Original article

Sex-Related Differences in Characteristics and Therapy of Heart Failure Patients

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Abstract

Aim: To determine the differences in comorbidities, therapy and echocardiographic measures among patients hospitalized for heart failure relative to gender.

Methods: The study included patients hospitalized for heart failure at the Department of Cardiovascular Diseases of the Clinical Hospital Center Osijek in the period from 1 January 2020 to 30 March 2021.

Results: There were 200 patients included in the study, of which 100 (50%) were male and 100 (50%) were female. Female patients were older, while male patients more frequently had a history of coronary artery disease. Men had a higher dose of loop diuretic on admission to the hospital. No significant difference was found in the representation of beta blockers and ACE inhibitors in therapy with regard to gender. On the other hand, men more frequently used MRA, sacubitril/valsartan and antiplatelet medication at hospital admission. Male patients had a larger left ventricular end-diastolic diameter, left ventricular end-systolic diameter and a lower left ventricular ejection fraction (EF). Regarding the type of heart failure according to EF, 72% of men had HFrEF, 20% HFmrEF and 8% HFpEF. In women, 47% had HFrEF, 33% HFmrEF and 20% HFpEF. During hospitalization due to heart failure, 22 patients died, an equal number of men and women.

Conclusion: This research confirmed the differences in risk factors and pathophysiology of heart failure between males and females. Medicine is progressing towards an individual approach to each patient, so further research will be needed to find the best therapy for both male and female patients

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Introduction

Heart failure (HF) is a clinical syndrome that includes symptoms and signs that arise due to structural and/or functional heart disorders. The most common cause is systolic (with or without diastolic) myocardial dysfunction. Other factors contributing to the development of HF include pathology of the heart valves and pericardium, heart rhythm and conduction disorders. According to the 2021 guidelines of the European Society of Cardiology with regard to ejection fraction (EF), HF is divided into: HF with reduced EF (HFrEF) (< 40%), mildly reduced EF (HFmrEF) (40–49%) and preserved EF (HFpEF) (≥ 50%) (1). It is believed that the prevalence of HF in the world is about 64.3 million. In developed countries, about 1–2% of the population is diagnosed with HF. About half of patients have preserved EF, and it is believed that this percentage is increasing (2).

Gender differences in patients with HF exist in disease distribution, outcome and risk factors that lead to HF. Women have a lower incidence of HF than men in all age groups, except those older than 74 years. However, women still make up half of HF patients in terms of disease prevalence because women have higher life expectancy. In addition, a smaller percentage of women undergo hospitalization for HF, but those who go on to be hospitalized, are hospitalized in more advanced stages of HF (3). Although the prognosis of HF is poor in both sexes, it is known that mortality is higher in men (4). The pathophysiology of HF differs in men and women. In men, the occurrence of HF is more common as a result of direct injury to the myocardium during ischemia, leading to focal fibrosis at the site of the injury and eccentric hypertrophy, i.e. dilation of the ventricles and ultimately reduced EF. On the other hand, HFpEF is more common in women, which is the result of chronic inflammation as part of comorbidities such as obesity, hypertension and diabetes mellitus, which leads to myocardial remodeling and interstitial fibrosis (5).

Although the number of patients with HF is equal with regard to gender, most studies do not emphasize the differences in the etiology, pathophysiology and treatment of HF in men and women. The aim of this study was to examine the differences in comorbidities, therapy and echocardiographic measurements of patients hospitalized for HF with regard to gender.

Patients and methods

Study design

The research was designed as a cross-sectional study with historical data at the Department of Cardiovascular Diseases of the Clinical Hospital Center Osijek. The research was approved by the Ethics Committee of the Osijek Faculty of Medicine of the Josip Juraj Strossmayer University of Osijek (CLASS: 602-04/20-08/07; REG. NO.: 2158-61-07-20-183).

Patients

The study included patients hospitalized for heart failure at the Department of Cardiovascular Diseases of the Clinical Hospital Center Osijek in the period from 1 January 2020 to 30 March 2021, when the target number of 200 subjects was reached. The exclusive criterion was patients with myocardial infarction and active malignant disease. During hospitalization due to heart failure, 22 patients died and therefore data on therapy at discharge were available for 178 patients.

Methods

Data on patients were collected by searching the hospital information system. The patients' age, gender, comorbidities (hypertension, diabetes mellitus, chronic obstructive pulmonary disease, aortic stenosis and atrial fibrillation), vital signs on arrival (systolic and diastolic arterial pressure, blood oxygen saturation and heart rate) and the number of prior hospitalizations were recorded. It was recorded if the patient had a beta blocker, angiotensin-converting enzyme (ACE) inhibitor, sacubitril/valsartan, mineralocorticoid receptor antagonist (MRA), loop diuretic, calcium channel blocker, antiplatelet and anticoagulant therapy at admission as well as at discharge. In laboratory findings at admission, the values of

leukocytes, neutrophils, lymphocytes, erythrocytes, red blood cell distribution width (RDW), hemoglobin, thrombocytes, glucose, creatinine, urate, C-reactive protein (CRP), albumin, N-terminal proB type natriuretic peptide (NT-proBNP), sodium and potassium

were monitored. During hospitalization, all patients underwent echocardiography, where data on left ventricular EF, left atrium diameter, left ventricular diameter in diastole and systole as well as tricuspid annular plane systolic excursion (TAPSE) were recorded. Patients were divided into two groups based on gender (male and female).

Statistical analysis

Categorical data were presented in absolute and relative frequencies. Differences in categorical variables were tested with the χ2-test. The normality of the distribution of numerical variables was tested with the Shapiro-Wilk test. Numerical data will be described by the arithmetic mean and standard deviation in the case of distributions that follow the normal and in other cases by the median and the limits of the interquartile range. Differences in numerical variables between two independent groups were tested with the Student's t-test in the case of distributions that follow the normal and in other cases by the Mann-Whitney U test. All P values are two-sided. The significance level was set at Alpha = 0.05. The statistical program MedCalc Statistical Software version 19.1.7.(MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2020) was used for statistical analysis

Results

There were 200 patients included in the study, of which 100 (50%) were male and 100 (50%) were female. The median age was 76 years, interquartile range (73–79 years). Regarding age, female patients were older than male patients (median 79 years vs. 72 years, P < 0.001, Mann-Whitney U test). The most common comorbidity was hypertension (172 patients, 86%), followed by atrial fibrillation (120 patients, 60%) and coronary artery disease (80 patients, 40%). Diabetes mellitus was present in 68 (34%) patients. A significantly higher incidence of coronary artery disease was observed in male patients (51% of men vs. 29% of women, P =0.002, χ2 test) (Table 1).

At hospital admission, most patients had in therapy a beta blocker (140 patients, 70%), an ACE inhibitor (119 patients, 59.5%) and a loop diuretic (121 patients, 60.5%). Male patients had a higher dose of loop diuretic at hospital admission (median 80 mg in men versus 40 mg in women, P < 0.001, Mann-Whitney U test). No significant difference was found in the representation of beta blockers and ACE inhibitors in therapy with regard to gender. On the other hand, male patients more frequently used MRA (39% of men and 23% of women, P = 0.01, χ2 test), sacubitril/valsartan (20% of men and 4% of women, P < 0.001, χ2 test) and

Table 1. Sex-related differences in comorbidities of heart failure patients

		Male N (%)	Female N (%)	*P*˚	Total N (%)
Comorbidity	Hypertension	90 (52.3)	82 (47.7)	0.1	172 (86)
	Diabetes mellitus	39 (57.4)	29 (42.6)	0.14	68 (34)
	CAD	51 (63.7)	29 (36.2)	**0.002**	80 (40)
	Aortic stenosis	22 (48.9)	23 (51.1)	0.87	45 (22.5)
	Atrial fibrillation	61 (50.8)	59 (49.2)	0.77	120 (60)
	COPD	18 (62.1)	11 (37.9)	0.16	29 (14.5)
First hospitalization		53 (47.7)	58 (52.3)	0.48	111 (55.5)
Total		100 (50)	100 (50)		200 (100)

CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease

Table 2. Sex-related differences in therapy on admission of heart failure patients

		Male N (%)	Female N (%)	*P**	Total N (%)
Therapy on admission	Beta blockers	73 (52.1)	67 (47.9)	0.36	140 (70)
	ACE inhibitors	61 (51.3)	58 (48.7)	0.67	119 (59.5)
	MRA	39 (62.9)	23 (37.1)	**0.01**	62 (31)
	Sacubitril / valsartan	20 (83.3)	4 (16.7)	**<0.001**	24 (12)
	Loop diuretic	60 (49.6)	61 (50.4)	0.89	121 (60.5)
	SGLT2 inhibitor	2 (50)	2 (50)	>0.99	4 (2)
	Other diuretics†	22 (53.7)	19 (46.3)	0.6	41 (20.5)
	CCB	20 (47.6)	22 (52.4)	0.73	42 (21)
	Antithrombotic	36 (66.7)	18 (33.3)	**0.004**	54 (27)
	Anticoagulant	38 (50)	38 (50)	>0.99	76 (38)
Total		100 (50)	100 (50)		200 (100)

MRA = mineralocorticoid receptor antagonist; SGLT2 = sodium-glucose cotransporter-2; CCB = calcium channel blockers

* $\chi 2$ test

† torasemide, indapamide, hydrochlorothiazide

antiplatelet drugs (36% of men and 18% of women, P = 0.004, $\chi 2$ test) at admission to the hospital (Table 2). During hospitalization due to heart failure, 22 patients died, an equal number of men and women.

At discharge from the hospital, 161 (80.5%) patients had a beta blocker, 117 (65.7%) an ACE inhibitor and 168 (94.4%) loop diuretic. No significant gender difference was found in the prescribed beta blockers. ACE inhibitors were more often prescribed to female patients (49% of men and 68% of women, P = 0.003, $\chi 2$ test), while male patients were more often prescribed sacubitril/valsartan (35% of men and 11% of women, P < 0.001, $\chi 2$ test) (Table 3).

Table 3. Sex-related differences in therapy on discharge of heart failure patients

		Male N (%)	**Female N (%)**	***P****	**Total N (%)**
Therapy on discharge	Beta blockers	80 (49.7)	81 (50.3)	0.77	161 (80.5)
	ACE inhibitors	49 (41.9)	68 (58.1)	**0.003**	117 (65.7)
	MRA	67 (54.5)	56 (45.5)	0.08	123 (69.1)
	Sacubitril / valsartan	35 (76.1)	11 (23.9)	**<0.001**	46 (25.8)
	Loop diuretic	83 (49.4)	85 (50.6)	0.52	168 (94.4)
	SGLT2 inhibitor	5 (83.3)	1 (16.7)	0.1	6 (3.4)
	Other diuretics†	10 (52.6)	9 (47.4)	0.81	19 (10.7)
	CCB	12 (37.5)	20 (62.5)	0.12	32 (18)
	Antithrombotic	26 (53.1)	23 (46.9)	0.62	49 (27.5)
	Anticoagulant	61 (52.1)	56 (47.9)	0.43	117 (65.7)
Total		100 (50)	100 (50)		200 (100)

MRA = mineralocorticoid receptor antagonist; SGLT2 = sodium-glucose cotransporter-2; CCB = calcium channel blockers

* $\chi 2$ test

† torasemide, indapamide, hydrochlorothiazide

Table 4. Sex-related differences in laboratory measurements of heart failure patients

	Male median (IQR)	Female median (IQR)	P*	Total median (IQR)
Age (years)	72 (62.5 – 81)	79 (69.5 – 84)	**<0.001**	76 (73 – 79)
Loop diuretic dose (mg)	80 (40 – 125)	40 (40 – 80)	**<0.001**	80 (40 – 80)
Heart rate (/min)‡	102 (29)	100 (31)	0.58†	101 (30)
Systolic blood pressure (mmHg)‡	130 (25)	133 (29)	0.37†	132 (27)
Diastolic blood pressure (mmHg)	80 (70 – 90)	79 (67 – 89)	0.16	80 (78 – 80)
Blood oxygen saturation (%)	96 (92 – 97)	93 (89 – 96)	**0.002**	95 (94 – 95)
Leukocytes (x10^9/L)	8.6 (6.6 – 11.8)	8.7 (7.1 – 11.7)	0.61	8.7 (8.3 – 9.4)
Neutrophils (%)	73 (67 – 79)	73 (66 – 81)	0.93	73 (72 – 74)
Lymphocytes (%)	16 (10 – 22)	16 (11 – 23)	0.95	16 (15 – 18)
Erythrocytes (x10^{12}/L)	4.6 (4.1 – 5.1)	4.2 (3.8 – 4.6)	**<0.001**	4.4 (4.2 – 4.5)
RDW (%)	14.6 (13.8 – 16.5)	15 (13.8 – 16.4)	0.59	14.9 (14.5 – 15.3)
Hemoglobin (g/L)	138 (120 – 150)	120 (107 – 132)	**<0.001**	127 (123 – 129)
Thrombocytes (x10^9/L)	191 (149 – 247)	224 (184 – 275)	**0.008**	210 (196 – 225)
Glucose (mmol/L)	7.1 (6.2 – 9.1)	8.1 (6.5 – 11)	**0.04**	7.8 (7.2 – 8.1)
Urea (mmol/L)	9.2 (7.1 – 14.4)	9.5 (7.5 – 13.9)	0.86	9.5 (9 – 10.5)
Creatinine (μmol/L)	118 (93.5 – 148)	101 (79 – 133)	**0.02**	110.5 (104 – 118)
C reactive protein (mg/L)	9.8 (5.7 – 23.5)	11.1 (5.1 – 22.2)	0.91	10.9 (9.1 – 12.9)
Urate (μmol/L)	512 (432 – 646)	466 (355 – 634)	0.06	489 (458 – 542)
Albumin (g/L)	36 (33 – 39)	36 (32 – 39)	0.76	36 (35 – 37)
Sodium (mmol/L)	139 (136 – 141)	139 (137 – 141)	0.48	139 (139 – 140)
Potassium (mmol/L)‡	4.3 (0.6)	4.2 (0.6)	0.5†	4.2 (0.6)
NT-proBNP (pg/L)	5,569 (2,362 – 12,134)	6,780 (2,724 – 12,477)	0.31	6,352 (5,211 – 7,565

IQR = interquartile range; RDW = red blood cell distribution width; NT-proBNP = N-terminal probrain natriuretic peptide

* Mann-Whitney U test

† Student's t-test

‡ expressed as arithmetic mean (standard deviation)

The arithmetic value (standard deviation) of systolic arterial pressure was 132 mmHg (27), and median diastolic arterial pressure was 80 mmHg (interquartile range 78–80 mmHg). No significant difference was found regarding gender. Male patients had significantly higher blood oxygen saturation (96% vs. 93%, P = 0.002, Mann-Whitney U test). Regarding laboratory findings, male patients had significantly more erythrocytes (4.6 vs. 4.2x1012/L, P < 0.001, Mann-Whitney U test),

Table 5. Sex-related differences in echocardiographic measurements of heart failure patients

	Male median (IQR)	Female median (IQR)	*P**	Total median (IQR)
LA (mm)	50 (45 – 53)	47 (44 – 52)	**0.04**	48 (47 – 50)
LVEDD (mm)‡	58.1 (8.7)	50.8 (9.6)	**<0.001**†	54.4 (9.8)
LVESD (mm)‡	47.7 (9.2)	39.9 (10.1)	**<0.001**†	43.8 (10.4)
EF (%)	33 (25 – 40)	40 (33 – 50)	**<0.001**	35 (34 – 38)
TAPSE (mm)	16 (14 – 20)	18 (14 – 21)	0.26	17 (15 – 18)

LA = left atrial diameter; LVEDD = left ventricular end-diastolic diameter; LVESD = left ventricular end-systolic diameter; EF = ejection fraction; TAPSE = tricuspid annular plane systolic excursion

* Mann-Whitney U test

† Student's t-test

hemoglobin (138 vs. 120 g/L, P < 0.001, Mann-Whitney U test) and creatinine (118 vs. 101 µmol/L, P = 0.02, Mann-Whitney U test), as well as significantly lower thrombocytes (191 vs. 224x109/L, P = 0.008, Mann-Whitney U test) and glucose (7.1 vs. 8.1 mmol/L, P = 0.04, Mann-Whitney U test) (Table 4). Regarding the echocardiographic measurements, male patients had a larger left atrial diameter (50 vs. 47 mm, P = 0.04, Mann-Whitney U test), left ventricular end-diastolic diameter (58.1 vs. 50.8 mm, P < 0.001, Student's t-test), left ventricular end-systolic diameter (47.7 vs. 39.9 mm, P < 0.001, Student's t-test) and lower left ventricular ejection fraction (33 vs. 40%, P < 0.001, Mann-Whitney U test). The function of the right ventricle was preserved with no difference regarding gender (Table 5). Regarding the type of HF according to EF, 72% of men had HfrEF, 20% HFmrEF and 8% HFpEF. In women, 47% had HFrEF, 33% HFmrEF and 20% HFpEF.

Discussion

In this study, differences in comorbidities, therapy and echocardiographic measurements of patients hospitalized for HF were examined with regard to gender. Regarding comorbidities, no significant difference was found, except for coronary artery disease, which was more common in men. Men were more often prescribed MRA, sacubitril/valsartan, an antiaggregation drug as well as higher doses of loop diuretic, while women were more often prescribed an ACE inhibitor at discharge which is in line with the previous results considering that more men have HFrEF than women. Significant differences in biochemical variables between men and women corresponded with expected sex-related variations. No significant difference was found in survival during hospitalization with regard to gender.

In this study, women were older than men, had a higher EF and less often had ischemic cardiomyopathy or coronary artery disease underlying HF, which is in line with previous studies on the typical presentations of women with HF (6–8). The main difference in the etiology of HF is the greater presence of ischemic heart disease in men, which leads to the activation of certain pathophysiological mechanisms and affects middle-aged men more often. Direct injury of myocytes by ischemia or myocarditis leads to inflammation that will end in eccentric hypertrophy (9). On the other hand, HFpEF is a slowly progressive disease in which no initial event that causes myocardial injury can be found but is a consequence of a long-term chronic pro-inflammatory condition in the setting of different comorbidities (2). This explains the greater proportion of men in patients with HFrEF and the greater proportion of women in patients with HFpEF. Furthermore, the protective role of the female gender and estrogen in certain remodeling patterns and further progression to HF is known. With aging, the protective role of estrogen is lost, which explains the similar incidence of HF in patients in advanced age groups, regardless of gender. In the study by Hall et al. early menopause and nulliparity have been found to increase the risk of developing HF, especially HFpEF (10). In our

study, no difference was found in the presence of hypertension and diabetes mellitus with regard to gender. Although it is known that women with HF more often have comorbidities (such as hypertension and diabetes mellitus), it is important to emphasize that the risk of developing HF in patients with the aforementioned comorbidities varies depending on gender. Namely, in the Framingham heart study, it was found that men with diabetes mellitus have twice the frequency of HF, while women have five times more (11). In a meta-analysis that included more than 12 million patients, the relative risk for developing HF in women with diabetes mellitus type 2 was 1.95 (95% CI 1.70–2.22), while in men it was 1.74 (95% CI 1.55–1.95) (12). Previous research has shown that women had more severe symptoms, more pronounced signs of congestion and a lower quality of life, and despite this, a similar number of hospitalizations due to heart failure (8). NT-proBNP values in our study do not correlate with the level of symptoms, which is in line with other research (13). No significant difference was found in the value of NT-proBNP depending on gender. In our study, the number of men and women treated with loop diuretic was equal, but men had a significantly higher dose. Given that it is known that women appear in advanced stages of HF, unlike men, it is possible that they did not show up on time for control examinations where there was an opportunity to increase the dose.

Guideline-directed medical therapy for HF according to the 2021 guidelines of the European Society of Cardiology is equal regardless of gender (1, 14, 15). Recently, studies have been conducted that show the shortcomings of this uniform approach to treatment, given that there are differences in pharmacokinetics and pharmacodynamics depending on gender, influencing the choice and the dose of the medication (16). Similarly, in previous studies, it was shown that women are not appropriately treated with guideline-directed medical therapy. Fonarow et al. studied gender differences in a total of 48,612 patients from the OPTIMIZE-HF registry and found that significantly fewer women had an ACE inhibitor, beta blocker and MRA in therapy while significantly more women had a loop diuretic (17). In our research, no significant difference was found in the prescribed ACE inhibitor and beta blocker at admission, depending on gender, which represents progress compared to previous research. Significantly more men had MRA on therapy at admission, which is likely a reflection of the higher proportion of HFrEF in men. At discharge from the hospital, significantly more men were prescribed sacubitril/valsartan than women. Studies on the use of sacubitril/valsartan in patients with HFmrEF and HFpEF did not find a significant reduction in heart failure hospitalizations and mortality (18). However, looking at women and men separately, women with HFpEF and HFmrEF benefited more from sacubitril/valsartan in reducing HF hospitalizations than men (19) which leaves room for further studies and emphasizes the need for an individual approach to the treatment of HF. In our study, only a minority of patients were treated with sodium-glucose cotransporter-2 (SGLT2) inhibitors because it was conducted before the results of the EMPULSE trial were published (20, 21).

Differences in echocardiographic measurements between women and men are a reflection of different pathophysiological mechanisms of the origin and progression of HF. Myocardial remodeling in men leads to left ventricular dilatation and fibrosis. On the other hand, women experience concentric hypertrophy and a decrease in the volume of the left ventricle (6, 22). In our study, women had a smaller diameter of the left atrium and a smaller diameter of the left ventricle in systole and diastole. On the other hand, they had higher TAPSE (tricuspid annular plane systolic excursion), i.e. better right ventricular function and left ventricular EF, which is in line with other studies. Women have a higher ejection fraction and TAPSE, which follow diastolic dysfunction and HFpEF, while in men the above measures are lower as a reflection of biventricular systolic dysfunction (23). Sex-related variations in echocardiographic measurements should be noted as confounding factors.

The research was conducted as a cross-sectional study, which is the main limitation of

this research. The therapy was observed at the time of admission and discharge of the patient, but the doses of drugs (except loop diuretic) were not recorded, which makes it impossible to draw more detailed conclusions regarding the differences in the therapy of men and women with HF. Furthermore, the BMI of the patients was not recorded, i.e. the presence of obesity as one of the important risk factors for the development of HF.

Heart failure is a heterogeneous clinical syndrome. Considering the existence of differences in pathophysiological processes between men and women, it is to be expected that there are also differences in risk factors and pathophysiology of HF, which was confirmed in this and other studies. Despite this, women are underrepresented in research on HF therapy. Medicine is progressing towards an individual approach to each patient, so further research will be needed to emphasize these differences and to find the best therapy for both men and women

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Spolno uvjetovane razlike u obilježjima i terapiji srčanih bolesnika

Sažetak

Cilj: Odrediti razlike u komorbiditetima, terapiji i ehokardiografskim mjerenjima među pacijentima hospitaliziranima zbog zatajenja srca u odnosu na spol.

Metode: Studija je uključila pacijente hospitalizirane zbog zatajenja srca na Odjelu za kardiovaskularne bolesti Kliničkog bolničkog centra Osijek u razdoblju od 1. siječnja 2020. do 30. ožujka 2021. godine.

Rezultati: U studiju je bilo uključeno 200 pacijenata, od kojih je 100 (50 %) bilo muškaraca i 100 (50 %) žena. Ženske pacijentice bile su starije, dok su muškarci češće imali povijest koronarne arterijske bolesti. Muškarci su na prijemu u bolnicu primali višu dozu diuretika Henleove petlje. Nije pronađena značajna razlika u zastupljenosti beta blokatora i ACE inhibitora u terapiji s obzirom na spol. S druge strane, muškarci su češće koristili MRA, sakubitril/valsartan i antitrombocitne lijekove pri prijemu u bolnicu. Muški pacijenti imali su veći krajnji dijastolički promjer lijeve klijetke, krajnji sistolički promjer lijeve klijetke i nižu ejekcijsku frakciju (EF) lijeve klijetke. S obzirom na tip zatajenja srca prema EF-u, 72 % muškaraca je imalo HFrEF, 20 % HFmrEF, i 8 % HFpEF. Kod žena, 47 % ih je imalo HFrEF, 33 % HFmrEF i 20 % HFpEF. Tijekom hospitalizacije zbog zatajenja srca, umrla su 22 pacijenta, jednak broj muškaraca i žena.

Zaključak: Ovo istraživanje potvrdilo je razlike u rizičnim čimbenicima i patofiziologiji zatajenja srca između muškaraca i žena. Medicina napreduje prema individualnom pristupu svakom pacijentu, stoga će biti potrebna daljnja istraživanja kako bi se pronašla najbolja terapija za muškarce i žene.