Revista Española de Cardiología

SUPPLEMENTARY MATERIAL

Noninferiority of heart failure nurse titration vs heart failure cardiologist titration. ETIFIC multicenter randomized trial

Table 1 of the supplementary data

Causes of loss to follow-up.

	Intervention	Follow-up
Causes of death	1. Multiple organ failure due to evolved myocardial infarction 2. Sudden cardiorespiratory arrest at home from unknown causes 3. Treatment withdrawal due to excessive alcohol consumption	1. Brain herniation after outpatient cardiorespiratory arrest 2. Cardiorenal failure in gastroenteritis and probable ischemic colitis 3. Cardiorenal failure in oncological process 4. Malignant pulmonary neoplasm
Loss to follow-up for other clinical reasons	1. Patient with a solitary kidney. Renal artery angioplasty for restenosis, transplant candidate (previous creatinine normal) 2. Septic shock due to urinary tract infection after renal calculi 3. Inotrope administration 4. Medical decision: medication that interferes with titration 5. Severe peripheral artery disease. Amputation. Need for inotropes	1. Fall. Head trauma. Admission to neurology department 2. Hip fracture 3. Renal failure. Dialysis complications
Other nonclinical causes	3: 1 HF unit closed during summer period 2 Medical decision	
Withdrawal of consent	2	3
Inability to attend visits	11: 5 Patient is going to live abroad 2 Work purposes 1 Medical assistance is not renewed. Does not attend. It is unknown whether the patient has returned to his/her country 1 Illness of the HF nurse 2 Patient cannot attend	5: 1 Patient lives far away, advanced age 1 Illness of the HF nurse 1 Patient works abroad 2 Patient is going to live abroad
Inability to take measurements: does not attend	4	4

HF, heart failure.

Table 2 of the supplementary data

Supplementary baseline measurements

Variables	HF nurse n = 164	HF Cardiologist n = 156	*P*
Educational level			
Reading and writing supplied by carer	5 (3.07)	1 (0.64)	.13
Reading and writing	33 (20.25)	26 (16.67)	.10
Up to 10 y	15 (9.2)	28 (17.95)	
Up to 14-16 y	74 (45.4)	65 (41.67)	
Further studies	36 (22.09)	36 (23.08)	
Supplied by carer + reading and writing + up to 10 y	53 (35.52)	55 (35.26)	.61
Patients aged ≥ 70 y	44 (26.83)	39 (25.00)	.71
Memory Impairment screening (0-8)	39, 6.41 ± 1.80; (0-8)	36, 6.80 ± 1.72; (2-8)	.34
Lawton instrumental activities of daily living scale score (0-8)	42, 5.61 ± 2.19; (0-8)	36, 5.86 ± 2.42; (0-8)	.62
Lawton < 5 (men) < 8 (women)	18 (46.15)	18 (50)	.74
Lawton, Inability to:			
Use the telephone	3 (6.82)	2 (5.13)	.75
Go shopping	14 (3.82)	14 (35.9)	.70
Prepare food	21 (47.73)	19 (48.72)	.93
Keep house	10 (22.73)	10 (25.64)	.76
Wash clothes	21 (47.73)	18 (46.15)	.89
Travel	13 (29.55)	10 (25.64)	.69
Be in charge of medication	17 (43.59)	16 (44.44)	.94
Use money	5 (11.36)	7 (17.95)	.40
CVRF			
Exsmoker < 1 y	10 (6.1)	14 (8.97)	.33
Exsmoker ≥ 1 y	32 (19.51)	41 (26.28)	.15
Dyslipidemia	69 (42.07)	53 (33.97)	.14
Heart disease, n (%)			
Pacemaker	3 (1.83)	4 (2.56)	.65
Automated implantable cardioverter defibrillator	4 (2.44)	7 (4.49)	.32
Cardiac resynchronization therapy	2 (1.22)	1 (0.64)	.59
LVEF % ≤ 35%	140 (85.37)	136 (87.18)	.64
First-degree AVB	5 (3.04)	2 (1.28)	.43
Charlson index			
AMI	34 (20.73)	38 (24.36)	.44
Peripheral arterial disease	12 (7.32)	10 (6.41)	.75
Stroke (ischemic/hemorrhagic)	6 (3.66)	10 (6.41)	.26

Dementia	2 (1.22)	0 (0)	.17
Chronic respiratory disease	18 (10.98)	23 (14.74)	.31
Connective tissue disease	4 (2.44)	5 (3.21)	.68
Gastroduodenal ulcer	4 (2.44)	1 (0.64)	.20
Mild chronic liver disease	3 (1.83)	7 (4.49)	.17
Diabetes	47 (28.66)	35 (22.44)	.20
Hemiplegia	0 (0)	0 (0)	< .001
Renal failure with Cr > 3 mg/dL or in dialysis	6 (3.66)	3 (1.92)	.35
Diabetes with end-organ damage	3 (1.83)	10 (6.41)	.04
Any malignancy	10 (6.1)	14 (8.97)	.33
Leukemia	0 (0)	1 (0.64)	.30
Lymphoma	1 (0.61)	2 (1.28)	.53
Severe-moderate chronic liver disease	1 (0.61)	1 (0.64)	.97
Metastatic solid tumor	0 (0)	0 (0)	< .001
AIDS	0 (0)	1 (0.64)	.30
Charlson Index ≥ 3	45 (27.44)	64 (41.03)	.01
Charlson index			
Charlson comorbidity index score, not age-adjusted	164, 2.08 ± 1.21; (1-8)	156, 2.31 ± 1.43; (1-10)	.13
Charlson comorbidity index score, adjusted by age	164, 4.74 ± 1.91; (2-11)	155, 4.86 1.97; (2-14)	.58
Vital signs			
Systolic blood pressure ≤ 90 mmHg	9 (5.49)	11 (7.1)	.55
Body mass index (kg/m^2)	163, 27.7 ± 4.87; (16-43.2)	155, 26.6 ± 4.97; (14.7-40.39)	.11
Laboratory tests (upon discharge)			
NT-proBNP > 1000 pg/mL	107 (73.79)	97 (69.78)	.45
eGFR 30-60 mL/min/1.73 m^2	39 (23.78)	26 (16.67)	.21
eGFR < 30 mL/min/1.73 m^2	5 (3.05)	3 (1.92)	.52
K, mEq/L	164, 4.51 ± 0.48; (3.08-6)	156, 4.43 ± 0.56; (2.9-6.4)	.12
K > 5.5 mEq/L	5 (3.05)	1 (0.61)	.11
K ≤ 3.5 mEq/L	4 (2.44)	9 (5.77)	.13
Sodium, mEq/L	164, 139.58 ± 3.15; (125-147)	156, 139.38 ± 3.38; (129-148)	.58
Urea, mg/dL	160, 56.62 ± 24.72; (5-169)	151, 52.17 ± 23.45; (13-143)	.10
Glycosylated hemoglobin (if diabetes mellitus)	50, 7.65 ± 1.82; (5-13)	42, 7.34 ± 1.54; (5-12.4)	.18
Other drugs that can possibly influence titration			
ARB + neprilysin Inhibitor	1 (0.61)	2 (1.28)	.53
Ivabradine	21 (12.8)	19 (12.18)	.87
Amiodarone	20 (12.2)	12 (8.33)	.26
Digitalis	9 (5.49)	9 (5.77)	.91
Diuretics (loop/thiazide)	132 (80.49)	130 (83.33)	.51

Dihydropyridine calcium-channel blockers	6 (3.66)	7 (4.49)	.71
Nitrates (not sublingual)/hydralazine	8 (4.88)	8 (5.13)	.92
Alpha-blockers	6 (3.66)	8 (5.13)	.52
Hypo- and hyperthyroidism medication	6 (3.66)	6 (3.85)	.93
K supplements	4 (2.44)	4 (2.56)	.94
NSAIDs or COX-2 inhibitors	1 (0.61)	1 (0.64)	.97
Corticosteroids	10 (6.1)	3 (1.92)	.06
Iron	4 (2.44)	10 (6.41)	.08
Inhaled bronchodilators	15 (9.15)	13 (8.33)	.80
Antidepressants	23 (14.02)	15 (9.62)	.22
Anxiolytics	27 (16.46)	16 (10.26)	.94
Hypnotics	5 (3.05)	5 (3.21)	.94
Neuroleptics	2 (1.22)	3 (1.92)	.61
Psychotropic drugs: antidepressants, anxiolytics, hypnotics, neuroleptics	44 (26.83)	31 (19.87)	.14
Other drugs			
Anticoagulants	55 (33.54)	51 (32.69)	.87
Antiplatelets	57 (34.76)	50 (32.05)	.61
Statins	96 (58.54)	74 (47.44)	.047
Oral antidiabetics	38 (23.17)	29 (25)	.70
Insulin	9 (5.49)	9 (5.77)	.91
Proton pump inhibitors	86 (52.44)	74 (47.44)	.37
Drug combination			
With 3 groups of drugs: BB + ACE inhibitor /ARB/ARB-neprilysin Inhibitors + MRA	124 (75.6)	117 (75)	.90
ACE inhibitors /ARB/ARB-neprilysin Inhibitors	157 (95.73)	144 (92.31)	.20
With 2 groups of drugs: BB + ACE inhibitors /ARB/ARB-neprilysin Inhibitors	29 (17.68)	23 (14.74)	.48
With 2 groups of drugs: BB + MRA	1 (0.61)	5 (3.21)	.09
With 2 groups of drugs: ACE inhibitors + MRA	1 (0.61)	0 (0)	.33
With 1 group of drugs: BB	5 (3.05)	7 (4.49)	.50
With 1 group of drugs: ACE inhibitors	2 (1.22)	4 (2.56)	.38
With any other rate-lowering drug (ivabradine/amiodarone/digoxin)	48 (29.27)	40 (25.64)	.47
With any other hypotensive drug (calcium-channel blockers, nitrates/hydralazine, alpha-blockers)	16 (9.76)	18 (11.54)	.61
European heart failure self-care behaviour scale (12-60)	163, 36.62 ± 12.15; (9-60)	154, 35.85 ± 11.37 (10-60)	.56
Question 10 irregular medication intake, score 3-5, n (%)	23 (14.11)	21 (13.63)	.90

Health-related quality of life			
Minnesota Living with HF Questionnaire (0-105)	162, 50.8 ± 22.61; (0-96)	155, 45.71 ± 22.21; (2-93)	.04
Physical dimension (0-40), renal calculi	162, 23.24 ± 11.23; (0-40)	155, 20.78 ± 10.86; (0-40)	.048
Emotional dimension (0-25)	162, 10.74 ± 6.97; (0-25)	155, 9.23 ± 6.9; (0-25)	.054
EQ-5D (total score)	159, 0.73 ± 0.23; (0.014-1.000)	152, 0.75 ± 0.24; (0-1)	.54
EQ-5D any problem 2/3	114 (70.37)	108 (69.57)	.89
Visual analog scale EQ-5D (0-100)	162, 58.27 ± 20.34; (0-100)	154, 56.98 ± 19.04; (0-100)	.56

ACE inhibitors, angiotensin-converting enzyme inhibitors; AMI, acute myocardial infarction; ARB, angiotensin receptor blocker; AVB, atrioventricular block; BB, beta-blockers; COX-2 inhibitors, cyclo-oxygenase-2 inhibitors; Cr, Creatinine; CVRF, cardiovascular risk factors; eGFR, estimated glomerular filtration rate; EQ-5 D, EuroQol-5 dimension; K, potassium; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NSAIDs, nonsteroidal anti-inflammatory drugs; NT-proBNP, N-terminal proBNP.

The data are expressed as No. (%), mean ± standard deviation, or No. ± standard deviation; (min-max).

Table 3 of the supplementary data

Dosage: baseline to 4-month follow-up (titration period)

Dosage. 4 mo	HF nurse n = 144	HF cardiologist n = 145	Diff. (95%CI)	*P*
BB dose				
Relative dose at baseline, %	144, 34.81 ± 18.16	145, 34.80 ± 20.6	00.1 (−4.48; 4.50)	> .99
Relative dose at 4 mo, %	144, 71.09 ± 31.49	145, 56.29 ± 31.32	14.80 (7.53; 22.07)	< .001
Relative dose baseline – 4-mo difference	36.28 ± 30.75; 41.81	21.49, 16.78 ± 26.20	14.78 (7.56; 22.01)	< .001
% of patients with 100% 4-mo target dose	70 (48.61)	37 (25.52)	23.09 (12.28; 33.91)	< .001
% of patients with ≥50% 4-mo target dose	110 (76.39)	92 (63.45)	12.94 (2.47; 23.41)	.02
BB titration changes				
Dose increased compared with baseline	113 (78.47)	88 (60.69)	17.78 (7.38; 28.19)	.001
Dose matched compared with baseline	23 (15.97)	50 (34.48)	−18.51 (−28.29; −8.73)	< .001
Dose decreased compared with baseline	8 (5.56)	7 (4.83)	0.73 (−4.39; 5.84)	.78
ACE inhibitors dose				
Relative dose at baseline, %	118, 45.92 ± 30.06	121, 40.13 ± 25.38	5.78 (−1.29; 12.87)	.11
Relative dose at 4 mo, %	115, 72.61 ± 29.80	115, 56.13 ± 30.37	16.48 (8.66; 24.30)	< .001
% of patients with 100% 4-mo target dose	55 (48.70)	29 (25.22)	23.48 (11.38; 35.58)	< .001
% of patients with ≥50% 4-mo target dose	96 (82.61)	80 (69.57)	13.04 (2.15; 23.94)	.02
ACE inhibitors titration changes				
Dose increased compared with baseline	70 (60.87)	61 (53.04)	7.83 (−4.93; 20.58)	.23
Dose matched compared with baseline	44 (38.26)	47 (40.87)	−2.61 (−15.24; 10.03)	.69
Dose decreased compared with baseline	2 (1.74)	7 (6.09)	−4.35 (−9.33; 0.63)	.09
ARB dose				
Relative dose at baseline, %	16, 29.15 ± 14.99	8, 43.20 ± 20.63	−14.04 (−29.31; 1.21)	.07
Relative dose at 4 mo, %	19, 44.48 ± 33.47	17, 43.51 ± 33.69	0.97 (−21.81; 23.75)	.93
% of patients with 100% 4-mo target dose	4 (21.05)	3 (17.65)	3.41 (−22.37; 29.18)	.80
% of patients with ≥50% 4-mo target dose	8 (42.11)	7 (41.18)	0.93 (−31.32; 33.18)	.96
ARB titration changes				

Dose increased compared with baseline	10 (52.63)	8 (47.06)	5.57 (−27.09; 38.24)	.74
Dose matched compared with baseline	7 (36.84)	6 (35.29)	1.55 (−29.86; 32.96)	.92
Dose decreased compared with baseline	1 (5.26)	3 (17.65)	−12.38 (−33.10; 8.33)	.24
ARM dose				
Relative dose at baseline, %	125, 61.4 ± 33.52	127, 63.18 ± 33.00)	−1.78 (−10.04; 6.46)	.66
Relative dose at 4 mo, %	125, 71 ± 32.12	127, 70.47 ± 29.78)	0.52 (−7.15; 8.21)	.86
Relative dose baseline - 4 mo difference	9.6, 3.79 ± 15.40	7.28, 1.29 ± 13.27	2.31 (−5.98; 10.61)	.58
% of patients with 100% 4-mo target dose	64 (51.6)	59 (46.46)	3.54 (−8.81; 15.90)	.41
% of patients with ≥ 50% 4-mo target dose	108 (87.10)	118 (92.91)	−5.82 (−13.21; 1.58)	.12
ARM titration changes				
Dose increased compared with baseline	43 (34.4)	25 (19.69)	14.71 (3.89; 25.53)	.008
Dose matched compared with baseline	69 (55.2)	93 (73.23)	−18.02 (−29.66; −6.39)	.003
Dose decreased compared with baseline	13 (10.4)	9 (7.09)	3.31 (-3.65; 10.28)	.35

ACE inhibitors, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker; BB, beta-blocker; MRA, mineralocorticoid receptor antagonist.

The data are expressed as No. (%), mean ± standard deviation, or No. ± standard deviation; (min-max).

To calculate the mean baseline doses of BB and MRA, the 4-month number was taken, that is, all patients (n) who had a prescription during the titration period (which included prescribed patients at any time in this period and patients with a zero dose because of drug withdrawal). To calculate the mean baseline doses of ACE inhibitors and ARB, only the patients (n) whi received a prescription at baseline were included in the analysis. To calculate the mean 4-month doses for all 4 groups (BB, ACE inhibitors, ARB, and MRA), the 4-month number was taken, that is, all patients (n) who had a prescription during the titration period (which included prescribed patients at any time in this period and patients with a zero dose because of drug withdrawal), except for those patients with ACE inhibitors/ARB who had a drug substitution (ARB, ARB + neprilysin inhibitor). Differences between ACE inhibitors, angiotensin-converting enzyme inhibitors and ARB relative doses baseline-4 months were not calculated due to multiple medication changes (from ACE inhibitors to ARB or ARB + neprilysin inhibitor or from ARB to ARB + neprilysin inhibitor) as indicated in the prescription tables included in this supplement. However, there were no statistically significant differences at baseline between the groups. The lowest level of the target dose range recommended in the guidelines or any value above it was as 100% of the target dose. The drugs not recommended in the European Guidelines for the treatment of HF were not taken into consideration for dose calculation.

Table 4 of the supplementary data

Variables potentially associated with titration. Baseline to 4-month follow-up

Variables potentially associated with titration 4 mo	HF nurse N = 144	HF cardiologist N = 145	Diff. (95%CI)	*P*
Systolic blood pressure				
Baseline, mmHg	144, 115.58 ± 17.33; (70-162)	144, 115.97 ± 19.82; (75-184)	−0.40 (−4.71; 3.92)	.86
4-mo, mmHg	144, 119.66 ± 17.47; (80-164)	144, 120.87 ± 19.86; (78-190)	−1.21 (−5.55; 3.13)	.58
Baseline-4-mo difference	144, 4.08 ± 19.29; (−33.00 to 65.00)	144, 4.90 ± 20.42; (−71.00 to 60.00)	−0.81 (−5.42; 3.80)	.73
SPB ≤ 100 mmHg				
Baseline,	27 (18.75)	35 (24.31)	−5.39 (−14.83; 4.05)	.27
4 m	24 (16.67)	24 (16.67)	0	> .99
Baseline-4-mo difference	3 (2.08)	11 (7.63)	−5.56 (−10.48; −0.63)	.03
Baseline with other hypotensive drugs	3 (2.08)	3 (2.06)		
4-mo with other hypotensive drugs	6 (4.16)	3 (2.06)	2.09 (−1.90; 6.10)	.31
Heart rate, bpm				
Baseline	143, 72.26 ± 13.2; (42-110)	144, 73.65 ± 14.76; (37-120)	−1.39 (−4.64; 1.87)	.40
4 mo	143, 65.7 ± 11.78; (46-112)	144, 66.85 ± 12.48; (42-116)	−1.15 (−3.98; 1.67)	.42
Baseline-4-mo difference	143, −6.56 ± 15.73; (−48.00 to 68.00)	144, −6.79 ± 14.19; (−57.00 to 26.00)	−0.06 (−0.10; −0.01)	.90
HR < 50 bpm				
Baseline	4 (2.80)	3 (2.08)	0.71 (−2.86; 4.28)	.70
4 mo	8 (5.59)	5 (3.47)	2.12 (−2.69; 6.93)	.41
Baseline-4-mo difference	4 (2.79)	2 (1.38)	1.41 (−1.90; 4.72)	.40
Baseline with BB + other rate-lowering drugs	3(2.08)	3(2.06)		
4-mo with BB + other rate-lowering drugs	4 (2.77)	1 (6.94)	2.08 (−0.9; 5.09)	.17
Heart rate >70 bpm and sinus rhythm				
Baseline	56 (39.16)	62 (43.06)	−3.89 (−15.27; 7.48)	.50
4-mo	31 (21.68)	41 (28.47)	−6.75 (−16.69; 3.19)	.19
Baseline-4-modifference	16 (11.18)	13 (9.02)	2.16 (−4.81; 9.13)	.54
4 mo, without 100% BB	5 (3.49)	18 (12.5)	9 (−2.81; −15.18)	.005
Heart rate ≥ bpm and sinus rhythm at 4 mo	15 (10.49)	28 (19.44)	−8.89 (−17.03; −0.76)	.03
Creatinine, mg/dL				
Baseline	142, 1.11 ± 0.47; (0.44-4.67)	144, 1.03 ± 0.52; (0.42-5.73)	0.08 (−0.03; 0.20)	.15
4 mo	142, 1.1 ± 0.46; (0.57-4.68)	144, 1.04 ± 0.52; (0.52-5.85)	0.05 (−0.06; 0.17)	.36
eGFR, mL/min/1.73 m²				

Baseline	143, 72.22 ± 21.28; (11-119)	144, 78.76 ± 21.49; (10-121)	−6.54 (−11.51; −1.57)	.01
4-mo	142, 74.08 ± 22.29; (11-126.7)	144, 79.07 ± 22.26; (9.8-126.7)	−4.98 ± −10.17; 0.20)	.06
Baseline to 4-mo difference	142, 1.91 ± 15.29;(−48.10 to 42.30)	144, 0.31 ± 14.91; (−45.90 to 35.00)	1.61 (−1.91; 5.12)	.37
eGFR < 60 mL/min/1.73 m^2				
Baseline	38 (26.76)	23 (15.97)	10.56 (1.09; 20.04)	.03
4-mo	33 (23.24)	28 (19.44)	3.52 (−6.02; 13.06)	.47
Baseline to 4-mo difference	5 (3.52)	−5 (−3.47)	6.99 (1.08; 12.66)	.02
eGFR at 4 mo				
Worsens	57 (40.14)	67 (46.53)	−6.62 (−18.01; 4.76)	.26
Matches	3 (2.11)	4 (2.78)	−0.68 (−4.22; 2.87)	.71
Improves	82 (57.75)	73 (50.69)	6.60 (−4.87; 18.07)	.26
Urea, mg/dL				
Baseline	140, 55.74 ± 23.4; (5-157)	140, 50.94 ± 22.26; (13-143)	4.80 (−0.57; 10.17)	.08
4-mo	134, 51.22 ± 19.99; (21-119)	133, 47.22 ± 17.38; (5-121)	4.01 (−0.51; 8.52)	.08
Sodium, mEq/L				
Baseline	144, 139.45 ± 3.11; (125-147)	145, 139.41 ± 3.21; (129-147)	0.04 (−0.69; 0.77)	.92
4-mo	142, 40.3 ± 3.34 (123-147)	144, 140.36 ± 3.17; (129-147)	−0.06 (−0.82; 0.70)	.88
Potassium, mEq/L				
Baseline	142, 4.52 ± 0.49; (3.08-6)	144, 4.43 ± 0.57; (2.9-6.4)	0.08 (−0.04; 0.21)	.18
4-mo	142, 4.7 ± 0.45; (3.5-5.8)	144, 4.62 ± 0.51; (3.2-6.3)	0.08 (−0.03; 0.20)	.15
Potassium > 5.5 mEq/L				
Baseline	4 (2.82)	1 (0.69)	2.12 (−0.92; 5.16)	.21
4-mo	7 (4.93)	6 (4.17)	0.76 (−4.07; 5.59)	.79
Baseline-4-mo difference	3 (2.11)	5 (3.52)	−1.36 (−5.17; 2.45)	.49
Potassium > 6 mEq/L				
Baseline	0 (0)	1 (0.69)	−0.69 (−2.05; 0.66)	> .99
4 mo	0 (0)	2 (1.39)	−1.39 (−3.30; 0.52)	.50
Hemoglobin, g/dL				
Baseline	144, 14.99 ± 8.33; (9.8-112)	145, 14.15 ± 2.19; (8.8-19)	0.83 (−0.57; 2.24)	.25
4-mo	138, 13.74 ± 1.82; (5.5-18.4)	141, 13.75 ± 1.61; (8.7-17.3)	0.00 (−0.41; 0.40)	.98
Hemoglobin < 12 (women), < 13 (men), g/dL				
Baseline	29 (20.14)	36 (24.83)	−4.69 (−14.30; 4.92)	.40
4-mo	33 (23.91)	31 (21.99)	1.93 (−7.94; 11.80)	.78
NYHA				
Baseline				
NYHA II	121 (84.03)	119 (82.07)	0.02 (−0.07; 0.11)	.66

NYHA III	23 (15.97)	26 (17.93)	−0.02 (−0.11; 0.07)	.66
4 mo				
NYHA I	39 (27.86)	40 (28.99)	−0.01 (−0.11; 0.10)	.92
NYHA II	99 (70.71)	90 (65.22)	0.07 (−0.04; 0.18)	.23
NYHA III	2 (1.43)	8 (5.8)	−0.04 (−0.08; 0.00)	.06
NYHA III Baseline-4-modifference	−21 (14.58)	−18 (12.59)	2.17 (−5.71; 10.05)	.59
AVB				
First-degree AVB at baseline	4 (2.78)	1 (0.69)	0.02 (−0.01; 0.05)	.17
Third-degree AVB with pacemaker at baseline	1 (0.69)	1 (0.69)	0.00 (−0.02; 0.02)	> .99
First-degree AVB at 4-month	9 (6.25)	2 (1.38)	4.86 (0.47; 9.25)	.03
Third-degree BAV with pacemaker at 4-mo	2 (1.39)	1 (0.69)	0.69 (−1.65; 3.04)	.56
Atrial fibrillation/atrial flutter				
Baseline	42 (29.17)	36 (24.83)	4.34 (−5.89; 14.56)	.43
4 mo	25 (17.36)	21 (14.48)	2.88 (−5.55; 11.31)	.52
Flexible diuretic regime/patients with a prescription	82 (69.49)	66 (55.00)	14.49 (2.32; 26.67)	.02
European Heart Failure Self-care Behaviour Scale (12-60 worse)	142, 19.35 ± 7; (12-54)	144, 20.66 ± 8.6; (12-51)	−1.31 (−3.14; 0.51)	.16
Question 10. Irregular medication intake score ≥3	4 (2.82)	8 (5.56)	−2.74 (−7.36; 1.89)	.25
Visits	**HF nurse group**	**HF cardiologist group**	**Diff. (95% CI)**	***P***
Nurse	141, 6.41 ± 2.82; 6 (1-15)	144, 3.87 ± 1.74; 4 (1-11)	2.54 (1.99; 3.08)	< .001
Cardiologist	141, 2.20 ± 1.21; 2 (1-6)	144, 2.81 ± 1.58; 2 (1-8)	−0.61 (−0.94; −0.28)	< .001
Nurse + cardiologist	141, 8.61 ± 3.11; 8 (1-17)	141, 6.69 ± 1.46; 7 (2-14)	1.92 (1.27; 2.58)	< .001
Titrating professional	141, 6.41 ± 2.82; 6 (1-15)	144, 2.81 ± 1.58; 2 (1-8)	4.45 (3.06; 4.13)	< .001
N ≤ 2 consultations with the professional who titrated, n (%) patients	7 (4.96)	77 (53.47)	−48.24 (−57.09; −39.39)	< .001
HF nurse consultations with HF cardiologists, without patient visit on titration in intervention group*	111, 1.55 ± 1.77			

AVB, atrioventricular block; eGFR, estimated glomerular filtration rate; HF, heart failure; NHYA, New York Heart Association.

The data are expressed as No. (%), mean ± standard deviation, No. ± standard deviation; (min-max), or No. mean ± standard deviation.

*Documented No. (%) patients with consultations on titration between HF nurse-HF cardiologist without a patient visit were 111/144 (77.08%). The reasons for lack of registration were: *a)* it was not on the design (short time needed); *b)* there were no such consultations. A total of 80% patients had n ≤2 consultations. There was wide heterogeneity between hospitals but higher numbers of consultations were not associated with greater dosage but rather with less HF nurse experience (no previous experience of titration).

Table 5 of the supplementary data

Drug prescription. Baseline to 4-month follow-up (titration period)

Prescribed drugs/active patients at 4 mo	HF nurse n = 144	HF cardiologist n = 145	Diff. (95%CI)	*P*
BB				
Baseline	140 (97.22)	141 (97.44)	−0.02 (−3.81; 3.76)	.99
4 mo	143 (99.31)	142 (99.50)	1.38 (−1.31; 4.06)	.32
***Started** in this period*	4	4		
***Withdrawn** (0 dose)*	1	3		
ACE inhibitors				
Baseline	119 (82.64)	121 (83.62)	−0.81 (−9.48; 7.84)	.85
4 mo	116 (80.56)	112 (77.24)	3.31 (−6.08; 12.71)	.49
***Started** in this period*	3	4		
***Withdrawn** (0 dose), without ARB/ARB-neprilysin inhibitor*	0	3		
***Change** to other medication: ARB/ARB-neprilysin inhibitor*	6	10		
*ACE inhibitors not recommended in guidelines for HF at baseline **	1 perindopril			
*ACE inhibitors not recommended in guidelines for HF at 4 mo**	1 Perindopril			
ARB				
Baseline	17 (11.81)	12 (8.29)	3.54 (−3.40; 10.45)	.32
4 mo	18 (12.50)	20 (13.79)	−1.29 (−9.08; 6.49)	.75
***Started** in this period*	3	10		
***Withdrawn** (0 dose), without ACE inhibitors /ARB-neprilysin inhibitor*	1	0		
***Change** to other medication: ARB-neprilysin inhibitor*	1	2		
*ARB not recommended in guidelines for HF at baseline**	1 Olmesartan	2 Irbesartan, 2 Olmesartan		
*ARB not recommended in guidelines for HF at 4 mo**		3 Olmesartan, 1 Irbesartan		

MRA				
Baseline	109 (75.69)	113 (78.09)	−2.24 (−11.99; 7.49)	.65
4 mo	117 (81.25)	121 (83.62)	-2.20 (-11.01; 6.59)	.62
***Started** in this period*	15	14		
Withdrawn	7	6		

ACE inhibitors, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker; BB, beta-blockers; MRA, mineralocorticoid receptor antagonist.

Unless otherwise specified, the data are presented as No. (%).

Table 6 of the supplementary data

Drug combination at 4 months (after titration)

Drug combination*	HF nurse n = 144	HF cardiologist n = 145	Dif. (95%CI)	*P*
With 3 groups of drugs: BB + ACE inhibitors /ARB/*ARB-neprilysin Inhibitor* + MRA	117 (81.25)	115 (79.13)	1.90 (−7.23; 11.11)	.68
Renin-angiotensin system/peptide modulators ACE inhibitors /ARB/*ARB-neprilysin Inhibitors*	140 (97.22)	137 (94.49)	2.74 (−1.84; 7.32)	.24
With 2 groups of drugs: BB + ACE inhibitors /ARB/ARB-neprilysin Inhibitor	22 (15.28)	21 (14.51)	0.80 (−7.43; 9.00)	.85
With 2 groups of drugs: BB + MRA	1 (0.69)	3 (2.07)	−1.38 (−4.07; 1.31)	.32
With 2 groups of drugs: ACE inhibitors /ARB/ ARB-neprilysin Inhibitor + MRA	0 (0.00)	2 (1.38)	−1.38 (−3.28; 0.52)	.16
With 1 group of drugs: BB	3 (2.08)	4 (2.76)	−0.68 (−4.23; 2.87)	.71

ACE inhibitors, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker; BB, beta-blockers; MRA, mineralocorticoid receptor antagonist.

Unless otherwise specified, the data are expressed as No. (%) of patients.

Table 7 of the supplementary data

Other drugs possibly influencing titration. Baseline to 4-month follow-up

Other drugs that may influence titration/active patients at 4 mo	HF nurse n = 144	HF cardiologist n = 145	Diff. (95%CI)	*P*
With any other rate-lowering drug				
Baseline	46 (31.94)	40 (27.59)	4.36 (−6.17; 14.89)	.42
4 mo	31 (21.53)	38 (26.21)	−4.68 (−14.49; 5.13)	.35
Ivabradine				
Baseline	19 (13.19)	18 (12.44)	0.78 (−6.94; 8.49)	.84
4 mo	8 (5.56)	18 (12.44)	−6.86 (−13.40; −0.32)	.04
Started	3	9		
Withdrawn	14	9		
Amiodarone				
Baseline	18 (12.50)	13 (8.98)	3.54 (−3.60; 10.66)	.33
4 mo	16 (11.11)	11 (7.60)	3.53 (−3.18; 10.23)	.30
Started	2	4		
Withdrawn	4	5		
Change from amiodarone to dronedarone	0	1		
Digitalis				
Baseline	9 (6.25)	9 (6.22)	0.04 (−5.54; 5.62)	.99
4 mo	7 (4.86)	9 (6.22)	−1.35 (−6.63; 3.92)	.62
Started	2	3		
Withdrawn	4	3		
Hypo- and hyperthyroidism medication				
Baseline	6 (4.17)	7 (4.84)	−0.66 (−5.45; 4.12)	.79
4 mo	6 (4.17)	7 (4.84)	−0.66 (−5.45; 4.12)	.79
Inhaled bronchodilators				
Baseline	13 (9.03)	11 (8.29)	0.75 (−5.74; 7.23)	.82
4 mo	14 (9.72)	9 (6.22)	3.52 (−2.72; 9.75)	.27

With other drugs that can affect BP (nondiuretics)				
Baseline	19 (13.19)	22 (15.20)	−1.98 (−10.04; 6.06)	.63
4 mo	26 (18.06)	26 (17.97)	0.00 (0.00; 0.00)	--
ARB + neprilysin Inhibitor				
Baseline	1 (0.69)	2 (1.38)	−0.69 (−3.02; 1.65)	.57
4 mo	6 (4.17)	5 (3.46)	0.72 (−3.70; 5.13)	.75
Started	5 (3.47)	4 (2.76)	0.72 (−3.30; 4.72)	.73
Withdrawn	0 (0.00)	1 (0.69)	−0.69 (−2.04; 0.66)	.32
Dihydropyridine calcium-channel blockers				
Baseline	5 (3.47)	7 (4.84)	−1.36 (−5.96; 3.24)	.56
4 mo	7 (4.86)	9 (6.22)	−1.35 (−6.63; 3.92)	.62
Started	3 (2.08)	2 (1.38)	0.71 (−2.31; 3.71)	.65
Withdrawn	1 (0.69)	0 (0.00)	0.70 (−0.66; 2.05)	.32
Nitrates (not sublingual)/hydralazine				
Baseline	8 (5.56)	6 (4.15)	1.42 (−3.54; 6.37)	.58
4 mo	6 (4.17)	6 (4.15)	0.00 (0.00; 0.00)	--
Started	0 (0.00)	1 (0.69)	−0.69 (−2.04; 0.66)	.32
Withdrawn	2 (1.39)	1 (0.69)	0.70 (−1.64; 3.04)	.56
Alpha-blockers				
Baseline	5 (3.47)	7 (4.84)	−1.36 (−5.96; 3.24)	.56
4 mo	7 (4.86)	6 (4.15)	0.72 (−4.06; 5.50)	.77
Started	2	1		
Withdrawn	0	2		
Diuretics (loop/thiazide)				
Baseline	115 (79.86)	121 (83.62)	−3.59 (−12.53; 5.33)	.43
4 mo	117 (81.25)	118 (81.54)	−0.13 (−9.14; 8.86)	.98
*Psychotropic drugs**				
Baseline	40 (27.78)	27 (18.66)	9.18 (−0.52; 18.84)	.07
At 4 mo	38 (26.39)	26 (17.97)	8.47 (−1.07; 17.99)	.08

ARB, angiotensin receptor blocker.

Unless otherwise specified, the data are expressed as No. (%) of patients.

* Psychotropic drugs: antidepressants, anxiolytics, hypnotics, neuroleptics

Table 8 of the supplementary data

Relative dose at 4 months/hospital.

Relative dose at 4 mo	HF nurse hospitals n = 20	HF cardiologist hospitals n = 20
BB		
≥ 70%	11	7
50%-70%	7	5
< 50%	2	7
ACE inhibitors		
≥ 70%	11	2
50%-70%	8	9
< 50%	1	8
ARB		
≥ 70%	2	4
50%-70%	5	1
< 50%	7	7
MRA		
≥ 70%	7	11
50%-70%	10	8
< 50%	3	0

ACE inhibitors, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist; BB, beta-blockers.

Table 9 of the supplementary data

Multivariate models: beta-blockers

						Type 3 tests of fixed effects			
	Estimate	Standard error	DF	t Value	Pr > |t|	Num DF	Den DF	F Value	Pr > F
Intercept	7.563	8.947	406	0.85	.398				
ETIFIC HF nurse vs ETIFIC HF Cardiologist	12.182	3.051	454	3.99	< .001	1	453	2.05	.153
Visit (baseline vs 4 mo)	−20.870	2.517	440	-8.29	< .001	1	440	272.56	< .001
Group* visit	−17.283	3.575	440	-4.83	< .001	1	440	23.37	< .001
Relative BB dose (baseline)	0.863	0.052	416	16.48	< .001	1	416	271.70	< .001
Age, y	−0.192	0.085	448	-2.27	.024	1	448	5.15	.024
More than 10 y of education (yes vs no)	4.138	2.241	446	1.85	.066	1	451	10.67	.065
Baseline HR, bpm	0.223	0.068	451	3.27	.001	1	451	10.67	.001
Amiodarone (baseline: no vs yes)	7.073	3.056	452	2.31	.021	1	452	5.36	.021
Visits with the professional who titrated	1.447	0.457	363	3.17	.002	1	363	10.04	.002

BB, beata-blocker; HF, heart failure; HR, heart rate.

Finally, after a backward modeling method, the variables that were considered to influence the relative BB dose reached at 4 months can be seen in the above table.

An effect of the group was assessed (group* visit: *P* < .001). At 4 months, the estimated difference was 12.18 points in favor of the ETIFIC HF nurse group (95%CI, 6.19-18.17) (*P* < .001).

The factors related to the BB dose achieved were its baseline level, age, educational level, baseline HR, amiodarone, and number of visits with the titrating professional (1.44 points for each visit made; *P* < .002).

Table 10 of the supplementary data

Multivariate models: ACE inhibitors

						Type 3 tests of fixed effects			
	Estimate	Standard error	DF	t Value	Pr > |t|	Num DF	Den DF	F Value	Pr > F
Intercept	3.207	8.027	449	0.40	.690				
ETIFIC HF nurse vs ETIFIC HF cardiologist	13.793	2.648	449	5.21	< .001	1	449	20.43	< .001
Visit (baseline vs 4 mo)	−16.057	2.561	449	−6.27	< .001	1	449	138.66	< .001
Group* visit	−10.864	3.649	449	−2.98	.003	1	449	8.86	.003
Relative ACE inhibitors dose (baseline)	0.700	0.034	449	20.91	< .001	1	449	437.24	< .001
Age, y	−0.184	0.079	449	−2.34	.020	1	449	5.47	.020
SBP (Baseline, mmHg)	0.252	0.051	449	4.92	< .001	1	449	24.17	< .001
eGFR <60 (no vs yes)	7.503	2.469	449	3.04	.003	1	449	9.23	.002

ACE inhibitors, angiotensin-converting enzyme inhibitors; HF, heart failure; SBP, systolic blood pressure; eGFR, estimated glomerular filtration rate.

Finally, after a backward modeling method, the variables considered to influence the relative ACE inhibitors dose achieved at 4 months can be seen in the above table.

An effect of the group was assessed (group* visit: $P = .003$). At 4 months, the adjusted difference in average relative dose between the 2 groups observed in a multivariate model was 13.79 points (8.58, 18.99) ($P < .001$) for ACE inhibitors.

The factors related to the ACE inhibitors dose achieved were its baseline level, age, baseline SBP, and eGFR < 60.

Table 11 of supplementary data

Multivariate models: MRA

						Type 3 tests of fixed effects			
	Estimate	Standard error	DF	t Value	Pr > |t|	Num DF	Den DF	F Value	Pr > F
Intercept	6.186	9.315	459	0.66	.507				
ETIFIC HF nurse vs ETIFIC Cardiologist	3.196	2.757	478	1.16	.247	1	481	0.80	.372
Visit (baseline vs 4 mo)	−6.548	2.709	474	−2.42	.016	1	474	17.10	< .001
Group* visit	−2.879	3.863	474	−0.75	.457	1	474	0.56	.456
Relative MRA dose (baseline)	0.692	0.031	277	22.11	< .001	1	277	488.66	< .001
Age, y	−0.059	0.087	446	−0.68	.499	1	446	0.46	.498
eGFR < 60 (no vs yes)	5.796	2.667	485	2.17	.030	1	485	4.72	.030
K (≤ 5.5 mEq/L vs > 5.5 mEq/L)	15.511	7.321	477	2.12	.035	1	477	4.49	.035
Mild events (no vs yes)	3.820	2.485	447	1.54	.125	1	447	2.36	.125

eGFR, estimated glomerular filtration rate; HF, heart failure; K, potassium; MRA, mineralocorticoid receptor antagonists.

Last, after a backward modeling method, the variables considered to influence the relative MRA dose achieved at 4 months can be seen in the above table. For MRA, the average value in both groups was higher at 4 months than at baseline (visit $P < .001$) while an effect of the group was not assessed (group* visit; $P = .46$). The difference at 4 months was 3.19 points (95%CI; −2.22; 8.61) without assessing significant differences between both groups ($P = .37$). There seemed to be a correlation with the relative baseline MRA dose ($P < .001$), eGFR, K ≤ 5.5 and the onset of mild events (although this last factor did not reach statistical significance).

Table 12 of the supplementary data

Reasons given for not reaching 100% dose after titration period (at 4 months)

Reason given/drug	HF nurse n = 144 n (%)	HF cardiologist n = 145 n (%)	Diff. (95%CI)	*P*
BB				
Adverse events	18 (12.50)	14 (9.65)	2.84 (−4.39; 10.08)	.44
Symptomatic hypotension	6 (4.17)	6 (4.14)	0.03 (−4.57; 4.63)	.99
HR < 50 bpm	10 (6.94)	7 (4.83)	2.12 (−3.31; 7.54)	.44
Worsening HF	2 (1.39)	1 (0.69)	0.70 (−1.64; 3.04)	.56
Second-degree, third-degree AVB without pacemaker	0 (0.00)	0 (0.00)	0.00 (0.00; 0.00)	
Other reasons				
SBP ≤ 100 mmHg, asymptomatic hypotension	3 (2.08)	17 (11.72)	−9.64 (−15.37; −3.91)	.001
HR 50-60 bpm	35 (24.31)	34 (23.45)	−0.53 (−10.36; 9.30)	.92
Other clinical reasons	2 (1.39)	2 (1.38)	0.01 (−2.68; 2.70)	.99
Clinical reason for not reaching target dose	58 (40.28)	67 (46.21)	−5.93 (−17.33; 5.47)	.31
Clinical reason for not reaching target dose + in target dose	128 (88.89)	104 (71.72)	17.16 (8.22; 26.11)	< .001
No. of visits ≤ 2	4 (2.78)	22 (15.17)	−12.39 (−18.82; −5.97)	< .001
Followed-up by other professionals, discrepancies	1 (0.69)	2 (1.38)	−0.68 (−3.02; 1.65)	.57
The patient does not attend/is confused/has low adherence	0 (0.00)	2 (1.38)	−1.38 (−3.28; 0.52)	.16
Unknown/unexplained	11 (7.64)	15 (10.34)	−2.71 (−9.29; 3.88)	.42
ACE inhibitors				
Adverse event	11 (9.48)	14 (11.86)	−2.38 (−10.29; 5.52)	.56
Symptomatic hypotension	6 (5.17)	11 (9.32)	−4.15 (−10.76; 2.47)	.22
*Worsening renal function**	2 (1.72)	2 (1.69)	0.03 (−3.29; 3.35)	.99
K > 5.5 mEq/l	3 (2.59)	1 (0.85)	1.74 (−1.59; 5.07)	.31
Other reasons				
SBP ≤ 100 mmHg, asymptomatic hypotension	29 (25.00)	34 (28.81)	−3.81 (−15.17; 7.54)	.51
Worsening renal function, 30%-50% higher than baseline Cr or CR > 1.9	4 (3.45)	4 (3.39)	0.06 (−4.60; 4.72)	.98
K 5.2-5.5 mEq/L	2 (1.72)	4 (3.39)	−1.67 (−5.70; 2.37)	.42
Other clinical reasons	0 (0.00)	3 (2.54)	−2.54 (−5.38; 0.30)	.08
Clinical reason for not reaching target dose	46 (39.66)	60 (50.85)	−12.05 (−24.70; 0.59)	.06
Clinical reason for not reaching target dose + in target dose	101 (87.07)	79 (66.95)	20.12 (9.66; 30.58)	< .001
No. of visits ≤ 2	1 (0.86)	14 (11.86)	−11.00 (−17.07; −4.93)	.001
The patient does not attend/is confused/shows poor adherence	5 (4.31)	2 (1.69)	2.62 (−1.75; 6.98)	.24
Unknown/unexplained	9 (7.76)	11 (9.32)	−1.56 (−8.72; 5.59)	.67

ARB				
Adverse event	4 (44.44)	0 (0.00)	21.05 (2.72; 39.38)	.045
Symptomatic hypotension	2 (10.53)	0 (0.00)	10.53 (−3.27; 24.33)	.17
Worsening renal function*	0 (0.00)	0 (0.00)	0.00 (0.00; 0.00)	
K > 5.5 mEq/L	2 (10.53)	0 (0.00)	10.53 (−3.27; 24.33)	.17
Other reasons				
SBP ≤100 mmHg, asymptomatic hypotension	3 (15.79)	2 (11.76)	4.02 (−18.41; 26.46)	.73
Worsening renal function, 30%-50% higher than baseline Cr or CR > 1.9	2 (10.53)	0 (0.00)	11.76 (−3.55; 27.08)	.15
K 5.2-5.5 mEq/L	0 (0.00)	0 (0.00)	0.00 (0.00; 0.00)	
Other clinical reasons (ARB not from guidelines)	0 (0.00)	4 (23.53)	−23.53 (−43.69; −3.37)	.03
Clinical reason for not reaching target dose	9 (60.00)	2 (14.29)	41.18 (12.94; 69.42)	.01
Clinical reason for not reaching target dose + in target dose	13 (68.42)	5 (29.41)	39.01 (8.91; 69.11)	.02
No. of visits ≤ 2	0 (0.00)	8 (47.06)	−6.96 (−11.61; −2.31)	.004
The patient does not attend/is confused/has low adherence	0 (0.00)	1 (5.88)	−5.88 (−17.07; 5.30)	.28
Unknown/unexplained	6 (40.00)	3 (21.43)	2.56 (−2.41; 7.54)	.31
MRA				
Adverse event	10 (8.06)	7 (5.51)	2.55 (−3.67; 8.78)	.42
Symptomatic hypotension	2 (1.61)	0 (0.00)	1.61 (−0.60; 3.83)	.15
Worsening renal function*	2 (1.61)	2 (1.57)	0.04 (−3.06; 3.14)	.98
K > 5.5 mEq/L	6 (4.84)	5 (3.94)	0.90 (−4.17; 5.97)	.73
Other reasons				
SBP ≤ 100 mmHg, asymptomatic hypotension	9 (7.26)	14 (11.02)	−3.77 (−10.87; 3.34)	.30
Worsening renal function, 30%-50% higher than baseline Cr or CR > 1.9	4 (3.23)	1 (0.79)	2.44 (−1.03; 5.91)	.17
K > 5.2 and < 5.5 mEq/L	8 (6.45)	8 (6.30)	0.15 (−5.89; 6.20)	.96
Other clinical reasons	5 (4.03)	5 (3.94)	0.10 (−4.74; 4.94)	.97
Clinical reason for not reaching target dose	36 (29.03)	35 (27.56)	1.47 (−9.67; 12.62)	.80
Clinical reason for not reaching target dose + in target dose	100 (80.65)	95 (74.80)	5.84 (−4.42; 16.11)	.27
No. of visits ≤ 2	5 (4.03)	20 (15.75)	−11.72 (−18.94; −4.50)	.002
The patient does not attend/is confused/has low adherence	2 (1.61)	1 (0.79)	0.83 (−1.87; 3.52)	.55
Unknown/unexplained	17 (13.71)	11 (8.66)	5.05 (−2.73; 12.83)	.20

ACE inhibitors, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker; AVB, atrioventricular block; BB, beta-blockers; Cr, Creatinine; HR, heart rate; K, potassium; MRA, mineralocorticoid receptor antagonist; SBP, systolic blood pressure. Worsening renal function*: baseline creatinine > 50% or > 3 mg, estimated glomerular filtration rate < 25.

Table 13 of the supplementary data

Events associated with titration.

Events persisting at 4-mo	HF nurse n = 144	HF cardiologist n = 145	Diff. (95%CI)	*P*
Symptomatic hypotension	12 (8.33)	13 (8.97)	−0.63 (−7.11; 5.85)	.85
Persistent	2 (1.39)	6 (4.14)	−2.75 (−6.51; 1.01)	.15
HR < 50 bpm	10 (6.94)	7 (4.83)	2.12 (−3.31; 7.54)	.44
Persistent	4 (2.78)	2 (1.38)	1.40 (−1.89; 4.69)	.41
*Worsening renal function**	3 (2.08)	2 (1.38)	0.70 (−2.30; 3.71)	.65
Persistent	1 (0.69)	2 (1.38)	−0.68 (−3.02; 1.65)	.57
Worsening renal function with K > 5.5 mEq/L*	1 (0.69)	4 (2.76)	−2.06 (−5.06; 0.93)	.18
Persistent	1 (0.69)	4 (2.76)	−2.06 (−5.06; 0.93)	.18
K > 5.5 mEq/Ll	6 (4.17)	3 (2.07)	2.10 (−1.90; 6.10)	.31
Persistent	3 (2.08)	2 (1.38)	0.70 (−2.30; 3.71)	.65
Worsening HF	2 (1.39)	1 (0.69)	0.70 (−1.64; 3.04)	.56
Persistent	1 (0.69)	0 (0.00)	0.69 (−0.66; 2.05)	.32
Total events	34 (23.61)	30 (20.69)	2.92 (−6.65; 12.49)	.55
Total persistent	12 (8.33)	16 (11.03)	−2.70 (−9.51; 4.11)	.44
Total patients with events	30 (20.83)	23 (15.86)	4.97 (−3.94; 13.88)	.28

Worsening renal function* Baseline creatinine > 50% or > 3 mg, estimated glomerular filtration rate < 25; HR, heart rate; K, potassium.

Table 14 of the supplementary data

Causes associated with events related to titration	HF nurse		HF cardiologist	
Symptomatic hypotension	3/12	1 Alcohol consumption 1 Other hypotensive drug 1 Baseline renal failure	0	
HR < 50 bpm	8/10	4 Amiodarone 1 Amiodarone + cardioversion 1 Ablation 1 Digoxin 1 Baseline renal failure	2/7	2 Amiodarone
Worsening renal function*	1/3	1 Diarrhea with renal failure due to metformin	0	
Worsening renal function* with K > 5.5	1/1	1 NSAIDs	1/4	1 K fruit intake (1 avocado/d)
K > 5.5 mEq/L	3/6	1 High fruit intake 1 Prednisone withdrawal 1 Baseline spironolactone 100 mg	0	
Total	**16/32**		**3/11**	

Causes associated with events related to titration

Worsening renal function*: baseline creatinine > 50% or >3 mg, estimated glomerular filtration rate < 25; HR, heart rate; K, potassium.

Table 15 of supplementary data

Causes of drug withdrawal

Drugs withdrawn	HF nurse	HF cardiologist
BB	1 After cardioversion, HR 47 bpm. BB withdrawn and amiodarone prescribed	1 Patient confused, stopped taking 1 Intolerance prescribed ivabradine 1 HR 44 bpm
ACE inhibitors		1 Septic shock due to pneumonia 1 SBP 87 mmHg 1 Gastroenteritis, potassium 6, glomerular filtration rate 21
ARB	1 SBP 80 mmHg	
MRA	Adverse event 1 Alopecia and blemishes 3 Potassium > 5.5 mEq/L Others: 1 Blood pressure 98 mmHg 1 eGFR 28 mL/min/1.73 m^2 1 Improvement	Adverse event 1 Skin rash 1 Septic shock, pneumonia 2 Baseline creatinine > 50% and potassium > 5.5 mEq/L 1 Potassium > 5.5 mEq/L Others: 1 Withdrawn by local cardiologist

ACE inhibitors, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker; BB, beta-blockers; eGFR, estimated glomerular filtration rate HR, heart rate; MRA, mineralocorticoid receptor antagonist; SBP, systolic blood pressure

Table 16 of the supplementary data

Baseline measurement events (not caused by titration, but possibly influenced by it) and other events not associated with titration

Baseline measurement events /persisting at 4 mo	HF nurse n = 144	HF cardiologist n = 145	Diff. (95%CI)	*P*
Symptomatic arterial hypotension	1 (0.69)	1 (0.69)	0.00 (−1.91; 1.92)	> .99
Persistent	0 (0.00)	0 (0.00)		
Heart rate < 50 bpm	3 (2.08)	3 (2.07)	0.01 (−3.27; 3.30)	.99
Persistent	1 (0.69)	0 (0.00)	0.69 (−0.66; 2.05)	.32
Potassium > 5.5 mEq/L	6 (4.17)	1 (0.69)	3.48 (−0.05; 7.01)	.06
Persistent	2 (1.39)	0 (0.00)	1.39 (−0.52; 3.30)	.15
Total	10 (6.94)	5 (3.45)	3.50 (−1.61; 8.60)	.18
Persistent	3 (2.08)	0 (0.00)	2.08 (−0.25; 4.42)	.08
Other events not directly related to titration (prescription, other causes)	20 (13.89)	22 (15.17)	−1.28 (−9.41; 6.84)	.76

Table 17 of the supplementary data

Factors associated with baseline measurement events

Factors that can influence titration Baseline measurement events	HF nurse		HF cardiologist	
Heart rate < 50 bpm	2/3	1 Amiodarone 1 Digoxin + ablation	3/3	1 Ivabradine 2 Amiodarone
Potassium > 5.5 mEq/L	1/6	1 High fruit intake	0	
Total	3/9		3/3	

HF, heart failure.

Table 18 of the supplementary data

Admission causes, baseline to 6 months

Admissions	HF nurse N=144		HF Cardiologist N=145	
	No. (%)	Cause	No. (%)	Cause
HF admissions	1 (0.69)		9 (5.51)	
Admissions due to other unplanned CV causes	1 (0.69)	1 Symptomatic bradycardia and later another admission for scheduled pacemaker	2 (1.38)	2 Stroke
Admissions due to planned CV causes	10 (6.94)	1 Catheterization 1 Cardioversion 1 Pacemaker 4 Ablation: 3 AF/[F1], 1 VT 1 ICD 2 CRT	11 (7.59)	2 PH study and transplant 5 Catheterization 2 Ablation: 1 AF/[F1], 1 VT 1 ICD reimplantation 1 Amputation
Admissions due to unplanned non-CV causes	8 (5.56)	1 Gastrointestinal bleeding 1 Hematuria 1 Respiratory infection 1 Infection in arm 1 Worsening respiratory disease 1 Renal failure of unknown cause 1 Sigmoid adenocarcinoma 1 Pneumonia	13 (8.96)	1 Respiratory infection, fever 1 Ankle fracture 1 Septic shock due to pneumonia 1 Foot pain 4 Non-CV admissions and 1 unknown cause 1 Head trauma due to fall 1 Non-CV internal medicine 1 Acute gastroenteritis
Admissions due to planned non-CV causes	1 (0.69)	1 Dialysis catheter implantation	3 (2.07)	1 Urology procedure, neoplasm 1 Kidney biopsy 1 Inguinal hernia surgical procedure

CRT, cardiac resynchronization therapy; CV, cardiovascular; ICD, implantable cardioverter defibrillator; PH, pulmonary hypertension.

MULTIVARIATE MODELS

Test the overall effect of ETIFIC on an intention-to-treat basis, we compared the changes in outcome variables (BB, ACE inhibitors, ARB and MRA relative doses) between the 2 groups in the 2 follow-up measurements (baseline and 4-month values), adjusted by the reference values (baseline values).

Generalized mixed longitudinal models were used to take into account that they were repeated measurements for each patient, as well as the hierarchical structure of the data, with patients nested in hospitals (SAS PROC MIXED ver. 9.4, SAS Institute, Cary, NC, United States).

These models were linear for the changes in BB, ACE inhibitors, ARB and MRA mean relative doses. Time evolution was considered to be a categorical variable in these models, with various correlated measurements for each individual. This last option was chosen as it is less restrictive and provided a better fit to our data.

The ETIFIC intervention, measurement time and time by intervention interaction were included in the models as fixed effects. Patients and centers were included as random effects in the intercept and in the slope of the different repeated measurements.

These models were also adjusted by the reference values of the outcome variables. Different covariance structures were used for repeated observations in the same patient and center, and restricted maximum likelihood procedure was used to determine the best covariance structure for our data. Equally, maximum likelihood procedure using the forward, backward and stepwise methods (significance criteria, $P < .05$) was used to simplify the fixed effects structure.

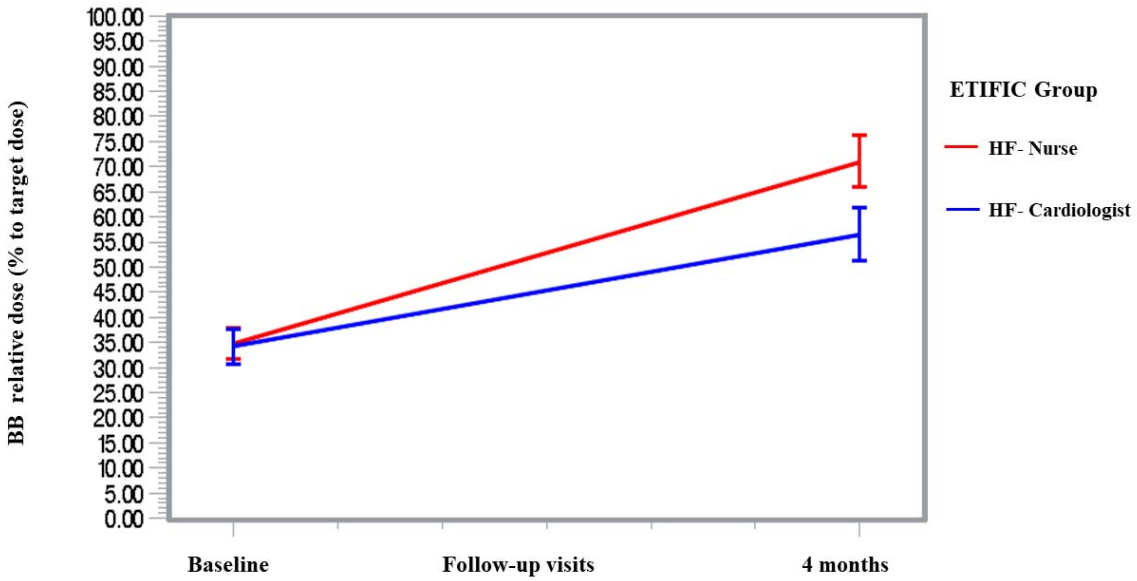
We assessed the overall effect of the ETIFIC program, testing the interaction between the intervention and measurement time. When this intervention by time interaction was significant (significance criteria, $P < .05$), planned contrasts were used to determine whether the changes between the baseline and follow-up at 4 months in the ETIFIC intervention group were significantly different to those observed in the control group ($P < .05$).

In addition to the random structure mentioned above, the random effects on the effect of the ETIFIC program at the center level were included to verify whether the effect attributable to the intervention varied between centers. Empirical Bayes estimators were calculated for each center, followed by a sensitivity analysis to assess the changes after excluding those centers whose populations significantly differed from the general average. Given the asymmetry of the continuous result variables, the sensitivity analysis was repeated, excluding those patients considered as possible atypical values, that is, those who exceeded 2 standard deviations.

No imputation methods were used to handle the missing data, since the mixed longitudinal models based on the maximum likelihood estimation used in this article are more appropriate for handling the missing data [Verbeke G, Molenberghs G (2000) Mixed linear models for longitudinal data. New York: Springer] than common imputation methods, as shown in the last observation, complete case analysis or other possible forms of imputation.

Figure 1 of the supplementary data

Trend in BB relative dose (baseline-4 months).



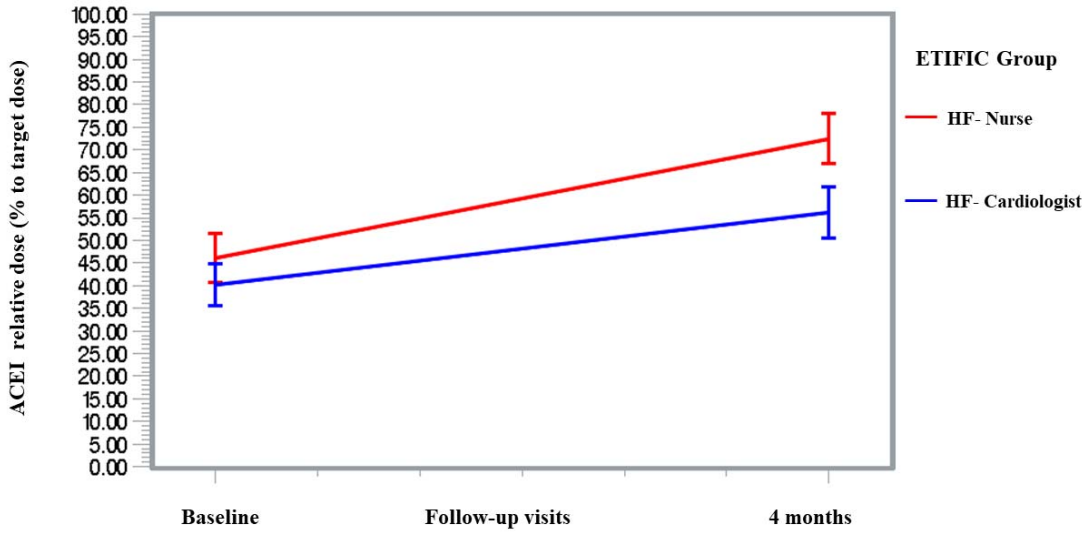
Multivariate models: beta-blockers. The graph shows the trend for the average value of the relative BB dose at the patient level; both groups started at a similar level and the ETIFIC nurse group slope is higher than that of the ETIFIC cardiologist group.

The variables introduced in the model were: group (ETIFIC nurse vs ETIFIC cardiologist), visit (baseline-4 months), group interaction by visit, relative BB dose at baseline visit, age (in years), sex (female vs male), patient education up to 10 years, chronic obstructive pulmonary disease, atrial fibrillation, ischemic heart disease, diabetes mellitus, baseline heart rate, baseline SBP, glomerular filtration rate, left ventricular ejection fraction, estimated glomerular filtration rate change (unchanged or improves vs deteriorates), baseline NT-proBNP, correct self-care, drugs at baseline visit:

combination of 3 drugs (BB, ACE inhibitors/ARB, MRA), rate-lowering drugs, amiodarone, ivabradine, digoxin, hypo- and hyperthyroidism therapies, inhaled bronchodilators, alpha-blockers, calcium-channel blockers, use of nitrates/hydralazine, use of diuretics, use of psychotropic drugs (hypnotics, neuroleptics, anxiolytics, antidepressants), mild events occurring during the titration process (yes vs no), number of visits with the professional who titrated. ACE inhibitors, angiotensin converting-enzyme inhibitors; ARB, angiotensin receptor blockers, BB, beta-blocker; HF, heart failure; MRA, mineralocorticoid receptor antagonist.

Figure 2 of the supplementary data

Trend in ACE inhibitor relative dose (baseline-4 months).

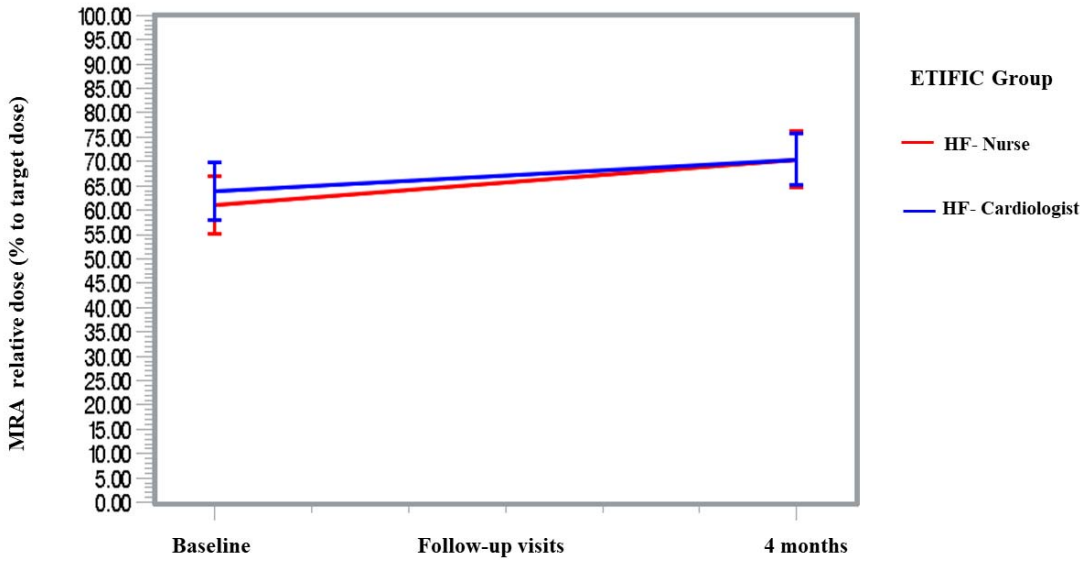


Multivariate models: ACE inhibitors. The graph shows the trend in the average value of the relative ACE inhibitors dose at the patient level. The average in patients in the ETIFIC nurse group at the baseline visit is higher than that of the ETIFIC cardiologist group and, additionally, the ETIFIC nurse group slope is higher than that of the ETIFIC cardiologist group. The variables introduced in the model were: group (ETIFIC nurse vs ETIFIC cardiologist), visit (baseline-4 months), group interaction by visit, relative ACE inhibitors dose at baseline visit, age (in years), sex (female vs male), patient education up to 10 years, chronic obstructive pulmonary disease, atrial fibrillation, ischemic heart disease, diabetes mellitus, baseline heart rate, baseline SBP, glomerular filtration rate, left ventricular ejection fraction, baseline potassium (>5.5 mEq/L), estimated glomerular filtration rate change (unchanged or improves vs deteriorates), baseline NT-proBNP, correct self-care, drugs at baseline visit: combination of 3 drugs (BB, ACE inhibitors /ARB, MRA), bradycardia-inducing drugs, amiodarone, ivabradine, digoxin, hypo- and hyperthyroidism therapies, inhaled

bronchodilators, alpha-blockers, calcium-channel blockers, use of nitrates/hydralazine, use of diuretics, use of psychotropic drugs (hypnotics, neuroleptics, anxiolytics, antidepressants), mild events occurring during the titration process (yes vs no), number of visits with the professional who titrated. ACE inhibitors, angiotensin converting-enzyme inhibitors; ARB, angiotensin receptor blockers, BB, beta-blocker; HF, heart failure; MRA, mineralocorticoid receptor antagonist.

Figure 3 of the supplementary data

Trend in MRA relative dose (baseline-4 months).

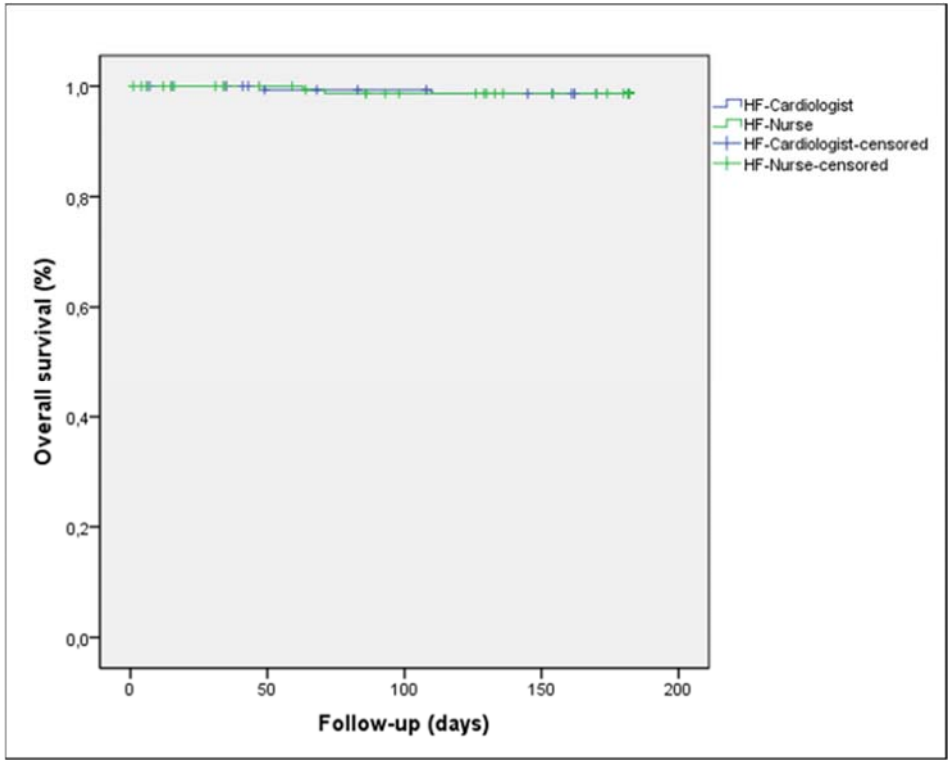


Multivariate models: MRA. The graph shows the trend in the average value of the relative MRA dose at patient level. The average of patients in the ETIFIC nurse group at the baseline visit was slightly lower than that of the ETIFIC cardiologist group, and the observed ETIFIC nurse group slope is similar to that of the ETIFIC cardiologist group. The variables introduced in the model were: group (ETIFIC nurse vs ETIFIC cardiologist), visit (baseline-4 months), group interaction by visit, relative MRA dose at baseline visit, age (in years), sex (female vs male), patient education up to 10 years, chronic obstructive pulmonary disease, atrial fibrillation, ischemic heart disease, diabetes mellitus, baseline heart rate, baseline SBP, estimated glomerular filtration rate, LVEF, baseline potassium (>5.5 mEq/L), estimated glomerular filtration rate change (unchanged or improves vs deteriorates), baseline NT-proBNP, correct self-care, drugs at baseline visit: combination of 3 drugs (BB, ACE inhibitors /ARB, MRA), bradycardia-inducing drugs, amiodarone, ivabradine, digoxin, hypo- and hyperthyroidism therapies, inhaled bronchodilators, alpha-blockers, calcium-channel

blockers, use of nitrates/hydralazine, use of diuretics and use of psychotropic drugs (hypnotics, neuroleptics, anxiolytics, antidepressants), mild events occurring during the titration process (yes vs no), number of visits with titrating professional. ACE inhibitors, angiotensin converting-enzyme inhibitors; ARB, angiotensin receptor blockers, BB, beta-blocker; HF, heart failure; MRA, mineralocorticoid receptor antagonist.

Figure 4 of the supplementary data

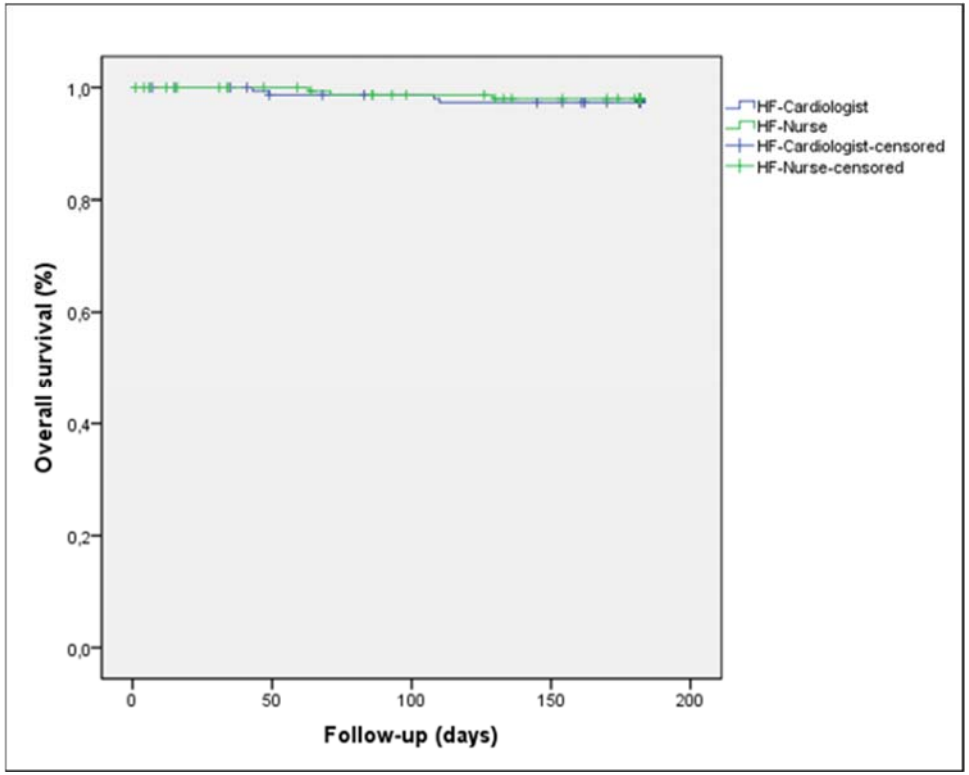
Kaplan Meier curves for cardiovascular mortality.



There were no differences in the 6-month survival rate between the 2 groups (HF cardiologist vs HF nurse), which was 98.6% and 98.7%, respectively (*P* = .98). HF, heart failure.

Figure 5 of the supplementary data.

Kaplan Meier curves for all-causes mortality.



There were no differences in the 6-month survival rate between the 2 groups (HF cardiologist vs HF nurse), which was 97.3% and 98.0%, respectively (*P* = .16).

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