survival differences associated with sex-mismatch were modified by differences in predicted heart mass (PHM) by a mathematical model. In a retrospective analysis of 31,634 patients, the authors found that a difference of 10 to 15% in PHM (undersized heart) between donor and recipient resulted in higher risk. In fact, when adjusting by PHM, they showed higher mortality in M/F group. The results of the International Society for Heart and Lung Transplantation (ISHLT) have also been analyzed several times (26, 30, 32). In 2012 (30) an increase in mortality in F/M was reported compared to M/M, influenced by early mortality. Later, Kackmarek et al. (26) analyzed 67,855 transplanted patients and found the worst annual survival rates in F/M group. The most recent analysis included 52,455 patients (32) and found that sex-mismatch increased mortality independently of weight match. The results of the University of Alabama – Cardiac Transplant Research database (CTRD), previously published, had found an interaction between sex, weight mismatch, and survival, especially in F/M. However, these differences were not observed when the weight mismatch was minimum (27).

A meta-analysis addressing sex-mismatch influence on one-year survival has been recently published (33). After an initial search, 556 articles were found, and 45 articles were selected for full-text assessment. Finally, only 10 articles were included for data extraction and quantitative synthesis. 76,175 patients were analyzed. In male recipients, sex-mismatch was related with increased one-year mortality (21.2 vs. 16.6%; OR = 1.38, 95% CI 1.31–1.44, $p < 0.001$). On the contrary in female recipient sex-mismatch was not a risk factor for one-year mortality (18.2 vs. 18.6%; OR = 0.93, 95% CI = 0.85–1.00, $p = 0.06$). The main limitations of this meta-analysis are the strong influence of the largest registry included in the results (26), the inability to determine the real influence of confounding factors and to determine the influence of early complications on long-term survival. However, it is the first meta-analysis on this field with studies of low bias, and the population included is representative of the HT population.

Influence on Rejection

The influence of sex-mismatch on rejection is unclear. Differences in the endocrine and immune system could lead to different adaptations to sex-mismatched heart (34). Women have a greater immune response (6, 35, 36) that leads to higher levels of immunoglobulins and autoimmune diseases (37) and are supposed to have higher rates of rejection (6–9, 38). In 1998, Prendergast et al. (11) found higher rates of acute rejection in recipients with a sex-mismatched heart, as also did Aliabadi et al. (23) in 2011. In 2012, Jalowiec et al. (20) reported higher rejection rates in M/F as had been previously published (39) and related lower survival to higher steroids requirements in the early post-transplant period. Patel et al. (40) reported, in a group of 1,299 patients, higher antibody-mediated rejection in M/F, but a recently published study found a higher risk in female recipients regardless of sex-mismatch (41). On the contrary, Bryan et al. (42) reported lower rejection rates in recipients of male hearts, mainly due to lower rates of the M/M group compared to the F/M group.

Influence on Cardiac Allograft Vasculopathy

The influence of sex-mismatch on cardiac allograft vasculopathy (CAV) has also been studied with heterogeneous results. A higher risk of CAV in F/M group was reported in different studies (38, 43). Whether these results were attributed to sex-mismatch, female donor or male recipient is not clear (44–46). Other studies showed this relationship regardless of the combination (23) or in the F/F group (22). Eifert et al. (13) failed in 2012 to show this relation. Immunological or size-mismatch could be the reason underlying this association (38, 43).

Influence on Primary Graft Failure

Primary graft failure (PGF) is an impairment of the transplanted heart that occurs in the first 24 h after transplantation (47). It is the main cause of death in the early post-transplant period with up to 22% mortality (48). In an analysis of the Spanish Registry of Cardiac Transplantation (25) an increase in mortality in F/M in the first 30 days was found, but PGF was related to female donors, as previously noted (49) but not with sex-mismatch. However, some studies found a relation of PGF with sex-mismatch in male recipients (50–52), although Young et al. (51) found this was particularly important when the size exceeded 30%.

In **Table 1** we present a summary of the main studies that show the influence of sex-mismatch on higher rates of mortality, rejection, CAV, and PGF.

DISCUSSION

Different analysis on sex-mismatch influence on prognosis have shown different results. Some of them found the worst survival in F/M group (11–15, 25–29, 33), while others did not. How

TABLE 1 | Summary of the main studies showing the influence of sex-mismatch on higher rates of mortality, rejection, cardiovascular allograft vasculopathy, and primary graft failure.

Reference	Type of study	Number of patients	Results
Sex-mismatch influences on survival			
Al-Khaldi et al. (15)	Single-center	869	- Recipient of female heart had worst survival (depending on donor/recipient age).
Ayesta et al. (33)	Meta-analysis	76,175	- Sex-mismatch affected 1-year survival in male recipients but not in female recipients.
Bello et al. (16)	Multicenter	3,316	- M/F was related with worst survival.
Eiffert et al. (13)	Single-center	1,000	- Multivariate analysis showed that F/F was a long-term survival predictor.
Kackzmarek et al. (26)	Multicenter (ISHLT Registry)	67,855	- F/M worst long-term survival.
Kittleson et al. (12)	Single-center	857	- Best survival in patients with sex-matched heart. - 5-year actuarial survival worst in F/M.
Khush et al. (30)	Multicenter (ISHLT Registry)	60,584	- F/M had higher risk of mortality.
Kirsch et al. (10)	Single-center	234	- Influence of sex-mismatch on early mortality.
Martínez-Sellés et al. (25)	Multicenter (Spanish Society of Cardiology Registry)	4,625	- F/M had higher early mortality, especially in those recipients with pulmonary gradient >13 mmHg.
Prendergast et al. (11)	Single-center	174	- F/M had worst annual survival.
Reed et al. (31)	Multicenter (UNOS Registry)	31,634	- M/F had worst 1 and 5-year survival.
Schelechta et al. (18)	Multicenter	609	- Sex-mismatch recipients had worst 3 and 5-year survival.
Stehlik et al. (27)	Multicenter (CTRD database)	7,321	- In F/M, older recipients and those higher size-mismatch had worst survival.
Weiss et al. (28)	Multicenter (UNOS Registry)	18,240	- F/M had worst 5-year survival - Multivariate: higher mortality in F/M vs. M/M.
Welp et al. (14)	Single-center	236	- F/M had worst survival.
Zeier et al. (29)	Multicenter	25,432	- Worst actuarial survival in F/M.
Sex-mismatch influences on rejection rates			
Aliabadi et al. (23)	Single-center	1,079	- Mismatch recipients had higher rates of acute rejection.
Bryan et al. (42)	Multicenter	279	- F/M vs. M/M had higher rates of rejection. - Female donor was related with higher risk of rejection.
Jalowiec et al. (20)	Multicenter	347	- M/F had higher rates of acute rejection.
Keogh et al. (39)	Single-center	313	- M/F had higher rates of acute rejection the first 3-months.
Patel et al. (40)	Single-center	1,299	- M/F had higher rates of antibody-mediated rejection.
Prendergast et al. (11)	Single-center	174	- Mismatch recipients had higher rates of acute rejection.
Sex-mismatch influences on cardiovascular allograft vasculopathy rates			
Aliabadi et al. (23)	Single-center	1,079	- Mismatch recipients had higher rates of CAV
Mehra et al. (43)	Single-center	36	- F/M was the combination with higher risk of CAV using intravascular ultrasound.
Sharples et al. (38)	Single-center	323	- F/M was the combination with higher risk of CAV.
Sex-mismatch influences on primary graft failure rates			
Russo et al. (50)	Multicenter (UNOS Registry)	16,716	- F/M was associated with higher risk of PGF.
Singh et al. (52)	Multicenter	450	- F/M was associated with higher risk of PGF.

UNOS, United Network for Organ Sharing; CAV, Cardiac Allograft Vasculopathy; CTRD, Cardiac Transplant Research Database; F/F, female donor and female recipient group; F/M, female donor and male recipient group; ISHLT, International Society for Heart and Lung Transplantation; PGF, Primary Graft Failure; M/M, male donor and male recipient group; M/F, male donor and female recipient group.

sex-mismatch could influence on mortality is still unknown. Hypothetically, it could be due to anatomic, immune, hormone, and genetic differences between women and men. Also, differences in donor and recipient age and the emergency of the transplant could be involved. Most importantly, size-mismatch between donor and recipient and pulmonary hypertension of the recipient could be the main factors underlying this relationship and are currently being studied. The heterogeneous results in the influence on CAV and PGF are probably due to different definitions until consensus was reached.

Anatomic and Physiological Differences

Anatomic and functional differences between women and men's hearts lead to different abilities to adapt to different hemodynamic situations (53–56). Also, in transplanted women with previous male pregnancies, the presence of male cells

could better explain the ability of women to adapt to a sex-mismatched heart (57). On the contrary, differences in endocrine and immune system could increase rejection in women (34–37). Advanced donor age is also related to mortality, mainly the first year after HT (58). In some studies, female donors older than male could be the reason under the worst survival of the F/M group (15, 18, 19, 24–26). However, some studies specifically addressed failed to show an interaction between age and sex-mismatch (15, 19, 22, 24–26). However, Al-Khaldi et al. (15) found an interaction between age and donor/recipient sex. Female recipients (younger) had no impact on multivariate analysis and the M/M group was the one with the best one-year survival. This confirmed the previously published data from the UNOS registry that showed that recipient <55 years-old and donor <30 years-old had the best long-term survival (59).

Urgent Transplant

The analysis of the UNOS Registry published in 2009 (28) showed higher mortality in F/M only valid for those transplanted in maximum urgency. A previous analysis published in Spain (60) had also shown higher mortality in the F/M, due to the higher rates of urgent transplant.

Undersizing Effect and Pulmonary Hypertension

The most currently discussed reason underlying the relation between sex-mismatch and survival is the "under-sizing" effect. A smaller female heart would not be able to keep the cardiac output required by a man, resulting in immediate right ventricular failure (61). The use of different cardiac size measures has attempted to minimize the effect of sex-mismatch by reducing size-mismatch. However, it is still not clear that sex-mismatch influence on prognosis is totally due to size-mismatch.

An analysis of the Spanish Registry of Heart transplantation (25) showed that sex-mismatch increased mortality only in men with pulmonary hypertension the first month after HT. However, there were no significant differences in weight relationship between donor and recipient in M/M vs. F/M. In the same way, the most recent analysis of ISHLT database (32) found that sex-mismatch increased mortality independently of weight match. They analyzed 52,455 transplants between 1994 and 2013 and defined three subgroups according to BMI: underweight, non-obese, and obese. Inappropriate weight match, defined as donor weight <70% of the recipient's weight, was associated with 30-day mortality and cumulative mortality. F/M and M/F had higher rates of cumulative mortality compared with sex-matched patients but increased early mortality only in F/M. They found no interaction between inappropriate weight match and sex-mismatch, which would be expected if size differences were the main reason for increased mortality in this group. Previous analysis of the ISHLT database (26) had focused on donor and recipient body mass index (BMI). They suggested an "undersizing effect" due to F/M worse results after correction of weight and height and an "oversizing effect" with better short-term results in M/F, especially when the recipient had high pulmonary pressures. Other analysis of this same database (30) adjusted the results based on weight mismatch, using three different parameters: donor and recipient weight, donor and recipient weight difference, and weight ratio of the recipient regarding donor weight. They found worse survival in F/M, but they did not find an interaction of the difference in weight in this survival. UNOS data published in 2009 (28) studied BMI ratio and body surface area (BSA) ratio between donors and recipients, finding a quite precise adjustment, probably due to a deliberate move to allocate the graft adjusting by cardiac size. Other studies were consistent with this adjustment and showed no difference among the four groups in donor/recipient BSA ratio (15, 18, 19).

However, a poor correlation between weight and heart size was shown, questioning the suitability of the measures used so far (31). Reed et al. (31) studied a new way of assessing this relationship with a mathematical formula. They conducted a retrospective study of 31,634 patients included in the UNOS registry, identifying undersizing pairs with increased risk. The formula calculated the PHM combining the predicted left ventricular and right ventricular cardiac mass. They found that a difference of 10–15% (undersized heart) resulted in a higher risk of mortality. In the adjusted analysis, the risk attributed to sex-mismatch in F/M disappeared and higher mortality was observed in M/F. These results would agree with the theory that cardiac size-mismatch is interacting with the worst survival in F/M. A most recent analysis of the UNOS registry (19,168 recipients between 2007 and 2016) assessed the ability of 5 size match metrics: PHM, weight, height, BMI, and BSA to predict 1-year mortality after HT (62). They found that PHM is the optimal donor-recipient size for the prediction of mortality. The increased mortality associated with donor-recipient PHM undersizing below 0.86 persisted after adjusting for other factors affecting mortality, including sex-mismatch (62). The authors analyzed the role of sex-mismatch and PHM in heart offer turndown from donor size/weight. Most of them were F/M and 17% of them would be acceptable using the PHM cut off. F/M did not have an increased risk of death. The thirty-sixth adult heart transplantation report of the ISHLT published in 2019 addressed this issue (63). The authors analyzed donor-recipient size match based on PHM. They found that most of donor-recipients with weight match ≤30% had an acceptable PHM of <20 to >20%, which may lead to an increase in the use of hearts. The Pearson correlation coefficient (R) for weight mismatch compared to PHM mismatch was moderate-strong. They also analyzed donor-recipient PHM match according to sex match. F/M tended to be undersized and M/F tended to be oversized. They concluded that differences in size matching may be a part of mortality differences seen in different sex-mismatch combinations. Donor-recipient size match by PHM was identified as a significant predictor of 1- and 5-year mortality after heart transplant (for both recipients of undersized and oversized donors). A recent analysis of the OPTN/UNOS Registry (64) analyzed 3,788 F/M from 2005 to 2018. They demonstrated that increasing donor BMI relative to recipient BMI up to 1.5 was associated with improved survival. They speculated that BMI difference may be useful as a surrogate for PHM difference (due to the complexity of PHM) and might help mitigate the impact of sex-mismatch in heart transplantation.

In patients with pulmonary hypertension, it is common practice to oversize donor hearts to prevent post-operative right ventricular failure. A recently published studied analyzed patients in the UNOS Registry (65) with moderate pulmonary hypertension. They found no benefit to oversizing donors. The unadjusted 1-year mortality was significantly higher for F/M compared with M/M but after propensity matching, there was no difference in mortality between female and male donors at 90 days and 1 year. However, a higher risk for 1-year mortality persisted among M/F in comparison with M/M. Also, there might be an interaction between weight difference, age, and recipient sex. A previous analysis of the CTRD had found an interaction between weight difference, age, and recipient sex, with higher one-year mortality in F/M with an older organ (more than 40 years) and a 30% weight difference (27). A single-center Portuguese study (24) showed the same survival in those patients with sex-mismatch due to a good selection of grafts based on cardiac size in those patients with high transpulmonary gradient. However, it is a single-center and small sample study so their results cannot be considered superior to those observed on large international bases.

The influence of donor/recipient sex-mismatch on survival after HT is still not clear and the reasons underlying are still under debate. Adjusting size-mismatch may help to improve results but there are still some other factors that should be clarified. Further studies, especially prospective ones, would be necessary to improve survival and allocate the best graft in this era with scarcity of organs.

CONCLUSION

The influence of sex-mismatch on prognosis after HT has been broadly studied. In brief, a worst survival of male recipients receiving female heart was noted. However, new evidence shows that the optimization of cardiac size match between donor and recipient with adequate measures could modify the effect of sex-mismatch.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

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REVIEW
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Sex and Heart Failure Treatment Prescription and Adherence

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Heart disease is the leading cause of death in both men and women in developed countries. Heart failure (HF) contributes to significant morbidity and mortality and continues to remain on the rise. While advances in pharmacological therapies have improved its prognosis, there remain a number of unanswered questions regarding the impact of these therapies in women. Current HF guidelines recommend up-titration of neurohormonal blockade, to the same target doses in both men and women but several factors may impair achieving this goal in women: more adverse drug reactions, reduced adherence and even lack of evidence on the optimal drug dose. Systematic under-representation of women in cardiovascular drug trials hinders the identification of sex differences in the efficacy and safety of cardiovascular medications. Women are also under-represented in device therapy trials and are 30% less likely to receive a device in clinical practice. Despite presenting with fewer ventricular arrythmias and having an increased risk of implant complications, women show better response to resynchronization therapy, with lower mortality and HF hospitalizations. Fewer women receive advanced HF therapies. They have a better post-heart transplant survival compared to men, but an increased immunological risk needs to be acknowledged. Technological advances in mechanical circulatory support, with smaller and more hemocompatible devices, will likely increase their implantation in women. This review outlines current evidence regarding sex-related differences in prescription, adherence, adverse events, and prognostic impact of the main management strategies for HF.

Keywords: heart failure, sex, treatment, treatment-drug, adherence-compliance-persistence, ventricular assist device, heart transplantation

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INTRODUCTION

Men and women have the same risk of developing heart failure (HF) throughout life. However, it is well-known that women develop the disease later in life. In addition, women have a higher prevalence of HF with preserved ejection fraction (HFpEF), the prevalence of which increases with age. This may partly explain the under-representation of women in pharmacologic and device therapy trials designed to treat HF with reduced EF (HFrEF) (1).

Sex based differences in pharmacokinetics and pharmacodynamics of pharmacological agents may explain the variable effects in men and women. However, given the smaller number of

women included in clinical trials of HFrEF, where they represent less than one-third of the study population, we do not have accurate information. Unfortunately, the results of large clinical trials are often not analyzed separately by sex and we only have subgroup analyses so they cannot be fully extrapolated to women (2). The same under-representation applies to clinical trials for devices. Heart transplantation shows good outcomes in women, with lower long-term, cardiovascular and malignancy risk. Nevertheless, sex needs to be taken into account in order to select a suitable donor, tailor post-transplant immunosuppression and surveillance and address specific quality of live concerns and address reproductive health.

SEX DIFFERENCES IN PHARMACODYNAMICS AND PHARMACOKINETICS

There are important sex-dependent differences in pharmacokinetics (PK) and pharmacodynamics (PD) that need to be acknowledged to understand how specific cardiovascular drugs can affect women and men differently. The differences can affect absorption, metabolism, distribution, and elimination.

Absorption

For orally administered drugs, two main factors need to be acknowledged: compared to men, women (1) produce less gastric fluid, which can lead to a decrease in the absorption of weak acids and an increase in the absorption of weak bases and (2) have longer intestinal transit time (3, 4). The influence of estrogen on enzymes such as CYP3A can modulate intestinal transport, elimination rate, and alcohol distribution volume (3). Transdermal absorption appears to be higher in women (3).

Distribution

Total body water is greater in men, while women have a higher proportion of adipose tissue. Therefore, distribution volume for hydrophilic or lipophilic drugs varies according to sex.

Plasmatic proteins involved in drug transport can be modulated by estrogens, resulting in a sex-dependent distribution (5, 6).

Metabolism

Lower hepatic flow in women, sex-dependent activity of metabolic enzymes, increased proportion of adipose tissue and lower basal metabolic rate can explain differences in drug metabolism (3, 7, 8).

Elimination

In general, glomerular filtration, tubular secretion, and tubular reabsorption are higher in men (3), however, during pregnancy, renal blood flow increases and an overall increase in glomerular filtration rate by about 50% is seen in pregnant women (9).

Liver enzyme activity decreases in presence of elevated female hormone levels which may decrease drug elimination. Therefore, metabolism can change throughout the menstrual cycle, during pregnancy, with oral contraceptives intake or after menopause (10).

SEX BASED DIFFERENCES IN PHARMACOKINETICS AND PHARMACODYNAMICS OF CARDIOVASCULAR DRUGS

Digoxin

An increased risk of death in women was reported in the DIG trial. Although it may have been related to higher digoxin levels in women, it could not be proven since digoxin levels were available in less than one third of the study patients (11).

Betablockers

Women have higher plasma levels of beta-blocker (BB) due to decreased renal clearance (Cl) and smaller distribution volume (Vd) (12). Despite this, BB have been shown to have greater therapeutic effect in men: In a chronic angina study with metoprolol, women had significantly higher heart rate and blood pressure both a rest and during exercise (13), despite similar effects on the reduction in the frequency of anginal episodes.

Inhibitors of the Renin-Angiotensin-Aldosterone System

Sex-based differences have not been identified on the antihypertensive effects of angiotensin-converting enzyme inhibitors (ACEI), angiotensin-receptor blockers (ARB) and aliskiren (3). Although higher ARB maximum serum concentration (C_{max}) and area under the curve (AUC) were found in women, the differences disappeared when adjusted for weigh (14).

Sacubitril/Valsartan

The potential effects of age and sex on the PK of Sacubitril/Valsartan were assessed in a study that enrolled 36 subjects, 50% male and 50% female: No sex-dependent differences were found in PK (15).

Diuretics

C_{max} and AUC of torsemide are 30–40% higher in women due to reduced elimination (16).

Nitrates

C_{max} and AUC of isosorbide-5-mononitrate are higher in women, likely requiring weight adjustment and titration based on symptoms (17).

Calcium-Channel Blockers

Sex-specific PK differences have been described for verapamil, nifedipine, and amlodipine. Oral clearance of verapamil and amlodipine is faster in women compared to men, due to the higher activity of CYP3A4 and lower activity of P-gp (18).

Thrombolytics, Antithrombotics, and Anticoagulants

Warfarin dosage is strongly associated with sex, with lower requirements in women. Exogenous estrogen and testosterone can influence warfarin protein binding, so dose adjustment may be needed if hormone replacement therapy is initiated (12).

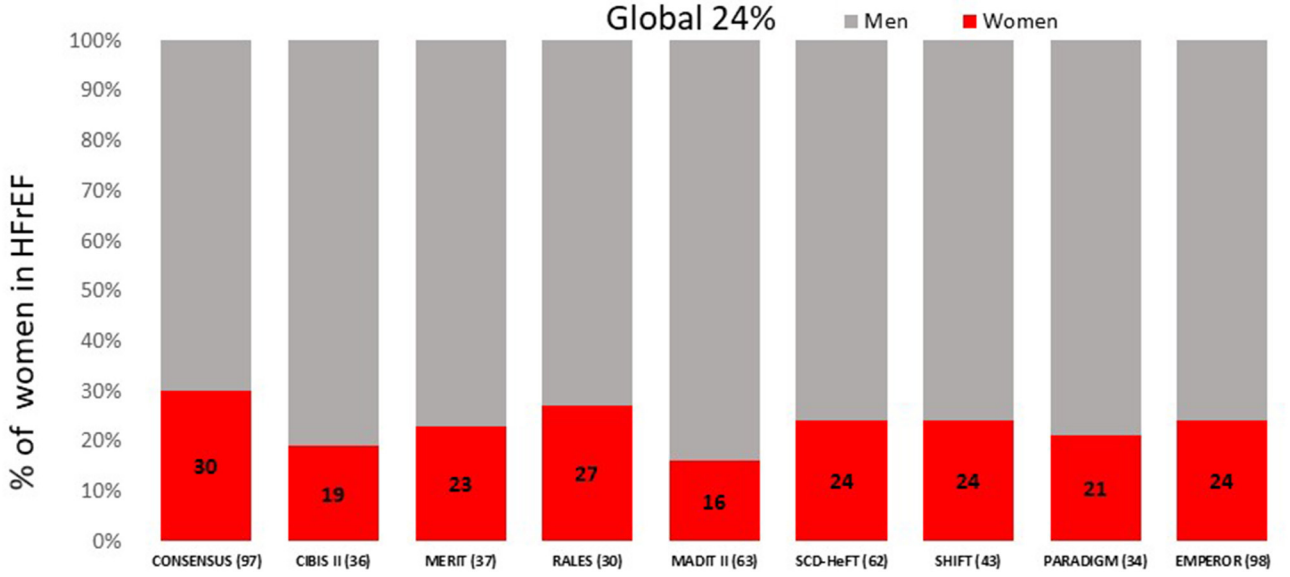

FIGURE 1 | Proportion of women included in the major HFrEF clinical trials. HFrEF, Heart Failure reduced Ejection Fraction.

There is limited data regarding sex differences in direct oral anticoagulants (DOACs). But safety and efficacy studies suggest the importance of dose adjustment based on body weight. In a DOAC meta-analysis including 66,389 patients (37.8% women), DOACs were associated with a significantly lower risk of major bleeding in women compared to men (RR 0.86; 95% CI 0.78–0.94) and a higher risk of stroke and systemic embolism compared with men (RR 1.19; 95% CI 1.04–1.35) (19).

SEX REPRESENTATION IN HEART FAILURE CLINICAL TRIALS

More than 30 years ago, the National Institutes of Health (NIH) established guidelines for the inclusion of women and minorities in clinical research. They recommend that clinical trials should enroll equal numbers of men and women in order to understand sex differences. Shortly thereafter, Congress approved these recommendations, and they became law. The Food and Drug Administration (FDA) published another regulation requiring detailed information by sex in clinical trials investigating new drugs, and therapies (20).

Clinical trials however, unfortunately, remain underpowered to identify statistically significant treatment effects in both sexes.

A recent study assessed the enrollment of women in 36 cardiovascular trials evaluating different drugs approved by FDA from 2005 to 2015. Adequacy between the percentage of women included in the trials and the prevalence of the female sex in the disease studied, was evaluated using the participation to prevalence ratio (PPR). A relationship between 0.8 and 1.2 was considered to reflect a good representation of women population. It should be noted that in the 3 HF trials included in this study women inclusion ranged from 22 to 40%. The overall PPR was 0.5, reflecting an inclusion of women in the trials well below their prevalence of the disease. More recent trials show the same pattern, ranging from 21 to 29% inclusion of women (21) (**Figure 1**).

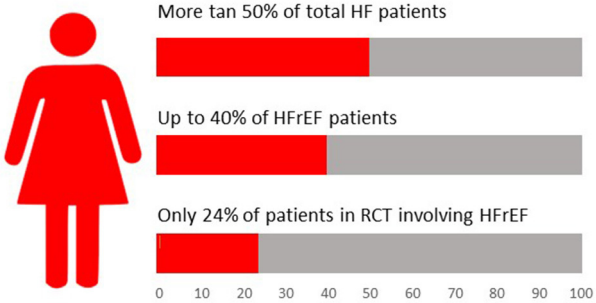

FIGURE 2 | Relevance of female sex in heart failure landscape. HF, Heart Failure; HFrEF, Heart Failure reduced Ejection Fraction; RCT, Randomized Controlled Trial.

In heart failure (HF) clinical trials, women represent approximately a quarter of patients with HFrEF and over half of those with HFpEF. However, epidemiologic data demonstrate a much higher proportion of women suffering the disease in the real world (22, 23) (**Figure 2**).

The differences between real world proportion of women with heart failure and their representation in clinical trials may depend on a variety of factors: more comorbidities, older age in women, fulfilling exclusion criteria more frequently, lower proportion of HFrEF, less investigator counseling or less personal availability, and willingness to enroll.

Sex Differences in Pharmacological Treatment of Heart Failure

Angiotensin-Converting Enzyme Inhibitors (ACEI)

The first clinical trials with ACEI date back to the late 1980s. A sub-analysis of the SOLVD trial (24) revealed a significant reduction in the combined outcome of CHF-related death and hospitalization in men (39.5 vs. 29.7% in the placebo and enalapril arm, respectively), but not in women (38.7 vs. 37.0%). Similar findings were reported other early trials with ACEI (CONSENSUS-1, SAVE) (25). A later meta-analysis including 30 randomized clinical trials on ACEI, evaluating data from more than 5,000 men and 1,500 women, showed a significant reduction in overall mortality and HF hospitalization in men, but not in women (26). The small proportion of women included in the trials may explain the lack of positive results (27).

Angiotensin II Receptor Blockers (ARB)

When large trials of ARB in HFrEF populations (ELITE, Val-HeFT, CHARM) explored sex-specific treatment effect they found no differences in mortality or HF hospitalization between women and men (16). ELITE II compared losartan with captopril in HFrEF patients and no difference based on sex was noted (28).

However, a population study comparing ACEI with ARB in HF, including 10,223 women (8,627 ACEI and 1,596 ARB) and 9,475 men (8,484 ACEI and 991 ARB), showed that women on ARBs had a better survival than those on ACE inhibitors, with a 31% relative risk reduction in all-cause mortality (adjusted HR 0.69, 95% CI 0.59–0.80, $p < 0.0001$). Conversely, there was no survival difference between ACEI or ARB in men (HR 1.10, 95% CI 0.95–1.30) (29).

Hormone effects on angiotensin II receptor expression or differences in adverse events may explain the potential superiority of ARB in women.

Mineralocorticoid Receptor Antagonists (MRA)

The studies assessing the role of mineralocorticoid receptor antagonist (MRA) in HFrEF (spironolactone in RALES and eplerenone in EPHESUS), showed no sex differences in prognosis (30, 31). In subgroup analysis of the EPHESUS study, female sex was associated with a reduction in all-cause mortality, while no differences were seen in men. Nevertheless, the interaction between the sex and the treatment arm was not significant.

In the TOPCAT trial, there were no sex-specific differences in the primary outcome (32). Nevertheless, in a secondary analysis of TOPCAT, restricted to 1,767 patients (49.9% women) enrolled in the Americas, spironolactone showed a reduction on mortality, with a trend toward greater reduction in cardiovascular mortality in women compared to men (9.0 vs. 13.2%, respectively, $p = 0.051$) (33).

Sacubitril-Valsartan

The PARADIGM-HF trial, showed superiority of sacubitril/valsartan compared to enalapril at reducing mortality and HF hospitalization in patients with HFrEF (34). In subgroup analyses, similar prognostic benefit was found for the primary endpoint in both men and women. When cardiovascular death was analyzed separately, sacubitril/valsartan showed a significant improvement in prognosis in men, but not in women (34), probably due to the small number of women included.

The PARAGON-HF trial, comparing sacubitril-valsartan and valsartan in patients with HFpEF, found no differences in primary composite end point of first and recurrent hospitalization for HF and death from CV causes. The primary composite endpoint occurred less frequently in women 0.73 (95% CI 0.59–0.90) compared to men 1.03 (0.84–1.25; $p = 0.017$) (35), primarily due to the reduction in HF hospitalization. Men were found to have a greater improvement in KCCQ-CSS than women. There were no sex differences in NYHA class, renal function, and adverse events.

In conclusion, PARAGONF_HF subanalysis suggest that sacubitril-valsartan may lead to greater reduction in HF hospitalizations in women with HFpEF.

Betablockers (BB)

Despite the low proportion of women included in BB trials (36–38) and lack of a specific design to study sex-differences, *post-hoc* pooled analysis confirmed similar and significant benefits of BB (bisoprolol, carvedilol, metoprolol) on combined end-point of all-cause mortality and all-cause hospitalizations in both women and men (39).

Interestingly, data from the earlier US-Carvedilol-Study (40), CIBIS II trial (41) and SENIORS study (42), suggest a greater survival benefit from BBs treatment in women, but no mechanistic explanation is described.

Ivabradine

The SHIFT trial, comparing ivabradine and placebo in patients with symptomatic chronic HFrEF (LVEF $\leq$35%) in sinus rhythm with heart rate >70 bpm, showed a reduction in the composite primary outcome of CV death or hospital admission for worsening HF. Subgroup analyses did not show any sex-differences in efficacy or safety of ivabradine (43).

Sodium-Glucose Cotransporter-2 Inhibitors (SGLT2i)

In the last 6 years, several large cardiovascular outcome trials evaluated the effect of iSGLT2 in patients with type 2 diabetes and established cardiovascular disease or those with high cardiovascular risk, they have consistently shown to reduce the risk of hospitalization for heart failure (44–49).

A meta-analysis of SGLT2i including patients with type 2 diabetes enrolled in the EMPA-REG OUTCOME, CANVAS Program, DECLARE TIMI-58, and CREDENCE trials, showed (50) no sex differences in safety or efficacy outcomes (all p interaction ≥ 0.17).

Recently, a meta-analysis condensing two single large-scale trials (DAPA-HF trial and EMPEROR-reduced trial) in patients with HFrEF with or without diabetes assessing the effects of SGLT2i on cardiovascular outcomes have been published. SGLT2i reduced hospitalizations for HF and death, with an improvement in renal outcomes, regardless of sex and other

conditions such as age, diabetes status, or baseline heart failure medications (51).

Other Heart Failure Medications

Diuretics

The effects of diuretics on mortality and morbidity in chronic heart failure have not been studied in large clinical trials. There are no reported sex-related differences with diuretic therapy. Observational studies have shown a relationship between diuretics dose and mortality risk, which was maintained after adjusting for sex (52).

Digoxin

In the DIG trial, digoxin was associated with a significantly higher risk of death among women (adjusted HR 1.23; 95% confidence interval, 1.02–1.47), with no increased risk in men (11). Subsequent retrospective analyses showed a strong relationship between serum digoxin concentrations and survival (53). Comprehensive analysis of data indicates a beneficial effect of digoxin on morbidity (HR 0.73, 95% CI 0.58–0.93, $p = 0.011$) and no excess mortality in women at serum concentrations between 0.5 and 0.9 ng/ml, whereas serum concentrations $\geq$1.2 ng/ml was harmful (HR 1.33, 95% CI 1.001–1.76, $p = 0.049$).

Overall, whereas higher digoxin levels tend to increase mortality in women, low concentrations seem to be safe and associated with improved symptoms.

Hydralazine-Isosorbide Dinitrate

The A-HEFT trial enrolled more than 5,000 black women (41% of total cohort) with moderate to severe heart failure (NYHA class III-IV) (54) to test treatment with hydralazine-isosorbide nitrate vs. placebo.

Treatment with hydralazine and isosorbide showed a significant reduction in mortality, first heart failure hospitalization, and change in quality of life at 6 months, with no differences between men and women.

SAFETY: HEART FAILURE DRUGS AND ADVERSE REACTIONS IN WOMEN

Women are known to have an increased adverse reaction (AR) to cardiovascular drugs compared to men (1.5–1.7-fold) (3) and have greater hospital admissions. Despite this fact, there is little emphasis on sex-specific differences in AR in drug trials. In a recent systematic review (55), only 7% of heart failure drug studies reported sex-based AR data. Differences in adverse events may be due to differences in absorption, body composition, drug distribution, physiological hormone changes and excretion (**Table 1**). These effects may be more pronounced in women with HF as they are older and have a higher prevalence of comorbidities and polypharmacy (60).

TABLE 1 | Heart failure drugs pharmacodynamics, efficacy and adverse events in women compared to men.

Drug	Summary	References
Digoxin	- ↑ Death risk with less benefit in hospitalization. Related to higher dosage in women, considering their lower body weight.	(11, 53)
Beta-blockers	- ↑ Plasma levels with the same doses due to lower distribution volume (hydrophilic drugs) and slower clearance. - Similar or higher benefit in women.	(12, 35–39, 41, 42)
ACE-inhibitors	- Less benefit in women in clinical trials, but underrepresented (bias?). - ↑ Angioedema and cough. - Teratogenic.	(25–27, 56)
ARB	- Little evidence of more benefit in women.	(16, 28, 29, 57)
Sacubitril/valsartan	- Similar pharmacokinetic parameters. - Similar results in HFrEF hospitalizations but less reduction in CV death (underrepresented, bias?). - Less HF hospitalizations in HFpEF.	(15, 34, 35)
Mineralocorticoid receptor antagonists	- Similar or more benefit in women. - Lower withdrawal.	(30–33, 58)
Diuretics	- ↑ Serum concentration due to reduced elimination. - More electrolyte imbalance.	(16, 52, 59)
Nitrates	- ↑ Serum concentration: need to adjust for weight.	(17)
Ivabradine	- No sex differences on effectiveness.	(43)
iSGLT2	- Similar effectiveness and adverse events.	(44–51)

ACE, angiotensin converting enzyme; ARB, angiotensin receptor blockers; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HFpEF heart failure with preserved ejection fraction; CV death, cardiovascular death; iSGLT2, sodium-glucose co-transportrer-2 (SGLT2) inhibitors; ↑, Increased.

Diuretics

Women experience greater electrolyte imbalance with diuretic use, which in turn increases the arrhythmic risk. For instance, women have an increased risk of drug-induced torsades de pointes (2.3-fold) related to a longer corrected QT interval induced by the effects of estradiol on potassium and calcium channel modulation (59).

Digoxin

A post hoc analyses of the DIG study (11) showed a 20% higher death risk in women (HR 1.2, CI 1.02–1.47), with no impact on mortality in men. Moreover, digoxin showed less benefit in reducing hospitalization in women, compared to men. This may be related to dosage, since differences disappeared when dose was adjusted for ideal body weight.

Beta-Blockers

Women present higher plasma levels of beta-blocker due to a lower distribution volume (higher percentage of fat in women,

beta-blockers are hydrophilic drugs) and a slower clearance. Dosage needs to be adjusted according to these differences to prevent AR.

Angiotensin-Converting Enzyme Inhibitors

An increased risk of angioedema and cough (2-fold) has been described in women (56). Moreover, their potential teratogenic effects need to be acknowledged in women during childbearing years.

Angiotensin II Receptor Blockers

No significant sex-differences in risk of kidney impairment, hypotension, or hyperkalemia have been described with the use of Losartan (57).

Mineralocorticoid Receptor Antagonists

There seems to be a higher withdrawal rate in men due to the appearance of gynecomastia (seen in 5.3% of the men) (58).

ADVANCED HEART FAILURE THERAPIES IN WOMEN: DEVICES AND HEART TRANSPLANTATION

Implantable Cardioverter Defibrillator

Implantable Cardioverter Defibrillators (ICD) have shown to reduce sudden death risk in heart failure patients with reduced ejection fraction, especially of ischemic etiology. Therefore, they have a class 1A indication according to current guidelines for primary prevention in patients with left ventricular ejection fraction (LVEF) <35% despite optimal medical therapy (61).

These recommendations are based on classical studies, such as SCD-HeFT (62), MADIT II (63), or DANISH (64), where female representation was small (23, 15, and 27%, respectively). In fact, women with heart failure (HF) are less likely to receive an ICD or counseling for ICD. In a large observational study (65) including 21,059 patients from 236 sites, 19.3% women vs. 24.6% men ($p < 0.001$) were offered ICD implantation. Of note, the same proportion of men and women underwent the implant once it was advised (63.1 vs. 62.3%, $p =$ ns). In another observational study 32.2 per 1,000 men and 8.6 per 1,000 women received ICD therapy. After controlling for demographic variables and comorbidity, men were 2.44 (95% CI 2.30–2.59) times more likely to receive an ICD compared to women.

The reduced rate of ICD implantations in women may be related in part to the controversies regarding efficacy and higher risk of complications in women compared to men.

Although some device studies show a similar survival benefit after ICD implantation in both men and women, most are underpowered to study sex differences. In a metanalyses including 4,744 primary prevention ICD patients (66) (19.6% female), there was a 22% reduction in mortality in men but no benefit in women. In fact, ventricular arrythmias may be less common amongst women. The risk of sudden death was 32% lower in women compared to men in 8,337 HF patients cohort with no ICD (67). Women have consistently shown to have fewer appropriate ICD shocks. In a metanalyses (68) including 7,229 patients (22% female), women had a HR for appropriate ICD shocks of 0.63 (95% CI 0.49–0.82, $p \leq 0.001$) compared to men and no significant benefit on mortality. In a European study (69) analyzing data from 14 registries in 11 countries (5,033 patients, 19% female), an appropriate ICD shock occurred in 8% of women vs. 14% of men, $p = 0.0002$. In the Ontario ICD Database (70) (6,021 patients, 22% female), women showed a HR 0.69 (95% CI 0.51–0.93) for ICD shock and HR 0.73 (95% CI 0.59–0.90) for appropriate antitachycardia pacing compared to men. Etiology of cardiomyopathy and scar burden may account in part for these differences. In addition, sex hormones and their influence on myocardial ion channels (Ca, K) could play a role as well (71).

ICD related complications have been reported more frequently in women. In the Ontario ICD Database (70) women were 1.9 times more likely to have a major complication within the first year after implant, including lead dislodgement. In the National Cardiovascular Data Registry (72) (38,912 initial single or dual-chamber ICD implants, 25% female) women showed higher odds of procedural complications within 90 days OR 1.30 (95% CI 1.26–1.53, $p < 0.001$). The reasons for the differences in the complication rate are unclear but could be related to delayed presentation or greater severity of illness. Smaller vessel size and a thinner walled right ventricle may explain a higher rate of pneumothorax or perforation. Increased bleeding risk have also been reported in women.

Overall, studies show sex differences in arrhythmic risk and ICD-related complications. Nevertheless, there is a risk of sudden death in women with HF and reduced LVEF that could be prevented by ICD implantation. Careful and individualized assessment is required to identify patients that would benefit the most from this therapy.

Cardiac Resynchronization Therapy

Cardiac Resynchronization Therapy (CRT) has shown to improve functional capacity and survival amongst patients with LVEF<35%, left bundle block >130–150 ms and NYHA functional class II-IV and therefore has a class 1A indication in current HF guidelines (73). Several studies have reported under-utilization of CRT in women (74). A recent study (75) using registry data of 311,009 patients undergoing CRT implantation between 2006 and 2012 showed that only 30% were women, and women were less likely to have an ICD associated to the CRT. Interestingly however, women had a higher CRT response score compared to men. These disparities increased over the study period. In a Swedish registry (76), female sex was again associated with lower CRT implantation. Despite this, most of the studies suggest similar if not better response to CRT in women.

The CARE-HF (77) ($n = 752$, 28% female) and COMPANION (78) ($n = 1{,}520$, 32% female) trials demonstrated similar reduction in mortality and time to hospitalization in both sexes after CRT implant. In the MASCOT (79) trial ($n = 393$, 21% female) women showed better left ventricular remodeling and lower mortality and HF hospitalizations after adjustment for cardiovascular risk factors. Remarkably, women showed wider QRS and smaller left ventricle size at enrollment. In another study that only included patients with non-ischemic cardiomyopathy ($n = 212$, 49.5% female) CRT response among women was greater (84 vs. 58%, $p < 0.001$) than in men, despite similar

baseline QRS duration (80). In fact, women showed better response compared to men at all QRS widths below 180 ms. In a retrospective analysis (81) of 619 consecutive patients (19% women) undergoing CRT implantation in a single center over a 10-year period, female sex was the only independent predictor of all—cause mortality (HR 0.44, 95% CI 0.21–0.90, $p = 0.025$) and showed a trend toward lower heart failure hospitalization. In a metanalyses (82) of 5 randomized control trials ($n = 3,496$, 23% female), QRS duration was the only independent predictor of CRT benefit. Further analysis showed the benefit was even more significant at lower height. There was a higher proportion of women amongst the wider QRS and shorter patients.

As we discussed for ICD, complication rate seems to be higher in women after CRT implant. In the MADIT-CRT trial, women were twice as likely as men to experience a major procedure-related adverse event (6.3 vs. 2.7%; $p < 0.001$) mainly related to pneumothorax, infection or bleeding. The main risk factor for complications seemed to be size and body mass index both in women and men.

Overall, women show a better response to CRT after adjusting for non-ischemic etiology of the cardiac disease. Reasons are not clearly established but this benefit could be related to a smaller ventricle size with easier conduction between the leads and presence of more typical left bundle branch block.

Ventricular Assist Device

Mechanical circulatory support has expanded significantly in the recent years, with over 13,000 implants in the INTERMACS registry (83) between 2014 and 2018, of which only 22% were women. Technical evolution has enabled devices to become smaller and to evolve from pulsatile flow first to axial-flow and now to centrifugal flow with full magnetic levitation. This has led to a significant decrease in morbidity and mortality and increase in implantations. Left ventricular assist devices (LVAD) are now smaller and more hemocompatible. Despite this, in the MOMENTUM3 (84) trial, HeartMate3's pivotal trial, only 21% of the participants were women.

There are no sex differences in survival either in pulsatile or continuous flow devices according to INTERMACS registry (85). Complications are frequent, and include driveline infection, bleeding, pump thromboses, right ventricular failure, and neurological events. There is scarcity of data on the incidence of these complications according to sex, although several reports suggest that there might be a higher incidence of neurological events in women. In an INTERMACS registry study ($n = 1,936$, 21% female) female sex was associated with an increased risk of first neurological event (HR 1.44, 95% CI 1.05–1.96; $p = 0.020$), with no difference in other complications. In a later paper focusing on stroke rates during support with continuous-flow LVAD, female sex was also a predictor of stroke (HR 1.51, 95% CI 1.25–1.82; $p < 0.001$). The same was reported in an analysis of more than 900 HeartMate II outpatients (86) (23% female), where female sex was a risk factor for both hemorrhagic and ischemic stroke. There is lack of data on the impact of sex in stroke rate with HeartMate3 since the event rate in MOMENTUM3 was too low to derive conclusions.

There is no clear explanation as to why fewer women receive LVAD compared to men. Some aspects to consider are smaller body surface area, smaller ventricles, older age at the time of HF diagnosis and a higher prevalence of HF with preserved ejection (87), which is not suitable for LVAD support. Since there might be a risk for selection bias, we need to be aware that women benefit as much as men from this life-saving therapy, with no significant increase in complications specially with the newer generation LVAD devices.

Heart Transplantation

Heart Transplantation (HT) is the therapy of choice to improve survival in patients with end-stage HF. Mean survival after HT nowadays is 12.5 years for the adult population and 12–21 years for the pediatric population (88). Rejection and infection are the most concerning complications in the first year post-HT, whereas the leading cause of death after the first year are coronary allograft vasculopathy and malignancy.

Women are again under-represented in the field of HT: according to the last report from the International Society for Heart and Lung Transplantation (88), only a quarter of the HT were performed in women (25% in Europe, 26% in the United States of America, and 24% in other countries). There is also a smaller proportion of women amongst the donors (37% in Europe, 30% in the United States, and 22% in other countries). Female HT receptors have shown a better life expectancy compared to male recipients: 12.2 vs. 11.4 years ($p < 0.001$) (89).

Women are younger than men at the time of listing (mean 48 year for women vs. 56 years for men), have less ischemic heart disease and more idiopathic dilated cardiomyopathy, and fewer cardiovascular risk factors such as smoking, diabetes mellitus, hypertension, or tobacco use (89). On the other hand, women are less likely to be transplanted in the higher emergency status, as they are also less frequently supported with temporary mechanical circulatory devices.

In the post HT period, women are at a lower risk of coronary allograft vasculopathy and malignancy. These differences could explain longer survival in female HT recipients.

Pre-HT sensitization and post-HT rejection risk are higher in women, related predominantly to the presence of circulating preformed HLA antibodies due to sensitization from previous pregnancies (90). Donor-recipient matching is key at the time of HT. Sex mismatch has been reported as a prognostic factor for HT outcomes, with best outcomes reported with female donor to female recipient and the worst with female donor to male recipient. A simple explanation for this fact, is the undersizing of female donor hearts when used for male recipients, however, outcome differences seem to persist even after adjustment for ventricular mass (91).

In summary, fewer women receive HT, despite their better long-term survival. Sex specificities need to be considered in the pre-HT evaluation (greater sensitization, fewer cardiovascular risk factors), at the time of transplant (sex and size donor-recipient matching) and in the long-term post-HT follow-up

TABLE 2 | Advanced heart failure therapies in women: summary and key messages.

Intervention	Summary	References
Implantable cardioverter device	- Women under represented in ICD trials (15–27%). - Less likely to receive counseling for ICD. - Fewer ventricular arrythmias and appropriate ICD shocks. - Higher rates of complications (pneumo/hemothorax).	(62–72)
Cardiac resynchronization therapy	- CRT under utilized in women (30%). - Women show better response to CRT (left ventricular remodeling, mortality and HF hospitalizations). - Wider QRS complex with classic left bundle branch block and smaller ventricles may explain better CRT response in women. - Higher rates of complications during implantation.	(73–82)
Mechanical circulatory support	- Fewer women (22%) receive MCS. - Similar overall outcomes as men in both pulsatile and continuous flow devices. - Greater risk of neurological events in women (ischemic and hemorrhagic). - New generation smaller and more hemocompatible devices could increase implant rates in women.	(83–87)
Heart transplantation	- Fewer HT are performed in women (25%). - Women have better post transplant survival, related to pre HT factors (younger age, less cardiovascular risk factors) and post HT factors (less allograft vasculopathy and malignancies). - Women have increased immunological risk (sensitization and rejection)	(88–90)

ICD, implantable cardioverter device; CRT, cardiac resynchronization therapy; MCS, mechanical circulatory support; HT, heart transplantation.

(increased risk of rejection but lower risk of graft vasculopathy and malignancies) (**Table 2**).

SEX DIFFERENCES IN ADHERENCE

Adherence to long-term therapies for chronic diseases in developed countries averages only about 50–75% (2). Inadequate adherence is associated with increased long-term mortality in patients with heart failure (92).

Few studies have aimed to assess the effect of sex on adherence to HF drugs. Granger et al. analyzed adherence among participants in the CHARM trial ($n = 7{,}599$) and they found that 11% were poor adherers (<80%, $n = 836$). Poor adherers were more likely to be women (12.7% of women vs. 10.2% of men; $p = 0.002$), have a higher heart rate, and a greater number of concomitant illnesses (93).

Kayiband et al. performed an inception cohort study of new users of evidence-based HF drug treatment. They included 28,067 Canadian patients (13,453 women, 14,614 men) between January 2000 and December 2008 who had a follow-up >1 year after HF drug treatment initiation. In this study women were more likely than men to be adherent to their treatment (52.8 and 50.1%, respectively, adjusted proportion ratios: 0.96, 95% CI: 0.94–0.99) (94). More recently, a retrospective, observational study was carried out in the Dutch population. Twenty-five thousand seven hundred and seventy-six patients with a diagnosis code for chronic HF between January 2012 and December 2014 were included in order to study the impact of sex differences in co-morbidities and medication adherence on a composite endpoint of all-cause mortality or HF admission. 11,259 (45%) women and 14,517 men, median age 76 and 72 years, respectively, were analyzed after a median follow-up of 3.3 years, and only slight differences in HF drugs adherence between women and men were found with no impact on the composite endpoint (95).

We can conclude that non-adherence to disease-modifying drugs is associated with an increased mortality and HF readmissions, but adherence seems to be similar between sexes (**Figure 3**).

DISCUSION

Although women represent 50% of the world population and despite similar overall prevalence of heart failure among men and women (96) women are significantly underrepresented in clinical trials for heart failure. The trend has not changed significantly over time, with similarly low inclusion rate for women in the newer HFrEF trials. For example, women represented 30% of the study population in the enalapril CONSENSUS trial (97), in 1987, and 19% in the bisoprolol CIBIS II trial in 1999 (36) and represented 24% of the study population in the EMPEROR trial (98), published in 2020. This may be due to a higher proportion of women with HFpEF, older age and more comorbidities, limiting their chances of being included in HFrEF trials. In HFpEF trials, such as PARAGON (99) or TOPCAT (32), women represent 50% of the study population, which is higher compared to HFrEF trials, but still low in comparison to the percentage of women in the population with HFpEF. In fact, HF is the discipline of cardiology in which women are most underrepresented (21) in clinical trials.

Women are generally more symptomatic than men when they present with HFrEF (100), which could in turn be related to a later medical contact, minimization of symptoms, acceptance of a poorer quality of life (101) and a prioritization of their social role as caregivers. Due to underrepresentation in clinical trials, we have limited information on the efficacy and adverse effects of therapies in women. In a recent study on the use of guideline recommended therapy for HF and its titration, women had a similar proportion of HF drug and dose prescription compared to men, at baseline and at 1-year follow up. Considering the differences in adherence, absorption, metabolism, body weight and adverse events between men and women, it would be reasonable to establish a more tailored therapy according to sex. The main limitation for an individualized approach

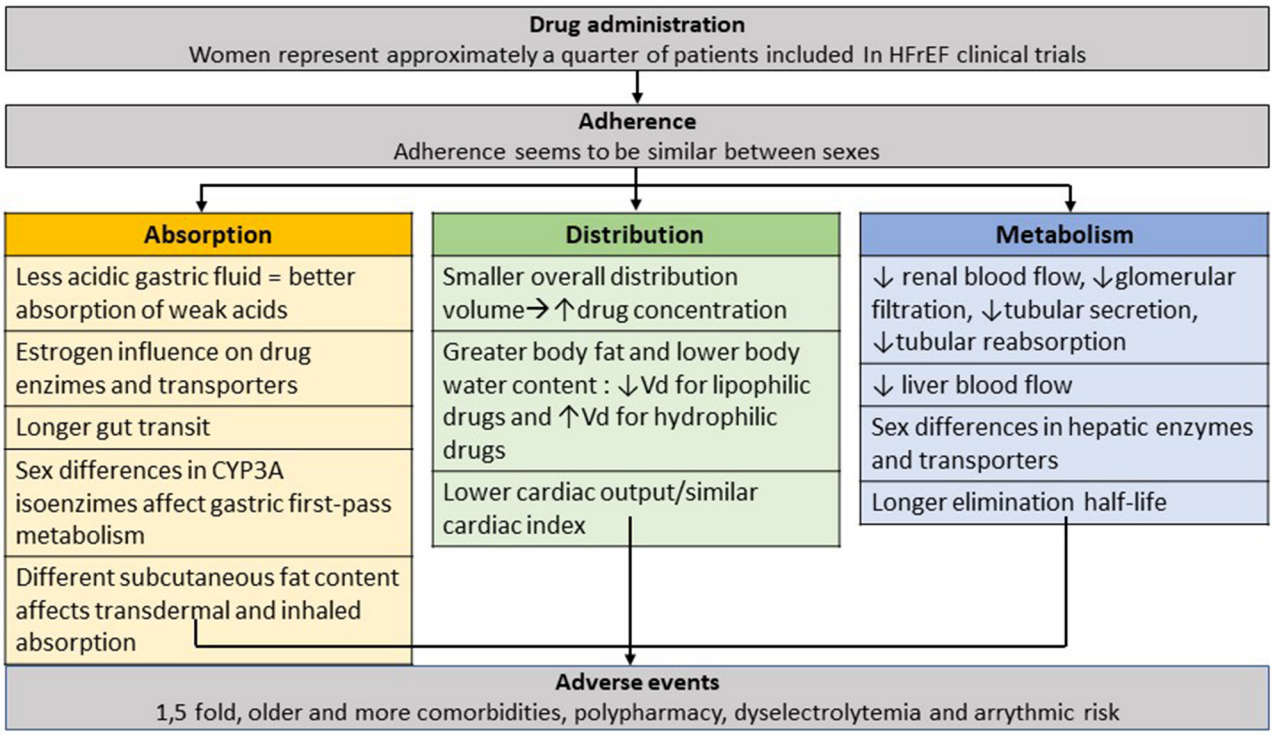

FIGURE 3 | Use of heart failure drugs in women. Sex-differences on prescription, adherence, effective circulation levels and adverse events. HFrEF, Heart Failure reduced Ejection Fraction.

remains to be the lack of reliable data. Santema et al. (102) showed how, despite achievement of similar target doses of HF guideline recommended therapy in men and women, the lowest hazards of death for men occurred at 100% of the recommended dose, whereas women showed 30% lower risk at 50% of the recommended dose, with no further decrease in risk at higher doses.

Women are also less likely to receive lifesaving therapies such as LVAD (103) and HT. LVAD therapy has shown similar survival benefits in women compared to men, but women tend to be more unstable at the time of implant, with worse INTERMACS profiles and more severe tricuspid regurgitation (104). In the HT arena, despite similar overall survival, women are more likely to receive hearts from higher risk donors (105).

Reproductive health counseling, teratogenic effect of HF medications and pregnancy management for women with HF are some important topics that affect women uniquely and that need to be a focus for future research and discussion, especially for those in need of advanced HF therapies and devices.

CONCLUSIONS AND FUTURE PERSPECTIVES

Despite high prevalence of HF in women, there is lack of data on the use of drugs and HF therapies, with limited enrolment in randomized control trials and limited access to lifesaving strategies. Future trials should focus on greater enrollment of women in heart failure therapeutics and devote resources to understand the pathophysiology of the sex differences and disparities in access to advanced therapies.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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GLOSSARY

AAG: alpha-1 acid glyconprotein
ACEI: angiotensin-converting enzyme (ACE) inhibitors
AR: Adverse reaction
ARB: angiotensin-receptor blockers
AUC: area under the curve
BB: Betablockers
BMR: basal metabolic rates
BSA: body surface area
CI: Confidence Interval
CI: cardiac index
Cl: clearance
CO: cardiac output
CRT: Cardiac Resynchronization Therapy
CYP3A4: cytochrome P450 3A4
CV: cardiovascular
DOACs: direct oral anticoagulants
FDA: Food and Drug Administration
HF: heart failure
HFpEF: Heart Failure preserved Ejection Fraction
HFrEF: Heart Failure reduced Ejection Fraction
HR: Hazard Ratio
HT: Heart transplantation
ICD: Implantable Cardioverter Defibrillator
LVEF: left ventricular ejection Fraction
LVAD: Left Ventricular Assist Device
MRA: Mineralocorticoid receptor antagonists
NIH: National Institutes of Health
PK: pharmacokinetics
PD: pharmacodynamics
PPR: participation to prevalence ratio
SGLT2i: Sodium-glucose cotransporter-2 inhibitors
Vd: volume distribution

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