

## **SUPPLEMENTARY DATA**

### **COLLABORATORS**

The authors acknowledge all other members of the ETIFIC research team, collaborators who took part in the study and reviewed the study protocol, developed the intervention content, obtained ethical approval from each hospital, managed the day-to-day running of the trial, and delivery of the intervention and collected the data:

Ascensión Martín, Josep Comín-Colet, Josep Roca, Cristina Enjuanes, Laia Rosenfeld, Marta Marichal, Arola Armengou, Pilar Ruiz-Rodríguez, Anna Linas, M. José Bernardo, José-Luis Lambert, Josefa González-Ordás, Amada Recio, Luis de-la-Fuente, Rebeca Sancho, Ana Correa, Carmen Bravo, Anna Arce, Ramón Bascompte, Mercè Faraudo, Paola Beltrán, Rosario Gracia-Ródenas, Francisco José Pastor-Pérez, Concepción Fernández-Redondo, Amparo Martínez-López, Carmen Duran, Concepción Recuerda, Gustavo Cortez, Carmen Rus, Ángela Ortega-López, Inés Gómez-Otero, Ana Seoane-Blanco, Montserrat Puga, Mercedes González-de-Molina, Luis Almenar, Inmaculada Husillos, Raquel López, Patricia Conejero, Pilar Iglesias, Ramón Bover, Alberto Esteban, Mónica Pérez, Alberto Giráldez, Patricia Atalaya, Carmen Larraondo, Ana López-Rodríguez, Manolo Gómez-Bueno, María Molina-Jiménez, Beatriz González-Fernández, Josefa Pérez-Romero, Beatriz Fernández-González, Leticia Napal, Jesús Berjón, Alfonso Varela, María Moure, Javier Segovia, Teresa Soria, Yolanda Sánchez-Paule, Julia Roure.

## **CONTRIBUTORS**

The authors as well as collaborators are members of the ETIFIC research team. Among them, there are HF-cardiologists, HF-nurses, Directors of HF and Cardiac Transplant Units, Directors of Departments of Cardiology, and Medical Directors. They have broad experience and expertise in managing HF patients and have taken part in several research studies on chronic and acute HF and heart transplant.

## **ACKNOWLEDGEMENTS**

We thank the Departments of Cardiology and Health Administrators of the 20 hospitals that took part in this study: Galdakao HU- Barrualde; Bellvitge HU; Dr. Josep Trueta HU; Del Mar HU; Burgos HU; Asturias HU; Germans Trias i Pujol HU; Valladolid H U; Navarra HU; Santa María-Lleida HU; Moisés Broggi H; Virgen de la Arrixaca HU; Puerta de Hierro HU; Andújar H; Virgen de la Victoria HU; Santiago HU; Virgen de las Nieves HU; La Fe de Valencia HU; San Carlos HU; Jerez HU. \*Hospital (H), University (U).

## **TRANSPARENCY**

The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned and registered have been explained.

## **DEFINITION GENDER/SEX**

The authors' definition of sex and gender for this article is based on the American Medical Association (AMA) guide, 11<sup>th</sup> edition:

***Sex** is defined as the classification of living things as male or female and is a “biological component, defined via the genetic complement of chromosomes, including cellular and molecular differences.”*

***Gender** comprises “social, environmental, cultural, and behavioural factors and choices that influence a person’s self- identity and health.”<sup>9</sup> The term gender “includes **gender identity** (how individuals and groups perceive and present themselves), **gender norms** (unspoken rules in the family, workplace, institutional, or **global culture** that influence individual attitudes and behaviours), **and gender relations** (the relations between individuals of different gender identities).”*

*(Christiansen SL, Iverson C, Flanagan A, et al. AMA manual of style, a guide for authors and editors, 11th edition, 2020. Jama network. Oxford University Press).*

Note from authors: although we agree in general with AMA definition and we have tried to apply it in the article, we had difficulties in choosing one term over another, sex, gender or both, due to the lack of research specifically directed to women, which could clarify the application of this definition. We did not prove but nor could we rule out the influence of both sex and gender in most of the study variables or factors influencing the titration process in women, the selection process, and some baseline characteristics. However, since the ETIFIC study was mainly an organizational trial carried out with close follow-up in HF clinics, that concluded that women, in that context, were able to achieve similar doses, no higher adverse events (even lower) and excellent clinical results, we have prioritized the term *gender* in the title, abstract, and

conclusions. Although the accuracy of some of our applied terms may not always have been the best option, we hope that our article has raised the urgent need for future research specifically directed to women and has opened ways for a better application of the terms *sex* and *gender*.

**Table 1 of the supplementary data**

Variables introduced in the multivariate analysis

Variables	BB	ACEI	MRA
Sex (female vs male)	X	X	X
Time (baseline vs 4 mo)	X	X	X
Group by titrating professional: HF nurse/HF cardiologist	X	X	X
No. visits with the titrating professional	X	X	X
Age, y	X	X	X
Patient education up to age ≤ 10 y	X	X	X
Baseline dose	X	X	X
SBP at baseline	X	X	X
Heart rate at baseline	X		
Glomerular filtration rate, at baseline	X	X	X
eGFR < 60 (no vs yes) at baseline	X	X	X
Potassium ≥ 5.5 mEq/L at baseline		X	X
Women with mild events (yes vs no) associated with titration	X	X	X
Atrial fibrillation	X	X	X
Ischemic heart disease	X	X	X
Diabetes mellitus	X	X	X
Respiratory disease	X		
NT-proBNP at baseline	X	X	X
LVEF at baseline	X	X	X
NYHAI/II/III at baseline	X	X	X
Combination of 3 drugs (BB, ACEI/ARB/sac-valsartan/MRA) at baseline	X	X	X
Other rate-lowering drugs at baseline	X		
BP lowering drugs at baseline	X	X	X
Psychotropic drugs at baseline	X	X	X

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta-blockers; HF, heart failure; eGFR, estimated glomerular filtration rate; MRA, mineralocorticoid receptor blocker; Nt-proBNP, N-terminal proBNP; NYHA, New York Heart Association; SBP, systolic blood pressure.

## Oyanguren J, et al. Gender differences in drug titration of heart failure patients with reduced ejection fraction from the XXX ETIFIC trial

Table 2 of the supplementary data

Exclusion, inclusion analysis

	Total	Women	Men	Diff (95%CI)	P
<i>Patients</i>					
Assessed for eligibility	824	221 (26.8)	603 (73.2)	-46.36 (-50.76 to -41.96)	< .001
Excluded	504	138 (27.38)	366 (72.62)	-45.24 (-50.94 to -39.53)	< .001
Excluded/assessed for eligibility		138/221 (62.44)	366/603 (60.70)	1.75 (-6.04 to 9.54)	.708
Included	320	83 (25.94)	237 (74.06)	-48.13 (-55.23 to -41.02)	< .001
Analyzed at 4 mo/total analyzed	289	76 (26.29)	213 (73.70)	-47.40 (-54.93 to -39.88)	< .001
Analyzed at 6 mo/total analyzed	274	74 (27.01)	200 (72.99)	-45.98 (-53.78 to -38.16)	< .001
<i>Included by hospital/total No. of included patients</i>					
In 6 hospitals that included ≥ 20 patients	182	53 (29.12) (12-37.20)	129 (70.88) (62-88)		
In 6 hospitals that included 10-19 patients	91	18/(19.78) (6.66-35.71)	73 (80.22) (64-93)		
In 8 hospitals that included < 10 patients	47	11 (23.40) (0-33)	36 (76.60) (33-100)		
<i>Women included by hospital</i>					
6 Hospitals ≥ 20: 01: 8/25 (32); 02:16/43 (37.20); 03:13/45 (28.88); 11: 7/22 (31.81); 15: 6/22 (27.27); 16: 3/25 (12)					
6 Hospitals 10-19: 10: 2/16 (12.5); 12: 3/16 (18.75);13:1/15 (6.66);14:5/14 (35.71);17: 4/17 (23.52); 18:3/13 (23.07)					
8 Hospitals < 10: 04: 1/7 (14.28); 05: 1/3 (33.33); 6: 2/7 (28.57); 7 2/3 (66.66); 8: 3/9 (33.33); 9: 0/1 (0); 19: 0/8(0); 20: 2/9 (22.22)					
<i>Men included by hospital</i>					
6 Hospitals ≥ 20: 01: 17/25 (68); 02:27/43 (62.80); 03:32/45 (71.12); 11: 15/22 (68.19); 15: 16/22 (72.73); 16: 22/25 (88)					
6 Hospitals 10-19: 10: 14/16 (87.5); 12: 13/16 (81.25); 13:14/15 (93.34); 14:9/14 (64.29); 17: 13/17(76.48); 18:10/13 (76.93)					
8 Hospitals < 10: 04: 6/7 (85.72); 05: 2/3 (66.67); 6: 5/7 (71.43); 7: 1/3 (33.34); 8: 6/9 (66.67); 9: 1/1 (100); 19: 8/8(100); 20: 7/9 (77.78)					

95%CI, 95% confidence interval; Diff, difference;

Unless otherwise indicated, the data are expressed as absolute numbers, No. (%), or No. (%) (min-max).

\* P value of the interaction between treatment and each subgroup.

Table 3 of the supplementary data

## Causes of exclusion

Causes of exclusion	Total N = 504	Women n = 138	Men n = 366	Diff (95%CI)	P*
<i>Not meeting inclusion criteria</i>	441	116 (84.06)	325 (88.80)	-4.73 (-12.15 to 2.67)	.199
Without need for BB titration prescription, 100% target dose or maximal tolerated dose	140	43 (31.16)	97 (26.50)	4.66 (-4.79 to 14.11)	.353
Scheduled surgical procedure	113	24 (17.39)	89 (24.32)	-6.93 (-15.13 to 1.27)	.123
Contraindication to BB	26	8 (5.8)	18 (4.91)	0.89 (-4.10 to 5.86)	.863
NYHA IV at discharge	1	0 (0)	1 (0.27)	-0.27 (-1.08 to 0.53)	.999
Inability to attend appointments; home-care patient	65	20 (14.49)	45 (12.29)	2.20 (-5.07 to 9.46)	.612
Incapacity for self-care not compensated by caregiver	42	6 (4.35)	36 (9.84)	-5.49 (-10.56 to -0.42)	.071
Life expectancy < 6 mo	34	5 (3.62)	29 (7.92)	-4.30 (-8.97 to 0.37)	.129
Living in a nursing home	15	8 (5.8)	7 (1.92)	3.88 (-0.76 to 8.53)	.046
Unable to stand up for 20 sec on weighing scale	4	2 (1.45)	2 (0.54)	0.91 (-1.73 to 3.53)	.649
Without telephone	1	1 (0.72)	0 (0)	0.72 (-1.19 to 2.64)	.612
<i>Consent form not signed</i>	45	14 (10.14)	31 (8.47)	1.67(-4.61 to 7.96)	.678
<i>Others</i>	18	8 (5.8)	10 (2.73)	3.07 (1.68 to 7.81)	.166

BB, beta-blockers; 95%CI, 95% confidence interval; Diff, difference; NYHA, New York Heart Association.

Unless otherwise indicated, the data are expressed as absolute numbers or No. (%).

\* P value of the interaction between treatment and each subgroup.

## Oyanguren J, et al. Gender differences in drug titration of heart failure patients with reduced ejection fraction from the XXX ETIFIC trial

Table 4 of the supplementary data

Supplementary baseline patient characteristics

Variables (at hospital discharge)	Women n = 83	Men n = 237	P*
<b>Educational level</b>			
Reading and writing supplied by carer	2 (2.41)	4 (1.69)	.769
Reading and writing	18 (21.69)	41 (17.37)	
Up to 10 y	11 (13.25)	32 (13.56)	
Up to 14-16 y	37 (44.58)	102 (43.22)	
Further studies	15 (18.07)	57 (24.15)	
<b>Patients ≥ 70 y</b>	30 (36.14)	53 (22.36)	.014
<b>Lawton Instrumental Activities of Daily Living Scale score (0-8)</b>	26 (7.81 ± 1.27)	49 (6.69 ± 2.41)	.031
Lawton < 5 (men) < 8 (women)	15 (57.69)	21 (42.86)	.221
Lawton test, inability			
Use telephone	1 (3.33)	4 (7.55)	.438
Shopping	10 (33.33)	18 (33.96)	.954
Food preparation	4 (13.33)	36 (67.92)	.000
Housekeeping	3 (10)	17 (32.08)	.024
Laundry	3 (10)	36 (67.92)	.000
Transportation	10 (33.33)	13 (24.53)	.389
Responsibility for own medications	10 (38.46)	23 (46.94)	.482
Handle finances	4 (13.33)	8 (15.09)	.827
<b>Cardiovascular risk factors</b>			
Hypertension	41 (49.4)	125 (52.74)	.600
Dyslipidemia	30 (36.14)	92 (38.82)	.666
Smoker	14 (16.87)	83 (35.02)	.002
Exsmoker < 1 y	4 (4.82)	20 (8.44)	.281
Exsmoker ≥ 1 y	11 (13.25)	62 (26.16)	.016
<b>Heart disease</b>			
AV block, first-degree	1 (1.2)	4 (1.69)	.495
Pacemaker	2 (2.41)	5 (2.11)	.872
Automated implantable cardioverter defibrillator	2 (2.41)	9 (3.8)	.550
Cardiac resynchronization therapy	1 (1.2)	2 (0.84)	.769
<b>Left ventricular ejection fraction (%) ≤ 35%</b>	69 (83.13)	207 (87.34)	.338
<b>Comorbidities, Charlson index</b>			
AMI	16 (19.28)	61 (25.74)	.236
Peripheral arterial disease	2 (2.41)	20 (8.44)	.062
Stroke	6 (3.66)	10 (6.41)	.259
Dementia	1 (1.2)	1 (0.42)	.436
Chronic respiratory disease	9 (1.84)	32 (13.5)	.533
Connective tissue disease	3 (3.61)	6 (2.53)	.608
Gastroduodenal ulcer	0 (0)	5 (2.11)	.182
Mild chronic liver disease	1 (1.2)	9 (3.8)	.243
Renal failure with Cr > 3 mg/dL or in dialysis	2 (2.41)	7 (2.95)	.796
Diabetes with end-organ damage	2 (2.41)	11 (4.64)	.375
Any malignancy	13 (15.66)	11 (4.64)	.001
Leukemia	0 (0)	1 (0.42)	.553
Lymphoma	2 (2.41)	1 (0.42)	.106
Severe-moderate chronic liver disease	0 (0)	2 (0.84)	.401

## Oyanguren J, et al. Gender differences in drug titration of heart failure patients with reduced ejection fraction from the XXX ETIFIC trial

Metastatic solid tumor	1 (1.2)	0 (0)	.091
Charlson comorbidity index score, not age-adjusted	2.17 ± 1.31	2.2 ± 1.33	.810
Charlson index, adjusted by age	5.11 ± 1.65	4.69 ± 2.03	.048
Charlson index ≥ 3	28 (33.73)	81 (34.18)	.942
BMI, kg/m <sup>2</sup>	26.49 ± 5.63	27.62 ± 4.64	.072
BMI < 19	6 (7.23)	6 (2.55)	.077
BMI 19-20.99	8 (9.64)	11 (4.68)	
BMI 21-39.9	68 (91.93)	216 (91.91)	
BMI ≥ 40	1 (1.20)	2 (0.85)	
Laboratory tests			
eGFR < 30 mL/min./1.73m <sup>2</sup>	3 (3.61)	5 (2.11)	
eGFR 30-60 mL/min./1.73m <sup>2</sup>	16 (19.28)	49 (20.68)	.735
Glycosylated hemoglobin (if diabetes mellitus) > 7.5	26 (35.14)	9 (50)	.244
Health-related quality of life			
Minnesota Living with HF Questionnaire (0-105) Total score	52.76 ± 21.14	46.76 ± 22.83	.038
<25	44 (18.72)	9 (10.98)	.341
25-40	51 (21.7)	14 (17.07)	
40-50	36 (15.32)	15 (18.29)	
50-74	55 (23.4)	25 (30.49)	
75-100	49 (20.85)	19 (23.17)	
EQ-5 D index	0.66 (0.24)	0.76 (0.23)	.001
Mobility (score 1,2,3)			
1	48 (58.54)	161 (68.8)	.201
2	33 (40.24)	72 (30.77)	
3	1 (1.22)	1 (0.43)	
Self-care (1,2,3)			
1	66 (80.49)	206 (88.03)	.169
2	13 (15.85)	25 (10.68)	
3	3 (3.66)	3 (1.28)	
Daily living tasks, (1,2,3)			
1	3947(56)	159 (67.95)	.040
2	33 (40.24)	65 (27.78)	
3	10 (12.19)	10 (4.27)	
Pain/discomfort (1,2,3)			
1	45 (54.88)	149 (64.22)	.194
2	34 (41.46)	71 (30.6)	
3	3 (3.66)	12 (5.17)	
Anxiety/ depression			
1	30 (36.59)	126 (53.62)	.002
2	37 (45.12)	93 (39.57)	
3	15 (18.29)	16 (6.81)	
Visual analog scale EQ-5D (0-100)	53.89 ± 17.73	58.94 ± 20.21	.047
Visual analog scale EQ-5D score			
< 25	4 (4.94)	12 (5.11)	.066
25-49.9	21 (25.93)	37 (15.74)	
50-74.9	47 (58.02)	134 (57.02)	
75-100	9 (11.11)	52 (22.13)	

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta-blockers; BMI, body mass index; BNP, B-type natriuretic peptide; EQ-5 D, EuroQol-5 Dimension; eGFR, estimated glomerular filtration rate; MRA, mineralocorticoid receptor blocker; NT-proBNP, N-terminal proBNP; NYHA, New York Heart Association; SBP, systolic blood pressure; VAS, visual analog scale.

The data are expressed as No. (%), mean ± standard deviation, or No.; median [interquartile range].

\*P value of the interaction between treatment and each subgroup.

Table 5 of the supplementary data

Differences in mean relative dose at 4 months and visits in women and men between titrating professionals: HF-nurse vs HF-cardiologist

Drug	HF nurse	HF cardiologist	Diff (95%CI)	P <sup>a</sup>
<b>BB</b>				
<i>Female patients</i>	40	36		
Relative dose %	68.44 ± 30.7	55.03 ± 29.5	13.40 (-0.38 to 27.19)	.057
<i>Male patients</i>	104	109		
Relative dose %	72.48 ± 31.7	56.71 ± 32	15.77 (7.17 to 24.37)	< .001
<b>ACEI</b>				
<i>Female patients</i>	30	27		
Relative dose %	68.75 ± 32.3	45.37 ± 30.6	23.38 (6.67 to 40.09)	.007
<i>Male patients</i>	85	88		
Relative dose %	73.2 ± 28.7	59.43 ± 29.7	13.77 (5.04 to 22.56)	.002
<b>ARB</b>				
<i>Female patients</i>	7	6		
Relative dose %	36.85 ± 30.8	30.92 ± 22.8	5.93 (-26.95 to 38.81)	.699
<i>Male patients</i>	12	11		
Relative dose %	48.93 ± 35.5	50.38 ± 37.5	-1.44 (-33.22 to 30.32)	.925
<b>MRA</b>				
<i>Female patients</i>	34	33		
Relative dose %	83.82 ± 26.7	75.76 ± 28.3	8.07 (-5.38 to 21.51)	.235
<i>Male patients</i>	91	94		
Relative dose %	66.21 ± 32.8	68.35 ± 30.5	-2.14 (-11.33 to 7.05)	.646
<b>Visits/professional</b>				
<i>Female patients</i>	39 <sup>b</sup>	36		
	6.28 ± 2.95	2.72 ± 1.56	3.56 (2.48 to 4.64)	< .001
<i>Male patients</i>	103 <sup>b</sup>	108 <sup>b</sup>		
	6.50 ± 2.80	2.84 ± 1.60	3.65 (3.03 to 4.28)	< .001
<b>Patients ≤ 2 visits with the titrating professional</b>				
<i>Female patients</i>	3/39 (7.69)	20/36 (55.55)	-47.86 (-68.79 to -26.93)	< .001
<i>Male patients</i>	4/103 (3.88)	58/108 (53.70)	-49.82 (-60.89 to -38.75)	< .001

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta blocker; 95%CI, 95% confidence interval; Diff, difference; HF, heart failure; MRA, mineralocorticoid receptor antagonist.

Unless otherwise indicated, the data are expressed as absolute numbers, No. (%) or mean ± standard deviation

<sup>a</sup>P value of the interaction between treatment and each subgroup.<sup>b</sup> The number of visits was missing in 3 patients (1 woman, 2 men).

Table 6 of the supplementary data

Differences in mean relative dose and visits in women and men between the professional who titrated: HF women cardiologist vs HF men cardiologist

Drug	HF female cardiologist	HF male cardiologist	Diff (95%CI)	P*
<b>BB</b>				
Female patients	18	18		
Relative dose %	65.28 ± 33.09	44.79 ± 21.09	20.49 (1.38 to 39.60)	.037
Male patients	47	62		
Relative dose %	62.37 ± 33.34	52.42 ± 30.52	9.95 (–2.40 to 22.30)	.113
<b>ACEI</b>				
Female patients	14	13		
Relative dose %	48.21 ± 32.84	42.31 ± 29.1	5.91 (–18.66 to 30.47)	.624
Male patients	39	49		
Relative dose %	61.35 ± 30.1	57.91 ± 30.27	3.44 (–9.23 to 16.11)	.591
<b>ARB</b>				
Female patients	2	4		
Relative dose %	22.75 ± 14.50	35 ± 27.1	–12.25 (–60.72 to 36.22)	.513
Male patients	2	9		
Relative dose %	43.75 ± 44.19	51.85 ± 38.76	–8.10 (–241.98 to 225.77)	.842
<b>MRA</b>				
Female patients	17	16		
Relative dose %	70.59 ± 30.92	81.25 ± 25.00	–10.66 (–30.59 to 9.27)	.283
Male patients	38	56		
Relative dose %	63.82 ± 39.50	71.43 ± 27.9	7.61 (–20.83 to 5.61)	.255
<b>Visits/professional</b>				
Female patients	18	18		
	3.22 ± 1.77	2.22 ± 1.17	1 (–0.02 to 2.02)	.054
Male patients	47	61		
	3.43 ± 1.65	2.39 ± 1.33	1.03 (0.44 to 1.62)	< .001
<b>Patients with ≤2 visits with the titrating professional</b>				
Female patients	8/18 (44.44)	12/18 (66.67)	–22.23 (–59.42 to 14.98)	.314
Male patients	18/47 (38.30)	40/61 (65.57)	–27.28 (–47.47 to –7.08)	.008

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta-blocker; 95%CI, 95% confidence interval; Diff, difference; HF, heart failure, MRA, mineralocorticoid receptor antagonist;

Unless otherwise indicated, the data are expressed as absolute numbers, No. (%), or mean ± standard deviation.

\*P value of the interaction between treatment and each subgroup.

## Oyanguren J, et al. Gender differences in drug titration of heart failure patients with reduced ejection fraction from the XXX ETIFIC trial

Table 7 of the supplementary data

Drug prescription. Baseline to 4 months (titration period)

Prescribed drugs/active patients at 4 months	Women n = 76	Men n = 213	Diff (95%CI)	P*
<b>BB</b>				
At baseline	73/76 (96.05)	208/213 (97.65)	-1.60 (-7.32 to 4.12)	.747
At 4 mo	75/76 (98.68)	210/213 (98.59)	0.09 (-2.92 to 3.10)	.953
Started in this period	3	5		
Withdrawn (0 dose)	1	3		
BB not recommended in guidelines for HF at baseline *	1	0		
<b>ACEI</b>				
At baseline	63/76 (82.89)	176/213 (82.62)	0.27 (-9.88 to 10.41)	1
At 4 mo	56/76 (73.68)	171/213 (80.28)	-6.60 (-18.74 to 5.55)	.298
Started in this period	1	6		
Withdrawn (0 dose), without ARB/ARB-neprilysin inhibitor	1	2		
Changed to other medication: ARB/ARB-neprilysin inhibitor	7	9		
ACEI not recommended in guidelines for HF at baseline *	0	1		
ACEI not recommended in guidelines for HF at 4 m*	0	1		
<b>ARB</b>				
At baseline	8/76 (10.52)	17/213 (7.98)	2.55 (-6.15 to 11.24)	.66
At 4 mo	13/76 (17.10)	22/213 (10.32)	6.78 (-2.62 to 16.18)	.120
Started in this period	6	6		
Withdrawn (0 dose), without ACEI/ARB-neprilysin inhibitor	0	1		
Changed to other medication: ARB-neprilysin inhibitor	1	0		
ARB not recommended in guidelines for HF at baseline*	1	4		
ARB not recommended in guidelines for HF at 4 mo*	1	3		
<b>MRA</b>				
At baseline	58/76 (76.31)	165/213 (77.46)	-1.15 (-13.13 to 10.83)	.964
At 4 mo	65/76 (85.52)	174/213 (81.69)	3.84 (6.52 to 14.19)	.560
Started in this period	9	20		
Withdrawn	2	11		

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB: beta-blockers; 95%CI, 95% confidence interval; Diff, difference; MRA, mineralocorticoid receptor antagonist.

Unless otherwise indicated, the data are expressed as absolute numbers or No. (%).

\*P value of the interaction between treatment and each subgroup.

**Table 8 of the supplementary data**

Drug combination at 4 months (after titration)

Patients with 3 groups of drugs Drug combination BB + (ACEI/ARB/ARB-neprilysin inhibitor) + MRA	Women n = 76	Men n = 213	Dif. (95%CI)	P*
HF-nurse group and HF-cardiologist group	64/76 (84.21)	168/213 (78.87)	5.34 (–5.42 to 16.09)	.403
HF-nurse group	33/40 (82.5)	84/104 (80.77)	1.73 (–14.00 to 17.46)	1
HF-cardiologist group	31/36 (86.11)	84/109 (77.06)	9.05 (–6.58 to 24.68)	.355

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta-blockers; 95%CI, 95% confidence interval; Dif, difference; MRA, mineralocorticoid receptor antagonist.

Unless otherwise indicated, the data are expressed as No. (%).

\* P value of the interaction between treatment and each subgroup.

Table 9 of the supplementary data

Other drugs that could possibly influence titration. Baseline to 4 months

Patients, n (%) with other drugs that could possibly influence titration/active patients at 4 months	Women n = 76	Men n = 213	Diff (95%CI)	P <sup>a</sup>
<i>With any other rate-lowering drug</i>				
Baseline	22 (28.94)	61 (28.64)	0.30 (-11.87 to 12.48)	.999
4 mo	16 (21.05)	52 (24.41)	-3.36 (-15.08 to 8.36)	.663
<i>Ivabradine</i>				
Baseline	14 (18.42)	23 (10.80)	7.62 (-2.04 to 17.28)	.088
4 mo	9 (11.84)	17 (7.98)	3.86 (-5.16 to 12.88)	.437
Started	3	9		
Withdrawn	8	15		
<i>Amiodarone</i>				
Baseline	5 (6.58)	26 (12.21)	-5.63 (-12.73 to 1.47)	.174
4 mo	4 (5.26)	23 (10.80)	-5.53 (-12.95 to 1.88)	.233
Started	1	5		
Withdrawn	2	7		
Change from amiodarone to dronedarone		1		
<i>Digitalis</i>				
Baseline	3 (3.95)	15 (7.04)	-3.09 (-8.66 to 2.47)	.338
4 mo	3 (3.95)	13 (6.10)	-2.16 (-7.59 to 3.28)	.481
Started	1	4		
Withdrawn	1	6		
<i>Hypo- and hyperthyroidism medication</i>				
Baseline	7 (9.21)	6 (2.82)	6.39 (-1.37 to 14.16)	.047
4 mo	6 (7.89)	7 (3.29)	4.61 (-2.80 to 12.02)	.180
<i>Inhaled bronchodilators</i>				
Baseline	12 (15.79)	13 (6.10)	9.69 (-0.01 to 19.38)	.019
4 mo	10 (13.16)	13 (6.10)	7.05 (2.09 to 16.20)	.088
<i>With other drugs that can affect blood pressure (nondiuretics)</i>				
Baseline	9 (11.84)	24 (11.27)	0.57 (-8.41 to 9.56)	.999
4 mo	10 (13.16)	36 (16.90)	-3.74 (-13.75 to 6.26)	.560
<i>ARB + neprilysin inhibitor</i>				
Baseline	1 (1.32)	2 (0.94)	0.38 (-2.87 to 3.62)	1
4 mo	4 (5.26)	7 (3.28)	1.98 (-4.48 to 8.43)	.672
Started	3	5		

Withdrawn	0	2		
<i>Dihydropyridine calcium-channel blockers</i>				
Baseline	3 (3.95)	9 (4.23)	-0.28 (-5.42 to 4.87)	.917
4 mo	3 (3.95)	13 (6.10)	-2.16 (-8.48 to 4.17)	.679
Started	0	5		
Withdrawn	0	1		
<i>Nitrates (not sublingual)/hydralazine</i>				
Baseline	6 (7.89)	9 (4.22)	3.67 (-3.86 to 11.20)	.349
4 mo	4 (5.26)	8 (3.76)	1.51 (-4.12 to 7.14)	.572
Started	0	1		
Withdrawn	2	2		
<i>Alpha-blockers</i>				
Baseline	1 (1.32)	11 (5.16)	-3.85 (-7.77 to 0.08)	.149
4 mo	0 (0.00)	13 (6.10)	-6.10 (-10.21 to -1.99)	.060
Started	0	3		
Withdrawn	1	1		
<i>Diuretics (loop/thiazide)</i>				
Baseline	66 (86.84)	170 (79.81)	7.03 (-2.29 to 16.35)	.174
4 mo	62 (81.58)	173 (81.22)	0.36 (-10.17 to 10.89)	.999
<i>Psychotropic drugs<sup>b</sup></i>				
Baseline	30/76 (39.47)	38 (17.84)	21.63 (8.61 to 34.66)	< .001
At 4 mo	27/76 (35.52)	37 (17.37)	18.16 (5.36 to 17.37)	.002

ARB, angiotensin receptor blocker; 95%CI, 95% confidence interval; Diff, difference.

<sup>a</sup>P-value of the interaction between treatment and each subgroup.

<sup>b</sup>Psychotropic drugs: antidepressants, anxiolytics, hypnotics, neuroleptics.

Table 10 of the supplementary data

Other variables potentially associated with titration

Variables potentially associated with titration 4 months	Women N=76	Men N=213	Diff (95%CI)	p*
<b>Systolic blood pressure</b>				
Baseline, mmHg	113.51 ± 18.08	116.58 ± 18.74	-3.07 (-7.96 to 1.81)	.217
4 mo, mmHg	117.71 ± 17.18	121.18 ± 19.15	-3.47 (-8.38 to 1.44)	.165
<b>SPB ≤100 mmHg</b>				
Baseline	21 (27.63)	41 (19.24)	8.38 (-3.87 to 20.64)	.172
4 mo	13 (17.10)	33 (15.49)	1.61 (-8.15 to 11.37)	.742
<b>Heart rate, beats/min</b>				
Baseline	73.24 ± 14.6	72.85 ± 13.79	0.38 (-3.31 to 4.08)	.838
4 mo	66.29 ± 11.40	66.27 ± 12.41	0.01 (-3.19 to 3.21)	.993
<b>HR &lt; 50 beats/min</b>				
Baseline	2 (2.63)	5 (2.35)	0.28 (-4.13 to 4.70)	.999
4 mo	3 (3.95)	10 (4.69)	-0.74 (-5.96 to 4.47)	.787
<b>Creatinine, mg/dL</b>				
Baseline	0.90 ± 0.38	1.13 ± 0.52	-0.24 (-0.37 to -0.11)	.0003
4 mo	0.93 ± 0.39	1.12 ± 0.51	-0.18 (-0.31 to -0.06)	.005
<b>Estimated glomerular filtration rate, mL/min/1.73 m<sup>2</sup></b>				
Baseline	73.45 ± 22.15	76.23 ± 21.40	-2.78 (-8.15 to 3.56)	.439
4 mo	73.55 ± 24.36	77.57 ± 21.58	-4.02 (-10.31 to 2.28)	.209
<b>eGFR &lt; 60 mL/min/1.73m<sup>2</sup></b>				
Baseline	16/75 (21.33)	46/212 (21.70)	-0.36 (-11.53 to 10.80)	.999
4 mo	20/75 (26.66)	42/212 (19.81)	6.86 (-5.40 to 19.11)	.282
<b>eGFR &lt; 30 mL/min/1.73 m<sup>2</sup></b>				
Baseline	3/75 (4)	4/212 (1.88)	2.11 (-3.59 to 7.81)	.559
4 mo	3/75 (4)	6/212 (2.83)	1.17 (-4.70 to 7.04)	.909
<b>eGFR, patients with change of level baseline-4 mo: a) ≥ 60; b) 30-59; c) &lt; 30</b>				
Improved	5/76 (6.58)	19/213 (8.92)	-2.34 (-9.99 to 5.31)	.694
Worsened	8/76 (10.53)	14/213 (6.57)	3.95 (-4.60 to 12.51)	.388
Remained similar	63/76 (82.89)	180/213 (84.51)	-1.61 (-12.27 to 9.04)	.883
<b>Sodium, mEq/L</b>				
Baseline	139.84 ± 2.87	139.34 ± 3.33	0.50 (-0.30 to 1.30)	.216
4 mo	140.87 ± 3.15	140.14 ± 3.26	0.73 (-0.12 to 1.57)	.092
<b>Potassium, mEq/L</b>				
Baseline	4.41 ± 0.58	4.49 ± 0.51	-0.08 (-23.80 to 0.06)	.245
4 mo	4.65 ± 0.48	4.67 ± 0.48	-0.01 (-0.14 to 0.11)	.844
<b>K &gt;5.5 mEq/L</b>				
Baseline	1 (1.32)	4 (1.89)	-0.56 (-3.74 to 2.62)	.750
4 mo	3 (3.95)	10 (4.73)	-0.78 (-6.02 to 4.54)	.792
<b>K &gt; 6 mEq/L</b>				

## Oyanguren J, et al. Gender differences in drug titration of heart failure patients with reduced ejection fraction from the XXX ETIFIC trial

Baseline	1 (1.32)	1 (0.47)	0.86 (−1.90 to 3.62)	.443
4 mo	1 (1.32)	1 (0.47)	0.86 (−1.90 to 3.62)	.443
<b>Hemoglobin, g/dL</b>	13.65 ± 1.92	14.89 ± 6.97	−1.24 (−2.84 to 0.36)	.128
Baseline	13.13 ± 1.40	13.96 ± 1.76	−0.83 (−1.28 to −0.38)	.0004
4 mo				
<b>Hemoglobin &lt; 12 (women), &lt; 13 (men), g/dL</b>				
Baseline	19 (25.00)	46 (21.60)	3.40 (−7.79 to 14.60)	.542
4 mo	15 (20.83)	49 (23.67)	−2.84 (−13.86 to 8.19)	.622
<b>NYHA</b>				
Baseline				
NYHA II	58 (76.32)	182 (85.45)	−9.13 (−20.69 to 2.43)	.100
NYHA III	18 (23.68)	31 (14.55)	9.13 (−1.54 to 19.80)	.068
4 mo				
NYHA I	14 (18.67)	65 (32.02)	−13.35 (−24.26 to −2.45)	.029
NYHA II	59 (78.67)	130 (64.04)	14.63 (3.25 to 26.01)	.020
NYHA III	2 (2.67)	8 (3.94)	−1.27 (−5.80 to 3.25)	.613
<b>Atrial fibrillation/atrial flutter</b>				
Baseline	14 (18.42)	64 (30.05)	−11.63 (−22.30 to −0.96)	.05
4 mo	9 (11.84)	37 (17.37)	−5.53 (−14.40 to 3.34)	.258
<b>BMI ≤ 19</b>	7 (9.21)	4 (1.87)	7.33 (−0.31 to 14.98)	.011
<b>Flexible diuretic regime/patients with a prescription</b>	39/62 (62.90)	113/173 (65.32)	−2.41 (−17.47 to 12.64)	.852
Flexible diuretic regime/patients with a prescription, HF-nurse group: 82/118	23/33 (69.70)	59/84 (70.24)	−0.54 (−19.56 to 18.48)	.999
Flexible diuretic regime/patients with a prescription, HF-cardiologist group: 66/119	15/29 (51.72)	51/89 (57.30)	−5.58 (−28.75 to 17.60)	.756
<b>European Heart Failure Self-care Behaviour Scale, (min-max) (12-60 worse)</b>	18.30 ± 6.35	20.62 ± 8.27	−2.32 (−4.38 to −0.26)	.027
Question 10. Irregular medication intake score ≥3	2 (2.63)	10 (4.76)	−2.13 (−6.74 to 2.48)	.427

BMI, body mass index; 95%CI, 95% confidence interval; Diff, difference; eGFR, estimated glomerular filtration rate; HR, heart rate; NYHA, New York Heart Association; K, Potassium; SBP, systolic blood pressure.

The data are expressed as No. (%) or mean ± standard deviation.

\*P value of the interaction between treatment and each subgroup.

### Supplementary data references

1. Olsen SL, Gilbert EM, Renlund DG, Taylor DO, Yanowitz FD, Bristow MR. Carvedilol improves left ventricular function and symptoms in chronic heart failure: A double blind randomized study. *J Am Coll Cardiol*. 1995;25:1225-1231.
2. Bristow MR, Gilbert EM, Abraham WT, et al. Carvedilol Produces Dose-Related Improvements in Left Ventricular Function and Survival in Subjects with Chronic Heart Failure. *Circulation*. 1996;94:2807-2816.
3. Packer M, Bristow MR, Cohn JN, et al. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. *N Engl J Med*. 1996;334:1349-55.
4. Packer M, Colucci WS, Sackner-Bernstein JD, et al. Double-blind, Placebo-Controlled Study of the Effects of Carvedilol in Patients with Moderate to Severe Heart Failure. The PRECISE Trial *Circulation*. 1996;94:2793-2799.
5. Australia/New Zealand Heart Failure Research Collaborative Group. Randomised placebo-controlled trial of carvedilol in patients with congestive heart failure due to ischaemic heart disease. *Lancet* 1997;349:375-380.
6. Cohn JN, Fowler MB, Bristow MR, et al. Safety and efficacy of carvedilol in severe heart failure. The U.S. Carvedilol Heart Failure Study Group. *J Card Fail*. 1997;3:173-179.
7. Packer M, Coats AJ, Fowler MB, et al. Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med*. 2001;344:1651-1658.
8. Cleland JG, Pennell DJ, Ray SG, et al. Myocardial viability as a determinant of the ejection fraction response to carvedilol in patients with heart failure (CHRISTMAS trial): randomized controlled trial. *Lancet*. 2003;362:14-21.
9. Dubach P, Myers J, Bonetti P, et al. Effects of bisoprolol fumarate on left ventricular size, function, and exercise capacity in patients with heart failure: Analysis with magnetic resonance myocardial tagging. *Am Heart J*. 2002;143:676-83.
10. Edes I, Gasior Z, Wita K. Effects of nebivolol on left ventricular function in elderly patients with chronic heart failure: results of the ENECA study. *Eur J Heart Fail*. 2005;7:631-639.
11. Van Veldhuisen DJ, Cohen-Solal A, Böhm M, et al. Beta-blockade with nebivolol in elderly heart failure patients with impaired and preserved left ventricular ejection fraction: Data from SENIORS (Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors With Heart Failure). *J Am Coll Cardiol*. 2009;53:2150-2158.
12. Poole-Wilson PA, Swedberg K, Cleland JG, et al. Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the carvedilol or metoprolol European trial (COMET): randomised controlled trial. *Lancet*. 2003;362:7-13.
13. Galatius S, Gustafsson F, Atar D, Hildebrandt PR. Tolerability of Beta-Blocker initiation and titration with bisoprolol and carvedilol in congestive heart failure- A randomized comparison. *Cardiology*. 2004;102:160-165.

14. Komajda M, Lutiger B, Madeira H, et al. Tolerability of carvedilol and ACE-Inhibition in mild heart failure. Results of CARMEN (Carvedilol ACE Inhibitor remodelling mild CHF evaluation). *Eur J Heart Fail.* 2004;6:467-475.
15. Willenheimer R, van Veldhuisen DJ, Silke B, et al. Effect on survival and hospitalization of initiating treatment for chronic heart failure with bisoprolol followed for enalapril, as compared with the opposite sequence. Results of the randomized cardiac insufficiency bisoprolol study (CIBIS) III. *Circulation.* 2005;112:2426-2435.
16. Edelmann F, Musial-Bright L, Gelbrich G, et al. Tolerability and feasibility of Beta-Blocker titration in HFpEF or HFrEF. Insights from the CIBIS-ELD trial. *JACC Heart Fail.* 2016;4:140-149.
17. Colucci WS, Packer M, Bristow MR, et al. Carvedilol Inhibits Clinical Progression in Patients with Mild Symptoms of Heart Failure. *Circulation.* 1996;94:2800-2806.
18. Doughty RN, Whalley GA, Gamble G, MacMahon S, Sharpe N. Left ventricular remodelling with carvedilol in patients with congestive heart failure due to ischemic heart disease. *J Am Coll Cardiol.* 1997;29:1060-1066.
19. Cohen-Solal A, Rouzet F, Berdeaux A, et al. Effects of carvedilol on sympathetic innervation in patients with chronic heart failure. *J Nucl Med.* 2005;46:1796-1803.
20. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet.* 1999;353:9-13.
21. SOLVD Investigators, Yusuf S, Pitt B, Davis CE, Hood WB, Cohn JN. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med.* 1991;325:293-302.
22. Gundersen T, Wiklund I, Swedberg K, Amtorp O, Remes J, Nilsson B. Effects of 12 weeks of ramipril treatment on the quality of life in patients with moderate congestive heart failure: results of a placebo-controlled trial. Ramipril Study Group. *Cardiovasc Drugs Ther.* 1995;9:589-594.
23. Granger CB, McMurray JJ, Yusuf S, et al. Effects of candesartan in patients with chronic heart failure and reduced left ventricular systolic function intolerant to angiotensin- converting-enzyme inhibitors: the CHARM alternative trial. *Lancet.* 2003;362:772-776.
24. Cohn JN, Tognoni G; Valsartan Heart Failure Trial Investigators. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med.* 2001;345:1667-175.
25. Konstam MA, Neaton JD, Dickstein K, et al. Effects of high-dose versus low-dose losartan on clinical outcomes in patients with heart failure (HEAAL study): a randomised double-blind trial. *Lancet.* 2009;374:1840-1848.
26. Cicoira M, Zanolla L, Rossi A, et al.. Long-term dose-dependent effects of spironolactone on left ventricular function and exercise tolerance in patients with chronic heart failure. *J Am Coll Cardiol.* 2002;40:304-310.
27. Pitt B, Remme W, Zannad F, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med.* 2003;348:1309-1321.
28. Zannad F, McMurray JJ, Krum H, et al. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med.* 2011;364:11-21.

29. Maggioni AP, Anker SD, Dahlström U, et al. Are hospitalized or ambulatory patients with heart failure treated in accordance with European Society of Cardiology guidelines? Evidence from 12,440 patients of the ESC Heart Failure Long-Term Registry. *Eur J Heart Fail.* 2013;15:1173–1184.
30. Thorvaldsen T, Benson L, Dahlström U, Edner M, Lund LH. Use of evidence-based therapy and survival in heart failure in Sweden 2003-2012. *Eur J Heart Fail.* 2016;18:503–511.
31. Gustafsson F, Schou M, Videbaek L, et al. Danish Heart Failure Clinics Network. Treatment with beta-blockers in nurse-led heart failure clinics: titration efficacy and predictors of failure. *Eur J Heart Fail.* 2007;9:910–916.
32. Driscoll A, Currey J, Tonkin A, Krum H. Nurse-led titration of angiotensin converting enzyme inhibitors, beta-adrenergic blocking agents, and angiotensin receptor blockers for people with heart failure with reduced ejection fraction. *Cochrane Database Syst Rev.* 2015;12.
33. Juillière Y, Suty-Selton C, Riant E, et al. Prescription of cardiovascular drugs in the French ODIN cohort of heart failure patients according to age and type of chronic heart failure. *Arch Cardiovasc Dis.* 2014;107:21–32.
34. De Groote P, Isnard R, Assyag P, et al. Is the gap between guidelines and clinical practice in heart failure treatment being filled? Insights from the IMPACT RECO survey. *Eur J Heart Fail.* 2007;9:1205-11.
35. Schou M, Gustafsson F, Videbaek L, et al. Extended heart failure clinic follow-up in low-risk patients: a randomized clinical trial (NORTHSTAR). *Eur Heart J.* 2013;34:432-442.
36. Barywani SB, Ergatoudes C, Schaufelberger M, Petzold M, Fu ML. Does the target dose of neurohormonal blockade matter for outcome in systolic heart failure in octogenarians? *Int J Cardiol.* 2015;187:666-672.
37. Elder DH, Mohan M, Cochrane L, Charles H, Lang CC. Characterizing patients with Chronic heart failure in Community care after hospitalization: a potential role for ivabradine. *Cardiovasc Ther.* 2015;33:104-108.
38. Hickey A, Suna J, Marquart L, et al. Improving medication titration in heart failure by embedding a structured medication plan. *Int J Cardiol.* 2016;224:99-106
39. Cohen Solal A, Leurs I, Assyag P, et al. Optimization of Heart Failure medical treatment after hospital discharge according to left ventricular ejection fraction: The FUTURE survey. *Arch Cardiovasc Dis.* 2012;105:355-365.
40. Calvert MJ, Shankar A, McManus RJ, Ryan R, Freemantle N. Evaluation of the management of Heart Failure in primary care. *Fam Pract.* 2009;26:145-153.
41. 6. Gheorghiade M, Albert NM, Curtis AB, et al. Medication dosing in outpatients with heart failure after implementation of a practice-based performance improvement intervention: from IMPROVE HF. *Congest Heart Fail.* 2012;18:9–17.
42. Marti CN, Fonarow GC, Anker SD, et al. Medication dosing for heart failure with reduced ejection fraction - opportunities and challenges. *Eur J Heart Fail.* 2019;21:286–296.

43. Shah KS, Xu H, Matsouaka RA, et al. Heart failure with preserved, borderline, and reduced ejection fraction: 5-year outcomes. *J Am Coll Cardiol* 2017;70(20):2476–86.
44. Franco J, Formiga F, Corbella X et al. (Grupo de investigadores RICA). De novo acute heart failure: Clinical features and one-year mortality in the Spanish nationwide Registry of Acute Heart Failure Med Clin. 2019;152(4):127-134.
45. Sicras-Mainar A, Sicras-Navarro A, Palacios B, Varela L, Delgado JF. Epidemiología y tratamiento de la insuficiencia cardíaca en España: estudio PATHWAYS-HF. *Rev Esp Cardiol*. 2020. <https://doi.org/10.1016/j.recesp.2020.09.014>.
46. Chioncel O, Lainscak M, Seferovic PM, et al. Epidemiology and one-year outcomes in patients with chronic heart failure and preserved, mid-range and reduced ejection fraction: an analysis of the ESC Heart Failure Long-Term Registry. *Eur J Heart Fail* 2017;19:1574–1585.
47. Fiuzat M, Wojdyla D, Kitzman D, et al. Relationship of beta-blocker dose with outcomes in ambulatory heart failure patients with systolic dysfunction: results from the HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training) trial. *J Am Coll Cardiol*. 2012;60:208-215
48. Güder G, Störk S, Gelbrich G, et al. Nurse coordinated collaborative disease management improves the quality of guideline-recommended heart failure therapy, patient reported outcomes and left ventricular remodelling. *Eur J Heart Fail*. 2015;17:442-452.
49. Greene SJ, Fonarow GC, DeVore AD et al. Titration of Medical Therapy for Heart Failure with Reduced Ejection Fraction. *J Am Coll Cardiol* 2019;73 (19):2365-2383.
50. Gürgöze MT, van der Galiën OP, Limpens MAM et al. Impact of sex differences in co-morbidities and medication adherence on outcome in 25776 heart failure patients. *ESC Heart Fail*. 2021;8:63-73.
51. Granger BB, Ekman I, Granger CB et al. Adherence to medication according to sex and age in the CHARM programme. *Eur J Heart Fail* 2009;11:1092–1098.
52. Lupón J, Díez-López C, de Antonio M, et al. Recovered heart failure with reduced ejection fraction and outcomes: a prospective study. *Eur J Heart Fail*. 2017;19:1615-1623.
53. Clarke CL, Grunwald GK, Allen LA, et al. Natural History of Left Ventricular Ejection Fraction in Patients with Heart Failure *Circ Cardiovasc Qual Outcomes*. 2013;6(6):680–686.
54. Wilcox JE, Fonarow GC, Yancy CW, et al. Factors associated with improvement in ejection fraction in clinical practice among patients with heart failure: Findings from IMPROVE HF. *Am Heart J*. 2012;163 (1):49-56.