



Effects of sacubitril/valsartan on exercise capacity: a prognostic improvement that starts during uptitration

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Abstract

Purpose Sacubitril/valsartan is a mainstay of the treatment of heart failure with reduced ejection fraction (HFrEF); however, its effects on exercise performance yielded conflicting results. Aim of our study was to evaluate the impact of sacubitril/valsartan on exercise parameters and echocardiographic and biomarker changes at different drug doses.

Methods We prospectively enrolled consecutive HFrEF outpatients eligible to start sacubitril/valsartan. Patients underwent clinical assessment, cardiopulmonary exercise test (CPET), blood sampling, echocardiography, and completed the Kansas City Cardiomyopathy Questionnaire (KCCQ-12). Sacubitril/valsartan was introduced at 24/26 mg b.i.d. dose and progressively uptitrated in a standard monthly-based fashion to 97/103 mg b.i.d. or maximum tolerated dose. Study procedures were repeated at each titration visit and 6 months after reaching the maximum tolerated dose.

Results Ninety-six patients completed the study, 73 (75%) reached maximum sacubitril/valsartan dose. We observed a significant improvement in functional capacity across all study steps: oxygen intake increased, at peak exercise (from 15.6 ± 4.5 to 16.5 ± 4.9 mL/min/kg; p trend = 0.001), while minute ventilation/carbon dioxide production relationship reduced in patients with an abnormal value at baseline. Sacubitril/valsartan induced positive left ventricle reverse remodeling (EF from 31 ± 5 to $37 \pm 8\%$; p trend < 0.001), while NT-proBNP reduced from 1179 [610–2757] to 780 [372–1344] pg/ml (p trend < 0.0001). NYHA functional class and the subjective perception of limitation in daily life at KCCQ-12 significantly improved. The Metabolic Exercise Cardiac Kidney Index (MECKI) score progressively improved from 4.35 [2.42–7.71] to 2.35% [1.24–4.96], $p = 0.003$.

Conclusions A holistic and progressive HF improvement was observed with sacubitril/valsartan in parallel with quality of life. Likewise, a prognostic enhancement was observed.

Keywords Sacubitril/valsartan · Heart failure · Exercise capacity · Cardiopulmonary exercise test · Biomarkers

Introduction

Heart failure with reduced ejection fraction (HFrEF) still represents a major issue in the general population with a continuously increasing prevalence [1] and a persistently high 5-year mortality rate, also in patients considered in “stable” clinical conditions [2, 3]. Sacubitril/valsartan therapy is a cornerstone of HFrEF pharmacological treatment due to its favorable effect on cardiovascular death and heart failure (HF)

hospitalizations [4–6]. Despite this positive prognostic impact, conflicting results have emerged on the effects of sacubitril/valsartan on exercise performance with some studies showing an improvement of exercise tolerance [7–13] and some others showing no significant effects [14–18]. These studies differ in terms of numerosity, study design (randomized vs. observational), and/or methodology. Indeed, exercise performance has been differently evaluated by means of maximal symptoms limited cardiopulmonary exercise test (CPET) [7–11, 14, 15, 17, 18], 6-min walking test [12, 13, 16, 19], and using exercise surrogates such as data obtained from accelerometer devices [14, 16]. Notably, little is known about exercise performance changes during sacubitril/valsartan uptitration [7].

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CPET is a valuable tool in HFrEF, allowing accurate assessment of patients' functional capacity and providing prognostically relevant parameters (e.g., oxygen intake at peak [peakVO₂] and at anaerobic threshold [AT], and minute ventilation/carbon dioxide production relationship [VE/VCO₂ slope]) [20, 21].

The aim of the present study was to prospectively evaluate the effects of sacubitril/valsartan on exercise performance, cardiac remodeling, functional status, and quality of life in a large population of HFrEF patients, after drug introduction and at different drug doses.

Materials and methods

We prospectively enrolled HFrEF outpatients referred to the HF Unit of three Italian Institutes between December 2018 and December 2019, who were eligible to start sacubitril/valsartan according to 2016 ESC Guidelines [22]. Study inclusion criteria were age > 18 years, males and females, New York Heart Association (NYHA) Class II–III in stable clinical condition, left ventricular ejection fraction (LVEF) ≤ 35%, and ability to perform CPET. Patients affected by chronic obstructive pulmonary disease or in need of oxygen supplement were excluded.

At baseline, each patient underwent all study procedures while taking their background guideline-directed

therapy for HF at the maximum tolerated dose. After 36 h of interruption of angiotensin-converting enzyme inhibitors (ACE-I) or angiotensin receptor blockers (ARBs), sacubitril/valsartan was introduced at 24/26 mg b.i.d. starting dose for all patients. After enrollment, the drug was progressively uptitrated in a standard monthly-based fashion to 97/103 b.i.d. or to the maximum tolerated dose.

All study procedures were performed at baseline, repeated at each titration visit and 6 months after the maximum tolerated dose was reached (except for echocardiography that was repeated only after 1 month and at the end of the study). Specifically, patients underwent clinical assessment, CPET, venous blood sample collection, and transthoracic echocardiography (TTE). Moreover, quality of life (QoL) was evaluated through Kansas City Cardiomyopathy Questionnaire (KCCQ-12) at each study visit, administrated before any other assessment (Fig. 1).

Cardiopulmonary exercise testing

In all laboratories patients were tested by a stationary ergospirometer (Quark PFT Cosmed, Rome, Italy) using an electronically braked cycle ergometer and wearing a standard CPET silicone mask, using a ramp protocol set to

* Only if dose was uptitrated

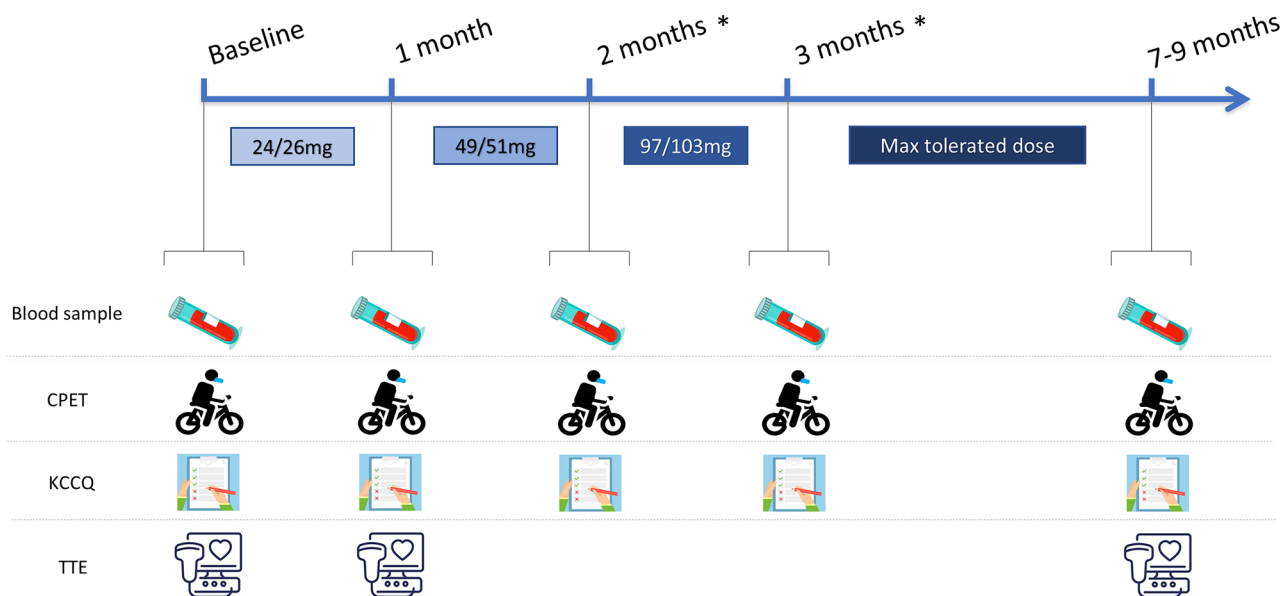


Fig. 1 Study protocol. The figure shows the study procedures performed at each study-step, during the progressive monthly-based drug uptitration and at the end of the study. Specifically, each patient underwent at each step a blood sample (renal function assessed by the MDRD equation, serum potassium and sodium, NT-proBNP, Hb), a maximal CPET with the same ramp protocol, and a QoL evaluation

through KCCQ-12. TTE was performed at baseline, after the first month, and at the end of the study. Abbreviations: MDRD, Modification of Diet in Renal Disease; NT-proBNP, N-terminal pro B-type natriuretic peptide; Hb, hemoglobin; CPET, cardiopulmonary exercise test; QoL, quality of life; KCCQ-12, Kansas City Cardiomyopathy Questionnaire, TTE, transthoracic echocardiography

achieve peak exercise in ~ 10 min [23]. To allow comparison among CPET results, the ramp protocol was chosen for each patient at the baseline visit and then applied to all the subsequent tests. In the absence of clinical events, the exercise was interrupted when patients stated that they had reached maximal effort. We performed a breath-by-breath analysis of expiratory gases and ventilation. The VO_2 /work rate relationship was measured throughout the entire exercise. The AT was identified using a V-slope analysis of VO_2 and CO_2 production (VCO_2), and it was confirmed by specific trends of ventilation vs VO_2 and ventilation vs CO_2 and of end-tidal pressure of oxygen and end-tidal pressure of CO_2 . AT was reported as absolute value and as percentage of the predicted maximum VO_2 [24, 25]. The VE/VCO_2 slope was calculated from 1 min after the beginning of the loaded exercise to the end of the isocapnic buffering period. Predicted values of peak VO_2 were calculated as “(height – age) × 20” for men and “(height – age) × 14” for women, with height expressed in centimeters and age in years [26].

Transthoracic echocardiography

TTE examinations were performed using Philips ultrasound machine (Epiq CVx – Philips Medical Systems, Andover, Massachusetts) equipped with an X5-1 probe. Complete standard 2D TTE analysis was performed. Left chambers' volumes and LVEF were measured from 4-chamber and 2-chamber views using the biplane Simpson's method [27]. All echocardiograms were performed by well-trained operators.

Kansas city cardiomyopathy questionnaire analysis

The KCCQ-12 was analyzed combining the reported Physical Limitation, Symptom Frequency, Quality of Life and Social Limitation scales into the Summary Score, calculated as the average of the available scale scores. In order to calculate the summary score, at least one of the four scale scores must be present [28, 29].

Prognostic score

As additive analysis, we included a multiparametric prognostic risk assessment through Metabolic Exercise Cardiac Kidney Index (MECKI) score calculation, to analyze the impact of sacubitril/valsartan introduction on two-year risk of death or urgent heart transplant/LVAD (left ventricle assist device) implantation. The MECKI score was calculated as previously described [30].

Statistical analysis

Statistical analyses were performed using SAS software, version 9.4 (SAS Institute, Cary, NC, USA). Continuous variables were expressed as means ± standard deviation (SD) or median and interquartile range [IQR] in case of non-normally distributed variables; categorical variables were reported as frequencies and percentages. Missing values (in V1, V2, and V3) were imputed by considering the value of the following visit, where present. Comparisons of observed values over time were performed by repeated-measures ANOVA, after log-transformation of variables with right-skewed distribution; single comparisons were performed by paired *t*-tests and Bonferroni's correction for multiple comparisons was applied. Pearson's or Spearman's correlation coefficient was calculated, as appropriate. All tests were two-sided, and a *p* value < 0.05 was required for statistical significance (after Bonferroni's correction where appropriate).

The present research protocol complies with World Medical Association Declaration of Helsinki, and it was approved by the Centro Cardiologico Monzino Ethical Committee (CCM 898) as the guiding study center as well as by the local Ethical Committee of satellites centers. Each subject provided written informed consent to the study. This observational cohort study was also registered into clinicaltrials.gov on June 16, 2020, with ID: NCT04434170.

Results

One hundred and thirteen HFrEF outpatients (81% males, age 64.5 ± 9.7 years) were enrolled in three Italian centers. Seventeen patients (15%) interrupted the protocol for the following reasons: 1 patient experienced sudden cardiac death; 5 patients had clinical worsening (1 renal function worsening and 4 symptomatic hypotension) and interrupted the study drug; 2 patients were diagnosed with cancer; 2 patients were excluded after unscheduled cardiac resynchronization therapy (CRT) implantation; 1 patient had SARS-CoV-2 infection with respiratory failure, for 4 patients, CPET was contraindicated due to ventricular arrhythmias/mobile left ventricular thrombosis; and 2 patients withdrew from the study for personal reasons. All these patients were excluded from the analysis.

Table 1 shows the main characteristics of the retained population and therapy at enrolment ($n = 96$). HFrEF was of ischemic etiology in 55% of patients, 59 patients (59%) had hypertension, and 38 (39%) chronic kidney disease with $\text{eGFR} \leq 60$ ml/min/1.73m². At a mean follow-up of 282 ± 63 days, 72 patients (75%) reached the maximum sacubitril/valsartan dose (97/103 mg b.i.d.) without safety concerns. After the baseline assessment, a further

Table 1 Basal characteristics of the retained study population ($n=96$)

	<i>Data at enrolment</i>
<i>Age (years)</i>	63.66 ± 9.80
<i>BMI (kg/m²)</i>	27.08 ± 4.24
<i>SBP (mmHg)</i>	117.60 ± 15.49
<i>Heart rate (bpm)</i>	66.92 ± 10.73
<i>Males (n, %)</i>	77, 80%
<i>Ischemic etiology (n, %)</i>	53, 55%
<i>Hypertension (n, %)</i>	57, 59%
<i>Diabetes (n, %)</i>	21, 22%
<i>Atrial fibrillation (n, %)</i>	23, 24%
<i>ICD (n, %)</i>	36, 38%
<i>CRT-D (n, %)</i>	21, 22%
<i>NYHA II (n, %)</i>	84, 88%
<i>NYHA III (n, %)</i>	11, 11%
<i>Hemoglobin (g/dL)</i>	14.04 ± 1.60
<i>Creatinine (mg/dL)</i>	1.16 ± 0.26
<i>GFR (ml/min/1.73 m²)</i>	68.92 ± 19.58
<i>Sodium (mmol/L)</i>	140.72 ± 2.79
<i>Potassium (mmol/L)</i>	4.40 ± 0.42
<i>ACE-I (n, %)</i>	72, 75%
<i>ARB (n, %)</i>	22, 23%
<i>BB (n, %)</i>	95, 99%
<i>MRA (n, %)</i>	69, 72%
<i>Loop diuretics (n, %)</i>	76, 79%

BMI body mass index, *SBP* systolic blood pressure, *ICD* implantable cardioverter defibrillator, *CRT-D* cardiac resynchronization therapy-defibrillator, *NYHA* New York Heart Association, *GFR* glomerular filtration rate assessed by Modification of Diet in Renal Disease (MDRD) equation, *ACE-I* angiotensin-converting-enzyme inhibitor, *ARB* angiotensin receptor blocker, *BB* beta blocker, *MRA* mineralocorticoid receptor antagonist

functional evaluation was not possible in 4 patients due to physical limitations and/or poor compliance/motivation to the test.

Compared to baseline (Table 1), NYHA functional class significantly improved at the end of study assessment with 34 (36%) patients in class 1, 57 (60%) in class 2 and only 4 (4%) in class 3 ($p < 0.001$) (Fig. 2). From the analysis of KCCQ-12 summary score, we observed a statistically significant improvement of the subjective perception of functional limitation in daily life, from a score of 3.95 ± 0.92 at baseline to 4.27 ± 0.81 at end of study (Fig. 2).

As regards safety concerns, we did not observe a significant change in renal function and electrolytes (eGFR from 69 ± 20 to 66 ± 20 ml/min/1.73m², potassium from 4.40 ± 0.42 to 4.36 ± 0.43 mmol/l, $p = \text{ns}$ for both) (Fig. 3A), while a statistically significant — however not clinically relevant — reduction in systolic blood pressure was observed during sacubitril/valsartan uptitration (from 118 ± 16 to 109 ± 14 mmHg, p for trend < 0.001). We recorded an almost

significant reduction in the prescription of loop diuretics during the whole study period (Fig. 3B).

On the average, we observed a significant improvement in functional capacity parameters. From baseline to the end of the study, peak VO₂ increased from 15.6 ± 4.5 to 16.5 ± 4.9 mL/min/kg ($p = 0.001$) with a progressive trend of improvement throughout all titration visits (p for trend = 0.001) (Fig. 4, Table 2). Notably, peak VO₂ changes were in parallel with NYHA class amelioration (Table 3). VO₂ at the AT, detectable in 80 patients, significantly improved, from 11.5 ± 3.3 ml/min/kg ($47 \pm 14\%$ of the predicted peak VO₂) to 12.2 ± 3.5 mL/min/kg ($51 \pm 15\%$) (p value baseline vs. end of study 0.028) (Fig. 4, Table 2). Peak workload increased as well across all the study steps (from 91 [67–120] to 97 [73–121] Watt, p for trend < 0.001). We did not observe a significant reduction in VE/VCO₂ slope values in the whole population (Table 2). Differently, considering only the frailer patients with pathological slope value at baseline (VE/VCO₂ ≥ 34 , $n = 34$), a significant amelioration was observed at the end of the study, from 39.5 ± 5.8 to 35.9 ± 7.1 (p for trend = 0.030).

In parallel, sacubitril/valsartan induced a positive cardiac reverse remodeling (Table 2). Specifically, LVEF increased (31 ± 5 vs. $37 \pm 8\%$; p for trend < 0.001); end-diastolic and end-systolic volumes (EDV and ESV) decreased [from 194 ± 66 to 170 ± 60 ml (p for trend < 0.001) and from 122 [104–160] to 101 [77–141] ml (p for trend < 0.001), respectively] along with systolic pulmonary artery pressure (PAPS) (from 34 ± 12 to 30 ± 14 mmHg, $p = 0.007$). We observed a significant reduction in left atrial (LA) volume from 44.3 [34.8–56.8] to 37.9 [33.0–51.3] mL/m², p for trend < 0.0001 . Of note, changes in peak VO₂ and LVEF were independent of each other (Table 3).

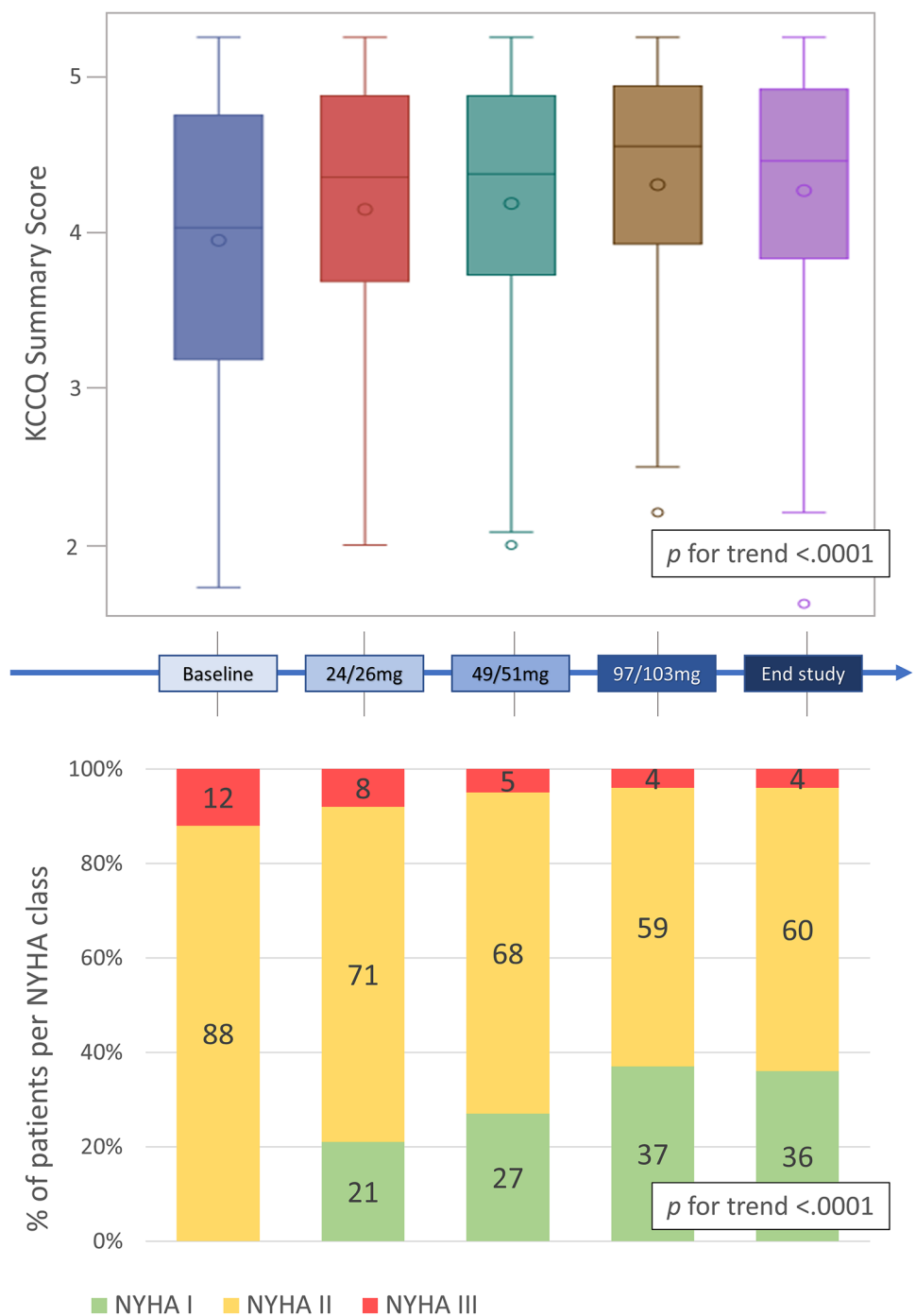
As regards cardiac biomarkers, NT-proBNP significantly reduced across the study steps from 1179 [610–2757] to 780 [372–1344] pg/ml (p for trend < 0.0001) (Table 2). Of note, we observed a statistically significant reduction ($p < 0.0001$) at all study steps compared to baseline values. Again, NT-proBNP amelioration was independent from LVEF improvement, but was in parallel with peak VO₂ and NYHA class changes (Table 3).

Finally, a global, multiparametric risk assessment was evaluated through MECKI score. We observed a statistically significant reduction from baseline of the calculated risk at 2 years, from 4.35 [2.42–7.71] to 2.35% [1.24–4.96], $p = 0.003$ (Table 2).

Discussion

The present study demonstrated a positive impact of sacubitril/valsartan on exercise capacity, reverse cardiac remodeling, NT-proBNP, and QoL in stable HF_{rEF} patients. Importantly, for the first time, we showed how these improvements, although not directly correlated with each other from

Fig. 2 Quality of life and NYHA class amelioration during the study. A progressive significant improvement in QoL (upper panel) and NYHA class (lower panel) was observed during the drug uptitration. KCCQ-12 summary score significantly improved from 3.95 ± 0.92 to 4.27 ± 0.81 . About one-fifth of patients report being asymptomatic (NYHA I) already after 1 month of treatment at the lower sacubitril/valsartan dose (24/26 mg b.i.d.), and more than one-third become asymptomatic at the end of the study. Abbreviations: QoL, quality of life; NYHA, New York Heart Association; KCCQ, Kansas City Cardiomyopathy Questionnaire

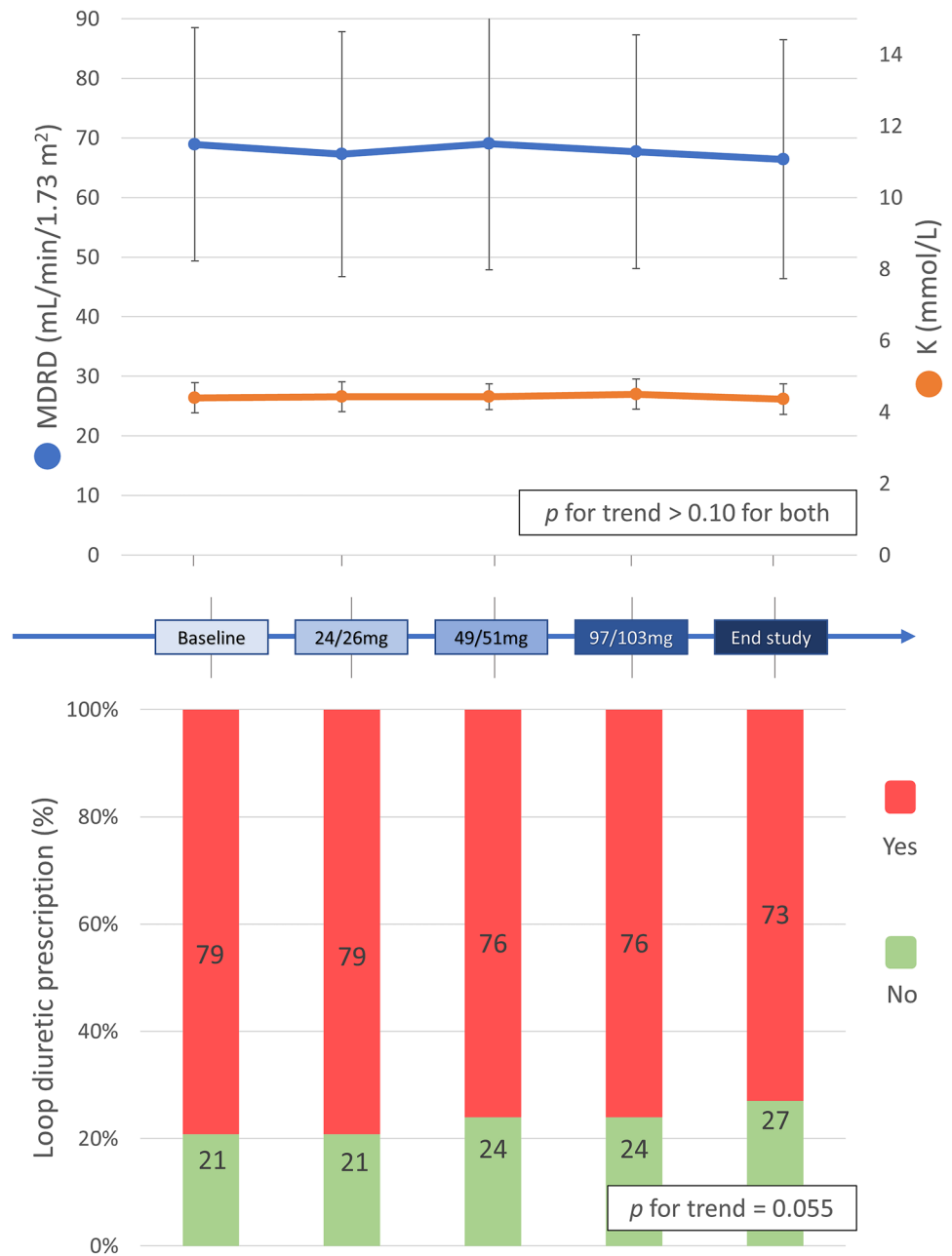


a statistical point of view, are consistent across the whole fixed monthly-based uptitration steps with the commercially available drug dosages (24/26 → 49/51 → 97/103 mg).

In particular, we evidenced an improvement of the strongest prognostically relevant CPET parameters, as shown by a significant increase in peak VO_2 , together with a reduction in VE/VCO_2 slope in frailer patients. Moreover, a tendency toward VO_2 improvement at AT was observed (p for trend ns; p value baseline vs end study 0.028). This result is in line

with the increased number of patients in which AT became detectable during the treatment (from 87 to 95% at the end of the study). This is particularly relevant being the presence of a non-detectable AT linked to a non-homogenous oxygen delivery to the working muscles to non-homogenous resistance to oxygen flow from the capillary to the mitochondria and muscle oxygen utilization. Moreover, the presence of a non-detectable AT is per se a well-known strong negative prognostic marker in HFrEF [25, 31].

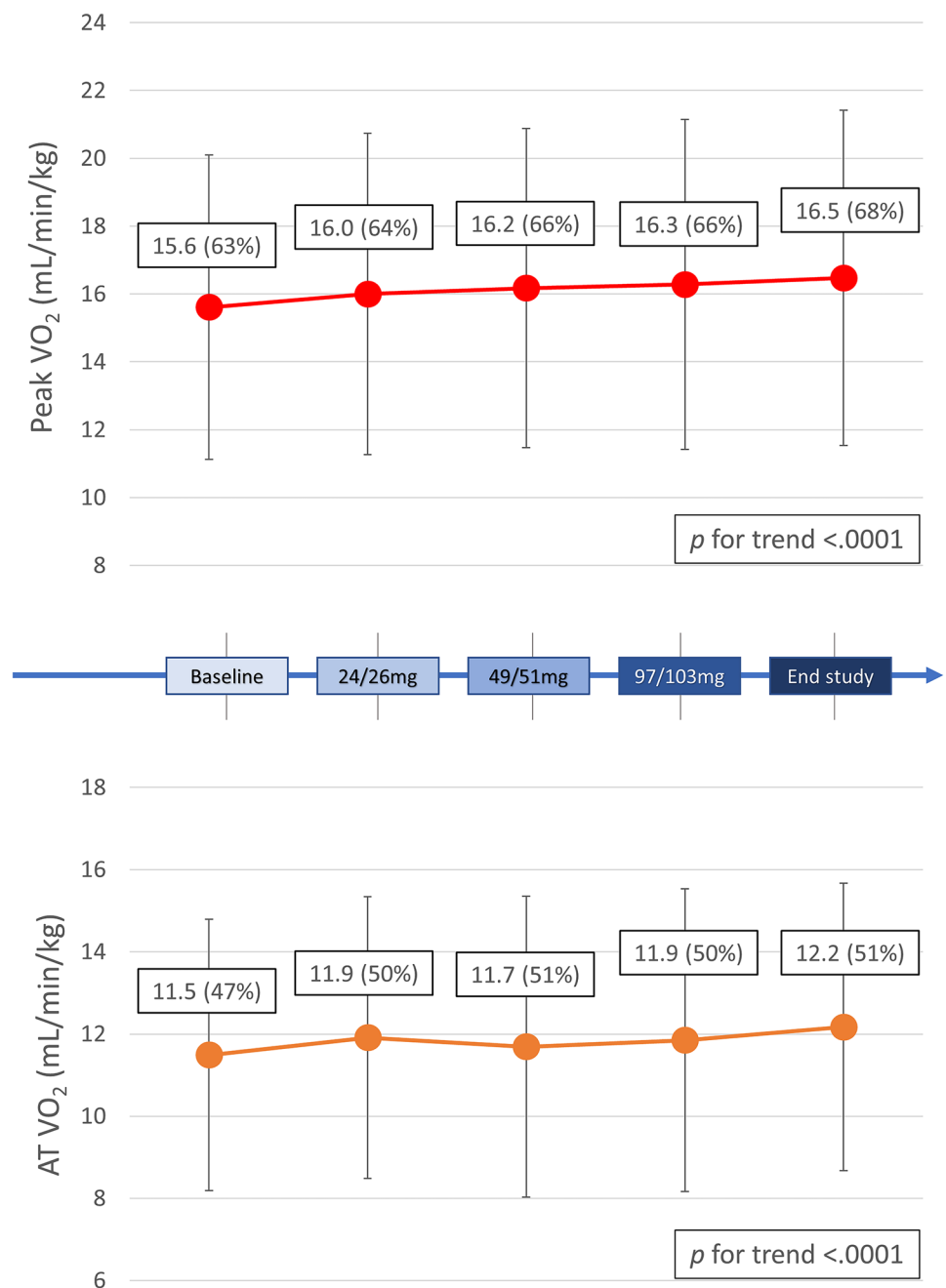
Fig. 3 Renal function, potassium values and loop diuretic prescription. The upper panels show how renal function (as assessed by MDRD) and serum potassium did not significantly change during the whole study. In the lower panel, a progressive, non-significant, reduction in the prescription of loop diuretics (e.g., furosemide) is shown. Abbreviations: MDRD, Modification of Diet in Renal Disease



These data should be read in relation to previous studies on this topic. In the ACTIVITY-HF study [14], a randomized controlled trial assessing functional capacity with CPET, sacubitril/valsartan failed to demonstrate a benefit on peak VO_2 compared with enalapril on a large multicenter population of HFrEF patients. Another randomized trial by Dos Santos et al. [15] reached the same conclusions, as another small Italian retrospective trial did [18]. One possible explanation is that the populations enrolled in these studies are different from ours, as evidenced by baseline peak VO_2 values, particularly low in ACTIVITY-HF (12.9 ± 3.0 ml/kg/min) and high in the Dos Santos et al.

study (19.35 ± 0.99 ml/kg/min). It is likely that, while maintaining a favorable prognostic effect, in patients who are too advanced or too “healthy,” sacubitril/valsartan may not be able to improve functional capacity, as our data seem to suggest this effect in an intermediate “sick” HF population (baseline peak VO_2 15.6 ± 4.5 ml/kg/min). In a comparable group of HFrEF patients (baseline peak VO_2 14.6 ± 3.3 ml/Kg/min) enrolled in a single arm prospective study, Vitale et al. [7] demonstrated an increase of 17.8% in peak VO_2 at 6.2-month follow-up and an improvement in other CPET parameters, as evidenced by a significant reduction in VE/VCO_2 slope values in frailer patients. On the other hand, a

Fig. 4 Oxygen intake progressive improvement. The figure shows the progressive significant improvement of VO_2 , both at peak exercise (upper part) and at the AT (lower part). As demonstrated by the p for trend values, the increase in VO_2 starts during the first up-titration steps and is maintained through the whole study protocol. Abbreviations: VO_2 , oxygen intake; AT, anaerobic threshold



previous small study conducted on a selected population of advanced HFrEF patients listed for heart transplantation seems to suggest a residual favorable effect of sacubitril/valsartan on exercise capacity [32]. All these data indicate that accurately predicting which patients are more likely to show an improvement in functional capacity during sacubitril/valsartan therapy is not straightforward. The treatment response is indeed variable also depending on phenotypic features of the disease underlying HFrEF, as evidenced in a trial by Nugara et al., in which functional benefit correlated with the presence of myocardial fibrosis

on cardiac magnetic resonance [33]. Therefore, the presence of a “sweet spot” in baseline VO_2 as a possible predictor for maximal benefit during sacubitril/valsartan treatment represents to date a fascinating hypothesis but requires further study to be definitely demonstrated.

Importantly, our trial was the first one designed to assess a dose/effect relationship with a fixed and progressive monthly-based up-titration of the drug dosages. We demonstrated how the more relevant CPET parameters, as well as NT-proBNP, NYHA class and QoL, start to improve since the first step (24/26 mg b.i.d.), maintaining a progressive

Table 2 Cardiopulmonary exercise test and echocardiographic parameters during the study

	<i>Baseline</i>	<i>24/26 mg</i>	<i>49/51 mg</i>	<i>97/103 mg</i>	<i>End study</i>	<i>p TREND</i>
<i>Peak HR (bpm)</i>	109 ± 24	108 ± 23	107 ± 23	109 ± 23	111 ± 23	0.334
<i>Peak HR (% pred)</i>	70.3 ± 15.3	70.1 ± 15.1	68.8 ± 14.3	71.0 ± 16.3	71.1 ± 13.5	0.429
<i>Peak power (watt)</i>	91 (67–120)	98 (72–123)	99 (68–125)	101 (71–122)	97 (73–121)	0.001
<i>VO₂ AT (mL/min/kg)</i>	11.5 ± 3.3	11.9 ± 3.4	11.7 ± 3.7	11.9 ± 3.7	12.2 ± 3.5	0.245
<i>VO₂ AT (% pred)</i>	47 ± 14	50 ± 17	51 ± 18	50 ± 15	51 ± 15	0.085
<i>Peak VO₂ (mL/min/kg)</i>	15.6 ± 4.5	16.0 ± 4.7	16.2 ± 4.7	16.3 ± 4.9	16.5 ± 4.9	0.001
<i>Peak VO₂ (% pred)</i>	63 ± 16	64 ± 17	66 ± 16	66 ± 17	68 ± 17	<0.0001
<i>VE/VCO₂ slope</i>	32.8 ± 6.8	31.6 ± 6.3	32.1 ± 6.3	31.8 ± 6.5	32.1 ± 6.0	0.952
<i>O₂ pulse (mL/b)</i>	11.9 ± 4.1	12.1 ± 3.4	12.4 ± 3.7	12.3 ± 3.8	12.1 ± 3.5	0.015
<i>LAVi (mL/m²)</i>	44.3 (34.8–56.8)	39.6 (34.0–51.2)			37.9 (33.0–51.3)	<0.0001
<i>MR grade</i>	1 (1–2)	1 (1–1.5)			1 (1–1)	<0.0001
<i>LVEDVi (mL/m²)</i>	94 (79–114)	90 (73–107)			84 (67–98)	<0.0001
<i>LVESVi (mL/m²)</i>	63 (54–80)	58 (45–72)			53 (39–68)	<0.0001
<i>LVEF (%)</i>	31.4 ± 4.7	34.3 ± 7.3			36.6 ± 8.1	<0.0001
<i>TAPSE (mm)</i>	20.4 ± 4.5	19.6 ± 4.3			19.8 ± 4.7	0.081
<i>PAPS (mmHg)</i>	33.7 ± 11.8	31.2 ± 15.1			29.9 ± 13.7	0.007
<i>MECKI score (%)</i>	4.35 (2.42–7.71)	2.95 (1.92–6.74)			2.35 (1.24–4.96)	<0.0001

HR heart rate, *VO₂* oxygen intake, *AT* anaerobic threshold, *VE/VCO₂* minute ventilation/carbon dioxide production relationship, *LAVi* left atrial volume indexed, *MR* mitral regurgitation, *LVEDVi* left ventricle end diastolic volume indexed, *LVESVi* left ventricle end systolic volume indexed, *LVEF* left ventricle ejection fraction, *TAPSE* tricuspid annular plane systolic excursion, *PAPS* systolic pulmonary artery pressure, *MECKI* Metabolic Exercise Cardiac Kidney Index

and sustained improvement during the entire follow-up. This suggests that also low doses of sacubitril/valsartan may already be important in conferring clinical and prognostic benefits, as also shown by an observational study by Corrado et al. [34].

The CPET changes were paralleled by a decrease of LV volumes (both EDV and ESV), LA volumes, PAPs and MR, as previously published by our group [35, 36]. Interestingly, we showed that 32 patients (33%) improved LVEF from < 40 to more than 40%, meeting the criteria for HF with improved EF (HFimpEF). This subset of HF patients is now properly classified as a new group by the HF American guidelines [37], with the aim to underline the prognostic relevance of a dynamic evaluation of the HF patients. Similarly, 42 patients (51%) improved EF from < 35 to more than 35%, losing the formal indication for ICD implantation in primary prevention [38], and confirming the results from a recently published article [39].

Parallel to the functional capacity improvement at CPET, we also observed an amelioration in patients' subjective perception of functional limitation during their daily life, assessed through NYHA class and, importantly, with the KCCQ-12 questionnaire (Fig. 3), a well-validated prognostic tool in the HFref field [40]. Interestingly, after the baseline evaluation in which only NYHA II and III HFref patients were enrolled, about one-fifth of patients reported being asymptomatic (NYHA I) already after 1 month of treatment at the lower sacubitril/valsartan dose (24/26 mg b.i.d.), and

more than one-third (36%) become asymptomatic by the end of the study (Fig. 3). These results are in line with a significant increase in peak workload at CPET, confirming that patients are able to tolerate more intense efforts with ongoing sacubitril/valsartan treatment. Even in the context of a general improvement of most of the variables evaluated, the significant correlation of *VO₂* with KCCQ changes and not with an echocardiographic variable such as LVEF is interesting, thus showing how the evaluation of functional capacity represents a fundamental, holistic approach which better represents the patient's state and wellness, beyond its prognostic aspect.

Looking into the need for a more dynamic evaluation of HFref (each patient's participation in our trial lasted about 9 months), all these changes are particularly relevant since they occurred "against the current," whereas the natural evolution of this disease would have been a progressive worsening. Moreover, while the standard background HF therapy was kept stable during the observation period, we noted a reduction in the prescription of furosemide (Fig. 3), showing how the observed favorable effects are independent from loop diuretic administration and actually allow a diuretic dose reduction which is considered a positive trend due to the diuretic drawbacks. Once again, sacubitril/valsartan safety and the tolerability were confirmed by stable renal function and potassium values over time, and by 75% of the patients being able to tolerate the 97/103 mg b.i.d dose without adverse reactions.

Table 3 Correlations

	Peak VO ₂ mL/min/kg	Peak VO ₂ % pred	AT VO ₂ % pred	AT VO ₂ mL/min/kg	LVEF	KCCQ summary score	NYHA
Peak VO₂ mL/min/kg	1	0.932	0.415	0.500	0.025	0.221	-0.123
		<.0001	0.000	<.0001	0.810	0.039	0.243
Peak VO₂ % pred	0.932	1	0.507	0.548	0.039	0.194	-0.170
	<.0001		<.0001	<.0001	0.714	0.071	0.105
AT VO₂ % pred	0.415	0.507	1	0.930	0.116	0.014	-0.166
	0.000	<.0001		<.0001	0.311	0.908	0.147
AT VO₂ mL/min/kg	0.500	0.548	0.930	1	0.041	0.039	-0.149
	<.0001	<.0001	<.0001		0.722	0.742	0.194
LVEF	0.025	0.039	0.116	0.041	1	-0.012	-0.103
	0.810	0.714	0.311	0.722		0.907	0.318
KCCQ summary score	0.221	0.194	0.014	0.039	-0.012	1	0.024
	0.039	0.071	0.908	0.742	0.907		0.823
NYHA	-0.123	-0.170	-0.166	-0.149	-0.103	0.024	1
	0.243	0.105	0.147	0.194	0.318	0.823	
NT-proBNP *	-0.226	-0.219	-0.162	-0.157	-0.079	-0.217	0.271
	0.045	0.052	0.190	0.205	0.479	0.055	0.013

Significant ($p < 0.05$) correlations are highlighted in red

VO₂ oxygen intake, AT anaerobic threshold, LVEF left ventricle ejection fraction, KCCQ Kansas City Cardiomyopathy Questionnaire, NYHA New York Heart Association Class

*Spearman correlation

The positive prognostic effects of sacubitril/valsartan were also confirmed by the risk assessment provided by the combination of metabolic, exercise, cardiac, and kidney function parameters into the MECKI score [30]. Specifically, the risk of death or urgent heart transplant/LVAD implantation at 2 years was almost halved, suggesting again how HF disease modifying drugs can greatly affect the trajectory of the disease with an even more pronounced effect on HF prognosis [41].

Limitations

This study was conducted before the introduction of SGLT2 inhibitors as a standard therapy for HFrEF, so it is not possible to estimate how well these results can be reproduced in a population also treated with these drugs. In addition, a chronic, stable and well-treated population from an outpatient setting, with normal right ventricular systolic function and capable of maximal exercise was included in the present study. Therefore, we do not know whether the same benefit can be expected in

frailer patients or those in whom sacubitril/valsartan is introduced during acute or sub-acute HF events. It is impossible to rule out whether part of the observed functional improvement at CPET is also secondary to better adaptation toward exercise along the whole protocol (“training” effect). However, this can be considered minimal since these stable patients were enrolled among the ones already undergoing regular clinical and CPET follow-up at HF units and therefore used to regular exercise protocols. Lastly, it was not possible to run, albeit desirable, a placebo control study for ethical reasons, being sacubitril/valsartan treatment strongly recommended by ESC HF guidelines (class I) [42], as well as by other guidelines [43, 44].

Conclusion

Our study confirmed the positive effect of sacubitril/valsartan on functional capacity. For the first time, with a fixed and progressive monthly-based uptitration, we

demonstrated how the more relevant CPET parameters, as well as echocardiographic measurements, biomarkers, NYHA class, and QoL, start to improve early, maintaining a progressive and sustained amelioration during the treatment. These results suggest a significant prognostic improvement as evidenced by the halving of the risk calculated with MECKI score.

Author contribution All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by MM, IM, ES, AG, SP, and DM. The first draft of the manuscript was written by MM, IM, ES, SP, and PA, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Availability of data and material Raw data will be available upon request on the website www.zenodo.org.

Code availability Not applicable.

Declarations

Ethics approval The present research protocol complies with World Medical Association Declaration of Helsinki, and it was approved by the Centro Cardiologico Monzino Ethical Committee (CCM 898). This observational cohort study was also registered to clinicaltrials.gov with ID: NCT04434170.

Consent to participate Each subject provided written consent to the study.

Consent for publication Not applicable

Conflict of interest The authors declare no conflict of interests.

Disclaimer All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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