BRIEF ORIGINAL

Sacubitril/valsartan-treated patients with exacerbated acute heart failure: approaches to care in the emergency department and on the ward

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Objectives. To describe the pattern of care usually given to patients with acute heart failure (AHF) who are taking sacubitril/valsartan (SV) and to explore the effects of care characteristics on clinical outcomes.

Methods. Exploratory study of AHF cases in patients taking SV who were included in the register for the Epidemiology of Acute Heart Failure in Emergency Departments during the sixth period of data collection (EAHFE-6). We extracted baseline and episode variables and information related to SV treatment. We also analyzed associations between the discontinuation of SV therapy and adverse events within 180 days (all-cause mortality) and after discharge (emergency revisits, admission for AHF, death from any cause, or a composite event).

Results. Fifty patients on SV were included. The median time on SV therapy was 81 days (interquartile range, 43–284 days). SV was discontinued in 19 cases (38%; 5 in the emergency department and 14 on the ward). Sixteen records specified the reason for discontinuing SV: renal insufficiency, 4 cases; arterial hypotension, 3; weakness/dizziness, 3; and exacerbated AHF, 3. SV discontinuation was associated with older age, absence of treatment with a betablocker, and hyperkalemia. The EAHFE-6 cases did not reveal significant differences related to SV discontinuation with respect to the rates of adverse events within 180 days or on discharge after the index event.

Conclusions. Long-term SV therapy is discontinued in over a third of patients who present with exacerbated AHF even though no association with clinical outcomes could be identified.

Keywords: Acute heart failure. Sacubitril/valsartan. Mortality. Revisiting. Emergency department, hospital.

Pacientes en tratamiento con sacubitrilo-valsartán que presentan una descompensación en forma de insuficiencia cardiaca aguda: análisis de la actitud en urgencias y durante la hospitalización

Objetivo. Identificar el patrón de práctica clínica habitual respecto al tratamiento crónico con sacubitrilo-valsartán (SV) durante los episodios de insuficiencia cardiaca aguda (ICA), sus determinantes y su efecto sobre la evolución.

Método. Estudio exploratorio de pacientes con ICA incluidos en el Registro EAHFE-6 en tratamiento crónico con SV. Se recogieron características basales, del episodio y del tratamiento con SV, y se identificaron factores relacionados con la interrupción de SV y su asociación con eventos adversos 180 días postevento índice (mortalidad por cualquier causa) y postalta (reconsulta a urgencias u hospitalización por ICA, muerte o evento combinado).

Resultados. Se incluyeron 50 pacientes (mediana desde inicio de SV: 81 días; RIC: 43-284) y SV se interrumpió en 19 casos (38%; 5 en urgencias, 14 en hospitalización). Se identificó un motivo de retirada en 16 casos (4 por insuficiencia renal; y 3 por hipotensión arterial, hiperpotasemia, debilidad/mareo y empeoramiento de ICA, respectivamente). La retirada de SV se asoció con edad avanzada, no estar en tratamiento con betabloqueantes e hiperpotasemia. No hubo diferencias significativas entre grupos en eventos adversos a los 180 días postevento índice o postalta.

Conclusión. En los pacientes en tratamiento crónico con SV que presentan ICA, este es suspendido en más de un tercio de casos, si ello no se asocia con cambios evolutivos.

Palabras clave: Insuficiencia cardiaca aguda. Sacubitrilo-valsartán. Mortalidad. Reconsulta. Servicios de urgencias.

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Introduction

Patients with heart failure (HF) commonly experience decompensations that require urgent care[1]. About 60-80% of acute HF episodes (AHF) treated in hospital emergency departments (EDs) require hospitalization[2], and about 95% of hospitalizations for AHF are performed through these EDs[3]. Therapeutic management of these decompensations is based essentially on the administration of oxygen, diuretics and, less frequently, vasodilators to treat congestion, and inotropes and vasopressors in the case of hypoperfusion[1,4].

On the other hand, regarding chronic treatment which modifies the course of HF with depressed ejection fraction, current clinical guidelines recommend the maintenance of treatment with inhibitors of the renin-angiotensin system (RAS) and with beta-blockers in those patients who were receiving them prior to de-

compensation, also coinciding with hospital admission, provided that their hemodynamic situation allows it[4]. Recently, the use of neprilisin inhibitor (sacubitril) associated with RAS inhibitor (valsartan) has been introduced into the market, as the PARADIGM-HF study showed that the initiation of this medication in patients with hemodynamically stable HF with persistent symptoms reduces the risk of death from any cause by 16% and hospitalization for AHF by 21% during a follow-up period of 27 months[5]. Therefore, ED consultation of patients with AHF who are being treated with sacubitril/valsartan (SV) is becoming common, although the frequency of this is unknown, and the attitude of ED physicians and hospital specialists towards maintaining or withdrawing this treatment is not known. It should be remembered that the PARADIGM-HF study also showed that the use of SV was associated with a higher frequency of hypotension and angioedema, and this could lead to a conservative attitude by withdrawing the drug during decompensation. However, the effect of drug withdrawal on non-ambulatory patients in terms of short-term evolution is also unknown. The aim of the present study was to explore the above-mentioned doubts.

Method

A secondary analysis was performed on the patients diagnosed with AHF included in the EAHFE-6 Registry, whose recruitment phase took place during the months of January and February 2018 in 33 Spanish EDs and included 4,579 consecutive patients. The characteristics of the Registry have been previously published in detail[6,7]. It should be emphasized that the registry includes the care of patients with AHF in the ED in real clinical practice and, although all the centres follow action protocols based on the clinical guidelines in force at the time of the study, it does not include any specific protocolised action and all patient care is carried out autonomously by the physician in charge.

Among the patients included in the EAHFE-6 Registry, those who were receiving treatment with SV prior to decompensation were identified. A distinction was made between those who were discharged from hospital after AHF treatment and those whose treatment was interrupted during the process. For all these patients, 40 different variables were collected: 19 related to the baseline situation, 17 referring to the acute episode, and 4 variables related to chronic treatment with SV (time since the start of treatment, dose, service responsible for introducing the treatment and causes for interruption of treatment during the episode of AHF).

In order to identify variables potentially related to the withdrawal of medication during the AHF episode, differences between patients whose medication was withdrawn and those whose treatment with SV was maintained were investigated using either the Fisher exact test or the Student test, depending on whether the variable was qualitative or quantitative. On the other hand, to investigate whether the withdrawal of SV could have any impact on the evolution of patients, mortality from any cause during the 180 days following the index event (primary objective) was compared with that of the patients who survived the index event (secondary objectives) and the patients in whom treatment was maintained. Kapplan-Meier curves were used for this purpose and were compared using the log-rank test. Given that a small sample was expected and that the study was designed as a secondary opportunity analysis, with a merely exploratory character, no sample size calculation was made and the analysis was exclusively univariate. It was accepted that the differences were statistically significant if the value of p was less than 0.05.

Results

A total of 50 patients were identified as being chronically treated with SV (1.1%). Treatment had begun a median of 81 days ago (IQR 43-284), and was initially prescribed by the cardiology service (90%) and the short-stay unit (10%). In 44% of cases the patient was treated with the 50 mg every 12 hours prescription, in 36% with the 100 mg every 12 hours prescription and in 20% with the 200 mg every 12 hours prescription. Patients on chronic treatment with SV had an average age of 71 years (SD 14), 28% were women, had a high number of comorbidities, and 65% were on treatment with beta-blockers (Table 1). In relation to the baseline situation, 43% were in a functional class of NYHA III or IV, the mean Barthel index was 89 points (SD 18) and the left ventricular ejection fraction was 32% (SD 11).

For 31 of the 50 patients (62%) on chronic treatment with SV, such treatment was maintained at discharge after the episode of AHF and in 19 (38%) it was suspended (Figure 1); among the latter, suspension was made in the ED in 5 cases (26%) during hospitalization in 14 (74%). The causes of withdrawal were worsening renal function (4 cases, 21%), low blood pressure (3 cases, 16%), hyperkalaemia (3 cases, 16%), weakness/dizziness (3 cases, 16%), worsening of AHF (3 cases, 16%) and death (1 case, 5%); in the remaining 2 cases (11%). No apparent cause was identified. Older age, not being on chronic treatment with beta-blockers and hyperkalaemia were associated with withdrawal of SV (Table 1).

When mortality at 180 days after the index event was analyzed, there were 6 deaths (10%, one of which was during hospitalization for the event), with no significant differences between patients in whom the drug had been withdrawn and those in whom it had been maintained (3 deaths in each group, 16% and 10%, respectively) (Figure 2). Among the 49 patients discharged alive after the index event, there were also no statistically significant differences between groups: there

Table 1. Characteristics of the patients included in this study, and comparison between those whose medication was not withdrawn and those who had sacubitrilo-valsartan (SV) withdrawn during the episode of acute heart failure

	Patients treated with SV N = 50 n (%)	Lost values n (%)	Withdrawal of SV N = 19 n (%)	No withdrawal of SV N = 31 n (%)	p
Epidemiological data					
Age [mean (SD)]	70.7 (14.0)	0 (0)	75.9 (9.9)	67.5 (15.3)	0.038
Female sex	14 (28.0)	0 (0)	5 (26.3)	9 (29.0)	1.00
Comorbidities					
High blood pressure	41 (82.0)	0 (0)	17 (89.5)	24 (77.4)	0.452
Diabetes mellitus	26 (52.0)	0 (0)	8 (42.1)	18 (58.1)	0.383
Ischemic Heart Disease	29 (58.0)	0 (0)	14 (73.7)	15 (48.4)	0.139
Chronic kidney disease (creatinine > 2 mg/Dl)	23 (46.0)	0 (0)	11 (57.9)	12 (38.7)	0.247
Cerebrovascular disease	5 (10.0)	0 (0)	1 (5.3)	4 (12.9)	0.637
Atrial fibrillation	27 (54.0)	0 (0)	13 (68.4)	14 (45.2)	0.148
Heart valve disease	10 (20.0)	0 (0)	4 (21.1)	6 (19.4)	1.00
Peripheral artery disease	8 (16.0)	0 (0)	4 (21.1)	4 (12.9)	0.459
Chronic obstructive pulmonary disease	11 (22.0)	0 (0)	5 (26.3)	6 (19.4)	0.727
Previous episodes of acute heart failure	45 (100)	5 (10)	18 (100)	27 (100)	NC
Chronic home treatment					
Diuretics	44 (8.0)	0 (0)	18 (94.7)	26 (83.9)	0.387
Beta-blocker	32 (65.3)	1 (2)	6 (33.3)	26 (83.9)	0.001
Mineralcorticoid receptor antagonists	27 (54.0)	0 (0)	7 (36.8)	20 (64.5)	0.081
Digoxin	9 (18.0)	0 (0)	3 (15.8)	6 (19.4)	1.00
Baseline situation					
NYHA Class III/IV	20 (42.6)	3 (6)	8 (50.0)	12 (38.7)	0.541
Barthel index (points) [mean (SD)	89 (18)	1 (2)	82 (21)	93 (15)	0.052
LVEF (%) [mean (SD)]	32.1 (10.7)	2 (4)	34.5 (12.2)	30.6 (9.5)	0.216
Clinical situation on arrival at the emergency department					
Systolic blood pressure (mmHg) [mean (SD)	124 (21)	0 (0)	126 (19)	122 (22)	0.551
Heart rate (bpm) [mean (SD)	81 (19)	2 (4)	81 (24)	81 (16)	0.883
Basal Pulse Oximetry (%) [mean (SD)	94 (4)	0 (0)	93 (5)	95 (5)	0.131
Severity of the episode (according to MEESSI scale)		23 (46.0)			0.721
Low risk	15 (55.6)		6 (60.0)	9 (52.9)	
Increased risk (intermediate/high/very high)	12 (44.4)		4 (20.0)	8 (47.1)	
Laboratory data					
Hemoglobin (g/L) [mean (SD)]	132 (18)	0 (0)	132 (16)	133 (18)	0.844
Blood sugar (mg/Dl) [mean (SD)]	127 (66)	1 (2)	148 (59)	113 (67)	0.073
Creatinine (mg/dl) [mean (SD])	1.53 (0.55)	1 (2)	1.66 (0.49)	1.45 (0.58)	0.186
Sodium (mmol/L) [mean (SD)]	138 (6)	2 (4)	139 (5)	138 (6)	0.656
Potassium (mmol/L) [mean (SD)]	4.32 (0.56)	4 (8)	4.57 (0.50)	4.20 (0.56)	0.033
Elevated troponin	10 (40.0)	25 (50)	5 (45.5)	5 (35.7)	0.622
NT-proBNP (pg/mL) [median (IQR)	3.675 (1.776-8.091)	13 (26)	5.716 (3.044-14.695)	6.658 (3.357-11.947)	0.583
Treatment and disposal in the emergency department					
Diuretic (IV)	40 (81.6)	1 (2)	13 (68.4)	27 (90.0)	0.072
Morphine (SC/IV)	1 (2.0)	1 (2)	1 (5.3)	0 (0)	0.388
Nitroglycerin (IV)	5 (10.2)	1 (2)	2 (10.5)	3 (10.0)	1.00
Inotropes or vasopressors (IV)	0 (0)	1 (2)	0 (0)	0 (0)	NC
Non-Invasive Ventilation	3 (6.1)	1 (2)	2 (10.5)	1 (3.3)	0.551
Hospital admission	36 (72.0)	0 (0)	15 (78.9)	21 (67.7)	0.522
Variables related to chronic treatment with SV					
Time of treatment (days) [median (IQR)	81 (42-269)	9 (18)	76 (25-166)	95 (51-304)	0.120
Dose of SV (mg)		0 (0)			0.877
50	22 (44.0)		9 (47.4)	13 (41.9)	
100	18 (36.0)		6 (31.6)	12 (38.7)	
200	10 (20.0)		4 (21.1)	6 (19.4)	

LVEF: left ventricular ejection fraction; NC: not calculable; SD: standard deviation; IQR: interquartile range.

were 16 re-visits to the ED (32%; 28% and 35% in each group respectively), 11 hospitalizations (22%; 28% and 19% respectively), 5 deaths (10%; 11% and 10% respectively) and 19 events combined (38%; 28% and 45% respectively) (Figure 2).

Discussion

This is the first study that analyses what is the usual clinical practice during episodes of AHF in patients being treated with SV regarding this drug, as well as the

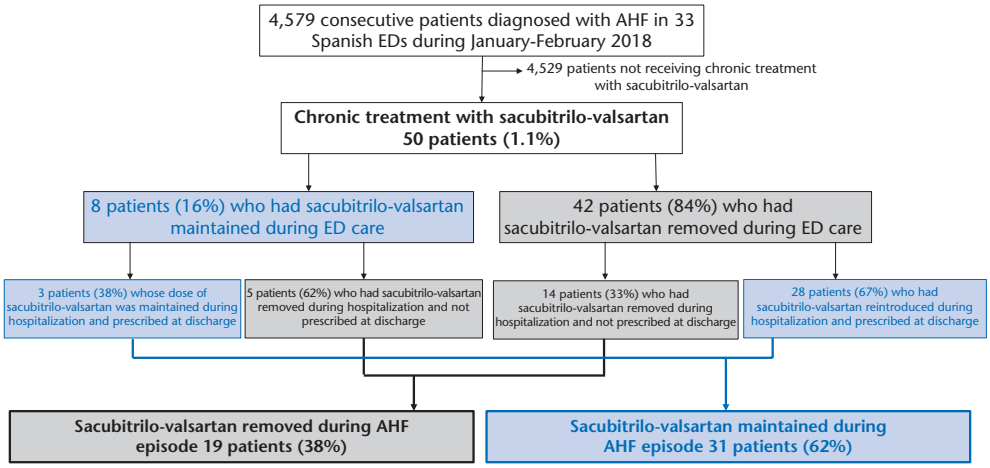
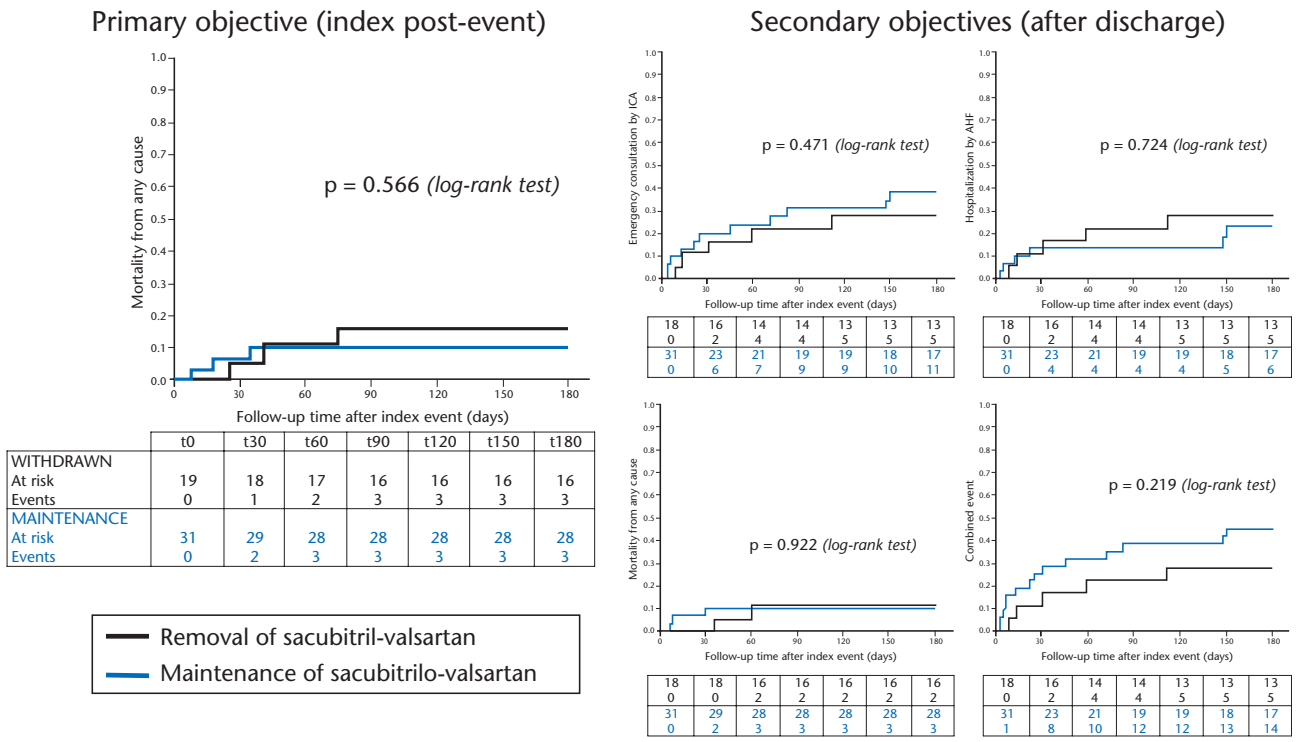


Figure 1. Patient inclusion flowchart. AHF: acute heart failure; ED: emergency department.

factors associated with making decisions about continuing or stopping treatment and its consequences. This is an exploratory study and its results should be taken with caution and interpreted exclusively as hypothesis generators.

The first conclusion is that more than a third of these patients are discharged from hospital for AHF without treatment with SV. Discontinuation is more frequent during hospitalization than during the ED stay. The latter is logical, since the stay in the ED is relatively short and therefore in many cases the decision as to whether the next dose of SV should be administered is already made in the hospitalization room. We do not currently have data with which to compare this first result, although it should be noted that it comes from a large sample of Spanish EDs. It should be checked whether this is also the case in other countries, or whether this attitude is maintained over time with the acquisition of greater experience with the drug during acute decompensation. It should be noted that just over 1% of patients with AHF who attended the ED were on treatment with SV, a percentage that reflects the slow implementation of this drug, for which there is also a tendency to use it in low rather than full doses[8], as we



	t0	t30	t60	t90	t120	t150	t180
WITHDRAWN							
At risk	19	18	17	16	16	16	16
Events	0	1	2	3	3	3	3
MAINTENANCE							
At risk	31	29	28	28	28	28	28
Events	0	2	3	3	3	3	3

Figure 2. Kapplan-Meier curves for the events analysed. AHF: acute heart failure.

also found in this study where only 20% of patients were on the 200 mg dose.

Secondly, it is important to note that drug withdrawal is associated with older age, probably because of a greater likelihood of adverse events[9], and especially with the most frequently described with SV: hypotension. However, it is noteworthy that the blood pressure figures, specifically, were not related to the decision of maintenance or withdrawal, or that hypotension was only the cause of drug withdrawal in 16% of cases. On the other hand, although SV was not associated with a higher incidence of hyperkalaemia than enalapril in the pivotal study[5], higher numbers of serum potassium were associated with drug withdrawal in the present study. In fact, hyperkalaemia was the cause of 16% of the withdrawals, as well as the development of renal failure in 21%. It is well known that renal and electrolyte disturbance are predictors of poor prognosis in patients with AHF[10], and the presence of these events leads to withdrawal of medications that may potentially be related to them or, in this case, medications newly introduced into the pharmacopoeia for which their effect on the acute patient is still poorly known. Specific studies will have to be carried out to confirm whether this fairly common clinical practice currently has any basis for it; especially taking into account the recent results of the PIONEER-HF study, which show that in HF patients with reduced ejection fraction who are hospitalised because of decompensation, the initiation of SV during such hospitalisation after haemodynamic stabilisation is not associated with worsening renal function, hyperkalaemia or symptomatic hypotension[11].

Against this clinical practice of SV withdrawal during the AHF episode is, in fact, our third finding: no increased risk of medium-term adverse events has been observed in those patients in whom the drug was maintained. If we add to this the fact that this drug has shown a highly beneficial effect as a treatment during the chronic phase of the disease[5], it could be considered that the attitude to be recommended during decompensations in the form of AHF should be the maintenance of treatment. The results of the PIONEER-HF[11] and TRANSITION[12] studies also seem to point in this direction. However, it will be necessary to evaluate this hypothesis in a study specifically designed to demonstrate such a recommendation. It should not be forgotten that the analysis of the present study was merely exploratory in a limited and univariate sample size, and it is not possible to exclude the presence of confounding factors. On the other hand, the results obtained in clinical trials are not always completely extrapolated to the real world, and several authors have highlighted the importance of taking into account the specific circumstances of patients when making decisions, especially therapeutic s[13-15].

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