Sacubitril/valsartan use in combination with inotropic support. An option for patients with acute heart failure

Uso combinado de sacubitrilo-valsartán con inotrópicos. Una opción en pacientes con insuficiencia cardiaca aguda

Dear Editor,

The therapeutic and prognostic paradigm of heart failure with reduced ejection fraction (HFrEF) has changed since the introduction of sacubitril/valsartan (SV). This dual angiotensin receptor-neprilysin inhibitor (ARNI) has shown efficacy and tolerability in HFrEF outpatients[1] and in those with acute decompensations and haemodynamic stability.[2,3] However, the recent use of inotropes was an exclusion criterion in PIONEER-HF and TRANSITION trials[2,3] and to date, no randomised trial has assessed the efficacy and safety of the use of SV combined with inotropes. The only published data in this setting comes from a case report and a small retrospective series of six patients,[4,5] in which this combination was started in the context of continuous invasive monitoring during admission in an intensive care unit. Inotropic support might enhance end-organ perfusion and optimise haemodynamic conditions for SV initiation and up-titration, minimizing the risk of developing symptomatic hypotension and renal dysfunction.

We retrospectively analysed our experience with the use of inotropic support to facilitate the initiation and/or up-titration of SV in patients admitted with decompensated HFrEF in a conventional cardiology ward. From September 2018 to February 2020, 105 patients admitted to our ward for acute HFrEF were treated with inotropes. In 12 of them, SV was initiated or up-titrated under inotropic support. In all cases, inotropes were started due to the presence of signs of a low cardiac output status or refractory congestion not responding to intensive diuretic therapy, or with the purpose to provide haemodynamic support to initiate SV (defined by a systolic blood pressure lower than 95 mmHg). Similarly, a contemporary cohort of 12 patients admitted for acute HFrEF and treated with inotropes but in which SV was not initiated nor titrated, and matched to cases by age, sex and aetiology of left ventricular dysfunction and with similar comorbidity, was used as a control group (Fig. 1A). Heart failure (HF) and HFrEF were defined according to the current ESC Guidelines.[6] Baseline and follow-up variables were recorded in a database.

In the ARNI group, the inotropic agent, the time between inotrope therapy instauration and SV initiation (or up-titration) and the initial and tolerated dose at discharge and at follow-up were characterised. Blood pressure, heart rate, serum creatinine, potassium and N-terminal pro-B-type natriuretic peptide (NT-proBNP) plasmatic levels at initiation of both inotropes and SV and at discharge were reported. Incidence of adverse events during hospitalisation in both groups were registered, including acute kidney injury, symptomatic hypotension, hyperkalaemia, angioedema or death, as defined in the PIONEER-HF trial.[3] In the long-term, HF readmissions and the need of mechanical circulatory support or eventual heart transplant were also analysed. This study was approved by the local Research Ethics Committee.

Categorical data were presented as frequencies (percentages) and continuous variables were expressed as mean (±standard deviation), or median (interquartile range), as appropriate. Comparisons were performed for continuous variables using Student's t or Mann–Whitney *U* tests, or χ^2 or Fisher's exact tests in the case of categorical variables, as appropriate. Wilcoxon's paired test was used to compare median values before and after treatment with SV. Statistical analyses were performed using SPSS, version 23.

Table 1 summarises baseline clinical characteristics and events during hospitalisation and follow-up. Mean age was 62.9 ± 10.4 years and 10 patients (83.3%) were male in each group. In the SV group, four patients (33.3%) were admitted due to a first HF episode and all of the remaining patients with previous HFrEF diagnosis were receiving optimal medical therapy, including renin–angiotensin system antagonists (100%), beta-blockers (100%) and mineralocorticoid receptor antagonists (100%). Three of the former (37.5%) were already receiving SV and 5 (62.5%) were carriers of an implanted cardioverter defibrillator (ICD), all of them for primary prevention.

In the SV group, levosimendan (single perfusion of 12.5 mg, without bolus) was used in 9 patients (75%), with a median duration of infusion of 3.0 (2–4) days. There was a concomitant use with dobutamine in 3 patients (25%). The median dose of dobutamine at initiation or up-titration of SV was 7.6 (5–8) μg/kg/min. The median time lapse between inotrope therapy initiation and SV initiation or up-titration was 10 (8–12) days.

In 9 patients (75%), the initial SV dose was 24/26 mg. At discharge, SV was withdrawn in 1 patient (8.3%), and 5 (41.7%) and 4 (33.3%) received the maximum and the intermediate dose, respectively. During follow-up, a higher proportion of patients tolerated 97/103 mg (58.3%) and three (33.3%) remained with the intermediate dose. In the 3 patients that had previously

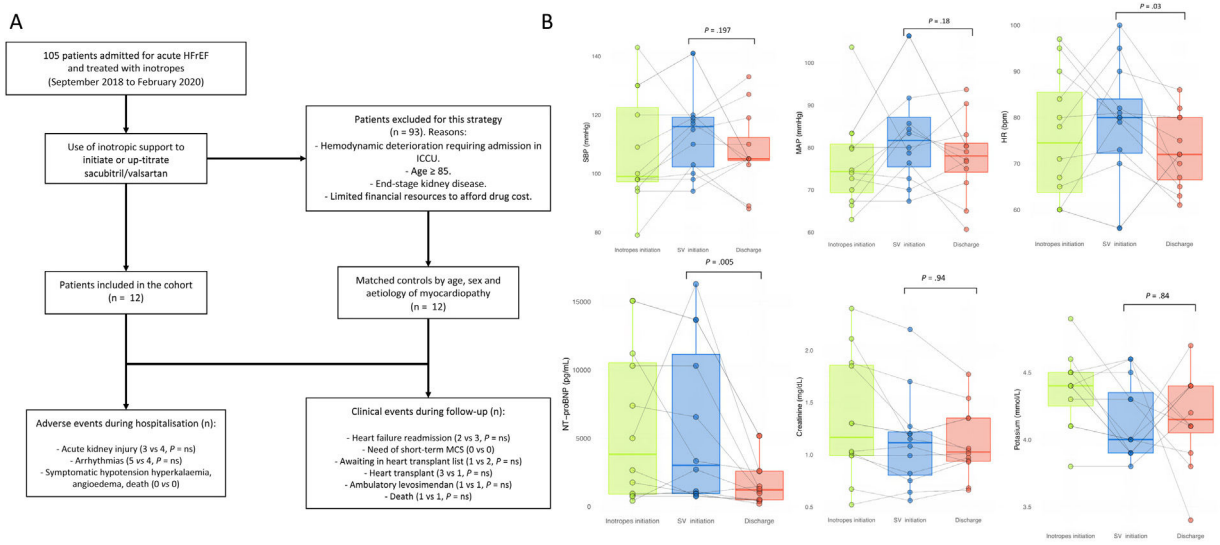

Fig. 1 – (A) Individual and median (interquartile range) values of systolic blood pressure (SBP), mean arterial pressure (MAP), heart rate, N-terminal pro-B-type natriuretic peptide (NT-proBNP) plasmatic levels, serum creatinine and potassium at initiation of inotropes and of sacubitril/valsartan (SV) (or up-titration) and at discharge. (B) Flowchart of the study. ICCU: intensive coronary care unit; ns, not significant.

received SV, treatment was not interrupted while on inotropes, and up-titration was possible (two were discharged on 49/51 mg and one on 97/103 mg).

Worsening renal function occurred in 3 patients (25%) in the SV group and in 4 patients (33.3%) in the control group ($P = .65$). In the ARNI group, acute kidney injury was transient and resolved in 24 h in 2 cases; in the third patient SV was withdrawn. Between SV initiation and hospital discharge (Fig. 1B), a reduction in NT-proBNP levels was observed (3016.5 [949.5–8743.8] *vs* 1212.5, [485.8–2583.5] pg/mL; $P = .005$), without significant variations in systolic (112.5 [102.3–118.3] *vs* 105 [101.5–112.3] mmHg; $P = .20$) and mean arterial pressure (81.7 [75.4–84.7] *vs* 76.8 [74.7–81] mmHg; $P = .18$), serum creatinine (1.1 [0.8–1.3] *vs* 1.03 [0.9–1.4] mg/dL; $P = .94$) or potassium (4.2 [3.9–4.4] *vs* 4.2 [4.1–4.4] mmol/L; $P = .84$). During inotropic support, arrhythmias were recorded in 5 patients (41.7%) in the ARNI group (1 *de novo* atrial fibrillation, 3 cases of non-sustained ventricular tachycardia, and 1 case of sustained ventricular tachycardia in the context of severe hypokalaemia, without recurrence after potassium correction) whereas in the control group, non-sustained ventricular tachycardias were recorded in 4 patients (25%), with no cases of sustained or *de novo* atrial fibrillation. There were no episodes of symptomatic hypotension, hyperkalaemia, angioedema, or death during hospitalisation in both groups.

During a median follow-up of 10.9 (9.7–13.7) months in the ARNI group, 2 patients (16.7%) were readmitted for HFrEF (mean time to readmission of 76.5 ± 2.1 days). Additionally, 1 patient (8.3%) received intermittent intravenous outpatient administration of levosimendan and another patient (8.3%) died presumably due to sudden cardiac death (elderly patient with end-stage HFrEF who did not tolerate SV at discharge and refused an ICD). Due to partial recovery of EF (≥ 35%) after SV initiation, ICD was avoided in two cases. In the control group (median follow-up of 11.5 [5.9–11.1] months), 3 patients (25%) were readmitted for HF (mean time to readmission of 35.5 ± 3.6 days), 2 patients (16.7%) were included in heart transplant waiting list, 1 was enrolled in intermittent intravenous ambulatory administration of levosimendan and 1 died due to end-stage heart disease.

Our data suggest that SV combined with inotropes might be safe in patients admitted for acute HFrEF. This combination may allow SV up-titration and might be routinely attempted when inotropes are needed. Ours is a single centre series and might not be representative of clinical practice in less complex scenarios. Also, although the ARNI group showed a trend towards a reduction in clinical events in the follow-up, the cohort size lacks an adequate power to detect statistical significance. Additionally, as right heart catheterisation was not performed systematically, invasive haemodynamic response to SV could not be evaluated. Finally, this investigational strategy was limited to a highly selected patient on inotrope treatment and could not be extrapolated to most of them.

We report, for the first time, the use of SV and inotropes in patients hospitalised for acute HFrEF in a cardiology ward. The rate of adverse events was low and similar to the reported in the pivotal trials. Similarly, SV withdrawal was low, and after hospital discharge, a high proportion of patients reached an optimal dose, suggesting that early introduction of SV under inotropes may increase the odds to reach target doses after discharge. Moreover, the reduction in NT-proBNP levels we found seems to correlate well with left ventricle reverse remodelling and improvement in EF. However, our findings should be confirmed in randomised prospective studies.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Table 1 – Baseline clinical characteristics, adverse events during hospitalisation and follow-up events of the groups.

	SV cohort ($n = 12$)	Controls ($n = 12$)	P
Body mass index (kg/m²)	27.4 ± 3.4	25.6 ± 4.25	.29
Comorbidities			
Hypertension	7 (58.3)	7 (58.3)	1
Hyperlipidemia	6 (50.0)	8 (66.7)	.41
Diabetes	6 (50.0)	4 (33.3)	.41
Smoking (current or former)	8 (66.7)	5 (41.7)	.41
Chronic kidney disease	4 (33.3)	2 (16.7)	.35
De novo HF	4 (33.3)	4 (33.3)	1
LVEF	20 ± 8	23.9 ± 5	.07
Non-ischaemic aetiology	6 (50.0)	6 (50.0)	1
QRS duration (ms)	118 ± 32	98 ± 27	.29
Atrial fibrillation	2 (16.7)	3 (25.0)	.35
Heart failure therapies			
ACE inhibitor/ARB	5 (41.7)	11 (66.7)	<.01
SV	3 (25.0)	0 (0)	.06
β-Blockers	8 (66.7)	9 (75.0)	.65
Mineralocorticoid receptor antagonist	8 (66.7)	7 (58.3)	.67
Digoxin	2 (16.7)	2 (16.7)	1
iSGLT-2	2 (16.7)	0 (0)	.14
Implantable cardioverter defibrillator	5 (41.7)	3 (25.0)	.03
Inotropes			
Dobutamine	3 (25.0)	3 (25.0)	1
Levosimendan	6 (50.0)	5 (41.7)	.7
Both	3 (25.0)	4 (33.3)	.65
Inotrope indication			
Low cardiac output status	7 (58.3)	9 (75.0)	.39
Refractory congestion	3 (25.0)	3 (25.0)	1
Haemodynamic support to initiate SV	2 (16.7)	0 (0)	–
Adverse events during hospitalisation			
Acute kidney injury	3 (25.0)	4 (33.3)	.65
Arrhythmia	5 (41.7)	4 (33.3)	.67
Symptomatic hypotension	0 (0)	0 (0)	–
Hyperkalaemia	0 (0)	0 (0)	–
Angioedema	0 (0)	0 (0)	–
Death	0 (0)	0 (0)	–
Clinical events during follow-up			
Heart failure readmission	2 (16.7)	3 (25.0)	.62
Need of short-term MCS	0 (0)	0 (0)	–
Awaiting in heart transplant list	1 (8.3)	2 (16.7)	.48
Heart transplant	3 (25.0)	1 (0)	.27
Death	1 (8.3)	1 (8.3)	1

ACE, angiotensin-converting enzyme; ARB, angiotensin-II AT_1 receptor blocker; LVEF, left ventricular ejection fraction; MCS: mechanical circulatory support; iSGLT-2, inhibitor of the sodium–glucose transporter-2; SV, sacubitril/valsartan.
Data are presented as mean (± standard deviation, SD) or frequencies (percentage), as appropriate.

Authors' contributions

C. Herrera formulated the idea, collected and analysed the data, and drafted the manuscript. All authors critically revised and approved the final version of the manuscript. F. Fernández-Avilés and M. Martínez-Sellés contributed equally to this work.

Conflicts of interest

None declared.

BIBLIOGRAFÍA

1. Mc Murray JJ, Packer M, Desai AS, et al. Angiotensin–neprilysin inhibition versus enalapril in heart failure. *N Engl J Med*. 2014;371:993–1004.
2. Wachter R, Senni M, Belohlavek J, et al. Initiation of sacubitril/valsartan in haemodynamically stabilised heart failure patients in hospital or early after discharge: primary results of the randomised TRANSITION study. *Eur J Heart Fail*. 2019;21:998–1007.

3. Velazquez EJ, Morrow DA, DeVore AD, et al. Angiotensin-neprilysin inhibition in acute decompensated heart failure. *N Engl J Med*. 2019;380:539–548.
4. Martyn T, Faulkenberg KD, Albert CL, et al. Acute hemodynamic effects of sacubitril–valsartan in heart failure patients receiving intravenous vasodilator and inotropic therapy. *J Card Fail*. 2021;27:368–372.
5. Bell TD, Mazer AJ, Miller PE, et al. Use of sacubitril/valsartan in acute decompensated heart failure: a case report. *ESC Heart Fail*. 2018;5:184–188.
6. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail*. 2016;18:891–975.

Cristian Herrera [a], Carlos Ortiz-Bautista [a], Javier Castrodeza [a], Eduardo Zatarain [a,b], Francisco Fernández-Avilés [a,b], Manuel Martínez-Sellés [a,b,c,*]

[a] *Servicio de Cardiología, Hospital General Universitario Gregorio Marañón, Instituto de Investigación Sanitaria Gregorio Marañón (IiSGM), Centro de Investigación Biomédica en Red - Enfermedades Cardiovasculares (CIBER-CV), Madrid, Spain*
[b] *Facultad de Medicina, Universidad Complutense, Madrid, Spain*
[c] *Facultad de Medicina, Universidad Europea, Madrid, Spain*

[*] *Corresponding author.*
E-mail address: mmselles@secardiologia.es (M. Martínez-Sellés).
2605-1532/

https://doi.org/10.1016/j.rccl.2021.03.003
Available online 28 April 2021

Predicción de mortalidad hospitalaria y reingreso a 30 días en la insuficiencia cardiaca con el aprendizaje automático

Prediction of in-hospital mortality and 30-day readmission in heart failure using machine learning

Sr. Editor:

La identificación de factores predictores de mortalidad intrahospitalaria y reingreso a 30 días en pacientes hospitalizados por insuficiencia cardiaca (IC) continúa siendo un problema no resuelto. Varios estudios en el ámbito de la población española han explorado este problema, el más reciente el realizado por Martínez Santos et al.[1], con una capacidad predictiva moderada en consonancia con la evidencia previa.

Los modelos de aprendizaje automático, aplicados al estudio de datos clínicos de diferente tipología, son una realidad[2], con mayor o menor mejoría respecto a los modelos estadísticos lineales tradicionales. El presente estudio aplica estas técnicas por primera vez, sobre los datos recogidos en el Conjunto Mínimo Básico de Datos durante los últimos 10 años en un hospital terciario con una unidad de cardiología de tipología 4[3]. Se obtuvo la aprobación del comité de ética para tal fin.

Se incluyeron todos los ingresos hospitalarios con diagnóstico principal de IC (códigos 398.91, 404.01, 404.91, 404.93 y 428.* del CIE-9 e I09.81, I11.0, I13.0, I13.2 e I50.* del CIE-10) entre enero de 2009 y noviembre de 2019. Se generaron como variables a predecir o «etiquetas»: a) si el paciente falleció durante el ingreso y b) si el siguiente reingreso desde el día del alta se produjo en 30 días o menos. Se incluyeron un total de 11.633 ingresos hospitalarios de un total de 7.360 pacientes (81 ± 10 años, 46,5% varones) con una media de 8,3 ± 6,6 días desde el ingreso hasta el alta. Un total de 1.297 (17,6%) pacientes fallecieron durante uno de sus ingresos (11,1% respecto al total de ingresos) y 2.089 (20,2%) de las altas tuvieron un reingreso a 30 días. En la figura 1 se puede observar la evolución por año tanto del número total de ingresos por IC como de fallecimientos y reingresos a 30 días.

Entre las variables (o atributos) incluidos para el ajuste de los modelos de aprendizaje automático, se recogieron 90 variables de carácter poblacional, históricas, relativas al ingreso hospitalario, de diagnósticos y de procedimientos. La selección de dichas variables se realizó por criterios médicos y metodológicos, agrupando diferentes códigos del CIE-9 y CIE-10 para obtener un conjunto de datos con un número amplio de variables lo suficientemente pobladas. Como algoritmos de aprendizaje automático se utilizaron 4 clasificadores: a) 2 (AdaBoost y CatBoost) típicamente empleados con conjuntos de datos compuestos por variables categóricas, ambos son de tipo ensemble y se basan en la combinación de un número de clasificadores débiles de tipo árbol de decisión para generar un clasificador con mayor robustez y b) 2 modelos lineales de regresión logística con un factor de regularización L2. La regularización L2 consiste en introducir una limitación a la magnitud que pueden tomar los coeficientes beta de la regresión, lo que generalmente mejora en mayor o menor medida el comportamiento del modelo al reducir su capacidad de sobreajuste. Uno de estos modelos empleó la totalidad de las