SUPPLEMENTARY DATA

COLLABORATORS

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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.

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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, 11th 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."9 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, Flanagin 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.

Table 2 of the supplementary data

Exclusion, inclusion analysis

	Total	Women	Men	Diff (95%CI)	*P*
Patients					
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
Included by hospital/total No. of included patients		Women	Men		
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)		
Women included by hospital					
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)					
Men included by hospital					
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**
Not meeting inclusion criteria	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
Consent form not signed	45	14 (10.14)	31 (8.47)	1.67(−4.61 to 7.96)	.678
Others	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.

Table 4 of the supplementary data

Supplementary baseline patient characteristics

Variables (at hospital discharge)	Women n = 83	Men n = 237	*P**
Educational level			
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)	
Patients ≥ 70 y	30 (36.14)	53 (22.36)	.014
***Lawton Instrumental Activities of Daily Living Scale* score (0-8)**	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
Cardiovascular risk factors			
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
Heart disease			
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
Left ventricular ejection fraction (%) ≤ 35%	69 (83.13)	207 (87.34)	.338
Comorbidities, Charlson index			
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

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^2	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^2	3 (3.61)	5 (2.11)	
eGFR 30-60 mL/min./1.73m^2	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*[a]
BB				
Female patients	40	36		
Relative dose %	68.44 ± 30.7	55.03 ± 29.5	13.40 (−0.38 to 27.19)	.057
Male patients	104	109		
Relative dose %	72.48 ± 31.7	56.71± 32	15.77 (7.17 to 24.37)	< .001
ACEI				
Female patients	30	27		
Relative dose %	68.75 ± 32.3	45.37 ± 30.6	23.38 (6.67 to 40.09)	.007
Male patients	85	88		
Relative dose %	73.2 ± 28.7	59.43 ± 29.7	13.77 (5.04 to 22.56)	.002
ARB				
Female patients	7	6		
Relative dose %	36.85 ± 30.8	30.92 ± 22.8	5.93 (−26.95 to 38.81)	.699
Male patients	12	11		
Relative dose %	48.93 ± 35.5	50.38 ± 37.5	−1.44 (−33.22 to 30.32)	.925
MRA				
Female patients	34	33		
Relative dose %	83.82 ± 26.7	75.76 ± 28.3	8.07 (−5.38 to 21.51)	.235
Male patients	91	94		
Relative dose %	66.21 ± 32.8	68.35 ± 30.5	−2.14 (−11.33 to 7.05)	.646
Visits/professional				
Female patients	39[b]	36		
	6.28 ± 2.95	2.72 ± 1.56	3.56 (2.48 to 4.64)	< .001
Male patients	103[b]	108[b]		
	6.50 ± 2.80	2.84 ± 1.60	3.65 (3.03 to 4.28)	< .001
Patients ≤ 2 visits with the titrating professional				
Female patients	3/39 (7.69)	20/36 (55.55)	−47.86 (−68.79 to −26.93)	< .001
Male patients	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
[a]*P* value of the interaction between treatment and each subgroup.
[b] 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**
BB				
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
ACEI				
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
ARB				
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
MRA				
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
Visits/professional				
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
Patients with ≤2 visits with the titrating professional				
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.

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**
BB					
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		
ACEI					
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		
ARB					
At baseline		8/76 (10.52)	17/213 (7.98)	2.55 (−6.15 to 11.24)	.66
At 4 m o		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		
MRA					
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; Diff, 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*[a]
With any other rate-lowering drug				
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
Ivabradine				
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		
Amiodarone				
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		
Digitalis				
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		
Hypo- and hyperthyroidism medication				
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
Inhaled bronchodilators				
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
With other drugs that can affect blood pressure (nondiuretics)				
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
ARB + neprilysin inhibitor				
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		
Dihydropyridine calcium-channel blockers				
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		
Nitrates (not sublingual)/hydralazine				
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		
Alpha-blockers				
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		
Diuretics (loop/thiazide)				
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
Psychotropic drugs[b]				
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.

[a]P-value of the interaction between treatment and each subgroup.
[b]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**
Systolic blood pressure				
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
SPB ≤100 mmHg				
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
Heart rate, beats/min				
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
HR < 50 beats/min				
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
Creatinine, mg/dL				
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
Estimated glomerular filtration rate, mL/min/1.73 m²				
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
eGFR < 60 mL/min/1.73m²				
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
eGFR < 30 mL/min/1.73 m²				
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
eGFR, patients with change of level baseline-4 mo: a) ≥ 60; b) 30-59; c) < 30				
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
Sodium, mEq/L				
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
Potassium, mEq/L				
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
K >5.5 mEq/L				
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
K > 6 mEq/L				

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
Hemoglobin, g/dL	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				
Hemoglobin < 12 (women), < 13 (men), g/dL				
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
NYHA				
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
Atrial fibrillation/atrial flutter				
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
BMI ≤ 19	7 (9.21)	4 (1.87)	7.33 (−0.31 to 14.98)	.011
Flexible diuretic regime/patients with a prescription	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
European Heart Failure Self-care Behaviour Scale, (min-max) (12-60 worse)	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.

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