## Scientific letters

### Early Sacubitril/Valsartan-driven Benefit on Exercise Capacity in Heart Failure With Reduced Ejection Fraction: A Pilot Study

### *Efecto inicial del sacubitrilo-valsartán sobre la capacidad funcional en pacientes con insuficiencia cardiaca con fracción de eyección reducida: estudio piloto*

**To the Editor,**

The hallmark clinical feature of heart failure (HF) is a severe reduction in exercise capacity, which limits patients' activities of daily living and is a crucial determinant of increased risk of adverse outcomes.[1] In patients with chronic HF and reduced ejection fraction (HFrEF), sacubitril/valsartan reduced the risk of the composite of cardiovascular death or first hospitalization for HF by 20% compared with enalapril at a median follow-up of 27 months.[2] However, evidence supporting the role of this treatment combination for improving short-term functional capacity is lacking.

In this work, the primary endpoint was to evaluate the short-term effects of sacubitril/valsartan on maximal exercise capacity evaluated by peak oxygen consumption (peak $VO_2$) in stable patients with symptomatic HFrEF. The secondary endpoint included changes in ventilatory efficiency during exercise ($VE/VCO_2$ slope).

From March 1, 2017 to July 1, 2017, we prospectively studied a cohort of patients with chronic HF, visited in the HF unit of a tertiary center in Spain. The inclusion criteria were: *a)* left ventricular ejection fraction $<$ 40%; *b)* stable New York Heart Association functional class $\geq$ II; *c)* ability to perform a valid baseline exercise test, and *d)* prior treatment with an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker.

For eligible patients, treatment with an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker was replaced by sacubitril/valsartan. All patients provided informed consent and the protocol was approved by the research ethics committee in accordance with the principles of the Declaration of Helsinki and national regulations.

At each visit (baseline assessment and after 30-day initiation of sacubitril/valsartan), we registered demographic information, medical history, vital signs, 12-lead electrocardiogram, cardiopulmonary exercise testing), quality of life (Minnesota Heart Failure Living questionnaire), standard laboratory data, and pharmacological treatments. Doses of sacubitril/valsartan were prescribed according to established recommendations.[1] By protocol, no treatment changes occurred between the 2 visits.

Maximal functional capacity was evaluated with incremental and symptom-limited cardiopulmonary exercise testing (CORTEX Metamax 3B) on a bicycle ergometer, beginning with a workload of 10 W and increasing stepwise at 10-W increments every 1 minute. Gas exchange data and cardiopulmonary variables were averaged every 10-second values. Peak $VO_2$ was considered the highest value of $VO_2$ during the last 20 seconds of exercise. The $VE/VCO_2$ slope was determined by measuring the slope across the entire course of exercise.

Continuous variables are expressed as mean $\pm$ standard deviation or median [interquartile range] as appropriate; discrete variables as percentages. In an ANCOVA design, changes in peak $VO_2$

**Table**
Baseline Characteristics of the Study Population

| Variables | Included patients (n = 16) |
|---|---|
| *Demographic, medical history and vital signs* | |
| Age, y | 72 [61-75] |
| Male | 12 (75) |
| Hypertension | 12 (75) |
| Diabetes mellitus | 6 (37.5) |
| Dyslipidemia | 14 (87.5) |
| Ischemic heart disease | 9 (56.3) |
| Baseline NYHA class III/IV | 6 (37.5) |
| Atrial fibrillation | 9 (56.3) |
| Systolic blood pressure, mmHg | 115 $\pm$ 20 |
| Diastolic blood pressure, mmHg | 64 $\pm$ 11 |
| Heart rate, bpm | 70 $\pm$ 13 |
| *Laboratory* | |
| Serum potassium, mEq/L | 4.3 $\pm$ 0.4 |
| Serum sodium, mEq/L | 139 $\pm$ 3 |
| Serum creatinine, mg/dL | 1.28 [0.9-1.72] |
| eGFR, mL/min/1.73 $m^2$ | 52.5 [41.7-75.2] |
| Hemoglobin, g/dL | 14.3 $\pm$ 1.5 |
| NT-proBNP, pg/mL | 2055 [792-4283] |
| *Echocardiography* | |
| LVDD, mm | 68 [63-74] |
| LAV, $mL/m^2$ | 88 [75-126] |
| LVEF, % | 32 $\pm$ 8 |
| E/e' ratio | 13 [11-16] |
| TAPSE | 20 [16-22] |
| *Treatment* | |
| Furosemide | 15 (93.8) |
| Beta-blockers | 16 (100) |
| Antialdosterone | 13 (81.3) |
| Starting dose of sacubitril/valsartan 24/26 mg | 10 (62.5) |
| *Exercise performance* | |
| 6-MWT, m | 315 [255-391] |
| *Quality of life* | |
| MLHF score | 29 [15-33] |
| *Cardiopulmonary exercise test* | |
| Peak $VO_2$, mL/min/kg | 11.6 $\pm$ 2.5 |
| $VE/VCO_2$ | 42.9 $\pm$ 8.3 |
| RER | 1.14 $\pm$ 0.13 |

bpm, beats per minute; eGFR, estimated glomerular filtration rate using the Modification of Diet in Renal Disease formula; LAV, left atrial volume by biplane modified Simpson; LVDD, left ventricular diastolic diameter; LVEF, left ventricular ejection fraction; MLHF, Minnesota Living with Heart Failure Questionnarie score; 6-MWT, 6-minute walk test; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association functional class; peak $VO_2$, peak oxygen consumption; RER, respiratory exchange ratio; TAPSE, tricuspid annular plane systolic excursion; $VE/VCO_2$ slope, relationship between minute ventilation and the rate of $CO_2$ elimination.
Data are expressed as No. (%), mean $\pm$ standard deviation or median [interquartile range].

were tested with a mixed-effects model for repeated-measures. The model included as covariates the sacubitril/valsartan doses and the baseline value of peak $VO_2$. A 2-sided *P* value of $< .05$ was set as the criterion for statistical significance.

A total of 33 consecutive HFrEF patients were screened for eligibility and 16 were finally included in this study (Figure 1 of the supplementary material). The main reasons for ineligibility were baseline systolic blood pressure $< 100$ mmHg (n = 7), estimated glomerular filtration rate $< 30$ mL/min/1.73 $m^2$ (n = 5), and orthopedic/neurological inability to perform a valid cardiopulmonary exercise test (n = 4).

Median [interquartile range] age was 72 years [61-75], 75% were men, 56.3% had prior ischemic heart disease, and 37.5% were in New York Heart Association functional class III. The mean ± standard deviation of left ventricular ejection fraction, peak $VO_2$, and $VE/VCO_2$ slope were 32 ± 8%, 11.6 ± 2.5 mL/min/kg, and 42.9 ± 8.3, respectively. The starting dose of sacubitril/valsartan was 24/26 mg in 10 patients (62.5%). Baseline characteristics are presented in the Table. Using raw values, an improvement of at least 10% of the baseline peak $VO_2$ and $VE/VCO_2$ slope were found in 5 (31.3%) and 4 (25%) patients, respectively.

Compared with baseline, peak $VO_2$ increased significantly at 30 days (+Δ = 0.92; 95% confidence interval, 0.06-1.77; *P* = .035), which corresponded to a 7.9% increase from the baseline value (Figure A). Likewise, a significant improvement in $VE/VCO_2$ slope was also found at 30 days (-Δ = 3.89; 95% confidence interval, 6.70-1.07; *P* = .007), which corresponded to a 9.1% of reduction, as shown in Figure B. In parallel, a significant improvement in other surrogates of severity such as quality of life and N-terminal pro-B-type natriuretic peptide (32.22% and 5.29% of reduction, respectively) was registered (Figure 2 of the supplementary material). No significant changes were detected in estimated glomerular filtration rate (Figure 2 of the supplementary material).

To the best of our knowledge, this is the first study suggesting that the initiation of sacubitril/valsartan, mostly at low doses, could lead to a short-term increase in peak $VO_2$. Interestingly, this beneficial effect was associated with a significant improvement in other cardiopulmonary exercise testing surrogates of severity such as ventilatory efficiency. Although the mechanisms by which sacubitril/valsartan might improve early exercise capacity in HFrEF remain unclear, we speculate that neprilysin inhibition mediated by sacubitril would acutely amplify the hemodynamic effects of natriuretic peptides and other vasoactive peptides,[3] resulting in an improvement of short-term exercise tolerance.

The main limitation of this study is the small sample size and the lack of a control group. However, we believe these encouraging findings open a new research path aimed at exploring the pathophysiological mechanism by which sacubitril/valsartan improves exercise tolerance in HFrEF. Indeed, a clinical trial evaluating the effect of sacubitril/valsartan on 6-month Exercise Tolerance in Patients With Heart Failure (NEPRIExTol) is currently ongoing (NCT03190304).

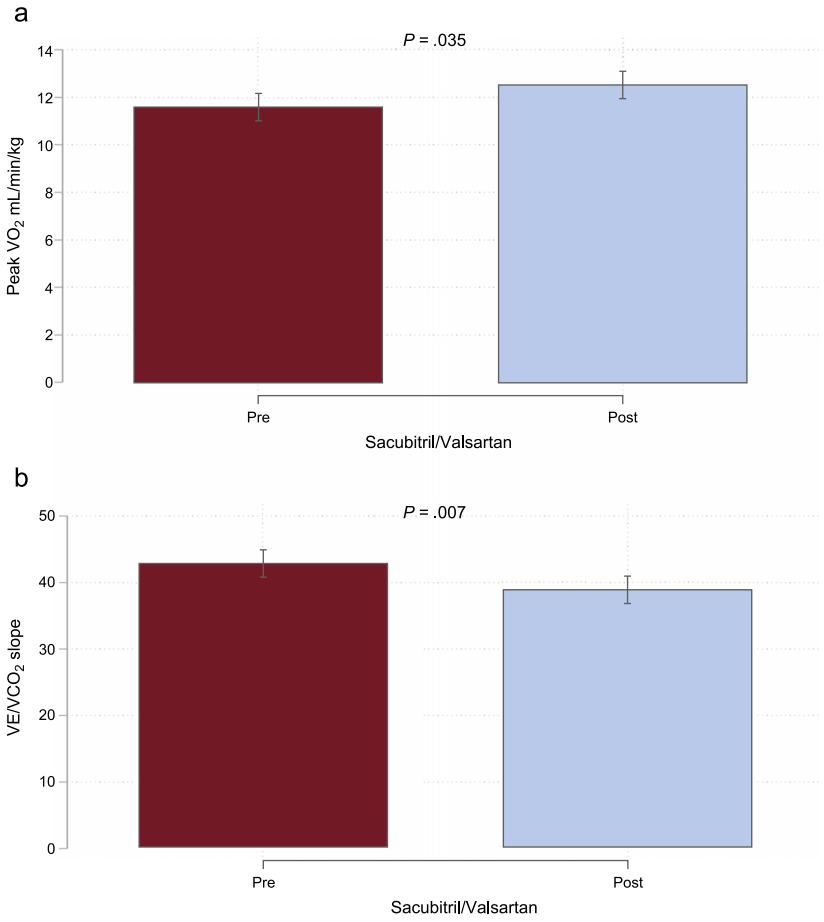


**Figure.** Thirty-day effects of sacubitril/valsartan on CPET parameters. A: changes in peak $VO_2$. B: changes in $VE/VCO_2$ slope. CPET, cardiopulmonary exercise test; peak $VO_2$, peak oxygen consumption; $VE/VCO_2$ slope, minute ventilation/carbon dioxide production. Adjusted for baseline values of both exposures.

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## SUPPLEMENTARY MATERIAL

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## Long-term Follow-up of Symptomatic Adult Patients With Noncompaction Cardiomyopathy

### *Seguimiento a largo plazo de pacientes sintomáticos adultos con miocardiopatía no compactada*

**To the Editor,**

Noncompaction cardiomyopathy (NCC) is thought to arise due to an arrest of the normal myocardial compaction process during intrauterine life.[1] Clinical manifestations include heart failure, embolic events, and arrhythmias.[2] Its prognosis varies considerably between studies and remains largely unknown.

Our aim was to better define the outcomes of symptomatic adult patients (defined as those > 18 years old, presenting with heart failure, atrial or ventricular arrhythmias, or embolic events) with NCC and compare them with those of a contemporary cohort of patients with idiopathic dilated cardiomyopathy (IDC).

This retrospective study included all consecutive patients who fulfilled echocardiographic criteria of NCC,[3] managed at 2 tertiary centers from 2001 to 2015. As a comparison group, we included all consecutive symptomatic patients with IDC managed at the Heart Failure Program of one of the participating centers from 2008 to 2015. We collected adverse events during follow-up, defined as sustained ventricular arrhythmias, cardioembolic events, cardiovascular death, or heart transplant. The study was approved by the clinical research ethics committees of both centers. Comparative analysis between the groups were performed with the Mann-Whitney test for continuous variables and the chi-square test for categorical variables. Survival analyses were performed with Kaplan-Meier curves and differences were tested using the log-rank test. To evaluate whether NCC predicted outcomes compared with IDC, we performed a backward step multivariate Cox proportional hazard analysis.

The Table shows the patients' baseline characteristics and treatment. Seventy-five patients with NCC fulfilled the inclusion criteria. In 65 (86.7%) patients, heart failure was the index complaint, whereas 9 (12%) had arrhythmias (6 atrial in origin and 3 ventricular tachycardia [2 sustained VT with hemodynamic stability and 1 with frequent runs of symptomatic nonsustained VT]) and 1 (1.3%) presented with an embolic event (stroke); 17% of the patients with NCC had a known family history of cardiomyopathy at diagnosis (but had not previously undergone family screening).

Patients with IDC were older and showed larger left ventricular end-diastolic diameters, as well as lower ejection fraction.

The patients were followed up for a median of 5 (2.4-6.7) years. During follow-up, 14 (18.7%) patients in the NCC group had a first adverse event (5 ventricular arrhythmias, 3 cardiovascular deaths, 4 cerebrovascular embolic events, and 2 heart transplants), whereas 35 (26.7%) patients had a first adverse event in the IDC group (13 ventricular arrhythmias, 12 cardiovascular deaths, 3 cerebrovascular embolic events, and 7 heart transplants). None of the patients with cerebrovascular events were under anticoagulant treatment prior to the event.

In the NCC group, 19 (25.3%) patients underwent an ICD placement, 12 as primary prevention and 7 as secondary prevention. In the IDC group, 48 patients (36.6%) underwent an ICD placement, 24 as primary prevention and 24 as secondary prevention. No statistically significant differences were found in terms of the ICD implantation rate between groups. Only patients in whom the indication was secondary prevention showed ICD therapies during follow-up.

The Figure shows the Kaplan-Meier survival curves free from a first event and free from cardiovascular death or heart transplant in both groups. Having an NCC did not predict a different outcome free from a first event compared with IDC (HR, 1.01; 95%CI, 0.49-2.10; $P$ = .98) after multivariate adjustment for age, left ventricular end-diastolic diameter, ejection fraction, and serum creatinine.

Our main finding is that symptomatic adult patients with NCC had a similar incidence of adverse events and survival compared with patients with IDC. The annual incidence of thromboembolic events was 1.06 percent per year in the NCC group and 0.62 percent per year in the IDC group. Interestingly, both groups showed a high incidence of anticoagulation therapy, even in sinus rhythm, but a diagnosis of NCC was not an indication for the use of anticoagulants. The low rate of thromboembolic events was probably related to this