



# Gender Differences in Comorbidities of Heart Failure Patients with Preserved or Reduced Left Ventricular Ejection Fraction

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**Corresponding Author:**

Ms. Nadezhda Hvarchanova,  
Assist. Prof., Department of Pharmacology, toxicology and pharmacotherapy, Faculty of Pharmacy, Medical University of Varna, 9000 - Bulgaria

**Submitting Author:**

Ms. Nadezhda Hvarchanova,  
Assist. Prof., Department of Pharmacology, toxicology and pharmacotherapy, Faculty of Pharmacy, Medical University of Varna, 9000 - Bulgaria

**Other Authors:**

Dr. Marieta Georgieva,  
Associate Professor, Department of Pharmacology, Toxicology and Pharmacotherapy, Faculty of Pharmacy, Medical University of Varna, Bulgaria, - Bulgaria

Dr. Branimir Kanazirev,  
Professor, Department of Propaedeutics of Internal Diseases, Faculty of Medicine, Medical University of Varna, Bulgaria, - Bulgaria

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# Gender Differences in Comorbidities of Heart Failure Patients with Preserved or Reduced Left Ventricular Ejection Fraction

**Author(s):** Hvarchanova N, Georgieva M, Kanazirev B

## Abstract

### Introduction/Aim

The aim of this study was to establish gender differences in the comorbidities of heart failure (HF) patients both with preserved (HFpEF) or reduced (HFrEF) left ventricular ejection fraction (LVEF).

### Materials and Methods

This is a retrospective study including 535 heart failure patients hospitalized in the period January, 2010 - December, 2014 with the rate of comorbidities in both groups - HFpEF and HFrEF being examined, including diabetes, hypertension, chronic obstructive pulmonary disease (COPD), atrial fibrillation, anemia and impaired kidney function based on the estimated glomerular filtration rate (eGFR).

### Results

In this study females with HF tended to be older, more numerous and more likely than men to have comorbid impaired renal function and both genders had similar occurrence of all other comorbidities. Patients with HFpEF had hypertension more often and atrial fibrillation less often, compared to those with HFrEF. Females with HFpEF had hypertension more often and atrial fibrillation less often, compared to their counterparts with HFrEF. Males with HFpEF and HFrEF exhibited no differences in comorbidities whatsoever. Females with HFpEF and HFrEF had more impaired renal function than males and more frequently atrial fibrillation, if with HFrEF.

### Conclusion

There was an increasing predominance of HFpEF, older age and female gender in HF hospitalizations over time. Registries and "real-life" investigations generally report higher prevalence of comorbidities compared to clinical trials but the impact on mortality seems to be different as mortality rates and causes of death are comparable between both sexes with slightly better survival in women, in contrast to their higher burden of comorbidities.

## Introduction

Heart failure (HF) is among the most widely spread cardiovascular pathologies with millions of patients worldwide (1). Its morbidity and mortality rates, hospitalization and rehospitalization rates and financial costs are constantly escalating (2). Several epidemiological studies have shown an increasing incidence of HF with preserved ejection fraction (EF), increased percentage of female patients, and increasing age of hospitalized HF patients (3,4). There are multiple comorbidities associated with HF especially in the group of patients with HF with preserved EF (HFpEF). Both groups have frequent hospitalizations and short-term rehospitalizations, while in the group of patients with HFpEF the lethal outcomes are more frequently related to non-cardiovascular factors compared to patients with HF with reduced EF (HFrEF) (3, 4). There are many differences between HF with reduced and with preserved EF. The latter group presents at a more advanced age, patients are more frequently female, more rarely with ischemic heart disease (IHD) and more often with hypertension (7, 8, 9). This study examines comorbidities associated with chronic HF - diabetes, hypertension, chronic obstructive pulmonary disease (COPD), impaired kidney function based on the estimated glomerular filtration rate (eGFR), atrial fibrillation, and their distribution among the patients with preserved and reduced EF.

## Materials and Methods

This is a retrospective study including 535 patients hospitalized in the period 2010-2014 and diagnosed with HF class III/IV NYHA and left ventricular EF verified by 2D echocardiography. Patients with symptoms and signs of HF with EF  $\geq 50\%$  were considered HFpEF and those with EF  $< 50\%$  were classified as HFrEF. Demographic data and prescribed medications at discharge were obtained from medical records and included gender, age, EF, comorbidities, such as diabetes, hypertension, COPD, impaired kidney function based on eGFR, atrial

fibrillation and anemia.

## The following criteria were used to identify and define comorbidities:

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Comorbidities	Criteria
Hypertension	Medical history of hypertension or blood pressure (BP) of more than 140/90 at hospital examination
Diabetes mellitus type 2 (T2DM)	Known diabetes mellitus with oral or insulin treatment, or newly discovered by blood sugar levels
Chronic obstructive pulmonary disease (COPD)	Medical history and/or hospitalizations for COPD
Chronic kidney disease (CKD)	Medical history and/or hospitalizations for CKD and eGFR less than 60 mL/min/m <sup>2</sup>
Impaired kidney function based on eGFR	eGFR less than 30 mL/min/m <sup>2</sup>
Atrial fibrillation	Atrial fibrillation on ECG
Anemia	Hemoglobin levels less than 130g/L for males and 120 g/L for females.

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## Statistics

A descriptive analysis was applied for the representation of the main characteristics of the sample and the indicators included in the research. The basis of the analysis consisted of nonparametric tests, such as cross tabulation and chi-square (Chi) when looking for significant differences in the frequency representation of category values. Continuous variables were compared using Student's t-test. A statistical significance in nonparametric tests was considered to be present when  $p \leq 0.05$ .

Correlation analysis was used to research the dependencies between the variables. The estimation of the degree of dependency between the variables was based on the results from the Pearson coefficient (r). It calculated the correlation on the basis of monotonous interrelations. The degree of association between the variables was defined as significant when  $0.5 < r < 0.7$ ; high when  $0.7 < r < 0.9$ , and extremely high when  $r > 0.9$  with  $p \leq 0.05$ .

## Tables

**Table 1. Distribution of males and females in HFpEF and HFrEF**

HF Patients	Females	Males	p-level
HFpEF (%)	61.5	38.5	$p=0.0003$

HFrEF (%)	40.1	59.9	$p=0.0001$
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On the other hand, the percentage of patients with HFpEF was higher for both sexes compared to HFrEF, and more strikingly and significantly so among women (Table 2).

**Table 2. Distribution of HFpEF and HFrEF by gender**

HF Patients	HFpEF	HFrEF	p-level
Males (%)	52	48	$p=0.1243$
Females (%)	72	28	$p=0.0001$

Comorbidities were quite common and CKD with  $eGFR < 60 \text{ ml/min/m}^2$  was the most common as 301 patients had reduced GFR and this constituted 56.3% of all patients. In the group as a whole, 261 (49%) had hypertension and 214 (40%) had diabetes mellitus. Patients with atrial fibrillation were 93 (17%), with COPD - 77 (14.4%) and with anemia 161 (30.1%) (Table 3).

**Table 3. Demographic data of hospitalized patients with heart failure for the period 2010-2014**

Parameters	All
Number	535
Gender (Females)	287 (53.6%)
Mean age	$71.2 \pm 11$
HFpEF	338 (63.2%)
Males with HFpEF	130 (52.4%)
Females with HFpEF	208 (72.5%)
Chronic kidney disease, $eGFR < 60 \text{ ml/min/m}^2$	301 (56.3%)
$eGFR < 30 \text{ ml/min/m}^2$	66 (12.3%)
Hypertension	261 (49%)
Diabetes mellitus	214 (40%)
Anemia	161 (30.1%)
Atrial fibrillation	93 (17%)
Chronic obstructive pulmonary disease (COPD)	77 (14.4%)

In Table 3 the most important comorbidities appear to be chronic kidney disease in 56.3% and diabetes mellitus in 40% of all patients. CKD undoubtedly will have an impact on the treatment with angiotensin-converting-enzyme inhibitors, angiotensin II receptor blockers and mineralocorticoid receptor antagonists and on hyperkalemia. Diabetes mellitus and heart failure are in a dangerous relationship therefore special attention should be paid to new treatments and to the adherence to guidelines. It is also important to note that almost 30% of the patients

have anemia and presumably some of them have iron deficiency as well.

In Table 4 both sexes were compared in terms of frequencies of comorbidities in all HF patients. It was kidney function expressed as eGFR that was significantly more impaired in women compared to men both in groups with eGFR < 60 ml/min/m<sup>2</sup> and eGFR < 30 ml/min/m<sup>2</sup>. There were no significant differences in the incidence of hypertension and diabetes mellitus though females showed a tendency to be more frequently affected.

Compared to the general population, the epidemiology of CKD in HF is not studied so well, since patients with CKD have often been excluded from HF trials. More than 40% and up to 70 % of HF patients have CKD and the close relationship between CKD and HF deteriorates their prognoses. CKD patients are far less likely to progress to end-stage renal disease than have a cardiovascular cause of death (14). In the majority of studies women had worse kidney function compared to men, although not significantly so (15).<sup>Â</sup>

**Table 4. Distribution of comorbidities according to gender among all HF patients**

Comorbidity	Females	Males	t 2	?-level
All	287 (53.6%)	248 (46.4%)	Â	Â
Hypertension	153 (58.6%)	108 (41.4%)	1.992	0.158
Atrial fibrillation	59 (20.6%)	34 (13.7%)	2.864	0.091
eGFR < 30 ml/min/m <sup>2</sup>	43 (15.0%)	23 (9.3%)	4.009	0.045
Chronic kidney failure, eGFR < 60 ml/min/m <sup>2</sup>	186 (64.8%)	115 (46.4%)	18.378	0.0001
COPD	41 (14.3%)	36 (14.5%)	0.187	0.665
Diabetes	122 (42.5%)	92 (37.1%)	0.280	0.597
Anemia	85 (29.6%)	76 (30.6%)	0.054	0.816

The<sup>Â</sup> <sup>Â</sup> Registry to Improve the Use of Evidence-Based Heart Failure Therapies in the Outpatient Setting (IMPROVE HF) in HF outpatients with reduced EF indicated that women were more likely to have advanced CKD. In contrast, the multicenter Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) registry involving 48 612 patients with HF showed a similar burden of comorbidity and outcomes for both genders. Data from large registries such as OPTIMIZE-HF, ADHERE, and GWTG-HF suggest a higher prevalence of diabetes of 30 to 44 % in real-world patients with HF (9,16, 17,18).

In Table 5 significant differences were found between patients with HFpEF and HFrEF as far as hypertension and atrial fibrillation were concerned. Hypertension was more frequent in patients with HFpEF and atrial fibrillation was found predominantly in patients with HFrEF.

**Table 5. Distribution of comorbidities according to HFpEF and HFrEF**

Comorbidity	HFpEF	HFrEF	t 2	?-level
All	Â 338 (63.2%)	197 (36.8%)	Â	Â
Hypertension	180 (53.2%)	81 (31.1%)	7.339	0.007
Atrial fibrillation	50 (14.7%)	43 (21.8%)	4.288	0.038

eGFR < 30 ml/min/m <sup>2</sup>	39 (11.5%)	27 (13.7%)	0.540	0.462
Chronic kidney failure, eGFR < 60 ml/min/m <sup>2</sup>	191 (35.5%)	110 (55.8%)	0.023	0.880
COPD	44 (13.1%)	33 (16.8%)	1.408	0.235
Diabetes	136 (40.2%)	78 (39.5%)	0.010	0.920
Anemia	99 (29.2%)	62 (31.4%)	0.259	0.611

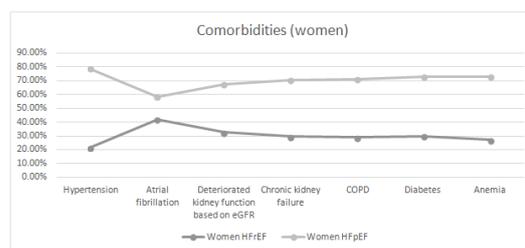
In Table 6 and Graph. 1 women with HFpEF had hypertension more frequently and atrial fibrillation less frequently compared to women with HFrEF.

**Table 6. Distribution of comorbidities in females with HFpEF or HFrEF**

Comorbidity	HFrEF	HFpEF	t 2	?-level
Females All	79 (27.5%)	208 (72.5%)	Â	Â
Hypertension	32 (40.5%)	117 (56.2%)	5.685	0.017
Atrial fibrillation	23 (29.1%)	32 (15.4%)	6.967	0.008
eGFR < 30 ml/min/m <sup>2</sup>	14 (17.7%)	29 (13.9%)	0.642	0.423
Chronic kidney failure eGFR < 60 ml/min/m <sup>2</sup>	55 (69.6%)	131 (63.0%)	1.107	0.293
COPD	11 (13.9%)	27 (12.9%)	0.044	0.833
Diabetes	35 (44.3%)	83 (39.9%)	0.458	0.499
Anemia	23 (29.1%)	62 (29.8%)	0.019	0.890

## Â Graphs

**Graph 1. Distribution of comorbidities among females with HFrEF and HFpEF**



In Table 7 and Graph. 2 there were no differences in comorbidities in men with HFpEF or HFrEF.

**Table 7. Distribution of comorbidities among males with HFpEF or HFrEF**

Comorbidity	HFrEF	HFpEF	t 2	?-level
Males all	118 (47.6%)	130 (52.4%)	Â	Â

Hypertension	49 (41.5%)	63 (48.5%)	1.202	0.273
Atrial fibrillation	20 (16.9%)	18 (13.8%)	0.459	0.498
eGFR< 30 ml/min/m <sup>2</sup>	13 (11.0%)	10 (7.7%)	0.813	0.367
Chronic kidney failure, eGFR< 60 ml/min/m <sup>2</sup>	55 (46.6%)	60 (46.2%)	0.005	0.943
COPD	22 (18.6%)	17 (13.1%)	1.447	0.229
Diabetes	43 (36.4%)	53 (40.1%)	0.418	0.518
Anemia	39 (33.1%)	37 (28.5%)	0.613	0.434

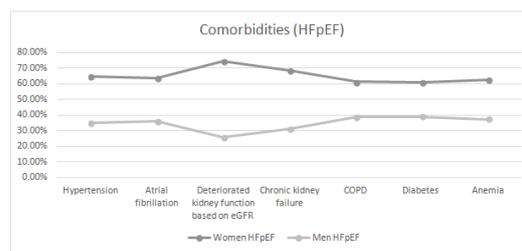


Table 9 and Graph. 4 show that for patients with HFrEF atrial fibrillation and chronic renal impairment were observed significantly more often in females than in males.

**Table 9. Distribution of comorbidities among HFrEF patients according to gender**

Comorbidity	Females	Males	t 2	?-level
HFrEF all	79 (40.1%)	118 (59.9%)	Â	Â
Hypertension	32 (40.1%)	49 (41.5%)	0.020	0.887
Atrial fibrillation	23 (29.1%)	20 (16.5%)	4.104	0.043
eGFR< 30 ml/min/m <sup>2</sup>	14 (17.7%)	13 (11.0%)	1.798	0.180
Chronic kidney failure, eGFR< 60 ml/min/m <sup>2</sup>	55 (69.6%)	55 (46.6%)	10.160	0.001
COPD	11 (13.9%)	22 (18.6%)	0.756	0.385
Diabetes	35 (44.3%)	43 (36.4%)	1.122	0.289
Anemia	23 (29.1%)	39 (33.1%)	0.340	0.560

**Graph 2. Distribution of comorbidities among males with HFrEF and HFpEF**

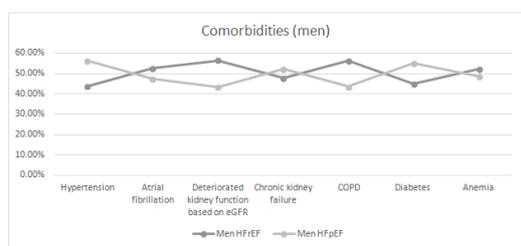


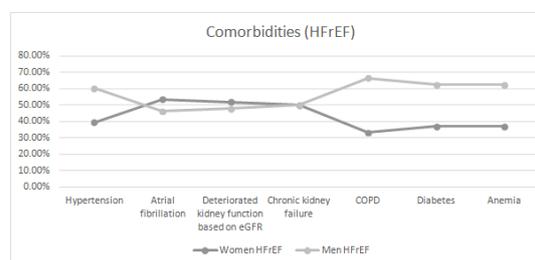
Table 8 and Graph 3 demonstrate that female patients with HFpEF had impaired glomerular filtration rate more often than men with HFpEF.

**Table 8. Distribution of comorbidities among HFpEF patients according to gender**

Comorbidity	Females	Males	t 2	?-level
HFpEF all	208 (61.5%)	130 (38.5%)	Â	Â
Hypertension	117 (56.2%)	63 (48.5%)	1.949	0.163
Atrial fibrillation	32 (15.4%)	18 (13.8%)	0.150	0.698
eGFR< 30 ml/min/m <sup>2</sup>	29 (13.9%)	10 (7.7%)	3.062	0.080
Chronic kidney failure, eGFR< 60 ml/min/m <sup>2</sup>	131 (63.0%)	60 (46.1%)	9.217	0.002
COPD	27 (13.0%)	17 (13.1%)	0.001	0.980
Diabetes	83 (39.9%)	53 (40.1%)	0.025	0.875
Anemia	62 (29.8%)	37 (28.5%)	0.085	0.770

**Graph 3. Distribution of comorbidities among patients with HFpEF**

**Graph 4. Distribution of comorbidities in patients with HFrEF**



There is a lack of gender-specific data on comorbidities in HF as a whole and in HFpEF and HFrEF separately. Despite the evidence that more than half of the patients with HF are women, randomized clinical trials have recruited predominantly male subjects.

Data from trials have demonstrated important gender differences in the etiology, risk factors, and clinical

presentation of HF, showing that women, compared to men, tend to be older, with higher blood pressure and non-ischemic HF etiology, as well as more comorbidities, such as diabetes, renal disease, and arthritis (19,20)

## Conclusion

Despite reported gender differences in the prevalence of hypertension and non-cardiovascular comorbidities in HF, the data remain incomplete and sometimes controversial. In this study females with HF tended to be older, more numerous and more likely than men to have comorbid impaired renal function and both genders had similar occurrence of all other comorbidities. Patients with HFpEF more often had hypertension and atrial fibrillation - less often, compared to those with HFrEF. Females with HFpEF had hypertension more often and atrial fibrillation less often, compared to their counterparts with HFrEF. Males with HFpEF and HFrEF had no differences in comorbidities whatsoever. Females with HFpEF and HFrEF had more impaired renal function than males and atrial fibrillation was more frequently observed, if with HFrEF.

Registries and real-life investigations generally report higher prevalence of comorbidities compared to clinical trials but the impact on mortality seems to be different as mortality rates and causes of death are comparable between both sexes with slightly better survival in women, in contrast to their higher burden of comorbidities.

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