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Original article

Gender differences in drug titration among heart failure patients with reduced ejection fraction in the ETIFIC trial

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ABSTRACT

Introduction and objectives: Optimal medical therapy decreases mortality and heart failure (HF) hospitalizations in HF patients with reduced left ventricular ejection fraction. Women have been underrepresented in clinical trials and not specifically evaluated. This study aimed to compare the safety and effectiveness of drug titration in women vs men.

Methods: This post hoc gender study of the ETIFIC multicenter randomized trial included hospitalized patients with new-onset HF with reduced ejection fraction and New York Heart Association II-III and no contraindications to beta-blockers. A structured 4-month titration process was implemented in HF clinics. The primary endpoint was the mean relative dose (% of target dose) of beta-blockers achieved by women vs men. Secondary endpoints included the mean relative doses of angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and mineralocorticoid receptor antagonists, adverse events, and other clinical outcomes at 6 months.

Results: A total of 320 patients were included, 83 (25.93%) women and 237 (74.06%) men (76 vs 213 analyzed). The mean ± standard deviation of the relative doses achieved by women vs men were as follows: beta-blockers 62.08% ± 30.72% vs 64.4% ± 32.77%, with a difference of −2.32% (95%CI, −10.58-5.94), $P = .580$; and mineralocorticoid receptor antagonists 79.85% ± 27.72% vs 67.29% ± 31.43%, $P = .003$. No other differences in drug dosage were found. Multivariate analysis showed nonsignificant differences. CV mortality was 1 (1.20%) vs 3 (1.26%), $P = 1$, and HF hospitalizations 0 (0.00%) vs 10 (4.22%), $P = .125$.

Conclusions: In a post hoc analysis from the HF-titration ETIFIC trial, we found nonsignificant gender differences in drug dosage, cardiovascular mortality, and HF hospitalizations.

Trial registry number: NCT02546856.

Diferencias de género en la titulación de fármacos de pacientes con insuficiencia cardiaca y fracción de eyección reducida del ensayo ETIFIC

Palabras clave:
Titulación
Fármaco
Insuficiencia cardiaca
Mujer
Género
Sexo
Diferencias

RESUMEN

Introducción y objetivos: El tratamiento óptimo disminuye la mortalidad y hospitalizaciones por insuficiencia cardiaca (IC) en pacientes con IC y fracción de eyección reducida. En los ensayos clínicos las mujeres estuvieron infrarrepresentadas y no fueron evaluadas específicamente. Este estudio buscó comparar la seguridad y efectividad de titulación (ajuste de dosis), de fármacos en mujeres y varones.

Métodos: Estudio *post hoc* de género del ensayo aleatorizado multicéntrico ETIFIC. Se incluyeron pacientes hospitalizados con IC *de novo y* fracción de eyección reducida. Proceso estructurado de titulación en unidades de IC. Objetivo principal: la dosis relativa media de bloqueadores beta (% de la

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dosis objetivo) alcanzada por mujeres frente a varones. Objetivos secundarios: dosis relativas medias de otros fármacos de IC, eventos adversos y resultados clínicos a 6 meses.

Resultados: Se incluyeron 320 pacientes, 83 (25,93%) mujeres y 237 (74,06%) varones. (76 frente a 213 analizados). Media ± desviación estándar de dosis relativa de bloqueadores beta mujeres frente a varones: 62,08 ± 30,72% frente a 64,4 ± 32,77%; diferencia −2,32%; IC95%, −10,58-5,94; p = 0,580, antagonistas del receptor de mineralocorticoides 79,85 ± 27,72% comparado con 67,29 ± 31,43%; p = 0,003, sin diferencias significativas en dosificación de otros fármacos. El análisis multivariante no encontró diferencias significativas. Mortalidad cardiovascular 1 (1,20%) frente a 3 (1,26%), p = 1 y 0 hospitalizaciones por IC (0,00%) frente a 10 (4,22%), p = 0,125.

Conclusiones: En un análisis *post hoc* del ensayo ETIFIC de titulación en IC no encontramos diferencias de género significativas en dosificación, mortalidad cardiovascular y hospitalizaciones por IC.

Número de registro: NCT02546856.

Abbreviations

ACEI: angiotensin-converting enzyme inhibitors
ARB: angiotensin II receptor blockers
BB: beta-blockers
HF: heart failure
HFrEF: heart failure with reduced ejection fraction
MRA: mineralocorticoid receptor antagonists

INTRODUCTION

Heart failure (HF) has a high prevalence, mortality, hospital admissions, and social and health system impacts. To improve prognosis and reduce mortality and HF hospitalizations, clinical practice guidelines recommend administration of beta-blockers (BB), renin angiotensin system inhibitors, mineralocorticoid receptor antagonists (MRA) and education and follow-up programs with multidisciplinary teams of specialized nurses and cardiologists in HF patients with reduced ejection fraction (HFrEF). Careful drug titration is recommended.[1–3] However, dose optimization is deficient in clinical practice. Women have been underrepresented in most original HFrEF trials. Their clinical characteristics, prescription, achieved dose and adverse events associated with titration have not been specifically analyzed. Few trials have evaluated the effects on mortality and hospitalization based on sex[4–10] (see references 1-42 of the supplementary data).

There is limited evidence on the differences between women and men from meta-analyses, systematic reviews, and observational studies.[4,11–23] It is recommended that sex and gender analysis be carried out in studies to deepen knowledge of possible differences, avoid harm due to inappropriate generalization of results, and increase the applicability of treatments in women.[4,12,16] To our knowledge, no results of the HF drug titration process in women vs men have been published within the framework of a clinical trial with a structured titration protocol and follow-up. The limited available evidence raises the need to deepen study of this topic.

ETIFIC was a multicenter randomized trial, which demonstrated noninferiority in the safety and effectiveness of drug titration by HF-nurses vs HF-cardiologists in patients with de novo HFrEF.[24,25] This post hoc analysis aimed to compare gender differences in drug titration, selection process, characteristics, prescription, achieved dose, adverse events and clinical results in women vs men.

METHODS

Study design and participants

ETIFIC was a randomized controlled open label trial carried out in 20 Spanish hospitals with HF units (2015-2018) to compare the safety and effectiveness of HF drug titration by HF-nurses vs HF-cardiologists. Its design and results have been previously published.[24,25]

Patients with de novo HFrEF and New York Heart Association (NYHA) II-III were included after hospitalization in a cardiology ward. Exclusion criteria were planned surgery, contraindication to BB or already receiving target or maximum tolerated dose, home or terminal care, or inability for self-care.

An active supervision system for recruitment, with centralized randomization, 4-month titration period, and a 6-month follow-up period after inclusion were established. A safety and clinical adjudication committee, blinded to the group assignment, monitored the safety of the research activity and evaluated all adverse events. Written informed consent forms were signed. The study was approved by the Clinical Research Ethics Committee of the Basque Country and complied with the Declaration of Helsinki.

ETIFIC confirmed the noninferiority safety and effectiveness of drug titration by HF-nurses vs drug titration by HF-cardiologists.

Study protocol

The previously published study protocol[24] was based on clinical practice guidelines.[1,2] The titrating professional was the HF-nurse vs the HF-cardiologist. In both cases, drug prescription was the responsibility of the cardiologist. HF-nurse tasks also included clinical assessment, education on self-care, psychosocial support, and care coordination. All HF-nurses and half of the HF-cardiologists were women.

The main objective of this post hoc substudy was to compare the safety and effectiveness of drug titration in women vs men from the ETIFIC study and to assess the possible factors associated with any differences.

Primary endpoint

To compare the achieved BB mean relative dose (% relative to target dose) after 4 months of titration in women vs men. The % of target dose was defined according to ESC HF guidelines.[24]

Secondary endpoints

To compare the following between women and men: *a)* patient selection process and baseline characteristics; *b)* mean relative

doses of angiotensin-converting enzyme inhibitors (ACEI), angiotensin II receptor blockers (ARB), and MRA at 4 months; *c)* percentage of patients with 100% and ≥ 50% of the target dose; *d)* mean relative doses and number of visits according to type and gender of the professional; *e)* percentage of adverse events associated with titration; *f)* variables influencing target dose achievement; *g)* rates of cardiovascular mortality and readmissions at 6 months; and *h)* changes in left ventricular ejection fraction (LVEF), NYHA class, 6-minute walk distance, N-terminal pro b-type natriuretic peptide (NT-proBNP) levels and quality of life scores throughout the study. Variables are shown in the design article.[2] Definitions of sex and gender are provided in the supplementary data.

Statistical analysis

The analysis was performed on an intention-to-treat basis. Both the Student t-test (or nonparametric Wilcoxon test if continuous data were not normally distributed) and the chi-square test (or Fisher exact test) were used to compare the baseline sociodemographic and clinical characteristics of patients in the 2 groups (women vs men). The effect attributable to the intervention was estimated by comparing the differences in the relative dose of BB, ACEI, ARB and MRA achieved between the groups, assessed at 4 months after the start of titration, and the 95% confidence interval was calculated. We performed a multivariate analysis for the primary and secondary endpoints as predefined in the original study design.[24] The model was adjusted by the variables established as relevant related factors with a possible effect on dosing, based on a review of the literature, shown in table 1 of the supplementary data. All analyses were performed considering the 2 target populations (women and men). All variables with a *P* value < .20 were included as explanatory variables in the multivariate model, with the relative dose as the response variable. The multivariate analysis was conducted using ANCOVA within the framework of a linear mixed regression analysis. To take into account the difference between baseline and end of the titration period at 4 months, mixed linear regression models with fixed effects and random effects (specific effect of each participant and center and the effect of time expressed as visit 1 (baseline) and visit 2 (at 4 months) were used. The models were adjusted for women, men, and the total number of patients. These models took into account the longitudinal structure of the 2 repeated measurements, as well as the hierarchical structure of the data. All the statistical analyses were performed using R (version 4.0.4): R Foundation (Statistical Computing, Vienna, Austria). Statistical significance was set at $P < .05$.

RESULTS

Patient population

A total of 824 patients with de novo HFrEF, 221 women and 603 men, were evaluated, and 320 patients were included, 83 women and 237 men. Finally, 289 patients (76 women and 213 men) were analyzed at 4 months, and 274 (74 women, 200 men) were analyzed at 6 months. The selection process and causes for exclusion are shown in figure 1, and in table 2 and 3 of the supplementary data.

Patient characteristics were generally well-balanced between the 2 groups, without significant differences in LVEF, ischemic heart disease, or NT-proBNP (table 1). However, women were older (4 years), had a higher proportion of systolic blood pressure (SBP) ≤ 100 mmHg, lower hemoglobin level, lower 6-minute walk distance, and worse quality of life. In contrast, men had a higher proportion of smokers, alcohol abuse, atrial fibrillation/flutter, and worse scores on the Lawton Instrumental Activities of Daily Living Scale and age-adjusted Charlson index.

Baseline prescription of HF guideline-recommended drugs did not differ significantly. Women more frequently took psychotropic drugs (table 4 of the supplementary data shows other baseline characteristics).

Primary endpoint

BB dosage

There were no significant differences between women and men in the mean relative doses of BB at 4 months or in the percentage of patients with 100% and ≥ 50% of target dose (table 2). Equally, there were also no differences between women and men in each group of titrating professional (table 3), or in the number of visits for women vs men (table 4).

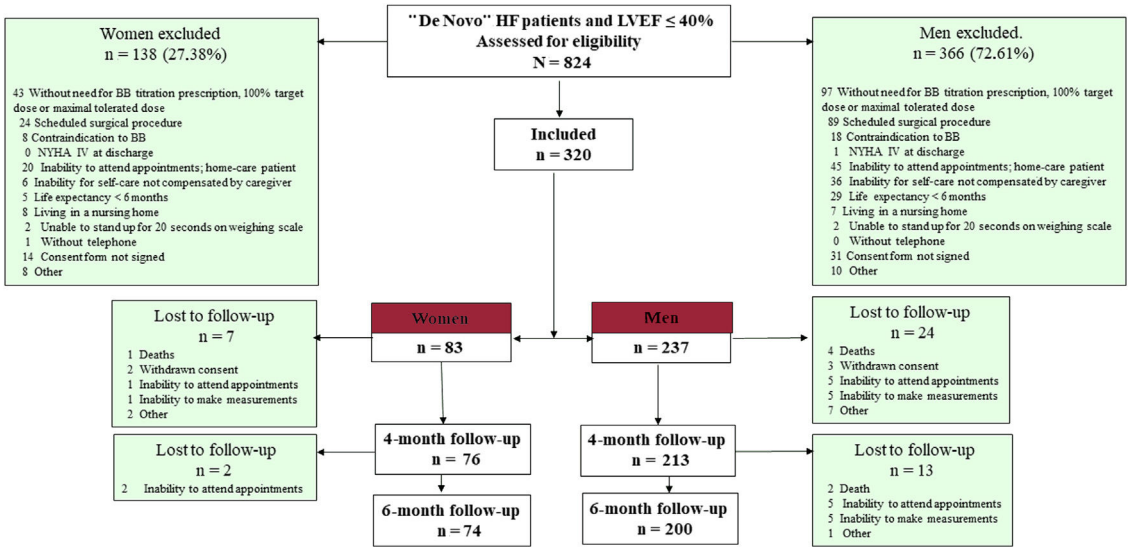


Figure 1. Patient flowchart. HF, heart failure; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

Table 1
Baseline patient characteristics

Variables (at hospital discharge)	Women n = 83	Men n = 237	*P*
Demographics	83 (25.93)	237 (74.06)	< .001
Age, y	64.83 ± 12.27	60.04 ± 11.95	.002
Education level, ≤ 10 y	31 (37.25)	77 (32.63)	.434
Patients ≥ 70 y	30 (36.14)	53 (22.36)	.0137
Memory impairment screening ≤ 4	4 (14.29)	8 (17.02)	.755
Lawton test: inability to administer medication	10 (38.46)	23 (46.94)	.482
Cardiovascular risk factors			
Hypertension	41 (49.4)	125 (52.74)	.600
Smoker	14 (16.87)	83 (35.02)	.002
Alcohol consumption > 2 units/d	7 (8.43)	87 (36.71)	.001
Diabetes	19 (22.89)	76 (32.07)	.115
Heart disease			
Ischemic heart disease	18 (21.69)	70 (29.54)	.168
Atrial fibrillation/flutter	14 (18.42)	78 (34.98)	.007
NYHA			
II	64 (77.11)	203 (85.65)	.071
III	19 (22.89)	34 (14.35)	.071
Left ventricular ejection fraction, %	28.02 ± 7.05	27.59 ± 6.9	.6232
Comorbidities			
Peripheral arterial disease	2 (2.41)	20 (8.44)	.062
Stroke	6 (3.66)	10 (6.41)	.259
Chronic respiratory disease	9 (10.84)	32 (13.5)	.533
Charlson index, adjusted by age	5.11 ± 1.65	4.69 ± 2.03	.048
Vital signs			
SBP mmHg	112.95 ± 18.65	116.39 ± 18.48	.147
SPB ≤ 100 mmHg	24 (28.92)	44 (18.64)	.049
Heart rate beats/min	72.41 ± 14.4	72.75 ± 13.84	.851
Laboratory tests			
NT-proBNP pg/mL	75; 1901 [1042; 4642]	207; 1590 [860; 3196]	.231
BNP pg/mL	5; 358 [126;404]	24; 352.5 [193.8; 835.2]	.544
Creatinine mg/dL	0.91 ± 0.39	1.14 ± 0.52	.001
eGFR mL/min/1.73 m^2	72.21 ± 22.75	75.55 ± 21.71	.234
eGFR < 60 mL/min/1.73 m^2	16 (19.28)	49 (20.68)	.735
Potassium > 5 mEq/L	7 (8.43)	29 (12.24)	.345
Hemoglobin g/dL	13.52 ± 1.99	14.3 ± 2.03	.0025
Anemia	22 (26.51)	60 (25.32)	.831
6-minute walk test, meters	318.29 ± 96.82	383.28 ± 102.85	.001
Meters ≤ 300	38 (46.34)	37 (16.23)	.001
European HF Self-care Behavior Scale (12-60)	37.6 ± 11.98	35.78 ± 11.68	.229
Question 10 Irregular medication intake (score 3-5)	18 (21.95)	26 (11.06)	.014
Quality of life			
Minnesota Living with HF Questionnaire (0-105)	52.76 ± 21.14	46.76 ± 22.83	.038
Physical dimension (0-40)	25.68 ± 10.32	20.77 ± 11.11	.001
Emotional dimension (0-25)	11.49 ± 7.35	9.49 ± 6.77	.025
EQ-5 D index	0.66 ± 0.24	0.76 ± 0.23	.001
Daily living tasks, score 2-3	43 (51.80)	75 (31.64)	.040
Anxiety and depression score 2-3	52 (62.65)	109 (45.99)	.002
VAS EQ-5D (0-100)	53.89 ± 17.73	58.94 ± 20.21	.047
Drugs			
BB	78 (93.98)	232 (97.89)	.078
ACEI	70 (84.34)	196 (82.7)	.732
ARB	9 (10.84)	23 (9.7)	.766
MRA	63 (75.9)	186 (78.48)	.627
Psychotropic drugs	32 (38.55)	43 (18.14)	.001
Antidepressants	17 (20.48)	21 (8.86)	.005
Anxiolytics	19 (22.89)	24 (10.13)	.003

Table 1 *(Continued)*
Baseline patient characteristics

Variables (at hospital discharge)	Women n = 83	Men n = 237	*P*
Hypnotics	6 (7.23)	4 (1.69)	.013
Neuroleptics	3 (3.61)	2 (0.84)	.080

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta-blockers; BNP, B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; EQ-5D, EuroQol-5 Dimension; HF, heart failure; MRA, mineralocorticoid receptor blocker; NT-proBNP, N-terminal probrain natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure; VAS, Visual analogue scale.
The data are expressed as No. (%), mean ± standard deviation, or No.; median [interquartile range].

However, women achieved significantly higher BB doses when titration was performed by a female HF-cardiologist compared with a male HF-cardiologists (*P* = .037) and higher BB doses, when comparing HF-nurses vs HF-cardiologists, and this result was almost significant (*P* = .057). This was associated with a higher number of visits (tables 5 and 6 of the supplementary data).

Secondary endpoints

ACEI/ARB dosage

There were no significant differences between women and men in the relative ACEI and ARB doses achieved at 4 months (table 2).

However, relative doses of ACEI were significantly lower in women vs men (*P* = .042) when titration was performed by HF-cardiologists but not by HF-nurses (table 3).

Women achieved significantly higher ACEI doses on comparison of titration by HF-nurses vs H-cardiologists, *P* = .007 (table 5 of the supplementary data).

The percentage of patients receiving ≥ 50% of the target dose of ACEI was significantly higher in men, *P* = .0226 (table 2).

MRA dosage

The relative MRA doses, the percentage of patients with 100% and ≥ 50% of the target dose at 4 months, were significantly higher

Table 2
Dosage: baseline to 4 months (titration period)

	Women n = 76	Men n = 213	Diff. (95%CI)	*P**
BB				
At baseline	76	213		
Relative dose %	34.54 ± 17.95	34.90 ± 19.89	−0.36 (−5.46 to 4.75)	.890
At 4 mo	76	213		
Relative dose %	62.08 (30.72)	64.4 (32.77)	−2.32 (−10.58 to 5.94)	.580
Patients with 100% target dose	24 (31.57)	83 (38.96)	−7.38 (−19.7 to 4.94)	.252
Patients with ≥ 50% target dose	54 (71.05)	149 (69.95)	1.09 (−10.8 to 13.01)	.857
ACEI				
At baseline	63	176		
Relative dose %	40.58 ± 27.61	43.93 ± 27.91	−3.35 (−11.40 to 4.70)	.413
At 4 mo	57	173		
Relative dose %	57.67 ± 48.81	66.21 ± 62.05	−8.54 (−18.42 to 1.35)	.089
Patients with 100% target dose	19 (33.33)	64 (36.99)	−3.66 (−17.85 to 10.53)	.617
Patients with ≥ 50% target dose	37 (64.91)	138 (79.76)	−14.85 (−28.61 to −1.09)	.023
ARB				
At baseline	8	16		
Relative dose %	30.70 ± 19.55	35.39 ± 17.55	−4.69 (−13.03 to 22.40)	.577
At 4 mo	13	23		
Relative dose %	34.11 ± 24.46	49.62 ± 35.62	−15.51 (−36.80 to 5.78)	.147
Patients with 100% target dose	1 (7.69)	6 (26.08)	−18.39 (−41.45 to 4.66)	.180
Patients with ≥ 50% target dose	3 (23.07)	12 (52.17)	−29.09 (−59.77 to 1.58)	.089
MRA				
At baseline	67	185		
Relative dose %	72.01 ± 36.55	59.10 ± 31.50	12.91 (3.66 to 22.16)	.006
At 4 mo	67	185		
Eplerenone	30/67 (44.77)	131/185 (70.81)	−26.03 (−40.64 to -11.43)	< .001
Relative dose %	79.85 ± 27.72	67.29 ± 31.43	12.55 (4.46 to 20.65)	.003
Patients with 100% target dose	42 (62.68)	81(43.78)	18.90 (4.28 to 33.53)	.012
Patients with ≥ 50% target dose	65 (97.01)	161 (87.02)	9.9 (2.64 to 17.33)	.039

95%CI, 95% confidence interval; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta-blocker; Diff., difference; MRA, mineralocorticoid receptor blocker.
The data are expressed as No. (%) or mean ± standard deviation.
* *P* value of the interaction between treatment and each subgroup.

Table 3
Mean relative dose by intervention group. Baseline to 4 months (titration period)

Drug No. Titrating professional Relative dose (%) at 4 mo Mean ± SD	Women n = 76	Men n = 213	Diff. (95%CI)	*P**
BB				
No.	76	213		
HF-nurse group (all women)	40	104		
Relative dose, %	68.44 ± 30.7	72.48 ± 31.7	− 4.03 (−15.54 to 7.46)	.486
HF-cardiologist group	36	109		
Relative dose, %	55.03 ± 29.5	56.71 ± 32	− 1.67 (−13.25 to 9.91)	.774
Female cardiologist	18	47		
Relative dose, %	65.28 ± 33.09	62.37 ± 33.34	2.91 (−15.83 to 21.65)	.754
Male cardiologist	18	62		
Relative dose, %	44.79 ± 17.53	52.42 ± 30.52	− 7.63 (−20.69 to 5.43)	.244
ACEI				
No.	57	173		
HF-nurse group	30	85		
Relative dose, %	68.75 ± 32.3	73.2 ± 28.7	− 4.45 (−17.90 to 8.93)	.504
HF-cardiologist group	27	88		
Relative dose, %	45.37 ± 30.6	59.43 ± 29.7	− 14.06 (−27.57 to − 0.55)	.042
Female cardiologist	14	39		
Relative dose, %	48.21 ± 32.84	61.35 ± 29.20	− 13.14 (−33.82 to 7.56)	.201
Male cardiologist	13	49		
Relative dose, %	42.31 ± 30.17	57.91 ± 30.27	− 15.6 (34.74 to 3.54)	.104
ARB				
No.	13	23		
HF-nurse group	7	12		
Relative dose, %	36.85 ± 30.8	48.93 ± 35.5	− 12.08 (−45.26 to 21.09)	.448
HF-cardiologist group	6	11		
Relative dose, %	30.92 ± 22.8	50.38 ± 37.5	− 19.46 (−50.78 to 11.85)	.205
Female cardiologist	2	2		
Relative dose, %	22.75 ± 14.50	43.75 ± 44.19	− 21 (−299.93 to 257.92)	.622
Male cardiologist	4	9		
Relative dose, %	35 ± 27.1	51.85 ± 38.76	− 16.85 (−59.69 to 25.99)	.393
MRA				
No.	67	185		
HF-nurse group	34	91		
Relative dose, %	83.82 ± 26.7	66.21 ± 32.8	17.61 (6.19 to 29.04)	.003
HF-cardiologist group	33	94		
Relative dose, %	75.76 ± 28.3	68.35 ± 30.5	7.41 (−4.28 to19.1)	.210
Female cardiologist	17	38		
Relative dose, %	70.59 ± 30.92	63.82 ± 39.50	6.77 (−12.10 to 25.65)	.471
Male cardiologist	16	56		
Relative dose, %	81.25 ± 25.00	71.43 ± 34.04	9.82 (−5.13 to 24.77)	.189

95%CI, 95% confidence interval; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta-blocker; Diff., difference; HF, heart failure; MRA, mineralocorticoid receptor blocker.
Unless otherwise indicated, the results are expressed as No. or mean ± standard deviation (SD).
* *P* value of the interaction between treatment and each subgroup.

Table 4
Visits according to titrating professional

Visits/professional (n women/n men)	Women n = 76	Men n = 213	Diff. (95%CI)	*P*
HF-nurse and HF-cardiologist, n *75/*211	4.57 ± 2.97	4.63 ± 2.91	−0.05 (−0.84 to 0.73)	.895
*HF-nurse (all women), n *39/*103*	6.28 ± 2.95	6.50 ± 2.80	−0.21 (−1.30 to 0.88)	.698
*HF-cardiologist, n 36/*108*	2.72 ± 1.56	2.84 ± 1.60	−0.12 (−0.72 to 0.48)	.692
Male cardiologist, n 18/47	3.22 ± 1.77	3.43 ± 1.65	−0.20 (−1.17 to 0.77)	.670
Female cardiologist, n 18/*61	2.22 ± 1.17	2.30 ± 1.33	−0.07 (−0.73 to 0.59)	.823
Patients with ≤ 2 visits according to the titrating professional				
HF-nurse and HF cardiologist	*23/75 (30.67)	*62/211 (29.38)	1.28 (−11.73 to 14.30)	.950
HF-nurse	*3/39 (7.69)	*4/103 (3.88)	3.81 (−7.12 to 14.73)	.616
HF-cardiologist	20/36 (55.55)	*58/108 (53.70)	1.85 (−18.76 to 22.46)	.999
Male cardiologist	8/18 (44.44)	18/47 (38.30)	6.15 (−24.53 to 36.82)	.865
Female cardiologist	12/18 (66.67)	*40/61 (65.57)	1.09 (−24.83 to 27.01)	.999

Diff., difference; HF, heart failure.
Unless otherwise indicated, the data are expressed as No. (%) or mean ± standard deviation.
* There were 3 patients (1 woman and 2 men) with the number of missing visits.

in women vs men (table 2). Women achieved higher MRA doses vs men when titration was performed by HF-nurses, *P* = .003 (table 3).

Variables potentially associated with higher drug doses at the end of the up-titration period

Significant differences were found between women and women. Women showed slightly better self-care, while men showed lower NYHA class and a lower proportion of patients with body mass index ≤ 19.

Moreover, the type and gender of the titrating professional, associated with their respective number of visits, influenced the achievement of higher doses, both among men and among women.

Although women had significantly lower creatinine at baseline and 4 months, estimated glomerular filtration rates (eGFR) showed no significant differences. No differences were found in other clinical variables or prescription (tables 5-10 of the supplementary data).

Multivariate analysis

A multivariate analysis disaggregated by sex was carried out, using mixed linear regression models with fixed effects and following the recommendations for Sex and Gender Equity in Research SAGER guidelines.[12] Factors related to the relative dose of BB, ACEI, MRA achieved by women, men and the total number of patients are shown in table 5.

Adverse events

There were no significant differences in terms of the occurrence of overall or individual adverse events between groups (figure 2).

Serious adverse events at 6 months

There were no statistically significant differences between women and men in all-cause and cardiovascular mortality or cardiovascular hospitalizations. No HF hospitalizations were observed in women, but this difference was not statistically significant. However, unplanned noncardiovascular hospitalizations were significantly more frequent in women (figure 3).

Clinical outcomes at 6 months

There were significant improvements in all clinical outcomes at 6 months, but without significant differences in the change from baseline to 6 months between the 2 groups, except in NYHA class, with men having better functional class at 6 months (table 6).

DISCUSION

In this post hoc study of HF drug titration in the ETIFIC trial, nonsignificant gender differences were found in BB/ACEI/MRA dosage in the multivariate analysis, cardiovascular mortality, HF hospitalizations, and other clinical outcomes at 6 months (figure 4).

Differences between women and men in the selection process and baseline characteristics

The possible barriers to women's participation were analyzed.[4,12] The proportion of women in ETIFIC (25.93%) could be considered underenrolment, given the established reference (< 32%) in a systematic review of 317 HFrEF trials.[4] However, participation was higher than that in trials of BB (23%), ACEI (21%), ARB (26%) and MRA (21%) (see references of the supplementary data: BB,1-20; ACEI 21-23; ARB 24,25 MRA 26-28), but lower than that in observational optimization studies (30%)[5–10] (see references 29-42 of the supplementary data). This may have been influenced by recruitment in cardiology wards (lower proportion of elderly patients or with comorbidity). The lower proportion of women in cardiology services vs other services is also reflected in the literature[20–26] (see references 43-46 of the supplementary data).

Some baseline differences between women vs men were observed in ETIFIC (table 1). No clinical trial or observational optimization study has evaluated the baseline characteristics of women.[5–10] (see references 1-42 of the supplementary data). These

Table 5
Multivariate linear mixed regression models

	Estimate	95%CI	*P*
Beta-blockers, all patients, n = 289			
Intercept	−53.02	(−146.97 to 40.92)	.269
Female sex	2.01	(−10.16 to 14.19)	.746
Time (baseline vs 4 mo)	29.29	(−29.71 to 88.28)	.331
Time (baseline vs 4mo), female sex*	−1.87	(−9.55 to 5.81)	.634
BB relative dose at baseline	0.83	(0.73 to 0.93)	< .001
Baseline heart rate, bpm	0.29	(0.16 to 0.41)	< .001
Visits with the titrating professional	1.23	(0.42 to 2.04)	.003
HF-nurse vs HF-cardiologist	4.63	(0.61 to 8.65)	.024
Beta-blockers, women, n = 76			
Intercept	−59.23	(−163.61 to 45.15)	.268
BB relative dose at baseline	0.83	(0.64 to 1.02)	< .001
Baseline heart rate, bpm	0.35	(0.12 to 0.58)	.004
Visits with the titrating professional	2.4	(1.15 to 3.66)	< .001
Time (baseline vs 4 mo)	27.42	(−37.29 to 92.12)	.408
Beta-blockers, men, n = 213			
Intercept	−45.76	(−151.84 to 60.32)	.398
BB relative dose at baseline	0.82	(0.71 to 0.92)	< .001
Baseline heart rate, bpm	0.29	(0.14 to 0.44)	< .001
HF-nurse vs HF-cardiologist	7.78	(3.72 to 11.85)	< .001
Atrial fibrillation	−5.44	(−9.99 to −0.88)	.02
Time (baseline vs 4 mo)	29.13	(−37.51 to 95.76)	.392
ACEI, all patients, n = 239			
Intercept	−31.77	(−119.52 to 55.98)	.478
Sex: female	4.09	(−8.5 to 16.68)	.525
Time (baseline vs 4 months)	22.83	(−31.98 to 77.65)	.415
Time (baseline vs 4 months) *Sex: female	−4.26	(−12.34 to 3.81)	.301
ACEI relative dose at baseline	0.7	(0.64 to 0.77)	< .001
SBP (baseline, mmHg)	0.26	(0.16 to 0.36)	< .001
eGFR < 60 (no vs yes)	−6.56	(−11.31 to −1.81)	.007
HF-nurse vs HF-cardiologist	7.1	(3.52 to 10.68)	< .001
Age, y	−0.18	(−0.33 to −0.02)	.025
ACEI, women, n = 63			
Intercept	−46.71	(−130.67 to 37.26)	.278
ACEI relative dose at baseline	0.72	(0.58 to 0.86)	< .001
SBP (baseline, mmHg)	0.31	(0.1 to 0.52)	.004
HF-nurse vs HF-cardiologist	11.14	(3.69 to 18.58)	.004
Diabetes mellitus	−12.08	(−22.15 to −2.02)	.02
Time (baseline vs 4 mo)	18.37	(−32.59 to 69.32)	.481
ACEI, men, n = 176			
Intercept	−27.17	(−105.39 to 51.04)	.999
ACEI relative dose at baseline	0.71	(0.64 to 0.78)	< .001
SBP (baseline, mmHg)	0.25	(0.14 to 0.36)	< .001
eGFR < 60 (no vs yes)	−5.65	(−10.95 to −0.34)	.038
HF nurse vs HF cardiologist	5.72	(1.65 to 9.79)	.006
Age, y	−0.23	(−0.41 to −0.05)	.012
Time (baseline vs 4 mo)	22.83	(−25.6 to 71.25)	.999
MRA, all patients, n = 252			
Intercept	14.71	(−29.88 to 59.3)	.999
Sex: female	3.03	(−10.17 to 16.24)	.653
Time (baseline vs 4 mo)	8.51	(−19.5 to 36.52)	.999
Time (baseline vs 4 mo) *Sex: female	−0.68	(−8.97 to 7.61)	.873
MRA relative dose at baseline	0.75	(0.68 to 0.83)	< .001
eGFR < 60 (no vs yes)	−6.28	(−11.15 to −1.41)	.012
K (≥ 5.5 mEq/L vs < 5.5 mEq/L)	−14.09	(−27.47 to −0.7)	.04
Combination of 3 drugs, baseline	−8.65	(−14.64 to −2.66)	.005

Table 5 *(Continued)*
Multivariate linear mixed regression models

	Estimate	95%CI	*P*
MRA, women, n = 67			
Intercept	14.5	(−75.86 to 104.86)	.754
MRA relative dose at baseline	0.69	(0.59 to 0.79)	< .001
Time (baseline vs 4 mo)	7.84	(−49.15 to 64.82)	.788
MRA, men, n = 185			
Intercept	31.28	(−148.71 to 211.27)	.999
MRA relative dose at baseline	0.77	(0.68 to 0.85)	< .001
K (≥ 5.5 mEq/L vs < 5.5 mEq/L)	−22.88	(−38.21 to −7.55)	.004
Combination of 3 drugs, baseline	−9.09	(−16.47 to −1.71)	.016
NYHA at baseline	−8.18	(−14.15 to −2.22)	.008
Time (baseline vs 4 mo)	8.43	(−105.05 to 121.9)	.999

95%CI, 95% confidence interval; ACEI, angiotensin-converting enzyme inhibitors; BB, beta-blockers; eGFR, estimated glomerular filtration; HF, heart failure; K, potassium; n, number of patients; MRA, mineralocorticoid receptor antagonists; NYHA, New York Heart Association; SBP, systolic blood pressure.
* Time and sex interaction.

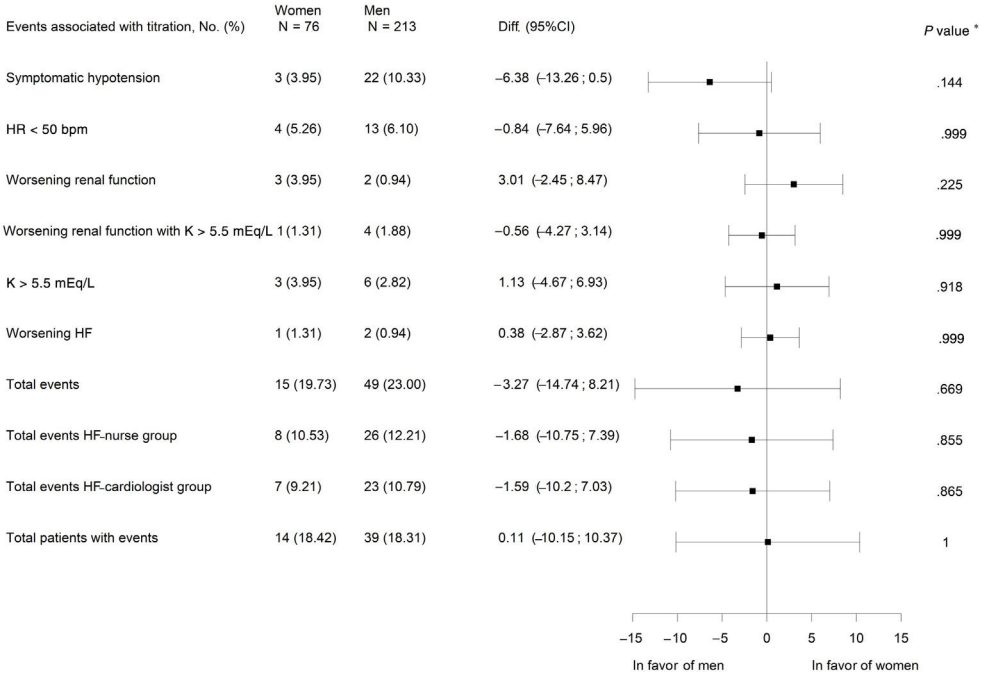


Figure 2. Adverse events associated with titration. 95%CI, 95% confidence interval; bpm, beats per minute; Diff., difference; HF, heart failure; HR, heart ratio; K, potassium; worsening renal function, creatinine >50% baseline, creatinine >3 mg/dL, estimated glomerular filtration rate< 25 mL/min/1.73 m^2; N total number of patients, No. (%), number of cases. * *P* value for difference between treatment groups.

were analyzed by 2 meta-analyses[17,18] and 6 studies with other objectives.[15,19–23] The HFrEF women generally had similar characteristics to those in ETIFIC (table 1): they were 1 to 4 years older,[15,17,18,20–22] had a lower proportion of smokers,[15,18,21] lower alcohol consumption,[15] less frequently had atrial fibrillation,[15,18,20,21] a lower 6-minute walk distance,[22] worse quality of life,[22,23] a higher proportion of NYHA III-IV,[17,18,20,21] and minimal differences in LVEF (0.5-2%) vs men.[15,17–19,21]

Drug prescription in ETIFIC showed no significant differences, except for greater prescription of psychotropic drugs in women. A lower prescription of BB[15,18] and ACEI in women vs men has been reported in the literature.[15,20]

Primary endpoint

BB relative dose

No gender differences were found in the mean relative doses of BB reached by all patients at 4 months (table 2) or in the

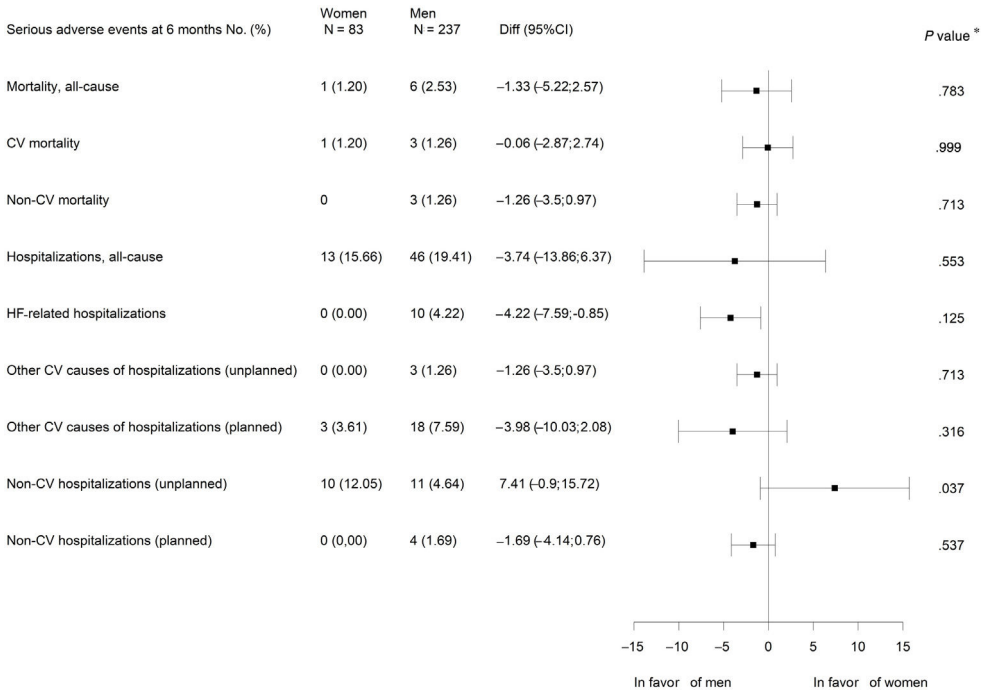


Figure 3. Serious adverse events. Mortality and hospitalizations evaluated at 6 months. 95%CI, 95% confidence interval; CV, cardiovascular; Diff., differences; HF, heart failure; N total number of patients, No. (%), number of cases. * *P* value for difference between treatment groups.

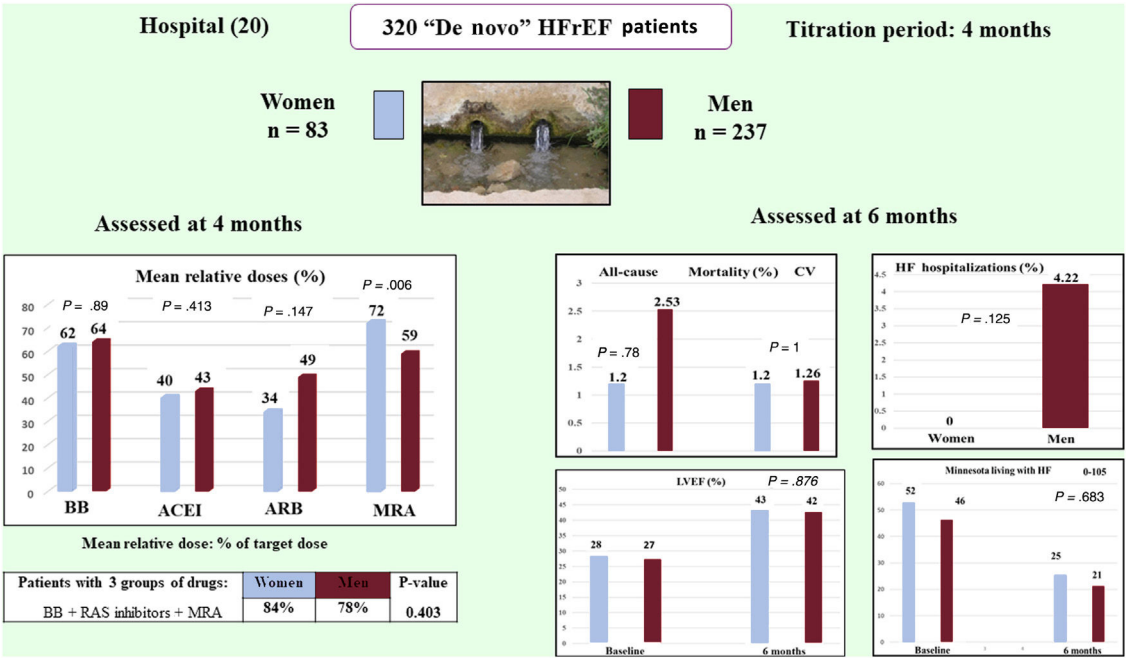
Table 6
Outcomes at 6 months

Variables	Women n = 74		Men n = 200		Difference of change from baseline to 6 months between groups (95%CI)	*P*
	Baseline	6 months	Baseline	6 months		
LVEF %	28.23 ± 7.17	43.09 ± 11.29	27.26 ± 6.94	42.58 ± 12.32	− 0.46 (−3.80 to 2.87)	.786
LVEF < 35%	57 (77.03)	15(20.27)	161 (80.50)	48 (24.00)	0.26 (−13.21 to 13.73)	.999
LVEF > 40%	0	44 (59.46)	0	96 (48.00)	11.46 (−2.62 to 25.54)	.121
NT-proBNP, pg/mL n 68/176	1654 [952-3850]	611 [195-1017]	1476 [789-2954]	526 [152-1277]	− 182 (−650 to 92)	.158
BNP, pg/ml, n 3/19	358 [200-381]	160 [155-166]	333 [188-762]	162 [71- 490]	33.5 (−967 to 992)	.999
NYHA class[a]						
I	0	18 (24.32)	0	84 (41.00)	− 16.68 (−30.53 to − 4.82)	.011
II	57 (77.03)	53 (71.62)	171 (85.50)	110 (55.00)	− 25.09 (−34.22 to 15.97)	< .001
III	16 (21.62)	2 (2.70)	29(14.50)	6 (3.00)	7.42 (−3.47 to 18.30)	.163
6-minute-walk test, meters	315.9 ± 94.59	359.59 ± 99.86	382.25 ± 97.41	433.20 ± 117.64	− 7.25 (−30.29 to 15.80)	.535
Minnesota score[b]	52.81 ± 21.48	26.07 ± 19.60	46.5 ± 22.73	21.11 ± 20.01	− 1.34 (−7.83 to 5.14)	.683
Physical dimension	25.42 ± 10.28	10.94 ± 9.08	20.8 ± 11.32	7.4 ± 8.66	− 1.08 (−14.48 to 2.40).	.540
Emotional dimension	11.60 ± 7.30	6.81 ± 6.08	9.46 ± 6.54	5.21 ± 5.91)	− 0.60 (−2.47 to 1.27).	.524
Euroqol-5 dimension index	0.65 ± 0.24	0.74 ± 0.24	0.77 ± 0.21	0.82 ± 0.21	0.04 (−0.02 to 0.11)	.210
Visual analogue scale	53.52 ± 18.50	66.19 ± 20.28	58.78 ± 19.85	71.65 ± 18.93	− 0.19 (−6.32 to 5.93)	.950

95%CI, 95% confidence interval; BNP, B-type natriuretic peptide; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal probrain natriuretic peptide; NYHA, New York Heart Association.
Unless otherwise indicated, the data are expressed as No. (%), mean ± standard deviation, or No.; median [interquartile range].
[a] There was 1 patient (woman) with NYHA missing.
[b] Minnesota Living with HF Questionnaire (0 better-105 worse).

multivariate analysis (table 5). Factors associated with dose were the relative dose of BB and heart rate at baseline for both women and men, and atrial fibrillation only for men (table 5), probably associated with a higher prevalence (table 1).

Both women and men achieved higher BB doses when they were titrated by HF-nurses vs HF-cardiologists. All HF-nurses were female. Female patients achieved higher BB doses when titrated by female cardiologists vs male cardiologists. In both cases, this was associated with a higher number of visits. The multivariate analysis also reflected the influence of these organizational issues (table 5, and tables 5 and 6 of the supplementary data). The association of the achieved dose with the titrating professional, and the number of visits was previously demonstrated in ETIFIC patients.[25] The possible influence of the professional's gender on the doses achieved by women has also been mentioned previously.[16]



Patients with 3 groups of drugs:	Women	Men	P-value
BB + RAS inhibitors + MRA	84%	78%	0.403

Figure 4. Post hoc analysis of the HF-titration ETIFIC trial: There were no significant gender differences regarding dosage of HF medications in the multivariate analysis, cardiovascular mortality or HF hospitalizations. ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker; BB, beta-blockers; CV, cardiovascular; HF, heart failure; HFrEF, heart failure patients with reduced ejection fraction; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor blocker; RAS, renin-angiotensin system.

No original BB trial has evaluated optimal doses for women or analyzed their prescription and the mean relative doses achieved (see references 1-20 of the supplementary data). These doses in women in ETIFIC, 62%, were lower (−15%), as with men, than the mean doses achieved by all patients in BB trials (more selected patients), although they were in the high dose range of observational optimization studies (33-63%)[5–10] (see references 29-42 of the supplementary data).

We found limited and heterogeneous information on the BB doses achieved by women vs men in other types of studies. As in ETIFIC, some studies found no dose differences, namely a meta-analysis,[17] a trial on exercise (see reference 47 of the supplementary data), and 3 observational studies,[9,10,21] while others reported lower target doses in women, namely, a HF program trial (see reference 48 of the supplementary data) and 2 observational studies[5] (see reference 40 of the supplementary data).

Secondary endpoints

No gender differences were found in the relative doses of ACEI/ARB (table 2). Equally, there were no significant differences between women and men during titration in SBP or eGFR (table 10 of the supplementary data), in symptomatic hypotension events (figure 2), or the mean relative dose of ACEI (table 2). However, there was a lower proportion of women with $\geq$ 50% the target dose of ACEI (table 2).

The multivariate analysis showed that the relative dose of ACEI at baseline and SBP were associated with the achieved doses of ACEI in both women and men (table 5). The association of achieved ACEI dose with the titrating professional, and the number of visits previously demonstrated in ETIFIC[25] was also confirmed for women, as shown in table 3 and table 5 (see also table 5 of the supplementary data).

Women achieved significantly higher relative MRA doses at 4 months, associated with higher use of spironolactone and lower use of eplerenone (table 2). No gender differences were found in the multivariate analysis including all patients (table 5). However, there were no differences in the potassium level at baseline and 4 months (table 10 of the supplementary data) or in adverse events associated with potassium levels (figure 2), but potassium $\geq$ 5 mEq/L was associated with a lower dose only in men in the multivariate analysis (table 5).

No original ACEI, ARB and MRA trial has reported the prescription and mean relative dose achieved disaggregated by gender. Both women and men achieved lower ACEI/ARB doses in ETIFIC than those achieved by all patients in trials. This difference could be explained by the selected population, a higher SBP and a lower prescription of MRA and BB in these trials compared with ETIFIC (see references 21-28 of the supplementary data).

We found limited and heterogeneous information from some observational studies, 2 of them showing lower ACEI and ARB doses achieved by women[6,10] but no other.[21] In contrast, higher MRA doses have been reported in women.[7]

The drug prescription rate in the ETIFIC trial was high for both women and men, without significant differences. In addition, the joint prescription of 3 groups of drugs (BB, renin angiotensin system inhibitors and MRA) was 84% in women vs 78% in men, far higher than in trials and observational studies[5–10] (see tables 7-9 and references 1-42,49 of the supplementary data).

Both women and men showed good self-care and adherence, although women showed slightly better results. Previous studies of adherence in HF have reported contradictory results in relation to gender (see table 10 and references 50, 51 of the supplementary data).

There were no differences between women and men in adverse events associated with titration (figure 2). Clinical trials and observational optimization studies did not report adverse events disagregated by sex[5–10] (see references 1-42 of the supplementary data).

Differences in pharmacodynamics and pharmacokinetics have been described in women that could lead to higher blood levels at the same drug dose, lower tolerance of higher doses or beneficial effects with lower doses. Moreover, differences in renal function could lead to greater adverse events, suggesting that optimal doses in women should be lower.[13,16,21] However, the ETIFIC trial showed no significant differences in women vs men in dosage and adverse events.

Other secondary endpoints

No gender differences were found in the mortality rate or cardiovascular admissions. Both were lower than in the literature, probably because the patients in this study had novo HF, received therapeutic optimization, close follow-up by the HF program, and showed good self-care and adherence.[1,3]

Although it did not reach statistical significance, probably due to the small number of events, it could be clinically relevant that there were no HF admissions in women, considering that there were no significant differences in cardiovascular mortality either (figure 3).

Three meta-analyses have shown the effectiveness of BB, ACEI and MRA in reducing mortality and admissions in women.[17,18,27] The BB and MRA meta-analysis[17,18] and the European Long-Term registry[28] observed fewer serious adverse events in women.

A substudy of BIOSTAT[21] observed a 30% reduction of death or hospitalization with 50% of the recommended doses of ACEI, ARB and 60% of BB, without finding a greater reduction with higher doses, although the authors reported that the optimal doses for women are unknown. No titration protocol, adverse events, number of visits or reasons for not reaching the target dose were described. Moreover, the BB and MRA prescription and BB doses achieved were significantly lower than in the ETIFIC trial.

A clear improvement in LVEF (14.86% vs 15.32%), NT-proBNP, NYHA, 6-minute walk test and quality of life, with no significant differences between women and men, was shown, except in NYHA class, where men had a better functional class at 6 months than women (table 6).

LVEF recovery has been associated with being female, nonischemic etiology, atrial fibrillation, adherence to BB and shorter duration of HF[19] (see references 52-54 of the supplementary data).

Similar improvements in women vs men have also been described in quality of life and 6-minute walk test, associated with the use of BB, ACEI, ARB, and a close follow-up in clinical studies.[22]

A paradox previously reported in the literature[15,20,29] was also observed in women who, despite being older, more symptomatic and having worse quality of life, had lower mortality and HF hospitalization. According to previous publications, this may be due to possible late diagnoses, less access to health care, socioeconomic and educational factors, and physicians' misperception of women's symptoms and consequent undertreatment.

Limitations

The ETIFIC clinical trial was not designed with the aim of evaluating gender differences in drug titration. Therefore, the sample in this post hoc analysis was not calculated for this purpose.

CONCLUSIONS

In a post hoc analysis of the HF-titration ETIFIC trial, multivariate analysis identified nonsignificant gender differences in the dosage of HF medications at 4 months after discharge. There were also nonsignificant differences in cardiovascular mortality, HF hospitalizations, and other clinical outcomes at 6 months.

To our knowledge, ETIFIC is the first study to show that a controlled environment such as a randomized trial in HF clinics, with a structured protocol, close follow-up and patient education allows women to tolerate a prescription and dosage without significant differences vs men, without a higher mortality rate or cardiovascular admissions and a clear improvement in clinical outcomes. Higher dosage was associated with HF-nurse involvement, female gender of the titrating professional, and the number of visits.

Sex and gender analysis should be carried out in clinical trials to gain greater in-depth knowledge of the possible differences and increase the applicability of treatments in women.

WHAT IS KNOWN ABOUT THE TOPIC?

- Women have been underrepresented in HFrEF trials. No original BB, ACEI, ARB, MRA trial has prospectively evaluated optimal doses by sex on a continuous scale, or specifically evaluated the characteristics, prescription, achieved doses and adverse events in women. Few trials have evaluated their effects on mortality and hospitalizations.
- Some studies (meta-analyses, systematic reviews, observational studies) have described differences between women and men in characteristics, drug prescription, dosage, and effects, but this evidence is limited by their design.

WHAT DOES THIS STUDY ADD?

- To our knowledge, ETIFIC is the first study to show that a controlled environment such as a randomized trial in a HF unit, with a structured protocol, close follow-up and patient education allows women to tolerate prescription and dosage without significant differences vs men, without a higher mortality rate or cardiovascular admissions and a clear improvement in LVEF, NT-proBNP, 6-minute-walk test, and quality of life.
- Higher dosage was associated with HF-nurse involvement, female gender of the titrating professional, and the number of visits.

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AUTHORS' CONTRIBUTIONS

All authors had full access to all the data (including statistical reports and tables) in the study and take responsibility for data

integrity and data analysis. All authors participated in the study design, writing and review of this manuscript and approval of the final version. P. Latorre-García, E. Arana-Arri, S. Pérez-Fernández were responsible for its methodological accuracy and statistical analysis. J. Oyanguren is the guarantor and attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

CONFLICTS OF INTEREST

None declared.

APPENDIX. SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.1016/j.rec.2021.11.002

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