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Article

The Effects of Sacubitril/Valsartan on Clinical, Bioumoral and Echocardiographic Parameters in Patients with Heart Failure with Reduced Ejection Fraction: The "Hemodynamic Reverse Remodeling"

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Abstract:

BACKGROUND: Sacubitril/valsartan has been shown to be superior to enalapril in reducing the risks of death and hospitalization for heart failure (HF). However the effect on cardiac performance remains unknown. We sought to evaluate the effects of sacubitril/valsartan on clinical, bioumoral and echocardiographic parameters in patients with HFrEF.

METHODS: Sacubitril/valsartan was administered to 205 HFrEF patients.

RESULTS: Among 230 patients (mean age 59 ± 10 years, 46% with ischemic heart disease) 205 (89%) completed the study. After a follow–up of 10.49 (2.93±18.44) months, the percentage of patients in NYHA class III changed from 40% to 17% (p<0.001). Median N–Type natriuretic peptide (Nt-proBNP) decreased from 1865 ± 2318 to 1514 ± 2205 pg/mL, (p=0.01). Furosemide dose reduced from 131.3 ± 154.5 to 120 ± 142.5 (p=0.047). Ejection fraction (from 27± 5.9% to 30 ± 7.7% (p<0.001) and E/A ratio (from 1.67 ± 1.21 to 1.42 ± 1.12 (p=0.002)) improved. Moderate to severe mitral regurgitation (from 30.1% to 17.4%; p=0.002) and tricuspid velocity decreased from 2.8 ± 0.55 m/sec to 2.64 ± 0.59 m/sec (p<0.014).

CONCLUSIONS: Sacubitril/valsartan induce "hemodynamic reverse remodeling" and in association with Nt-proBNP concentrations lowering improve NYHA class despite a diuretic dose reduction.

Keywords: Heart failure; Sacubitril/valsartan; Neprilysin inhibition; Reduced ejection fraction; echocardiography, Nt-Pro-BNP, hemodynamic, remodeling.

1. Introduction

Combining renin-angiotensin-aldosterone system (RAAS) blockade with natriuretic peptide system enhancement may deliver specific therapeutic benefits to patients with heart failure and reduced ejection fraction (HFrEF). The first-in-class angiotensin receptor neprilysin inhibitor (ARNI) sacubitril/valsartan combines the angiotensin II type-1 receptor blocker (ARB) valsartan with the neprilysin inhibitor sacubitril. Sacubitril/valsartan was superior to enalapril in reducing risks of death and hospitalization for HF in patients with HFrEF in the Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) study [1]. However the effect of sacubitril/valsartan on cardiac performance in patients with HFrEF remains unknown. Therefore, in this study, we sought to evaluate the effects of sacubitril/valsartan on clinical, bioumoral, echocardiographic, parameters in HFrEF patients.

2. Experimental Section

Study Design and Patient Selection.

The study was conducted in our outpatient HF clinic center between September 1st, 2017 through Jenuary 15th, 2019 and was approved by the ethics committee in 14.01.17 (project code IRBB 23/16) of the Istituto Mediterraneo per i Trapianti e Terapie ad Alta Specializzazione (ISMETT) center in Palermo, Italy.

All patients provided informed consent for participation. The protocol was approved by the research ethics committee in accordance with the principles of the Declaration of Helsinki and national regulations.

In this prospective observational single center study, sacubitril/valsartan was administered to patients with HFrEF, in addition to recommended therapy.[2] The aim of the study was to evaluate the effects of sacubitril/valsartan on clinical, bioumoral and echocardiographic parameters, recorded at baseline and after follow-up.

Patients were included in the study in accordance with the following inclusion criteria:

(1) symptomatic heart failure defined as New York Heart Association (NYHA) class II-III.

(2) left ventricular ejection fraction (LVEF) below 35% measured by echocardiography;

(3) pretreatment with an individual optimal dose of angiotensin-converting enzyme inhibitor (ACE-I) or ARB for at least 6 months;

(4) arterial blood pressure ≥100 mmHg;

(5) serum potassium (K+) level <5.4 mEq/L.

Exclusion criteria were as follows:

(1) hospitalization for HF within 90 days before ambulatory evaluation.

(2) Myocardial revascularization within 180 days before ambulatory visit.

(3) Concomitant initiation of cardiac resynchronization therapy (CRT) and/or percutaneous mitral valve treatment during study follow-up or in the previous 6 months.

(4) Presence of congenital heart disease.

(5) Severe liver insufficiency (Child-Pugh C).

(6) History of angioedema.

Study Procedures: To assess clinical stability, patients were assessed in our outpatient clinic at the enrolment phase (baseline visit). Medical history, physical exam, weight, blood pressure, NYHA class, 12-lead electrocardiogram (ECG), and laboratory analysis comprehensive of biomarkers including N-terminal pro-brain natriuretic peptide (NT-proBNP) were obtained every 1 month to undertake sacubitril/valsartan dose up-titration and then every 6 months. Doses of sacubitril/valsartan were prescribed according to established recommendations [2]. The recommended starting dose was 49/51 mg twice-daily. Patients were switched from an ACE-I after a 36-hour washout period. For patients with severe renal impairment (estimated glomerular filtration rate [eGFR] <30 mL/min), moderate liver insufficiency (Child-Pugh B), hypotensive (<110 mmHg), or taking low doses of ACE-I or ARB, the starting dose was 24/26 mg twice-daily. Up-titration was

performed every 4 weeks if tolerated by the patient. Changes in the doses of diuretics were allowed during follow-up. Safety and tolerability assessments were performed, including monitoring and recording of all adverse events and their relationship to the study drug. Two hundred thirty were initially enrolled. After the run-in phase (one month), eight patients discontinued sacubitril/valsartan because of hypotension , four because of worsening renal function and two because of skin erythema: Two hundred and sixteen patients were finally evaluated.

Echocardiography: A standard 2-Dimensional and Doppler transthoracic echocardiogram was performed at two time points (baseline assessment and 6 months after the initiation of sacubitril/valsartan) in all patients. All ultrasound examinations were done with a commercially available echocardiographic instrument (Vivid 9 System, Vingmed, General Electric Healthcare and Philips Medical Systems, EPIC). LVEF and volumes were measured from apical views using the modified biplane Simpson method, as previously described [3].Volumes and mass were indexed to the body surface area. The right ventricular (RV) longitudinal systolic function was assessed by tricuspid annular plane systolic excursion (TAPSE). ColorDoppler was used to qualitatively assess mitral regurgitation (MR) degree. Assessment of diastolic function was made by trans-mitral early (E wave velocity) and late (A wave velocity) Doppler flow waves, E/A ratio, and E deceleration time, and by measuring the early diastolic pulsed wave tissue Doppler (PW-TDI) at the medial and lateral mitral annulus (e'). E/e' ratio was used as a parameter of LV end-diastolic filling pressure (LVEDP)[4].Tricuspid regurgitation (TR) velocity was mesured as mesure of sistolic pulmonary arterial pressure and inferiore vena cava diameter variation as surrogate of central venous pressure. Images were analyzed offline by two expert investigators blinded to clinical factors.

Statistical analysis was performed using SPSS Statistics 25 software (IBM). Continuous variables are described by mean (SD), or by median and interquartile range, in case of non-normal distribution. Categorical variables were expressed as number (percentages). One hundred and sixty-one patients were followed-up in our outpatient clinic, and changes from baseline were tested by paired t-test or McNemar test, respectively. A *P*-value <0.05 was considered statistically significant.

3. Results

3.1 Baseline Evaluations

A total of 216 patients were prospectively enrolled. However Five patients discontinued sacubitril/valsartan because experienced hypotension, four patients because acute on chronic HF and two patients had ventricular arrhythmia. Therefore, 205 (89%) patients were included in the final analysis with a median follow-up of 10.49 m (range 2.93-18.44) months. The mean age was 59 ± 10 years, 15% females, 46% with ischemic heart disease, 62 % with NYHA functional class II and 17% on atrial fibrillation. Baseline characteristics of patients are presented in Table 1.

TABLE 1

PATIENTS CHARACTERISTICS,	N (%)
Pazients	205
Age (mean ± SD)	59 ± 10
Female sex	31 (15)
BSA (mean ± SD)	2 ± 0.2
ETIOLOGY	
Ischemic	95 (46)
Non Ischemic	110 (54)
NYHA	
II	128 (62)
III	77 (38)
COMORBIDITY	
hypertension	90 (45)

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Diabetes	63 (32)
Atrial fibrillation	35 (17)
COPD	7 (3)
MEDICAL THERAPY	
FUROSEMIDE	180 (88)
MRA	174 (85)
ACE- I /ARB	100 (205)
β-BLOCKERS	197 (96)
IVABRADINE	37 (18)
ELECTRICAL THERAPY	
ICD	164 (80)
CRT	51 (25)

Values are mean ± standard deviation. BSA, Body surface area; NYHA, New York Heart Association; COPD, chronic obstructive pulmonary disease; MRA, mineralocorticoid receptor antagonist; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ICD, intracardiac defibrillator; CRT, cardiac resynchronization therapy.

The mean (SD) of systolic blood pressure was 118.5 ± 15mm Hg. The median of NT-proBNP levels, eGFR (Modification of Diet in Renal Disease [MDRD] Study) equation dosages, creatinine concentrations and serum potassium at baseline were 1865 ± 2318pg/mL, 69.4 ± 23.1 mL/min/1.73 m^2, 1.2 ± 0.35 mg/dl, 4.14 ± 0.44 mEq/L respectively. Beta-blockers, mineralocorticoid receptor antagonist, and furosemide were administered in 96%, 85%, and 88% of patients, respectively. The mean daily furosemide dose was 131.3 ± 154.5mg. Eighty percent of patient underwent to cardiac defibrillator (ICD) implantation and 25% of patients received CRT device with ICD. The starting dose of sacubitril/valsartan was 24/26 mg twice daily in 77% of patients. The dose of 49/51 mg was administered in 23 % of patients. Mean baseline values of LVEF, E/A ratio, left atrial volume index (LAVi), were 27 ± 5.9 %, 1.67 ± 1.21, 54.2 ± 22.6mL respectively. The percentage of patients with moderate to severe functional MR was 30.1% and the mean baseline values of TR velocity was 2.8 ± 0.55 m/sec. (table 2).

TABLE 2

Changes in CLINICAL, sacubitril/valsartan dose, BIOUMORAL and echocardiographic PARAMETHERS

	Baseline	Follow-up	p value
SBP (mmHg)	118,5 ± 15	115,4 ± 16,9	0.042
DBP (mmHg)	73 ± 10,3	67,5 ± 9,3	<0.001
NT-proBNP (pg/ml)	1865 ± 2318	1514 ± 2205	0.01
Creatinine (mg/dl)	1,2 ± 0,35	1,31 ± 0,57	0.052
eGFR (ml/min/1,73m2)	69,4 ± 23,1	65,3 ± 23,2	0.012
potassium (mEq/l)	4,14 ± 0,44	4,17 ± 0,44	0.611
Furosemide dose (mg)	131,3 ± 154,5	120 ± 142,5	0.047
SACUBITRIL/VALSARTAN			
24/26 (mg/bid)	77	39	
49/51 (mg/bid)	23	34	
97/103 (mg/bid)	0	27	
FE (%)	27 ± 5,9	30 ± 7,7	<0.001
EDVi (ml/m2)	120,5 ± 31,4	120,7 ± 33	0,932

MR mod/sev (%)	30.1	17.4	0.002
E/A	1,67 ± 1,21	1,42 ± 1,12	0,002
E/e'	14,79 ± 6,10	13,85 ± 6,09	0.194
LAVi (ml/m2)	54,2 ± 22,6	52,4 ± 19,1	0.202
TR velocity (m/s)	2,8 ± 0,55	2,64 ± 0,59	0.014
TAPSE (mm)	19,03 ± 4,55	19,28 ± 3,62	0.472

SBP: Systolic blood pressure; DBP: Diastolic blood pressure; Nt-pro-BNP, N-terminal pro–B-type natriuretic peptide. eGFR, estimated glomerular filtration rate; EF, ejection fraction; EDVi, endiastolic volume index.; MR, mitral regurgitation from moderate to severe grade; E/A: peak e-wave velocity/ peak a-wave velocity ratio; E/e' peak: e-wave velocity divided by mitral annular e' velocity (average) ratio; LAV-i, left atrial volume index; RA, right atrium; TR velocity: tricuspid regurgitation peak velocity; TAPSE, tricuspid annular plane systolic excursion.

3.2 Change in Clinical Characteristics, ARNI dose and Laboratory Data.

After a median follow–up of 10.49 months (2.93±18.44) days, percentage of patients HYHA class II increase from 60% to 73% and the number of patients in NYHA class III decrease from 40% to 17% (p<0.001).

Systolic and diastolic blood pressure decreased with treatment (*P = 0*.009 and *P* <0 .001, respectively). The dose of sacubitril/valsartan 49/51 mg twice daily was administered in 34% of patients. In 39% patients the initial dosage of 24/26 mg twice daily was maintained. In the 27% of patients the dose was up titrated until 97/103 mg twice daily. The median furosemide dose decreased from 131.3 ± 154.5 mg at baseline to 120 ± 142.5 mg after follow-up (P = 0.047), see table 2. Initiation and titration of sacubitril-valsartan was associated with a reduction in NT-proBNP concentration (1514 ± 2205 pg/ml; p =0.01). We observed significant changes, but not clinically relevant, in eGFR (65.3 ± 23.2 ml/min/1.73 m2; *p* = 0.012;). In fact no variation in creatinine concentrations and in serum potassium (1.31 ± 0.57 mg/ml; *P = 0.052*) (4.17 ± 0.44 mEq/L, p= 0.611) were founded, see table 2.

3.3 Change in Echocardiographic Measurements.

Patients exhibited a mild but significant improvement in LVEF (30 ± 7,7%; *P =0* .001). The changes in the E/A-wave ratio from baseline to follow up were (1.42 ± 1.12; *p =0* .002), on the contrary there was no significant change in E/e' (from 14.79 ± 6,10 to 13.85 ± 6.09; P=0.194). Treatment with sacubitril-valsartan was also associated with significant reduction of the percentage of patients with moderate to severe MR (from 30.1% to 17.4%, *P* = 0.002) . In addition TR velocity decrease from 2.8 ± 0.55 m/sec to 2.64 ± 0.59 m/sec (p<0.014), (Table 2).

3.4 Safety

During follow-up 5 (2%) patients discontinued sacubitril/valsartan because experienced hypotension, 4 (2%) patients because acute on chronic HF. In 2 (1%) patients worsening renal function was observed.

4. Discussion

This prospective observational study of patients with HFrEF showed that: switching to sacubitril/valsartan may generate "hemodynamic reverse remodeling" by reducing left ventricular filling pressure, MR and finally pulmonary artery systolic pressure; This hemodynamic effect in association with the reduction of Nt-proBNP may ameliorate functional class capacity and identify patients in which diuretic withdrawal could be safely performed (figure 1).

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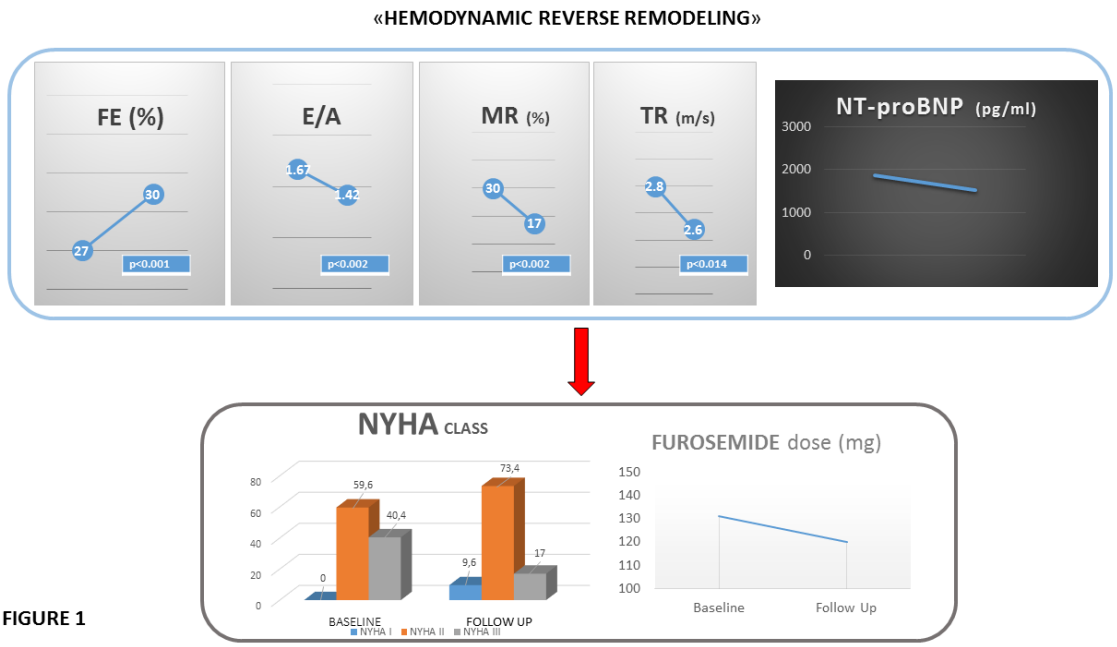

FIGURE 1

Figure 1. Hemodynamic reverse remodeling". Sacubitril/valsartan improved EF, reduced E/A ratio, MR, TR velocity and Nt-ProBNP concentration. This hemodynamic effect ameliorate NYHA class and reduce diuretic dose at follow up.

EF, ejection fraction; MR, mitral regurgitation from moderate to severe grade; E/A: peak e-wave velocity/ peak a-wave velocity ratio; TR velocity: tricuspid regurgitation peak velocity.

In this study, we evaluated the effect of switching to sacubitril/valsartan therapy in HFrEF patients through a multiparametric approach, that is NT-proBNP levels, echocardiography, and NYHA Class and all collected data were used to test the hypothesis that sacubitril/valsartan may confer an early comprehensive and global benefit to HFrEF patients.

In addition to their vasodilatory, natriuretic, and diuretic effects, natriuretic peptides inhibit the RAAS, sympathetic nervous system, and consequent release of antidiuretic hormone, improve myocardial relaxation and vagal tone, and have antifibrotic and antihypertrophic properties [5,6]. Mechanistically, sacubitril is implicated in attenuating cardiomyocyte cell death, hypertrophy, and impaired myocyte contractility [7]. Based on these preclinical and mechanistic evaluations of sacubitril, the incremental beneficial effect systolic and diastolic function might seem more intuitive than expected. However prospective data regarding sacubitril-valsartan and cardiac remodeling are limited: Martens and colleagues [8]reported a 5% mean improvement in LVEF after a follow-up period of 4 months. The recent PROVE-HF study [9] adds information regarding associations between ARNI therapy, change in NT-proBNP, and cardiac remodeling. Reduction in NT-proBNP following treatment with sacubitril-valsartan was associated with an increase in LVEF, and reductions in indexed LV and LA volumes as well as E/e' ratio. In line with this findings we found a mild but significant improvement in cardiac function measured by LVEF, confirming the potential LV reverse remodeling effect mediated by sacubitril/valsartan.

Moreover, at the best of our knowledge this is the first study to report a reduction in E/A ratio as well as improvement of MR severity. Both are important prognostic measures, reflecting the magnitude and chronicity of elevated cardiac filling pressures, LV negative remodeling and fluid congestion. This improvement determine reduction in TR velocity and in the pulmonary artery systolic pressure. The observed benefit of ARNI in inducing not only left ventricular reverse remodeling but also E/A ratio, MR degree reduction and pulmonary pressure lowering is unique and fascinating because it is crucial in the clinical management and of HFrEF patients, and above all because it is consistent with the significant improvement in NYHA class observed in our population.

Coherently with echocardiographic measurements, neprilysin inhibition mediated by sacubitril acutely amplified the hemodynamic effects of natriuretic peptides determining natriuresis and vasodilation [10,11] which resulted in decreased neurohormonal activation as our data have demonstrated by NT-proBNP concentrations abatement at follow-up.

In facts reduction in NT-proBNP concentration was strongly associated with outcomes in PARADIGM-HF [1]. On the other hand, studies have suggested that a lack of NT-proBNP reduction after therapy for HFrEF is associated with worse left ventricular size and function [12,13]

Our results suggest that patients with NT-proBNP reduction following ARNI initiation are likely to experience reverse cardiac remodeling.

Improving in filling pressure, MR degree and pulmonary pressure in tandem with a small yet significant improvement in EF, that is "hemodynamic reverse remodeling", effectively improved NYHA class and exertional dyspnea.

In a recent metanalysis of twenty studies enrolling 10 175 patients, ARNI improved functional capacity in patients with HFrEF, including increasing NYHA class and 6-minute walking distance. Moreover ARNI outperformed angiotensin-converting enzyme inhibitors/angiotensin receptor blockers in terms of cardiac reverse remodeling with striking changes in left ventricular EF, diameter, and volume [14].

Confirming these data, we found a reduction of percentage of patients in NYHA class III and an increasing number of patients in NYHA class I and II at follow up (Figure 1).

These data are in line with our previously published results showing a significant improvement in well known surrogates of cardiac performance such as peak VO_2 and O_2 pulse as well as others main prognostic-relevant CPET parameters after initiation of sacubitril/valsartan [15] .

Furthermore this "hemodynamic reverse remodeling" in association with Nt-proBNP concentration reduction, could lead to identify patients in which diuretic withdrawal strategy can be safely undertaken [16] . As we founded in our study reducing the mean diuretic dose, allows to avoid a significant deterioration of renal function, [17] and electrolyte imbalance.

Interestingly treatment with sacubitril/valsartan was associated with more loop diuretic dose reductions and fewer dose increases compared with enalapril in the PARADIGM-HF study [18], suggesting that treatment with sacubitril/valsartan may reduce the relative requirement for loop diuretics in patients with heart failure with reduced ejection fraction. The reduced relative need for diuretics in patients treated with sacubitril/valsartan may potentially be secondary to the natriuretic effects of sacubitril or the presumed improvement in haemodynamics that may occur with sacubitril/valsartan.

Loop diuretic use has been associated in prior studies with worse outcomes in heart failure. Several mechanisms have been proposed by which loop diuretics may increase risk of mortality: neurohormonal activation electrolytes depletion, serious cardiac arrhythmias [19,20], as well as an increased risk of cardio-renal syndrome [21] have all been reported in the literature. For this reason, as we have already demonstrated [16] diuretic therapy can and should be suspended in well-selected, asymptomatic, patients with HFrEF after adequate therapeutic neuro-hormonal modulation to preserve renal function.

Study limitation: This study has a number of limitations. Firstly, the study was not randomized. However, prospective longitudinal studies with multiple blinded assessors are a well-accepted design for evaluating echocardiographic and cardiopulmonary changes. Secondly, an important limitation of this study is the relatively small sample size and lack of a control group.

5. Conclusions

In summary, our findings are strongly suggestive of "hemodynamic reverse remodeling" in which a modulation of neurohormonal activation determined by sacubitril/valsartan may lead to a hemodynamic effect that may impact cardiac performance and in association with Nt-proBNP concentration abatement could lead to a ameliorate NYHA class and reduce diuretics administration and consequently to preserve renal function..

Author Contributions: For research articles with several authors, a short paragraph specifying their individual contributions must be provided. The following statements should be used "conceptualization, FC. and FM S.;

methodology, CM, DB.; software, DB and VA.; validation, LA., GC.; formal analysis, DB AND VA.; resources, GD, CF.; data curation, SS, VA.; writing—original draft preparation, GR.; writing—review and editing, GR, GV.; visualization, EL.; supervision, EC, FC.; project administration, DB.;

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Conflicts of Interest: "The authors declare no conflict of interest."

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