

# Safety of sacubitril/valsartan initiated during hospitalization: data from a non-selected cohort

Juan Carlos López-Azor<sup>1</sup>, Lourdes Vicent<sup>1</sup>, María Jesús Valero-Masa<sup>1</sup>, Alberto Esteban-Fernández<sup>2</sup>, Manuel Gómez-Bueno<sup>3</sup>, Ángel Pérez<sup>4</sup>, Pablo Díez-Villanueva<sup>5</sup>, Javier De-Juan<sup>6</sup>, Ángel Manuel-Iniesta<sup>7</sup>, Ramón Bover<sup>8</sup>, Susana del Prado<sup>6</sup> and Manuel Martínez-Sellés<sup>1,9\*</sup>

<sup>1</sup>Servicio de Cardiología, Hospital Universitario Gregorio Marañón, CIBERCV, Calle Doctor Esquerdo, 46, 28007, Madrid, Spain; <sup>2</sup>Servicio de Cardiología, Hospital Universitario de Móstoles, Madrid, Spain; <sup>3</sup>Servicio de Cardiología, Hospital Universitario Puerta de Hierro, CIBERCV, Madrid, Spain; <sup>4</sup>Servicio de Cardiología, Hospital de Burgos, Burgos, Spain; <sup>5</sup>Servicio de Cardiología, Hospital de La Princesa, Madrid, Spain; <sup>6</sup>Servicio de Cardiología, Hospital Universitario 12 de Octubre, Madrid, Spain; <sup>7</sup>Servicio de Cardiología, Hospital Universitario La Paz, Madrid, Spain; <sup>8</sup>Servicio de Cardiología, Hospital Universitario Clínico de San Carlos. Instituto de Investigación Sanitaria del Hospital Clínico San Carlos (IdiSSC), Madrid, Spain; and <sup>9</sup>Servicio de Cardiología, Universidad Complutense, Universidad Europea, Madrid, Spain

## Abstract

**Aims** Sacubitril/valsartan is safe when initiated during hospitalization in a clinical trial setting. Its safety in real-life population is not established. We compared the initiation of sacubitril/valsartan during hospitalization in a non-selected population, in the PIONEER-HF trial, and in non-selected outpatients.

**Methods and results** Multicentre registry included 527 patients: 100 were started on sacubitril/valsartan during hospitalization (19.0%) and 427 as outpatients (81.0%). Compared with those in the pivotal trial, inpatients in our cohort were older ( $71 \pm 12$  vs.  $61 \pm 14$  years;  $P < 0.001$ ); had more frequently Functional Class II (41 [41.0%] vs. 100 [22.7%];  $P < 0.001$ ), higher levels of N-terminal pro-B type natriuretic peptide (4044 [1630–8680] vs. 2013 [1002–4132] pg/mL;  $P < 0.001$ ), better glomerular filtration rate ( $63.5$  [51.0–80.0] vs.  $58.4$  [47.5–71.5] mL/min;  $P = 0.01$ ), and higher systolic blood pressure ( $121$  [110–136] vs.  $118$  [110–133] mmHg;  $P = 0.03$ ); and received angiotensin-converting enzyme inhibitors/angiotensin receptor blockers more frequently (92 [92.0%] vs. 208 [52.7%];  $P < 0.001$ ). Compared with non-selected outpatients, inpatients were older ( $71 \pm 12$  vs.  $68 \pm 12$  years,  $P = 0.02$ ), had more frequent Functional Class III–IV (58 [58.0%] vs. 129 [30.3%],  $P < 0.001$ ), had higher levels of N-terminal pro-B type natriuretic peptide (4044 [1630–8680] vs. 2182 [1134–4172];  $P < 0.001$ ), and were receiving angiotensin-converting enzyme inhibitors/angiotensin receptor blockers target dose less frequently (55 [55.0%] vs. 335 [78.5%];  $P < 0.001$ ). They also started sacubitril/valsartan with a low dose (50 mg/12 h) more frequently (80 [80.0%] vs. 209 [48.8%],  $P < 0.001$ ). The initiation of sacubitril/valsartan in outpatients was an independent predictor of high-dose use (OR 3.1; 95% confidence interval 1.7–5.6,  $P < 0.001$ ). The follow-up time in both cohorts, including all patients enrolled, was similar ( $7.0 \pm 0.1$  vs.  $7.2 \pm 2.6$  months,  $P = 0.72$ ). All-cause admissions during follow-up were more frequent in inpatients (30 [30.0%] vs. 68 outpatients [15.9%],  $P = 0.001$ ), with no relevant differences in all-cause mortality. There was no significant difference in sacubitril/valsartan withdrawal rate (17 inpatients [17.0%] vs. 49 outpatients [11.5%],  $P = 0.13$ ). The incidence of adverse effects was also similar: hypotension (16 inpatients [16.0%] vs. 71 outpatients [16.7%],  $P = 0.88$ ), worsening renal function (7 inpatients [7.0%] vs. 29 outpatients [6.8%],  $P = 0.94$ ), and hyperkalaemia (1 inpatient [1.0%] vs. 21 outpatients [4.9%],  $P = 0.09$ ). We did not register any case of angioedema.

**Conclusions** It is safe to initiate sacubitril/valsartan during hospitalization in daily clinical practice. Inpatients have a higher risk profile and receive low starting doses more frequently than outpatients.

**Keywords** Heart failure; Sacubitril/valsartan; Reduced ejection fraction; Hospitalization

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\*Correspondence to: Manuel Martínez-Sellés, Servicio de Cardiología, Hospital Universitario Gregorio Marañón, CIBERCV, Calle Doctor Esquerdo, 46, 28007 Madrid, Spain. Email: mmselles@secardiologia.es

## Introduction

Sacubitril/valsartan combines an angiotensin receptor blocker with a neprilysin inhibitor. This treatment has changed the management of heart failure with reduced ejection fraction, demonstrating to be more effective than enalapril in reducing cardiovascular mortality and hospital admission when started in a stable phase in outpatients.<sup>1</sup> Two randomized studies have recently found that sacubitril/valsartan is safe when initiated during admission. This will predictably permit to extend its use to inpatients.<sup>2,3</sup> However, the profile of patients included in clinical trials often differs from that of real clinical practice, limiting the extrapolation of results to heterogeneous populations. In this framework, Phase 4 studies are necessary.

The first aim of our study is to compare the characteristics and clinical profile of a non-selected cohort of patients who initiate sacubitril/valsartan during hospital admission with those included in PIONEER-HF trial (Comparison of Sacubitril-Valsartan versus Enalapril on Effect on N-terminal pro-B type natriuretic peptide in Patients Stabilized from an Acute Heart Failure Episode).<sup>2</sup> The second objective of our work is to compare the safety and tolerance of sacubitril/valsartan in two real-life cohorts. In one,

sacubitril/valsartan was initiated during hospital admission and in the other in outpatients.

## Methods

We performed a multicentre registry with prospective follow-up in 17 Spanish hospitals including all the patients with heart failure with reduced ejection fraction who initiated sacubitril/valsartan. The inclusion was performed in two phases: outpatients who initiated sacubitril/valsartan were included from October 2016 to March 2017, and inpatients from December 2017 to May 2018. Hospitals recruiting patients in the registry were grouped in three categories: heart transplant hospitals (48%), hospitals  $\geq 1000$  beds without heart transplant (33%), and medium/small-sized hospitals (19%). We recorded demographic variables and medical background including prior treatment, baseline New York Heart Association functional class, vital signs, laboratory results, and left ventricular ejection fraction at inclusion. The indication of sacubitril/valsartan was made by the local cardiologist according to the specifications of the European Medicines Agency: heart failure with reduced ejection fraction,

**Table 1** Comparison of baseline characteristics of our inhospital non-selected cohort with those of the PIONEER-HF (Comparison of Sacubitril-Valsartan versus Enalapril on Effect on NT-proBNP in Patients Stabilized from an Acute Heart Failure Episode) trial<sup>2</sup>

	Non-selected inhospital cohort <i>n</i> = 100	PIONEER-HF <i>n</i> = 440	<i>P</i>
Age, years	71 (65–80)	61 (51–71)	<0.001
Female	16 (16.0)	113 (25.7)	0.03
Hypertension	79 (79.0)	384 (87.3)	0.04
Diabetes	53 (53.0)	79 (18.0)	<0.001
Dyslipidaemia	64 (64.0)	159 (36.1)	<0.001
Smoking	17 (17.0)	92 (20.9)	0.49
LVEF, %	28 (21–32)	24 (18–30)	0.03
Systolic blood pressure, mmHg	121 (110–136)	118 (110–133)	0.03
Heart rate, b.p.m.	71 (63–84)	81 (72–92)	<0.001
NYHA functional class			<0.001
I	1 (1.0)	4 (0.9)	
II	41 (41.0)	100 (22.7)	
III	45 (45.0)	283 (64.3)	
IV	13 (13.0)	39 (8.9)	
Serum creatinine, mg/dL	1.08 (0.90–1.32)	1.28 (1.07–1.51)	0.02
Estimated GFR, mL/min	63.5 (51.0–80.0)	58.4 (47.5–71.5)	0.01
Serum potassium, mmol/L	4.22 (4.00–4.6)	4.20 (4.00–4.50)	0.89
NT-proBNP, ng/mL	4044 (1630–8680)	2883 (1610–5403)	<0.001
Prior treatment			
ACE inhibitor or ARB <sup>a</sup>	92 (92.0)	208 (47.3)	<0.001
Beta-blocker	88 (88.0)	262 (59.5)	<0.001
MRA	46 (46.0)	48 (10.9)	<0.001
ICD	29 (29.0)	80 (18.2)	0.01
CRT	9 (9.0)	43 (9.8)	0.80

*n* (%) for categorical variables and median (inter-quartile range) for continuous variables.

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CRT, cardiac resynchronization therapy; GFR, glomerular filtration rate; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B type natriuretic peptide; NYHA, New York Heart Association; SV, sacubitril/valsartan.

<sup>a</sup>No patient received both drugs.

Functional Class  $\geq$  II, and systolic blood pressure  $\geq$  100 mmHg and with serum potassium  $\leq$  5.4 mmol/L.<sup>4</sup> At least one consultation was scheduled in the first month after the initiation of sacubitril/valsartan in which vital signs and laboratory results were recorded. In the subsequent follow-up, we recorded functional class, left ventricular ejection fraction, treatment changes and titration, de-escalation or removal of sacubitril/valsartan, potential adverse effects attributed to sacubitril/valsartan (symptomatic hypotension, renal failure, hyperkalaemia, and angioedema), unexpected hospital

admissions, and all-cause death. The TITRATION 'conservative' regimen was recommended to start and uptitrate sacubitril/valsartan.<sup>5</sup> General patient management was carried out according to the recommendations of the clinical practice guidelines for heart failure with reduced ejection fraction.<sup>6,7</sup>

The investigation conforms with the principles outlined in the *Declaration of Helsinki* and was approved by the ethics committee of the coordinating centre (Hospital General

**Table 2** Comparison of the characteristic of non-selected inpatients and outpatients who initiated sacubitril/valsartan

	Inpatients n = 100	Outpatients n = 427	Total n = 527	P
<b>Baseline characteristics</b>				
Age, years	71 (65–80)	69 (61–77)	70 (62–78)	0.02
Female	16 (16.0)	126 (29.5)	142 (26.9)	0.006
Hypertension	79 (79.0)	317 (74.2)	396 (75.1)	0.37
Diabetes	53 (53.0)	170 (39.8)	223 (42.3)	0.02
Dyslipidaemia	64 (64.0)	278 (65.1)	342 (65.0)	0.93
Smoking	17 (17.0)	110 (25.8)	127 (24.1)	0.07
Obesity	21 (21.0)	106 (24.9)	127 (24.2)	0.52
Ischaemic heart disease	66 (66.0)	225 (52.8)	291 (55.3)	0.02
LVEF, %	28.0 (21.0–32.0)	30.0 (25.0–35.0)	30.0 (25.0–34.0)	0.04
Systolic blood pressure, mmHg	121 (110–136)	120 (105–130)	120 (106–130)	0.17
Diastolic blood pressure, mmHg	70 (61–77)	70 (62–78)	70 (62–78)	0.51
Heart rate, b.p.m.	71 (63–84)	66 (60–75)	67 (60–75)	<0.001
Hospitalization 6 months before inclusion	38 (38.0)	162 (37.9)	200 (38.0)	0.13
HF admission 6 months before inclusion	27 (27.0)	99 (23.2)	126 (23.9)	0.08
NYHA functional class				<0.001
I	1 (1.0)	5 (1.2)	6 (1.1)	
II	41 (41.0)	292 (68.5)	333 (63.3)	
III	45 (45.0)	115 (27.0)	160 (30.4)	
IV	13 (13.0)	14 (3.3)	27 (5.1)	
Serum creatinine, mg/dL	1.1 (0.9–1.3)	1.1 (0.9–1.4)	1.1 (0.9–1.4)	0.46
Estimated GFR, mL/min	63.5 (51.0–80.0)	60.0 (45.8–76.0)	60.0 (47.9–77.0)	0.04
Serum potassium, mmol/L	4.2 (4.0–4.6)	4.5 (4.2–4.9)	4.5 (4.2–4.8)	<0.001
NT-proBNP, ng/mL	4044 (1630–8680)	2013 (1002–4132)	2263 (1060–4764)	<0.001
<b>Previous treatment</b>				
ACE inhibitor	60 (60.0)	293 (69.4)	353 (67.6)	0.07
ARB	32 (32.0)	111 (26.4)	142 (27.4)	0.3
High dose of ACE inhibitor/ARB*	55 (55.0)	335 (78.5)	390 (74.0)	<0.001
Naïve for ACE inhibitors/ARB	8 (8.0)	21 (4.9)	29 (5.5)	0.05
Beta-blocker	88 (88.9)	388 (91.5)	476 (91.0)	0.42
MRA	72 (72.0)	259 (61.4)	331 (63.5)	0.02
ICD	29 (29.0)	230 (54.3)	259 (49.4)	<0.001
CRT	9 (9.0)	109 (25.9)	118 (22.7)	<0.001
<b>Starting dose of SV</b>				
50 mg b.i.d.	80 (80.0)	209 (48.8)	289 (54.8)	<0.001
100 mg b.i.d.	20 (20.0)	183 (42.8)	203 (38.5)	
200 mg b.i.d.	0 (0.0)	35 (8.2)	35 (6.6)	
<b>Adverse effects</b>				
Hypotension	16 (16.0)	71 (16.7)	87 (16.5)	0.88
Renal failure	7 (7.0)	29 (6.8)	36 (6.8)	0.94
Hyperkalaemia	1 (1.0)	21 (4.9)	22 (4.2)	0.09
Angioedema	0	0	0	1.00
<b>Mortality and readmissions</b>				
All-cause death	5 (5.0)	12 (2.8)	17 (3.2)	0.34
Cardiovascular death	1 (1.0)	9 (2.1)	10 (1.9)	0.70
Hospital admissions	30 (30.0)	68 (15.9)	98 (18.6)	0.001
Discontinuation of SV	17 (17.0)	49 (11.5)	66 (12.5)	0.13

n (%) for categorical variables and median (inter-quartile range) for continuous variables.

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CRT, cardiac resynchronization therapy; GFR, glomerular filtration rate; HF, heart failure; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B type natriuretic peptide; NYHA, New York Heart Association; SV, sacubitril/valsartan.

\*Equivalent to a total daily dose of  $\geq$  10 mg of enalapril or  $\geq$  160mg of valsartan

Universitario Gregorio Marañón). Patients included signed informed consent.

## Statistical methods

Continuous variables are summarized using the median and inter-quartile range. Categorical variables are expressed as frequencies and percentages. Categorical variables are compared using the  $\chi^2$  test or Fisher's exact test. Student's *t*-test, Mann–Whitney U-test, or the paired *t*-test is used to compare continuous variables.

A statistical modelling simulation was used to generate a population of random numbers with a distribution superimposable to patients randomized to sacubitril/valsartan in PIONEER-HF trial ( $n = 440$ ). Data and variables of PIONEER-HF were extracted from the supplementary material published. After this process, the simulated cohort and our cohort of inpatients were compared.<sup>8,9</sup>

We performed a multivariable logistic regression (backward selection) to determine which variables were independently related to the initiation of sacubitril/valsartan at high-dose ( $\geq 100$  mg twice a day) vs. low doses (50 mg twice a day) in the whole cohort, according to the criteria used in the TITRATION study.<sup>5</sup> We adjusted for all variables that, from the clinical point of view, could be expected to influence the initiation of sacubitril/valsartan at high dose: (i) dichotomous variables: sex, ischaemic heart disease, prior hospitalization, previous target dose of angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, previous treatment with mineralocorticoid receptor antagonists and beta-blockers, presence of implantable cardioverter defibrillator or cardiac resynchronization therapy, and initiation of sacubitril/valsartan as inpatient/outpatient; and (ii) continuous variables: age, functional class, left ventricular ejection fraction, systolic blood pressure, heart rate, creatinine, and N-terminal pro-B type natriuretic peptide. Statistical significance was established considering a value of  $P < 0.05$  bilateral. For statistical analysis, Stata package Version 14.0 (Stata Corp, College Station, Texas USA) was used.

## Results

We included 427 outpatients who initiated sacubitril/valsartan ambulatorily and 100 inpatients. Inpatients' main reason for admission was decompensated acute heart failure (82–82.0%), followed by arrhythmia (8–8.0%) and acute coronary syndrome (5–5.0%). Forty-two inpatients (42%) had at least a hospital admission in the previous 6 months.

Table 1 compares the baseline characteristics of inpatients with those of PIONEER-HF population. Our inpatients were 10 years older than the ones from the pivotal trial and had

a lower prevalence of diabetes and hypertension. They also had higher left ventricular ejection fraction, more often a baseline Functional Class II, and better renal function. N-terminal pro-B type natriuretic peptide levels were higher, and heart failure treatment was more frequently received in our inpatient cohort than in PIONEER-HF. Twenty inpatients (20.0%) were started on sacubitril/valsartan at a dose of 100 mg b.i.d.; the remaining 80 (80.0%) at a dose of 50 mg b.i.d.

Table 2 compares baseline characteristics and events during follow-up in our inpatient and outpatient cohorts. Both cohorts had a similar follow-up ( $7.0 \pm 0.1$  months inpatients vs.  $7.2 \pm 2.6$  months outpatients,  $P = 0.72$ ). We found a large proportion of men in both groups. Inpatients were older and had a higher prevalence of ischaemic heart disease and diabetes. They also had a worse baseline functional class, higher heart rate, worse left ventricular ejection fraction, and higher levels of N-terminal pro-B type natriuretic peptide. Inpatients received lower doses of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers but were treated with mineralocorticoid receptor antagonists more frequently than outpatients. The prevalence of device (implantable cardioverter defibrillator/cardiac resynchronization therapy) was also lower in inpatients than in outpatients. Inpatients started sacubitril/valsartan at a low dose more frequently than outpatients. Adverse effects and sacubitril/valsartan withdrawal were similar in both groups.

Seventeen inpatients withdrew sacubitril/valsartan during follow-up and four before discharge. In twelve, withdrawal was due to adverse effects: hypotension in nine and renal dysfunction in three. Of the other five cases, four discontinued sacubitril/valsartan owing to financing problems and one owing to left ventricular ejection fraction recovery. During follow-up, inpatients had more hospital admissions than outpatients, but there were no relevant differences in all-cause mortality. Sacubitril/valsartan initiation during hospitalization was independently associated with a lower starting dose (Table 3).

The characteristics of all patients who were on sacubitril/valsartan at the end of follow-up (including those who died if they were receiving the drug the day before

**Table 3** Independent predictors of introduction of sacubitril/valsartan at high dose (100 or 200 mg b.i.d.) in 527 non-selected inpatients and outpatients

	OR (95% CI)	<i>P</i>
Outpatient	3.08 (1.70–5.58)	<0.001
Male sex	1.97 (1.23–3.16)	0.005
ICD	2.24 (1.50–3.36)	<0.001
Serum creatinine, mg/dL	0.45 (0.26–0.78)	0.005
Previous treatment with target dose of ACE inhibitor/ARB	3.76 (2.25–6.29)	<0.001
Previous treatment with MRA	0.55 (0.36–0.83)	0.005

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CI, confidence interval; ICD, implantable cardioverter defibrillator; MRA, mineralocorticoid receptor antagonist; OR, odds ratio; SV, sacubitril/valsartan.

death) in both the inpatient and outpatient groups are compared in *Table 4*. The follow-up time was similar ( $7.2 \pm 2.6$  months inpatients vs.  $7.1 \pm 0.3$  months outpatients,  $P = 0.48$ ). Hospitalized patients had higher systolic blood pressure and higher levels of N-terminal pro-B type natriuretic peptide than had the outpatients. Inpatients also received a low sacubitril/valsartan dose more frequently than did outpatients.

## Discussion

To our knowledge, we present the largest non-selected cohort of patients with heart failure with reduced ejection fraction with prospective follow-up in which sacubitril/valsartan has been initiated, including both inpatients and outpatients. Our main finding is that, in real-life clinical practice, it is as safe to initiate sacubitril/valsartan during hospital admission as it is in outpatients.

Two studies have recently shown that the initiation of sacubitril/valsartan during hospitalization for acute decompensated heart failure is safe and that this drug is more effective than enalapril in reducing N-terminal pro-B type natriuretic peptide levels.<sup>2,3</sup> However, patients included in clinical trials frequently do not represent the real-life population.<sup>10–12</sup> This has been demonstrated specifically with sacubitril/valsartan,<sup>13,14</sup> and only limited data are available, from small cohorts, regarding the initiation of sacubitril/valsartan in non-selected hospitalized patients.<sup>15,16</sup> We have confirmed that our inpatients are different from those included in the PIONEER-HF trial. However, despite being older and having higher levels of N-terminal pro-B type natriuretic peptide at inclusion, the tolerance of sacubitril/valsartan was good (96% maintained the drug at discharge and 83% at 7 month follow-up). In fact, sacubitril/valsartan withdrawal was even lower than in the pivotal trial, in which 12% withdrew sacubitril/valsartan during admission and 19% at a shorter follow-up period of 8 weeks. This better real-life tolerance could be related with a more frequent previous intake of angiotensin-converting enzyme inhibitors/angiotensin

**Table 4** Characteristics of non-selected inpatients and outpatients who maintained sacubitril/valsartan at 7 month follow-up

	Inpatients <i>n</i> = 83	Outpatients <i>n</i> = 378	<i>P</i>
LVEF, %	31 (25–40)	30.0 (25.0–37.0)	0.40
Variation in LVEF, %	2.0 (0.0–13.0)	1.0 (0.0–5.8)	0.04
Systolic blood pressure, mmHg	120 (104–135)	110 (100–121)	0.002
Variation in systolic blood pressure, mmHg	–5 (–19 to 12)	7 (–2 to 19)	0.02
Heart rate, b.p.m.	65 (58–75)	65 (60–72)	0.83
NYHA functional class			<0.001
I	27 (32.9%)	279 (74.6)	
II	49 (59.8%)	74 (19.8)	
III	6 (7.3%)	17 (4.5)	
IV	0 (0.0%)	4 (1.1)	
Improvement of NYHA functional class	52 (64.2%)	306 (72.8%)	0.001
Serum creatinine, mg/dL	1.2 (0.9–1.4)	1.1 (0.9–1.4)	0.51
Variation in serum creatinine, mg/dL	0.0 (–0.2 to 0.2)	0.0 (–0.1 to 0.1)	0.91
Estimated GFR, mL/min	60.0 (49.0–67.0)	60.0 (45.0–73.7)	0.97
Variation in estimated GFR, mL/min	2.0 (–5 to 18)	0.0 (–5 to 6.5)	0.07
Serum potassium, meq/L	4.5 (4.2–4.7)	4.5 (4.2–4.8)	0.55
Variation in serum potassium, meq/L	–0.3 (–0.6 to 0.1)	0.1 (–0.1 to 0.3)	0.55
NT-proBNP, ng/mL	1809 (767–4117)	1326.0 (618–2673)	0.05
SV dose			<0.001
<50 mg b.i.d.	4 (4.8)	0 (0.0)	
50 mg b.i.d.	32 (38.6)	93 (24.6)	
100 mg b.i.d.	20 (24.1)	141 (37.3)	
200 mg b.i.d.	27 (32.5)	138 (36.5)	
Other treatments			
Beta-blockers	76 (91.6)	Not available	
MRAs	59 (71.1)	Not available	
Loop diuretics	64 (77.1)	Not available	
ICD	51 (61.4)	Not available	
CRT	14 (16.9)	Not available	
Mortality and admissions			
All-cause death	2 (2.4)	6 (1.6)	0.63
Cardiovascular death	0	3 (0.8)	0.41
Hospital admissions	24 (28.9)	43 (11.4)	<0.001

*n* (%) for categorical variables and median (inter-quartile range) for continuous variables.

CRT, cardiac resynchronization therapy; GFR, glomerular filtration rate; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B type natriuretic peptide; NYHA, New York Heart Association; SV, sacubitril/valsartan.

receptor blockers, and to the fact that our patients received lower doses of sacubitril/valsartan.

As expected, our inpatients had markers associated with a more advanced staged of heart failure than our outpatients, and this could raise concerns about the tolerability and safety of sacubitril/valsartan.<sup>17</sup> However, we did not register relevant differences in the incidence of adverse effects. Our data suggest that the uptitration of sacubitril/valsartan is suboptimal in both groups. Interestingly, cost was the second cause of sacubitril/valsartan withdrawal during the follow-up of the inpatient cohort. This may even be the main limitation to use sacubitril/valsartan to some populations.

Our study has some limitations: our data come mainly from large academic hospitals and might not be representative of the clinical practice of less complex centres, with a

lower level of specialization, experience, and awareness of the use of evidence-based therapies. Regarding the introduction or not of sacubitril/valsartan, it was left to the choice of the local medical team, so this decision may have been influenced by factors not registered in this study.

In conclusion, it is safe to initiate sacubitril/valsartan during hospitalization in daily clinical practice. Inpatients have a higher risk profile and receive low starting doses more frequently than have outpatients.

## Conflict of interest

M. Martínez-Sellés reports personal fees from Novartis and Rovi outside the submitted work.

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