SUPPLEMENTARY DATA

Statistical analysis

The effect size, calculated as the standardized mean difference (Cohen's d),[1] served as the basis for estimating the sample size using a 2-sample *t*-test comparing mean NT-proBNP levels at 6 months between the ARNI maintenance and de-escalation groups. Although the effect size of 0.4 was derived from the NT-proBNP level at 6 months in the continuation and withdrawal groups of the TRED-HF study,[2,3] we expected an effect size of 0.6 based on investigator judgment and clinical expectations in our study. Assuming an effect size of 0.6, a significance level of 0.05 and statistical power of 80%, the required sample size was calculated to be 45 participants per group. Considering a dropout rate of 10%, this study planned to recruit a total of 100 participants (50 participants per group). The block randomization table was made using the SAS program (version 9.4).

Data for continuous variables are presented as the mean ± standard deviation or median [interquartile range], as appropriate based on the normality of their distribution. Categorical variables are described as numbers and relative frequencies (%). Group comparisons were performed using the Student *t*-test or the Mann-Whitney U test for continuous variables, and the chi-square test or Fisher exact test for categorical variables. To evaluate within-group changes from baseline to follow-up, paired *t*-tests or Wilcoxon signed-rank tests were used for continuous and ordinal variables, and the McNemar test was applied for paired binary categorical variables. The Shapiro-Wilk test was used to test the normality assumption for continuous variables.

For the analysis of longitudinal primary outcomes measured at 6 and 12 months, a linear mixed-effects model was used to evaluate the interaction between treatment allocation and timepoint on log-transformed NT-proBNP levels, adjusting for age, sex, ischemic etiology, atrial fibrillation, and chronic kidney disease, with a random intercept specified for each participant. The significance of fixed effects was assessed using the Wald test. Furthermore, given the nonnormal distribution of the 12-month-to-baseline NT-proBNP ratio, a Box-Cox transformation ($\lambda = 0.356$) was performed, and linear regression models were subsequently used to assess interactions between treatment allocation and

baseline characteristics.

To assess group-by-timepoint interaction effects for other clinical endpoints, including New York Heart Association class, medication use, and echocardiographic parameters, generalized linear mixed-effects models and linear mixed-effects models were applied to binary and continuous outcomes, respectively.

Statistical analyses were performed using R statistical software (version 4.1.0; R Foundation for Statistical Computing, Vienna, Austria), with a 2-sided *P* value < 0.05 considered statistically significant.

Table S1 Assignment table

No.	Assignment	
1	valsartan	participation
2	sacubitril/valsartan	participation
3	valsartan	participation
4	sacubitril/valsartan	participation
5	valsartan	participation
6	sacubitril/valsartan	participation
7	valsartan	Participation
8	sacubitril/valsartan	Refuse
9	valsartan	Participation
10	sacubitril/valsartan	Participation
11	valsartan	Participation
12	valsartan	Participation
13	sacubitril/valsartan	Participation
14	valsartan	Participation
15	sacubitril/valsartan	Participation
16	sacubitril/valsartan	Participation
17	sacubitril/valsartan	Participation
18	sacubitril/valsartan	Participation
19	sacubitril/valsartan	Participation
20	valsartan	Participation
21	sacubitril/valsartan	Participation
22	valsartan	Participation
23	valsartan	Participation

24	valsartan	Participation
25	valsartan	participation
26	sacubitril/valsartan	participation
27	sacubitril/valsartan	participation
28	valsartan	participation
29	valsartan	participation
30	valsartan	participation
31	sacubitril/valsartan	participation
32	sacubitril/valsartan	participation
33	sacubitril/valsartan	participation
34	sacubitril/valsartan	participation
35	valsartan	participation
36	sacubitril/valsartan	participation
37	valsartan	participation
38	sacubitril/valsartan	participation
39	valsartan	participation
40	valsartan	participation
41	sacubitril/valsartan	participation
42	valsartan	participation
43	valsartan	participation
44	sacubitril/valsartan	participation
45	valsartan	participation
46	sacubitril/valsartan	participation
47	sacubitril/valsartan	participation
48	valsartan	participation

49	valsartan	participation
50	sacubitril/valsartan	participation
51	sacubitril/valsartan	participation
52	valsartan	participation
53	sacubitril/valsartan	participation
54	valsartan	participation
55	sacubitril/valsartan	participation
56	valsartan	participation
57	sacubitril/valsartan	participation
58	sacubitril/valsartan	participation
59	valsartan	participation
60	valsartan	participation
61	valsartan	participation
62	valsartan	participation
63	sacubitril/valsartan	refuse
64	sacubitril/valsartan	participation
65	valsartan	participation
66	sacubitril/valsartan	participation
67	sacubitril/valsartan	participation
68	sacubitril/valsartan	participation
69	valsartan	participation
70	sacubitril/valsartan	participation
71	valsartan	participation
72	valsartan	participation
73	sacubitril/valsartan	participation

74	valsartan	participation
75	valsartan	participation
76	valsartan	participation
77	sacubitril/valsartan	participation
78	valsartan	refuse
79	sacubitril/valsartan	participation
80	sacubitril/valsartan	participation
81	sacubitril/valsartan	participation
82	valsartan	participation
83	sacubitril/valsartan	participation
84	valsartan	participation
85	sacubitril/valsartan	participation
86	valsartan	participation
87	sacubitril/valsartan	participation
88	valsartan	participation
89	valsartan	participation
90	sacubitril/valsartan	participation
91	sacubitril/valsartan	participation
92	valsartan	participation
93	valsartan	participation
94	valsartan	participation
95	sacubitril/valsartan	participation
96	sacubitril/valsartan	participation
97	sacubitril/valsartan	participation
98	valsartan	participation

99	sacubitril/valsartan	participation
100	valsartan	participation
101	sacubitril/valsartan	participation
102	sacubitril/valsartan	participation
103	valsartan	participation

Table S2. Reasons for medication switch to ARNI in de-escalation group

No.	Reason for medication change
1	Creatinine level worsens from normal to 1.27 mg/dL and symptoms worsen from NYHA class I to II
2	Complaints of nausea and difficulty breathing
3	No worsening of objective indicators or worsening of symptoms, but attending physician decision

ARNI, angiotensin receptor-neprilysin inhibitor; NYHA, New York Heart Association.

Table S3. Sensitivity analysis: change in NT-proBNP (pg/mL) during follow-up period among patients without CRT

	Population	Whole population (n = 75)	De-escalation group Intention-to-treat: n = 34 Per-protocol: n = 41	Maintenance group Intention-totreat: n = 31 Per protocol: n = 41	*P*	*Adjusted P*
Baseline	Intention-to-treat (n = 75)	51.3 [23.0-104.5]	37.3 [21.4-123.0]	53.0 [30.4-91.6]	.911	.999
	Per-protocol (n = 72)	49.5 [21.9-94.8]	33.3 [21.4-98.2]	53.0 [30.4-91.6]	.513	.999
6 mo	Intention-to-treat (n = 75)	40.2 [14.9-109.0]	41.5 [17.8-99.0]	37.9 [14.1-109.0]	.649	.999
	Per-protocol (n = 72)	35.4 [13.8-99.0]	35.1 [13.8-92.1]	37.9 [14.1-109.0]	.915	.999
12 mo	Intention-to-treat (n = 75)	51.8 [19.1-114.0]	52.9 [26.3-120.0]	50.7 [19.0-88.3]	.590	.999
	Per-protocol (n = 72)	49.7 [19.1-90.4]	47.9 [24.0-112.0]	50.7 [19.0-88.3]	.880	.999

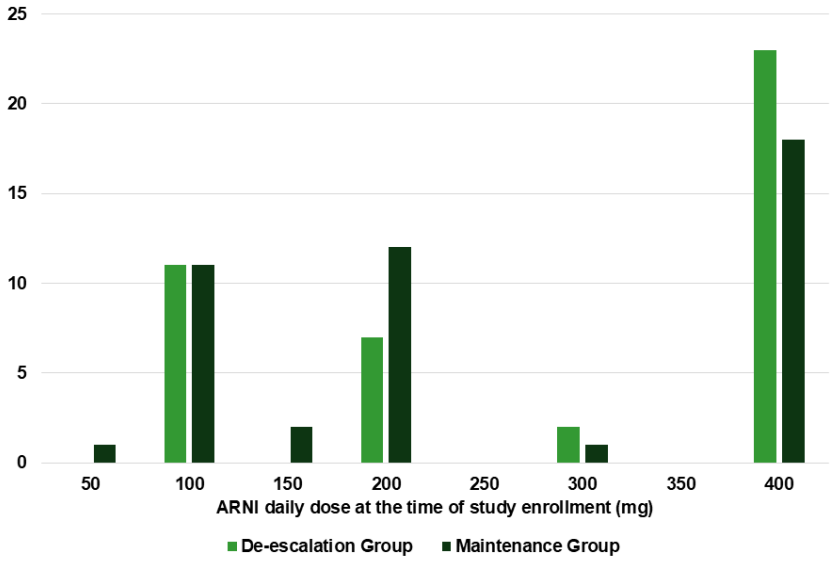
CRT, cardiac resynchronization therapy; NT-proBNP, N-terminal pro b-type natriuretic peptide.

Data are presented as median [25th percentile-75th percentiles].

P-values were calculated using the Mann-Whitney U test. Adjusted *P*-values were derived using the Bonferroni correction to account for multiple comparisons among the 3 timepoints.

FIGURE LEGENDS

Figure S1. ARNI daily dose at the time of study enrolment.



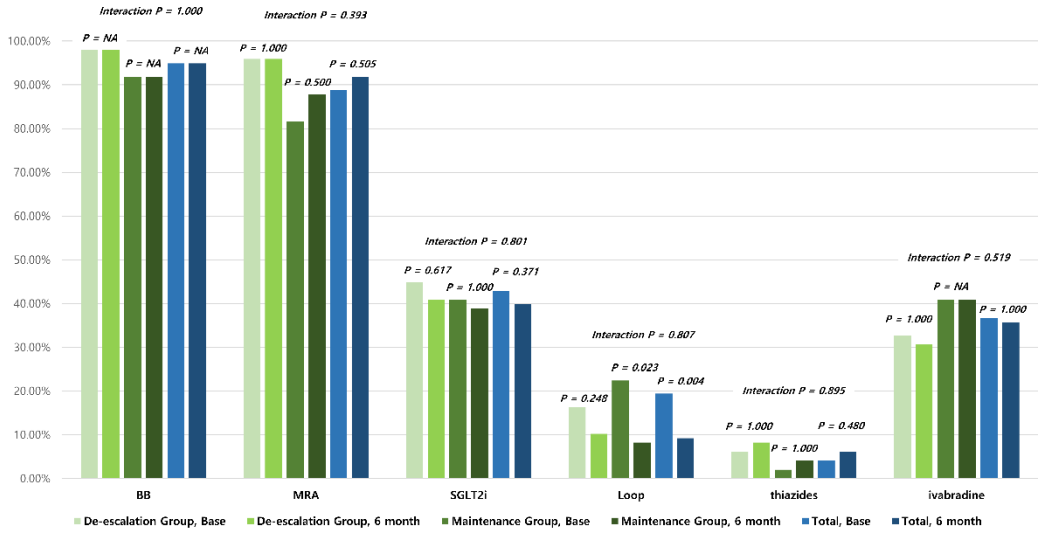
ARNI, angiotensin receptor-neprilysin inhibitor

Correcciones a la figura

Cambiar "enrollment" a "enrolment"

Cambiar "Group" a "group"

Figure S2. Changes in medication use over time in the de-escalation and maintenance groups**.**



BB, beta-blocker; MRA, mineralocorticoid receptor antagonist; SGLT-2 inhibitor, sodium-glucose cotransporter 2 inhibitor.

Within-group changes (*P*) in medication use over time were evaluated using the McNemar test. Interaction effects between group and timepoint (Interaction *P*) were assessed using generalized linear mixed-effects models.

Correcciones a la figura

Cambiar "Group" a "group"

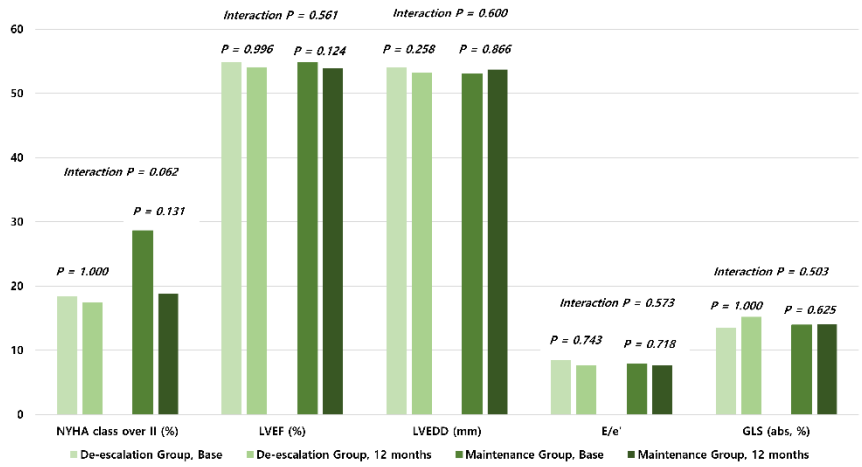
Eje vertical: Cambiar "thiazides" a "Thiazides" y "ivabradine" a "Ivabradine"

Cambiar "*P* = 1.000" a "*P* = .999"

Cambiar "Base" a "baseline"

Quitar zero delante del punto decimal en los valores de P

Figure S3. Distribution of symptom scale and echocardiographic parameters over 12 months in the de-escalation and maintenance groups (related to table 5).



Within-group changes (*P*) over time were evaluated using McNemar's test for paired binary categorical variables and the Wilcoxon signed-rank test for continuous variables. Interaction effects between group and timepoint (Interaction *P*) were assessed using generalized linear mixed-effects models for binary outcomes and linear mixed-effects models for continuous outcomes.

GLS, global longitudinal strain; LVEDD, left ventricular end diastolic dimension; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association

Correcciones a la figura

Cambiar "Group" a "group"

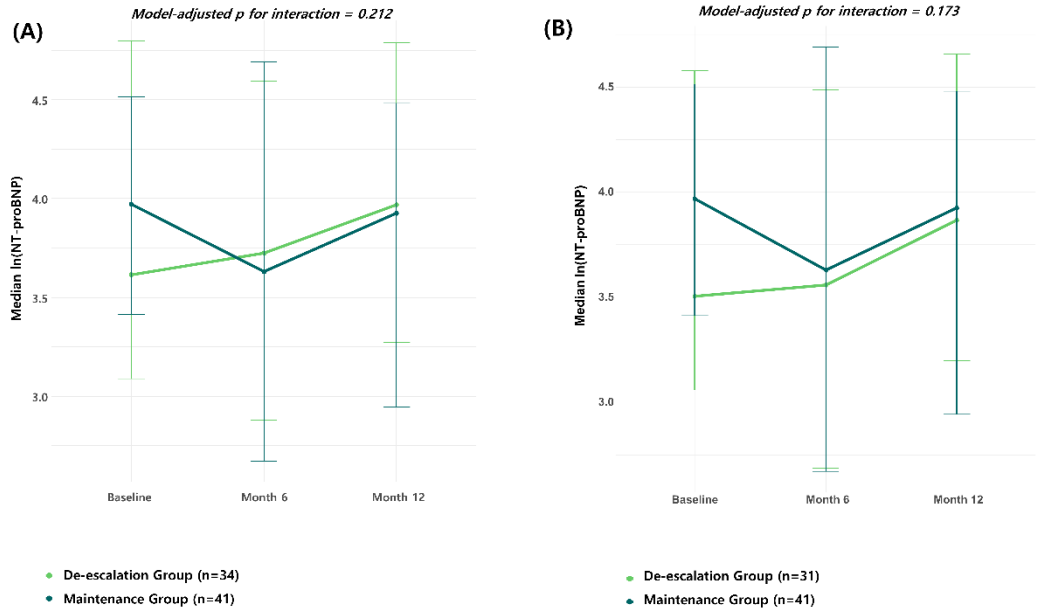
Eje vertical: Cambiar "over II" a "> II"

Cambiar "*P* = 1.000" a "*P* = .999"

Cambiar "Base" a "baseline"

Quitar zero delante del punto decimal en los valores de P

Figure S4. Sensitivity analysis: longitudinal changes in ln(NT-proBNP) levels among patients without CRT according to treatment strategy. (A) Intention-to-treat analysis (n = 75); (B) per-protocol analysis (n = 72).



CRT, cardiac resynchronization therapy; NT-proBNP, N-terminal pro b-type natriuretic peptide.

Cambiar “Group” a “group”

Poner espacios a ambos lados de “=”

Cambiar “p for” a “*P* for”

REFERENCES OF THE SUPPLEMENTARY DATA

1. Cohen J. Statistical Power Analysis for the Behavioral Sciences. Burlington: Elsevier Science; 2013.
2. Halliday BP, Wassall R, Lota AS, et al. Withdrawal of pharmacological treatment for heart failure in patients with recovered dilated cardiomyopathy (TRED-HF): an open-label, pilot, randomised trial. *Lancet.* 2019;393:61-73.
3. Aoki S. Effect sizes of the differences between means without assuming variance equality and between a mean and a constant. *Heliyon.* 2020;6.