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# Sex Differences in Heart Failure Mortality with Preserved, Mildly Reduced and Reduced Ejection Fraction: A Retrospective, Single-Center, Large-Cohort Study

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**Abstract:** Background: Heart failure (HF) is one of the leading causes of death worldwide. Studies show that women have better survival rates than men despite higher hospitalizations. However, little is known about differences in mortality and predictors of death in women and men with HF with preserved (HFpEF), mildly reduced (HFmrEF), and reduced ejection fraction (HFrEF). Methods: From February 2017 to September 2020, mortality and predictors of death were analyzed in women and men with HF. Baseline data included clinical characteristics and echocardiographic findings. Results: A total of 11,282 patients, 63.9 ± 14.4 years, including 6256 (55.4%) males, were studied. Females were older, had a higher baseline mean left ventricular ejection fraction (LVEF) and lower left ventricular diastolic diameter. During follow-ups, 1375 (22%) men and 925 (18.4%) women died. Cumulative incidence of death was higher in men with HFrEF but similar for HFmrEF and HFpEF. Cox regression for death showed renal dysfunction, stroke, diabetes, atrial fibrillation, age, LVEF, valve disease, MI, and hypertensive CMP as independent death predictors for all HF patients. Conclusions: Women had a better prognosis than men in HFrEF and similar mortality for HFmrEF and HFpEF, but sex was not an independent predictor of death for all HF subtypes.

**Keywords:** heart failure; cardiomyopathy; left ventricular ejection fraction; prognosis; women; men

## 1. Introduction

Heart failure (HF) is one of the leading causes of death and hospitalization from cardiovascular disease worldwide and years lived with disability [1]. In Brazil, despite the decline in the mortality rate, HF is still the leading cause of hospitalization and hospital death [2]. The HF incidence increases markedly after 60 years but more significantly in men [3]. The lifetime risk of developing HF is much higher in men, probably due to the higher prevalence of comorbidities such as myocardial infarction (MI), hypertension, diabetes, and chronic kidney disease (CKD) [4]. Women with HF are more likely to be older,

hypertensive, with preserved systolic function, and have a lower incidence of coronary artery disease [5]. HF in women presents more frequently with preserved left ventricular ejection fraction (HFpEF) rather than with reduced ejection fraction (HFrEF), which occurs predominantly in men [6,7]. Myocardial dysfunction in HF activates sympathetic and renin-angiotensin-aldosterone systems, increasing LV end-diastolic pressure and afterload in women and men. Nevertheless, there are sex differences in HF pathophysiology, which depend on estrogen, gene expression, inflammation, and comorbidities. In women, these differences may be related to endogenous estrogen-mediated mechanisms [8]. Estrogen protects the epicardial and microvasculature endothelial response to injury and reduces the activation of the sympathetic and renin-angiotensin-aldosterone systems. Estrogen's beneficial effects protect the left ventricle from remodeling and maintain diastolic function. Low estrogen levels activate these systems that favor the rise of reactive oxygen species and collagen synthesis, drops in nitric oxide, and diastolic dysfunction [9]. HF diagnosis requires typical signs and symptoms associated with increased BNP plasma concentration and a non-invasive cardiac imaging test, most often by a transthoracic echocardiogram showing left ventricular dysfunction [10]. There is evidence of a gender-associated risk of dying of HF in different HF subtypes [11,12]. The lifetime risk also differs in the HF spectrum, with HFrEF higher in men but similar in women and men for HFpEF [13]. Studies show that women have better survival rates than men for all HF subtypes, despite higher hospitalizations [14,15]. Men with HFrEF have higher cardiovascular mortality than women [16]. In HF with mid-range ejection fraction (HFmrEF) and HFpEF, women still show better survival differences than HFrEF. Nevertheless, sex-specific data are scarce concerning the epidemiology, comorbidities, hospitalizations, prognosis, and treatment of the different HF subtypes in populations of women and men. This study analyzed sex differences in all causes of death in HF subtypes in women and men.

## 2. Materials and Methods

This retrospective and single-center large cohort study analyzed clinical characteristics, laboratory data, and prognosis of 11,282 outpatients with HF aged $\geq$18 years, including 6256 (55.4%) men. This study was performed at the Instituto do Coração (InCor), Hospital das Clínicas, Faculdade de Medicina da Universidade de São Paulo, from February 2017 to September 2020. The Hospital Medical Information Unit provided the patients' data. The patients of interest were those diagnosed with HF. The Framingham criteria for diagnosing HF [17] and echocardiographic measurements were used. The echocardiographic data were those of the patients with both the baseline and the closest echocardiogram available at the end of the study. HF was categorized according to LVEF in HFrEF for LVEF $\leq$ 40%, HFmrEF for LVEF of 41–49%, and HFpEF for LVEF $\geq$ 50%. We excluded patients with HF from congenital heart disease and Chagas disease. The primary outcome was all-cause mortality which included cardiovascular and non-cardiovascular death. Cardiovascular death included fatal myocardial infarction, stroke, or other cardiovascular deaths. Non-cardiovascular deaths included cancer and infection-related deaths. From March to September 2020, COVID-19 infection-related deaths may have occurred in the study population, but the exact number of COVID-19 deaths was unavailable. The mortality data were obtained from the patient's medical record or the individual registration status on the Federal Revenue's website [18]. The clinical characteristics analyzed were age, the prevalence of comorbidities, the number of HF hospitalizations, and any cardiac surgical intervention. The comorbidities analyzed were diabetes (glycemia $\geq$ 126 mg/dL or under hypoglycemic drug), significant CKD (creatinine $\geq$ 2 mg/dL), atrial fibrillation (AF), previous MI, and stroke. The cardiac surgical interventions analyzed were percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG), valve repair or replacement, pacemaker implantation, cardiac resynchronization therapy (CRT), implantable cardioverter defibrillators (ICD), and heart transplants.

*Statistical Analysis*

The continuous variables were presented as mean, standard deviation, and categorical variables as frequencies and percentages. Normality was tested using the Kolmogorov–Smirnov test. The Student's *t*-test and analysis of variance were used to compare groups with continuous variables and chi-square for categorical variables. A two-sided probability of <0.05 will consider the statistical significance. We used the Kaplan–Meier (K-M) method with Šidák multiple-comparison adjustment to analyze the cumulative incidence of all-cause death. Cox proportional hazards models were used to examine variables independently associated with all-cause death. The chi-square score of the Cox proportional hazards model defined the most robust predictors of all-cause death. The dependent variable in Cox proportional hazards model was death. Covariates were age, sex, MI, diabetes, stroke, CKD, AF, PCI, CABG, LVEF, all coronary surgical intervention (percutaneous coronary intervention (PCI) + coronary artery bypass graft (CABG)), and all devices implantation (pacemaker + cardiac resynchronization therapy + implantable cardioverter-defibrillator). We used the SAS® Studio package (SAS Institute, Cary, NC, USA) for statistical analyses.

## 3. Results

Table 1 shows the clinical characteristics and echocardiographic data from all patients, in women and men.

**Table 1.** Clinical characteristics and echocardiographic data of the women and men with heart failure.

| | **All Patients N = 11,282** | **Women N = 5026 (44.6)** | **Men N = 6256 (55.4)** | *p* |
|---|---|---|---|---|
| Age (Years) | 63.9 ± 14.4 | 65.1 ± 15.0 | 63.0 ± 13.8 | <0.0001 |
| Ischemic CMP | 3248 (28.8) | 1126 (22.4) | 2122 (33.9) | <0.0001 |
| Idiopathic CMP | 4598 (4S0.8) | 1989 (39.6) | 2609 (41.7) | <0.0022 |
| Hypertensive CMP | 1934 (17.1) | 1033 (20.6) | 901 (14.4) | <0.0001 |
| Valve disease | 1502 (13.3) | 878 (17.5) | 624 (10.0) | <0.0001 |
| Myocardial infarction | 1670 (14.8) | 557 (11.1) | 1113 (17.8) | <0.0001 |
| Diabetes | 214 (19.0) | 934 (18.6) | 1207 (19.3) | 0.427 |
| CKD | 1202 (10.7) | 416 (8.3) | 786 (12.6) | <0.0001 |
| Atrial fibrillation | 2241 (19.9) | 948 (18.9) | 1293 (20.7) | 0.019 |
| Stroke | 512 (4.5) | 196 (3.9) | 316 (5.1) | 0.010 |
| Number of comorbidities | 5378 (47.7) | 2225 (44.3) | 3153 (50.4) | <0.0001 |
| N = 1 | 3372 (29.9) | 1482 (29.5) | 1890 (30.2) | 0.476 |
| N = 2 | 1463 (13.0) | 556 (11.1) | 907 (14.5) | <0.0001 |
| N = 3 | 446 (3.9) | 155 (3.1) | 291 (4.7) | 0.149 |
| N ≥ 4 | 97 (0.8) | 32 (0.6) | 65 (1.0) | 0.489 |
| PCI | 397 (3.5) | 140 (2.8) | 257 (4.1) | <0.0001 |
| CABG | 884 (7.8) | 285 (5.7) | 599 (9.6) | <0.0001 |
| Valve replacement | 988 (8.8) | 534 (10.6) | 454 (7.3) | <0.0001 |
| Valvoplasty | 125 (1.1) | 81 (1.6) | 44 (0.7) | <0.0001 |
| Pacemaker | 622 (5.5) | 339 (6.7) | 283 (4.5) | <0.0001 |
| ICD | 265 (2.4) | 72 (1.4) | 193 (3.1) | <0.0001 |

**Table 1.** *Cont.*

| | All Patients N = 11,282 | Women N = 5026 (44.6) | Men N = 6256 (55.4) | *p* |
|---|---|---|---|---|
| CRT | 317 (2.8) | 151 (3.0) | 166 (2.7) | 0.181 |
| Transplantation | 176 (1.6) | 62 (1.2) | 114 (1.8) | 0.007 |
| Hospitalization | 3207 (28.4) | 1474 (29.3) | 1733 (27.7) | <0.0001 |
| LVEF baseline | 45.3 ± 15.9 | 49.2 ± 16.0 | 42.3 ± 15.1 | <0.0001 |
| LVEF final | 46.4 ± 15.0 | 49.9 ± 14.5 * | 43.7 ± 14.7 * | <0.0001 |
| LVDD baseline | 57.7 ± 9.6 | 54.4 ± 8.8 | 60.1 ± 9.5 | <0.0001 |
| LVDD final | 56.8 ± 10.0 | 53.7 ± 9.0 * | 59.3 ± 10.0 * | <0.0001 |
| HFrEF | 4310 (38.2) | 1488 (29.6) | 2822 (45.1) | <0.0001 |
| HFmrEF | 1826 (16.2) | 653 (13.0) | 1173 (18.8) | <0.0001 |
| HFpEF | 5146 (45.6) | 2885 (57.4) | 2261 (36.1) | <0.0001 |
| Death | 2300 (20.4) | 925 (18.4) | 1375 (22.0) | <0.0001 |

* $p < 0.05$ for LVEF and LVDD baseline vs. final intragroup comparisons. Numbers in brackets mean percentage; *p* values: women vs. men; CABG: coronary artery bypass graft; CKD: chronic kidney disease; CMP: cardiomyopathy; CRT: cardiac resynchronization therapy; HFmrEF: HF with mildly reduced ejection fraction; HFpEF: HF with preserved ejection fraction; HFrEF: HF with reduced ejection fraction; ICD: implantable cardioverter-defibrillator; LVDD: left ventricular diastolic diameter; LVEF: left ventricular ejection fraction; PCI: percutaneous coronary intervention.

Women were older and had a higher prevalence of hypertensive CMP and valve disease. The comorbidities were higher in men than women, as well as PCI, CABG, ICD, and transplant. Women had higher pacemaker implantation, hospitalizations, baseline, and final LVEF. The baseline and final LVDD were lower in women. In women, final LVEF and LVDD decreased compared with baseline LVEF and LVDD, respectively. In men, LVEF increased and LVDD decreased. During the follow-up period, 1375 (22%) men and 925 (18.4%) women died ($p < 0.0001$). The cumulative incidence of death was higher in men (K-M: log-rank $p = 0.0001$) (Figure 1).

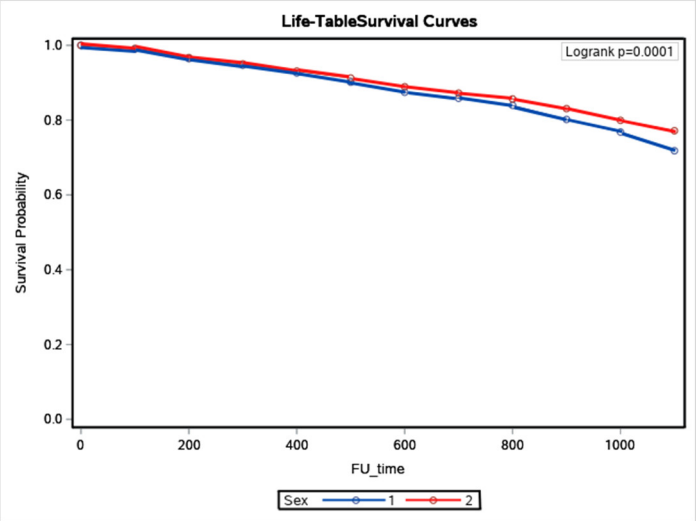



**Figure 1.** Kaplan–Meier survival curves in women and men with heart failure (Sex 1 means men and 2 women).

Table 2 shows the clinical characteristics and echocardiographic data of the patients with HF with preserved (HFpEF), mid-range (HFmrEF), and reduced (HFrEF) left ventricular ejection fraction.

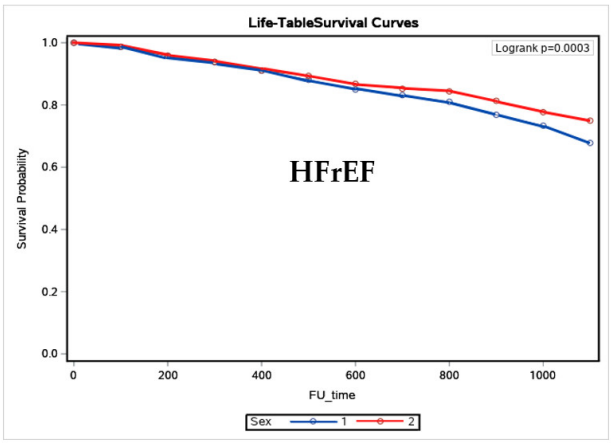
**Table 2.** Clinical characteristics of the patients with heart failure with preserved (HFpEF), mid-range (HFmrEF), and reduced (HFrEF) left ventricular ejection fraction.

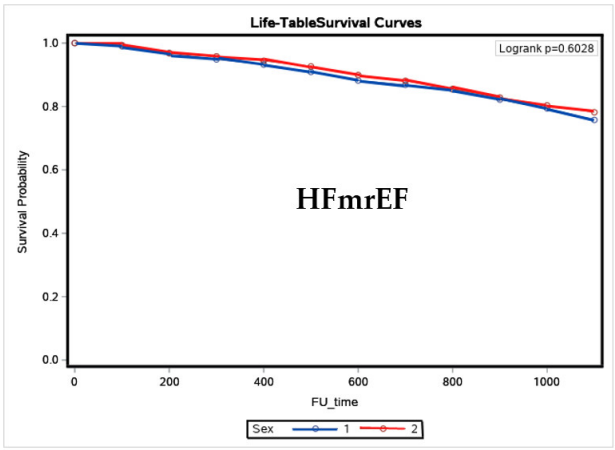
| | **HFrEF N = 4310 (38.2)** | **HFmrEF N = 1826 (16.2)** | **HFpEF N = 5146 (45.6)** | ***p*** |
|---|---|---|---|---|
| Age (Years) | 60.2 ± 13.7 | 64.1 ± 13.5 | 66.9 ± 14.6 | <0.0001 |
| Female | 1488 (34.5) | 653 (35.8) | 2885 (56.1) | <0.0001 |
| Cardiomyopathy | | | | |
| Ischemic | 1173 (27.2) | 632 (34.6) | 1443 (28.0) | <0.0001 |
| Idiopathic | 2353 (54.6) | 754 (41.3) | 1491 (29.0) | <0.0001 |
| Hypertensive | 616 (14.3) | 314 (17.2) | 1004 (19.5) | <0.0001 |
| Valve disease | 168 (3.9) | 126 (6.9) | 1208 (23.5) | <0.0001 |
| Myocardial infarction | 667 (15.5) | 359 (19.7) | 644 (12.5) | <0.0001 |
| Diabetes | 772 (17.9) | 364 (19.9) | 1005 (19.5) | 0.044 |
| CKD | 544 (12.6) | 212 (11.6) | 446 (8.7) | <0.0001 |
| Atrial fibrillation | 670 (15.6) | 363 (19.9) | 1208 (23.5) | <0.0001 |
| Stroke | 217 (5.0) | 80 (4.4) | 215 (4.2) | 0.129 |
| Number of comorbidities | 1931 (44.8) | 915 (50.0) | 2532 (49.2) | <0.0001 |
| N = 1 | 1167 (27.1) | 538 (29.5) | 1667 (32.4) | 0.153 |
| N = 2 | 547 (12.7) | 272 (14.9) | 644 (12.5) | <0.0001 |
| N = 3 | 180 (4.2) | 82 (4.5) | 184 (3.6) | 0.157 |
| N ≥ 4 | 37 (0.9) | 23 (1.2) | 37 (0.7) | 0.118 |
| PCI | 114 (2.7) | 76 (4.2) | 207 (4.0) | 0.0004 |
| CABG | 271 (6.3) | 173 (9.5) | 440 (8.6) | <0.0001 |
| Valve replacement | 119 (2.8) | 87 (4.8) | 782 (15.2) | <0.0001 |
| Valvoplasty | 6 (0.1) | 8 (0.4) | 111 (2.7) | <0.0001 |
| Pacemaker | 129 (3.0) | 99 (5.4) | 394 (7.7) | <0.0001 |
| ICD | 178 (4.1) | 39 (2.1) | 48 (0.9) | <0.0001 |
| CRT | 258 (6.0) | 30 (1.6) | 29 (0.6) | <0.0001 |
| Transplantation | 126 (2.9) | 7 (0.4) | 43 (0.8) | <0.0001 |
| Hospitalization | 1148 (26.6) | 452 (24.7) | 1607 (31.2) | <0.0001 |
| LVEF baseline | 28.7 ± 6.2 | 43.6 ± 2.9 | 61.3 ± 6.3 | <0.0001 |
| LVEF final | 36.5 ± 12.9 * | 44.2 ± 11.3 | 56.5 ± 11.1 * | <0.0001 |
| LVDD baseline | 64.8 ± 8.4 | 57.6 ± 6.5 | 51.0 ± 6.6 | <0.0001 |
| LVDD final | 62.7 ± 10.4 * | 58.0 ± 7.8 * | 51.8 ± 7.4 * | <0.0001 |
| Death | 1054 (24.5) | 342 (18.7) | 904 (17.6) | <0.0001 |

* *p* values for comparisons between baseline and final means in the same group; CABG: coronary artery bypass graft; CKD: chronic kidney disease; CMP: cardiomyopathy; CRT: cardiac resynchronization therapy; HFmrEF: HF with mildly reduced ejection fraction; HFpEF: HF with preserved ejection fraction; HFrEF: HF with reduced ejection fraction; ICD: implantable cardioverter-defibrillator; LVDD: left ventricular diastolic diameter; LVEF: left ventricular ejection fraction; PCI: percutaneous coronary intervention.

Patients with HFpEF were older and there was a greater number of women. They had a higher prevalence of valve disease, comorbidities, surgical procedures for valve disease, pacemaker implantation, and hospitalizations. On the other hand, patients with HFrEF had a higher prevalence of idiopathic CMP and higher rates of surgical procedures such as ICD and CRT implantation and transplants. In the same group comparisons, HFrEF

patients had an increase in final LVEF and a decrease in LVDD. In patients with HFmrEF, final LVDD increased compared to baseline LVDD. In patients with HFpEF, final LVEF decreased, and LVDD increased compared with respective baseline values. During the follow-up period, 1054 (24.5%) patients with HFrEF, 342 (18.7) with HFmrEF, and 904 (17.6) with HFpEF died ($p < 0.0001$). The cumulative incidence of death was higher in men with HFrEF compared to HFmrEF ($p < 0.001$) but similar for HFmrEF and HFpEF in women and men (Figure 2).



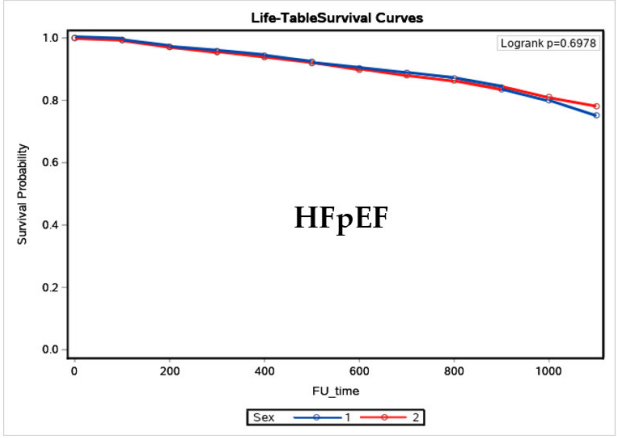




**Figure 2.** Kaplan–Meier survival curves in women and men with heart failure with reduced (HFrEF), mildly reduced (HFmrEF), and preserved (HFpEF) ejection fraction (Sex 1 means men and 2 women).

Table 3 shows the clinical characteristics and echocardiographic data of women and men with HF with preserved (HFpEF), mid-range (HFmrEF), and reduced (HFrEF) left ventricular ejection fraction.

**Table 3.** Clinical characteristics of women and men with heart failure with preserved (HFpEF), mid-range (HFmrEF), and reduced left ventricular ejection fraction (HFrEF).

| | **HFrEF N = 4310 (38.2)** | | **HFmrEF N = 1826 (16.2)** | | **HFpEF N = 5146 (45.6)** | |
|---|---|---|---|---|---|---|
| | **Women N = 1488 (34.5)** | **Men N = 2822 (65.5) *** | **Women N = 653 (35.8)** | **Men N = 1173 (64.2) *** | **Women N = 2885 (56.1)** | **Men N = 2261 (43.9) *** |
| Age (Years) | 60.7 ± 14.1 | 60.0 ± 13.5 | 64.0 ± 14.1 | 64.1 ± 13.2 | 67.5 ± 15.1 | 66.2 ± 13.9 * |
| Cardiomyopathy | | | | | | |
| Ischemic | 320 (21.5) | 853 (30.2) * | 174 (26.7) | 458 (39.1) * | 632 (21.9) | 811 (35.9) * |
| Idiopathic | 847 (56.9) | 1506 (53.4) * | 295 (45.2) | 459 (39.1) * | 847 (29.4) | 644 (28.5) |
| Hypertensive | 264 (17.7) | 352 (12.5) * | 130 (19.9) | 184 (15.7) * | 639 (22.2) | 365 (16.1) * |
| Valve disease | 57 (3.8) | 111 (3.9) | 54 (8.3) | 72 (6.1) | 767 (26.6) | 441 (19.5) * |
| Myocardial infarction | 174 (11.7) | 493 (17.5) * | 97 (14.8) | 262 (22.3) * | 286 (9.9) | 358 (15.6) * |
| Diabetes | 274 (18.4) | 498 (17.7) | 199 (18.2) | 245 (20.9) | 541 (18.8) | 464 (20.5) |
| CKD | 162 (10.9) | 382 (13.5) * | 67 (10.3) | 145 (12.4) | 187 (6.5) | 259 (11.5) * |
| Atrial fibrillation | 166 (11.2) | 504 (17.9) * | 108 (16.5) | 255 (21.7) * | 674 (23.4) | 534 (23.6) |
| Stroke | 62 (4.2) | 155 (5.5) | 23 (3.5) | 57 (4.9) | 111 (3.9) | 104 (4.6) |
| Number of comorbidities | 588 (19.5) | 1343 (57.3) * | 288 (39.8) | 627 (50.2) * | 1349 (46.8) | 1183 (44.5) * |
| N = 1 | 372 (25.0) | 795 (28.2) | 181 (27.7) | 357 (30.4) | 929 (32.2) | 738 (32.6) |
| N = 2 | 155 (10.4) | 392 (13.9) | 79 (12.1) | 193 (16.5) | 322 (11.2) | 322 (14.2) |
| N = 3 | 53 (3.6) | 127 (4.5) | 20 (3.1) | 62 (5.3) | 82 (2.8) | 102 (4.5) |
| N ≥ 4 | 8 (0.5) | 29 (1.0) | 8 (1.2) | 15 (1.3) | 16 (1.6) | 21 (0.9) |
| PCI | 36 (2.4) | 78 (2.8) | 19 (2.9) | 57 (4.9) * | 85 (3.0) | 122 (5.4) * |
| CABG | 72 (4.8) | 199 (7.1) * | 47 (7.2) | 126 (10.7) * | 166 (5.8) | 274 (12.1) * |
| Valve replacement | 35 (2.4) | 84 (3.0) | 35 (5.4) | 52 (4.4) | 464 (16.1) | 318 (14.1) * |
| Valvoplasty | 1 (0.1) | 5 (0.2) | 4 (0.6) | 4 (0.3) | 76 (2.6) | 35 (1.6) * |
| Pacemaker | 46 (3.1) | 83 (2.9) | 39 (6.0) | 60 (5.1) | 254 (8.8) | 140 (6.2) * |
| ICD | 46 (3.1) | 132 (4.7) * | 12 (1.8) | 27 (2.3) | 14 (0.5) | 34 (1.5) * |
| CRT | 124 (8.3) | 134 (4.8) * | 13 (2.0) | 17 (1.5) | 14 (0.5) | 15 (0.7) |
| Transplantation | 43 (2.9) | 83 (2.9) | 1 (0.2) | 6 (0.5) | 18 (0.6) | 25 (1.1) |
| Hospitalization | 381 (25.6) | 626 (22.2) | 152 (23.3) | 231 (19.7) | 941 (32.6) | 528 (23.9) * |
| LVEF baseline | 29.2 ± 5.9 | 28.5 ± 6.3 * | 43.7 ± 3.0 | 43.6 ± 2.9 | 62.2 ± 6.1 | 60.1 ± 6.3 * |
| LVEF final | 38.0 ± 12.9 | 35.7 ± 12.8 * | 44.7 ± 11.0 | 43.9 ± 11.5 | 58.2 ± 10.1 | 54.3 ± 11.8 * |
| LVDD baseline | 62.6 ± 7.8 | 66.0 ± 8.4 * | 56.0 ± 6.1 | 58.4 ± 6.5 * | 49.4 ± 5.8 | 53.1 ± 6.8 * |
| LVDD final | 60.3 ± 9.8 | 64.1 ± 10.4 * | 56.6 ± 7.5 | 58.8 ± 7.9 * | 50.0 ± 6.6 | 54.2 ± 7.6 * |
| Death | 308 (20.7) | 746 (26.4) * | 120 (18.4) | 222 (18.9) | 497 (17.2) | 407 (18.0) |

Numbers in parenthesis mean percentage; * $p < 0.05$: comparisons between women vs. men in the same HF subtype. CABG: coronary artery bypass graft; CKD: chronic kidney disease; CMP: cardiomyopathy; CRT: cardiac resynchronization therapy; HFmrEF: heart failure with mildly reduced ejection fraction; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; ICD: implantable cardioverter-defibrillator; LVDD: left ventricular diastolic diameter; LVEF: left ventricular ejection fraction; PCI: percutaneous coronary intervention.

In HFrEF, men had a higher prevalence of ischemic CMP, comorbidities, CABG, and ICD surgical procedures. Men also had higher baseline and final LVDD. Women had a higher prevalence of idiopathic and hypertensive CMP and CRT implantation. The baseline and final LVEF were also higher in women. In HFmrEF, men had a higher prevalence of ischemic CMP, comorbidities, PCI, CABG, and baseline and final LVEF. Women had a higher prevalence of idiopathic and hypertensive CMP. In HFpEF, women were older and had a

higher prevalence of hypertensive CMP and valve disease, comorbidities, valve surgery, and hospitalizations. Women also had a higher baseline and final LVEF. Men had a higher prevalence of ischemic CMP, MI, CKD, PCI, CABG, pacemaker, and ICD implantation. Men also had a higher baseline and final LVDD. In the HFrEF women and men, final LVEF increased, and LVDD decreased compared with respective baseline values. In HFmrEF women, final LVEF and LVDD increased compared with respective baseline values. In HFpEF women and men, final LVEF decreased, and LVDD increased compared with respective baseline values. During the follow-up period, death was higher in HFrEF men (26.4%) than in women (20.7%) ($p < 0.0001$). The cumulative incidence of death was higher in men than women in HFrEF but similar in other HF subtypes (Figure 2). In women, the variable comparisons of the different HF subtypes showed statistically significant differences for most of the variables analyzed, except for diabetes, stroke, CABG, and PCI (Table 3). Ischemic CMP and MI were more prevalent in HFmrEF than other HF subtypes. Idiopathic, hypertensive CMP and valve disease, CKD, AF, number of comorbidities, valve surgery, and pacemaker implantation were more prevalent, in descending order, in HFrEF and HFmrEF than HFpEF. ICD implantation, CRT, and heart transplants were more frequent in HFrEF than in other HF subtypes. The hospitalizations were higher in women with HFrEF and HFpEF. Mortality was higher in decreasing order in HFrEF and HFmrEF compared to HFpEF.

In men, the comparison of variables for the different HF subtypes showed statistically significant differences for most of the variables analyzed, except for CKD and stroke. Ischemic CMP and diabetes were more prevalent in HFmrEF and HFpEF than in HFrEF. MI was more prevalent in HFrEF and HFmrEF than in HFpEF. Idiopathic, the number of comorbidities, ICD, and CRT implantation were more prevalent, in descending order, in HFrEF, HFmrEF, and HFpEF. Hypertensive CMP and valve disease, AF, valve surgery, and pacemaker implantation were more prevalent in HFrEF and HFmrEF than in HFpEF. Heart transplants occurred more in HFrEF than in other HF subtypes. The hospitalizations were higher in women with HFrEF and HFpEF. Mortality was higher in HFrEF but similar in HFmrEF and HFpEF.

Multivariable regression analysis for all patients adjusted for several covariates showed CKD, stroke, diabetes, AF, age, baseline LVEF, valve disease, MI, hypertensive CMP, and PCI + CABG but not sex as the independent predictors of all-cause death (Table 4).

**Table 4.** Cox regression analysis for death from heart failure adjusted for age, sex, ischemic cardiomyopathy, idiopathic cardiomyopathy, hypertensive cardiomyopathy (HCMP), valve disease, myocardial infarction (MI), diabetes, stroke, chronic kidney disease (CKD), atrial fibrillation (AF), baseline left ventricular ejection fraction (LVEF), percutaneous coronary intervention (PCI) + coronary artery bypass graft (CABG), and pacemaker + cardiac resynchronization therapy + implantable cardioverter-defibrillator.

| | **Hazard Ratio** | **95% Confidence Limits** | | | **Score Chi-Square** | ***p*** |
|---|---|---|---|---|---|---|
| Age | 1.02 | 1.01 | 1.02 | CKD | 1302 | <0.0001 |
| HCMP | 0.81 | 0.72 | 0.92 | Stroke | 340 | <0.0001 |
| Valve disease | 1.65 | 1.45 | 1.87 | Diabetes | 259 | <0.0001 |
| MI | 1.29 | 1.16 | 1.43 | AF | 244 | <0.0001 |
| Diabetes | 2.06 | 1.88 | 2.26 | Age | 72 | <0.0001 |
| Stroke | 2.49 | 2.20 | 2.81 | Valve disease | 66 | <0.0001 |
| CKD | 2.76 | 2.51 | 3.03 | LVEF baseline | 57 | <0.0001 |
| AF | 1.87 | 1.71 | 2.04 | MI | 37 | <0.0001 |
| LVEF baseline | 0.76 | 0.72 | 0.81 | HCMP | 11 | 0.0009 |
| PCI + CABG | 1.24 | 1.02 | 1.50 | PCI + CABG | 5 | 0.027 |

Multivariable regression analysis for HF subtypes, adjusted for several covariates, showed CKD, stroke, diabetes, AF, hypertensive CMP, baseline LVEF, age, MI, valve disease, and PCI + CABG as the independent predictors of death for HFrEF. CKD, diabetes, stroke, AF, MI, age, valve disease, and PCI + CABG were independent predictors of death for HFmrEF. CKD, AF, age, diabetes, stroke, valve disease, and MI were independent predictors of death for HFpEF. Sex was not an independent predictor of death in all HF subtypes (Table 5).

**Table 5.** Cox regression analysis for death from heart failure of preserved (HFpEF), mid-range (HFmrEF), and reduced (HFrEF) left ventricular ejection fraction adjusted for age, sex, ischemic cardiomyopathy, idiopathic cardiomyopathy, hypertensive cardiomyopathy (HCMP), valve disease, myocardial infarction (MI), diabetes, stroke, chronic kidney disease (CKD), atrial fibrillation (AF), baseline left ventricular ejection fraction (LVEF), percutaneous coronary intervention (PCI) + coronary artery bypass graft (CABG), and pacemaker + cardiac resynchronization therapy + implantable cardioverter-defibrillator.

| | | Hazard Ratio | 95% Confidence Limits | | | Score Chi-Square | *p* |
|---|---|---|---|---|---|---|---|
| HFrEF | Age | 1.01 | 1.01 | 1.02 | CKD | 489 | <0.0001 |
| | HCMP | 0.69 | 0.57 | 0.84 | Stroke | 176 | <0.0001 |
| | Valve disease | 1.51 | 1.15 | 1.98 | Diabetes | 128 | <0.0001 |
| | MI | 1.28 | 1.10 | 1.49 | AF | 78 | <0.0001 |
| | Diabetes | 2.08 | 1.82 | 2.38 | HCMP | 24 | <0.0001 |
| | Stroke | 2.65 | 2.21 | 3.18 | Age | 23 | <0.0001 |
| | CKD | 2.70 | 2.35 | 3.09 | LVEF baseline | 22 | <0.0001 |
| | AF | 1.80 | 1.57 | 2.06 | MI | 7 | 0.0049 |
| | LVEF baseline | 0.97 | 0.96 | 0.98 | Valve disease | 8 | 0.0031 |
| | PCI + CABG | 1.24 | 1.02 | 1.50 | PCI + CABG | 5 | 0.027 |
| HFmrEF | Age | 1.02 | 1.01 | 1.03 | CKD | 245 | <0.0001 |
| | Valve disease | 2.00 | 1.40 | 2.86 | Diabetes | 65 | <0.0001 |
| | MI | 1.78 | 1.39 | 2.27 | Stroke | 48 | <0.0001 |
| | Diabetes | 2.33 | 1.86 | 2.93 | AF | 40 | <0.0001 |
| | Stroke | 2.48 | 1.82 | 3.38 | MI | 20 | <0.0001 |
| | CKD | 2.89 | 2.28 | 3.68 | Age | 14 | 0.0002 |
| | AF | 1.94 | 1.53 | 2.45 | Valve disease | 15 | 0.0001 |
| | PCI + CABG | 1.50 | 1.13 | 2.60 | PCI + CABG | 6 | 0.027 |
| HFpEF | Age | 1.03 | 1.03 | 1.04 | CKD | 565 | <0.0001 |
| | Valve disease | 1.88 | 1.60 | 2.20 | AF | 161 | <0.0001 |
| | MI | 1.22 | 1.01 | 1.46 | Age | 120 | <0.0001 |
| | Diabetes | 2.08 | 1.80 | 2.40 | Diabetes | 79 | <0.0001 |
| | Stroke | 2.14 | 1.76 | 2.61 | Stroke | 64 | <0.0001 |
| | CKD | 2.87 | 2.46 | 3.35 | Valve disease | 57 | <0.0001 |
| | AF | 1.94 | 1.69 | 2.23 | MI | 4 | 0.0344 |

## 4. Discussion

Our study showed a better prognosis in women with HFrEF, but after multivariate analysis adjusted for several covariates, sex was not an independent death predictor in all HF subtypes. Women with HFrEF had a lower prevalence of ischemic CMP and comorbidities. The LVEF was higher, and LVDD was lower in women than men. Our results were similar to those observed in large prospective cohort studies [6,13]. Gerber et al. showed higher but discrete cardiovascular mortality in men in a study conducted to estimate the HF incidence rates and outcomes after HF diagnosis between 2000 and 2010 in Olmsted County, Minnesota [6]. HF subtypes definition used the cutoff value of 50% for HFpEF ($\geq$50%) or HFrEF (<50%), and the authors did not include the HFmrEF subtype but distributed it in HFrEF and HFpEF subtypes. The mortality was higher in HFrEF than in HFpEF and increased with aging. Men also had higher cardiovascular death that could be related to a more significant reduction in the incidence of HFrEF in women during the study period. Nevertheless, all-cause mortality was similar between women and men. In data analysis of two large cohort studies, Pandey et al. also showed almost two times higher lifetime risk of HFrEF (EF < 45%) in men compared to women aged >40 years but a similar lifetime risk for HFpEF (EF $\geq$ 45%) [13]. Patients with previous MI had a significantly increased lifetime risk for all HF subtypes. The lifetime risk increased by 2.5-fold for the incidence of HFpEF and 4-fold for HFrEF in the presence of previous MI. Men had a higher MI prevalence than women for all ten-year age groups, from 45 years old and for patients over 75 years. Patients with ischemic CMP had a higher death rate than other HF etiologies [19]. Likewise, mortality from ventricular arrhythmias in ischemic cardiomyopathy is higher in men than in women. HF associated with ventricular arrhythmia, which is more common in men, is associated with a worse prognosis and higher mortality [20,21]. These findings may explain the higher risk of death in men with HFrEF. Estrogen modulating various pathophysiologic processes in women may also partly explain why women have a better prognosis than men in HF [22,23]. Estrogen exerts a cardioprotective effect in HF by inhibiting sympathetic activity and the renin-angiotensin-aldosterone system. Estrogen decreases renin levels, angiotensin-converting enzyme activity, AT1 receptor density, and aldosterone production, and increases AT2 receptor density. Estrogen increases natriuretic peptides that intensify the inhibition of the renin-angiotensin-aldosterone system. Estrogen promotes better endothelial response to injury, prevents left ventricular remodeling and diastolic function, and protects the myocardial microvasculature. Estrogens' protection at the cellular level is primarily carried out through increasing anti-oxidative defenses and maintaining mitochondrial integrity [24]. It is known that endogenous estrogens attenuate the inflammatory response and the expression of circulating MMP, which is directly associated with more significant ventricular dysfunction.

Our study also showed a higher prevalence of comorbidities in men for all HF subtypes, namely MI, CKD, and AF. These results agreed with the literature that showed a higher prevalence of comorbidities in men with HFrEF, while women have a higher prevalence of hypertension and diabetes but better renal function [16,25]. Women in all HF subtypes of our study had a higher prevalence of idiopathic and hypertensive CMP, similar to those observed in previous studies [26,27]. Our study also showed a higher prevalence of HFpEF in women. They were older and had a higher prevalence of hypertensive MCP and valvular disease, but in multivariate analysis, death in HFpEF patients was similar in women and men. Our results are similar to those in the literature for almost all clinical characteristics, echocardiographic data, and HF mortality [28–30]. Lam et al. showed a higher CV and all-cause death in women, but the risk of all-cause events was similar in women and men after adjusting to AF and renal dysfunction. On the other hand, Magnussen et al. showed higher mortality from HF in men than in women, even after adjusting for covariates that included the main risk factors for HF [30]. However, the population had baseline preserved renal function, and the authors did not include the renal function changes during the follow-up period in the multivariate analysis. It is well known that AF and CKD are comorbidities associated with higher mortality in women than men [31,32]. Our study showed a higher

prevalence of comorbidities in women with HFpEF, including AF, compared to HFrEF and HFrEF. A high number of comorbidities in HFpEF could justify the same mortality observed in women and men. The worse prognosis in women with AF may also be related to inadequate treatment, such as less use of anticoagulants and fewer ablation procedures [33].

In our study, HFmrEF and HFpEF patients showed similar mortality in women and men. These findings differed from those in the literature, where mortality in patients with HFmrEF is intermediate between HFrEF and HFpEF [14,34–37]. The same mortality observed in patients with HFmrEF and HFpEF may be associated with a more significant number of comorbidities, such as MI and CKD, in HFmrEF patients. On the other hand, as observed in some studies, our study also showed that HFmrEF patients had similar characteristics to those with HFrEF and HFpEF [38,39]. In the HFmrEF group, patients were younger and had a higher prevalence of ischemic and hypertensive CMP and MI, which resembled those of the HFrEF group. The HFmrEF group was similar to HFpEF for hypertensive CMP, diabetes, and AF prevalence.

Our study has some limitations. First, it is a retrospective study in a single specialized tertiary care center where selection biases may occur and which includes patients with a more complex clinical picture. Second, an adequate definition of symptoms must be included, especially the NYHA functional class of dyspnea and other variables associated with a worse prognosis (ventricular arrhythmia, 6-min walk test). Third, we were unable to detail the cause of death adequately. Therefore, our analysis included cardiac and non-cardiac causes, including the deaths from COVID-19 which occurred between the pandemic months of March to September 2020. Finally, adequate information regarding drug treatment and dosages is needed.

## 5. Conclusions

Our large cohort study with many patients showed that women with HFrEF had a better prognosis than men. Nevertheless, after adjusting for several covariates in the multivariable analysis, death was similar in all women and men patients and also in women and men in the HF subtypes. Contrary to most previous studies, this study showed that sex was not an independent variable of all-cause mortality in HF subtypes. Our more recent data may result from improving the guideline-based therapy on women, reducing the previously existing therapeutic gap between women and men. CKD, stroke, diabetes, AF, MI, and age are the most critical variables of worse prognosis shared by all HF subtypes. Therefore, intensifying primary prevention of these comorbidities is essential to reduce HF morbidity and mortality. Future prospective cohort studies are needed to establish the actual HF subtypes prognosis in women and men.

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## References


1. Savarese, G.; Becher, P.M.; Lund, L.H.; Seferovic, P.; Rosano, G.M.C.; Coats, A. Global burden of heart failure: A comprehensive and updated review of epidemiology. *Cardiovasc. Res.* **2022**, cvac013. [CrossRef] [PubMed]
2. Arruda, V.L.; Machado, L.M.G.; Lima, J.C.; Silva, P.R.S. Trends in mortality from heart failure in Brazil: 1998 to 2019. *Rev. Bras. Epidemiol.* **2022**, *25*, E220021. [CrossRef] [PubMed]
3. Rodgers, J.L.; Jones, J.; Bolleddu, S.I.; Vanthenapalli, S.; Rodgers, L.E.; Shah, K.; Karia, K.; Panguluri, S.K. Cardiovascular Risks Associated with Gender and Aging. *J. Cardiovasc. Dev. Dis.* **2019**, *6*, 19. [CrossRef] [PubMed]
4. Lloyd-Jones, D.M.; Larson, M.G.; Leip, E.P.; Beiser, A.; d'Agostino, R.B.; Kannel, W.B.; Murabito, J.M.; Vasan, R.S.; Benjamin, E.J.; Levy, D. Lifetime risk for developing congestive heart failure: The Framingham Heart Study. *Circulation* **2002**, *106*, 3068–3072. [CrossRef] [PubMed]
5. Roger, V.L.; Weston, S.A.; Redfield, M.M.; Hellermann-Homan, J.P.; Killian, J.; Yawn, B.P.; Jacobsen, S.J. Trends in heart failure incidence and survival in a community-based pop-ulation. *JAMA* **2004**, *92*, 344–350. [CrossRef]
6. Gerber, Y.; Weston, S.A.; Redfield, M.M.; Chamberlain, A.M.; Manemann, S.M.; Jiang, R.; Killian, J.M.; Roger, V.L. A contemporary appraisal of the heart failure epidemic in Olmsted County, Minnesota, 2000 to 2010. *JAMA Intern. Med.* **2015**, *175*, 996–1000. [CrossRef]
7. Tsao, C.W.; Lyass, A.; Enserro, D.; Larson, M.G.; Ho, J.E.; Kizer, J.R.; Gottdiener, J.S.; Psaty, B.M.; Vasan, R.S. Temporal Trends in the Incidence of and Mortality Associated with Heart Failure with Preserved and Reduced Ejection Fraction. *JACC Hear. Fail.* **2018**, *6*, 678–685. [CrossRef] [PubMed]
8. Zhao, Z.; Wang, H.; Jessup, J.A.; Lindsey, S.H.; Chappell, M.C.; Groban, L. Role of estrogen in diastolic dysfunction. *Am. J. Physiol. Heart Circ. Physiol.* **2014**, *306*, H628–H640. [CrossRef] [PubMed]
9. Beale, A.L.; Meyer, P.; Marwick, T.H.; Lam, C.S.; Kaye, D.M. Sex Differences in Cardiovascular Pathophysiology. *Circulation* **2018**, *138*, 198–205. [CrossRef]
10. Ho, J.E.; Gona, P.; Pencina, M.J.; Tu, J.V.; Austin, P.C.; Vasan, R.S.; Kannel, W.P.; D'Agostino, R.P.; Lee, D.S.; Levy, D. Discriminating clinical features of HF with preserved vs. reduced ejection fraction in the community. *Eur. Heart J.* **2012**, *33*, 1734–1741. [CrossRef]
11. Wang, X.; Vaduganathan, M.; Claggett, B.L.; Hegde, S.M.; Pabon, M.; Kulac, I.J.; Vardeny, O.; O'Meara, E.; Zieroth, S.; Katova, T.; et al. Sex Differences in Characteristics, Outcomes and Treatment Response with Dapagliflozin across the Range of Ejection Fraction in Patients with Heart Failure: Insights from DAPA-HF and DELIVER. *Circulation* **2022**. [CrossRef]
12. Butler, J.; Filippatos, G.; Siddiqi, T.J.; Ferreira, J.P.; Brueckmann, M.; Bocchi, E.; Böhm, M.; Chopra, V.K.; Giannetti, N.; Iwata, T.; et al. Effects of Empagliflozin in Women and Men with Heart Failure and Preserved Ejection Fraction. *Circulation* **2022**, *146*, 1046–1055. [CrossRef]
13. Pandey, A.; Omar, W.; Ayers, C.; LaMonte, M.; Klein, L.; Allen, N.B.; Kuller, L.H.; Greenland, P.; Eaton, C.B.; Gottdiener, J.S.; et al. Sex and Race Differences in Lifetime Risk of Heart Failure with Preserved Ejection Fraction and Heart Failure with Reduced Ejection Fraction. *Circulation* **2018**, *137*, 1814–1823. [CrossRef] [PubMed]
14. Stolfo, D.; Uijl, A.; Vedin, O.; Strömberg, A.; Faxén, U.L.; Rosano, G.M.C.; Sinagra, G.; Dahlström, U.; Savarese, G. Sex-Based Differences in Heart Failure Across the Ejection Fraction Spectrum: Phenotyping, and Prognostic and Therapeutic Implica-tions. *JACC Heart Fail* **2019**, *7*, 505–515. [CrossRef]
15. Savarese, G.; Vedin, O.; D'Amario, D.; Uijl, A.; Dahlström, U.; Rosano, G.; Lam, C.S.P.; Lund, L.H. Prevalence and Prognostic Implications of Longitudinal Ejection Fraction Change in Heart Failure. *JACC Heart Fail* **2019**, *7*, 306–317. [CrossRef] [PubMed]
16. Dewan, P.; Rørth, R.; Jhund, P.S.; Shen, L.; Raparelli, V.; Petrie, M.C.; Abraham, W.T.; Desai, A.S.; Dickstein, K.; Køber, L.; et al. Differential Impact of Heart Failure with Reduced Ejection Fraction on Men and Women. *J. Am. Coll. Cardiol.* **2019**, *73*, 29–40. [CrossRef]
17. McKee, P.A.; Castelli, W.P.; McNamara, P.M.; Kannel, W.B. The Natural History of Congestive Heart Failure: The Framingham Study. *N. Engl. J. Med.* **1971**, *285*, 1441–1446. [CrossRef] [PubMed]
18. Brasil. Receita Federal. Brasília. 2022. Available online: https://servicos.receita.fazenda.gov.br/Servicos/CPF/ConsultaSituacao/ConsultaPublica.asp (accessed on 11 April 2022).
19. Spitaleri, G.; Zamora, E.; Cediel, G.; Codina, P.; Santiago-Vacas, E.; Domingo, M.; Lupón, J.; Santesmases, J.; Diez-Quevedo, C.; Troya, M.I.; et al. Cause of Death in Heart Failure Based on Etiology: Long-Term Cohort Study of All-Cause and Cardiovascular Mortality. *J. Clin. Med.* **2022**, *11*, 784. [CrossRef]
20. Alenazy, B.; Tharkar, S.; Kashour, T.; Alhabib, K.F.; AlFaleh, H.; Hersi, A. In-hospital ventricular arrhythmia in heart failure patients: 7 year follow-up of the multi-centric HEARTS registry. *ESC Hear. Fail.* **2019**, *6*, 1283–1290. [CrossRef]
21. Li, L.; Tu, B.; Liu, S.; Zhang, Z.; Xiong, Y.; Hu, Z.; Yao, Y. Sex differences in ventricular arrhythmias epidemiology, risk factors, and mortality in congestive heart failure. *Int. J. Cardiol.* **2022**. [CrossRef] [PubMed]
22. Oneglia, A.; Nelson, M.D.; Merz, C.N.B. Sex Differences in Cardiovascular Aging and Heart Failure. *Curr. Hear. Fail. Rep.* **2020**, *17*, 409–423. [CrossRef]
23. Komukai, K.; Mochizuki, S.; Yoshimura, M. Gender and the renin-angiotensin-aldosterone system. *Fundam. Clin. Pharmacol.* **2010**, *24*, 687–698. [CrossRef]
24. Ventura-Clapier, R.; Moulin, M.; Piquereau, J.; Lemaire, C.; Mericskay, M.; Veksler, V.; Garnier, A. Mitochondria: A central target for sex differences in pathologies. *Clin. Sci.* **2017**, *131*, 803–822. [CrossRef]

25. Dunlay, S.M.; Roger, V.L. Gender Differences in the Pathophysiology, Clinical Presentation, and Outcomes of Ischemic Heart Failure. *Curr. Hear. Fail. Rep.* **2012**, *9*, 267–276. [CrossRef] [PubMed]
26. Hsich, E.M.; Piña, I.L. Heart Failure in Women: A Need for Prospective Data. *J. Am. Coll. Cardiol.* **2009**, *54*, 491–498. [CrossRef] [PubMed]
27. De Bellis, A.; De Angelis, G.; Fabris, E.; Cannatà, A.; Merlo, M.; Sinagra, G. Gender-related differences in heart failure: Beyond the "one-size-fits-all" paradigm. *Hear. Fail. Rev.* **2019**, *25*, 245–255. [CrossRef]
28. Ho, J.E.; Brouwers, F.P.; Enserro, D.; Shah, S.J.; Psaty, B.M.; Bartz, T.M.; Santhanakrishnan, R.; Lee, D.S.; Liu, K.; Blaha, M.J.; et al. Abstract 11958: Predicting Heart Failure with Preserved and Reduced Ejection Fraction: The International Collaboration on Heart Failure Subtypes. *Circulation* **2015**, *132*, A11958. [CrossRef]
29. Lam, C.S.; Carson, P.E.; Anand, I.S.; Rector, T.S.; Kuskowski, M.; Komajda, M.; McKelvie, R.S.; McMurray, J.J.; Zile, M.R.; Massie, B.M.; et al. Sex differences in clinical characteristics and outcomes in elderly patients with heart failure and preserved ejection fraction: The Irbesartan in Heart Failure with Preserved Ejection Fraction (I-PRESERVE) trial. *Circ. Hear. Fail.* **2012**, *5*, 571–578. [CrossRef] [PubMed]
30. Magnussen, C.; Niiranen, T.J.; Ojeda, F.M.; Gianfagna, F.; Blankenberg, S.; Vartiainen, E.; Sans, S.; Pasterkamp, G.; Hughes, M.; Costanzo, S.; et al. Sex-Specific Epidemiology of Heart Failure Risk and Mortality in Europe: Results from the BiomarCaRE Consortium. *JACC Heart Fail* **2019**, *7*, 204–213. [CrossRef]
31. Madan, N.; Itchhaporia, D.; Albert, C.M.; Aggarwal, N.T.; Volgman, A.S. Atrial Fibrillation and Heart Failure in Women. *Hear. Fail. Clin.* **2018**, *15*, 55–64. [CrossRef]
32. Bibbins-Domingo, K.; Lin, F.; Vittinghoff, E.; Barrett-Connor, E.; Grady, D.; Shlipak, M.G. Renal insufficiency as an independent predictor of mortality among women with heart failure. *J. Am. Coll. Cardiol.* **2004**, *44*, 1593–1600. [CrossRef] [PubMed]
33. Thompson, L.E.; Maddox, T.M.; Lei, L.; Grunwald, G.K.; Bradley, S.M.; Peterson, P.N.; Masoudi, F.A.; Turchin, A.; Song, Y.; Doros, G.; et al. Sex Differences in the Use of Oral Anticoagulants for Atrial Fibrillation: A Report from the National Cardiovascular Data Registry (NCDR®) PINNACLE Registry. *J. Am. Hear. Assoc.* **2017**, *6*, e005801. [CrossRef]
34. Martínez-Sellés, M.; Doughty, R.N.; Poppe, K.; Whalley, G.A.; Earle, N.; Tribouilloy, C.; McMurray, J.J.; Swedberg, K.; Køber, L.; Berry, C.; et al. Gender and survival in patients with heart failure: Interactions with diabetes and aetiology. Results from the MAGGIC individual patient meta-analysis. *Eur. J. Hear. Fail.* **2012**, *14*, 473–479. [CrossRef]
35. Farre, N.; Lupón, J.; Roig, E.; González-Costello, J.; Vila-Domènech, J.S.; Perez, S.; De Antonio, M.; Gonzalez, E.S.; Sánchez-Enrique, C.; Moliner, P.; et al. Clinical characteristics, one-year change in ejection fraction and long-term outcomes in patients with heart failure with mid-range ejection fraction: A multicentre prospective observational study in Catalonia (Spain). *BMJ Open* **2017**, *7*, e018719. [CrossRef]
36. Savarese, G.; Stolfo, D.; Sinagra, G.; Lund, L.H. Heart failure with mid-range or mildly reduced ejection fraction. *Nat. Rev. Cardiol.* **2021**, *19*, 100–116. [CrossRef]
37. Grupper, A.; Freimark, D.; Murad, H.; Olmer, L.; Benderly, M.; Ziv, A.; Friedman, N.; Kaufman, G.; Silber, H.; Kalter-Leibovici, O. Sex related differences in the characteristics and outcomes of heart failure: A sub analysis of heart failure disease management study. *Front. Cardiovasc. Med.* **2022**, *9*, 1012361. [CrossRef]
38. Koh, A.S.; Tay, W.T.; Teng, T.H.K.; Vedin, O.; Benson, L.; Dahlstrom, U.; Savarese, G.; Lam, C.S.; Lund, L.H. A comprehensive population-based characterization of heart failure with mid-range ejection fraction. *Eur. J. Hear. Fail.* **2017**, *19*, 1624–1634. [CrossRef] [PubMed]
39. Lund, L.H.; Claggett, B.; Liu, J.; Lam, C.S.; Jhund, P.; Rosano, G.M.; Swedberg, K.; Yusuf, S.; Granger, C.B.; Pfeffer, M.A.; et al. Heart failure with mid-range ejection fraction in CHARM: Characteristics, outcomes and effect of candesartan across the entire ejection fraction spectrum. *Eur. J. Hear. Fail.* **2018**, *20*, 1230–1239. [CrossRef] [PubMed]