Sacubitril/Valsartan in heart failure with reduced ejection fraction: clinical and echocardiographic insights from a real world population

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Background: Following the PARADIGM trial, some studies have identified cardiac remodeling as major background for hard end point benefits of Sacubitril/Valsartan (S/V), but few adopted a well described definition in the literature.

Purpose: We aimed at a comprehensive evaluation of the effects of S/V on echo-derived measures of cardiac remodeling along with clinical and laboratory data over a medium-term follow-up pointing to a real-world HFrEF population.

Methods: This is a prospective observational study of HFrEF patients on optimal medical therapy (OMT) initiated with S/V at Heart Failure Clinic of our institute (January 2017-January 2020). In 62 HFrEF, echocardiographic, laboratory and clinical data were collected at baseline and over 10 (Q1-Q3 8–13) months after S/V initiation. Mean age was 68±12 years, 79% men. Left ventricular reverse remodeling (LVRR) was defined as: 1) an absolute increase in LVEF $\geq$10 points or a LVEF $\geq$50% at follow-up and 2) a relative decrease in indexed left ventricular end-diastolic diameter of at least 10% or an indexed left ventricular end-diastolic diameter $\leq$33 mm/m^2.

Results: Compared to baseline, S/V promoted a significant improvement of LV ejection fraction (LVEF, from 30% to 37%; p<0,0001) with an absolute median increase in LVEF of 8 points. Parallel significant reductions in left ventricular and atrial volumes, lower mitral regurgitation degree and a better diastolic dysfunction along with clinical improvement (NYHA class and NT-proBNP values) were observed at follow up. sPAP (systolic Pulmonary Arterial Pressure) was significantly decreased at follow-up evaluation (37 mmHg vs 31 mmHg p=0,005) (Table 1). Overall, LVRR as defined above was observed in 30% of patients. Younger age (64 vs 74 years, p=0,007), a shorter duration of the disease (7 vs 23 months, p=0,009), and non ischaemic etiology (79% vs 33% p=0,003), along with a smaller baseline LAESVi (Left Atrial End Systolic Volume, 41 vs 48 ml/m^2 p=0,012) were more common in patients with LVRR. sPAP and Right Ventricular (RV) function estimated by tricuspid annular plane systolic excursion (TAPSE) were significantly better in LVRR patients along with TAPSE/sPAP ratio (Table 2).

Conclusions: Our data point to a remarkable medium-term reverse remodeling effect by S/V in HFrEF. Findings reinforce the concept that the main benefits of S/V on hard end-points are mediated by its cardiac-related effects. Both a left and right reverse remodeling occur in HFrEF patients who start S/V in the most adaptable phase of the disease supporting an early administration.

Table1. Comparison between baseline and follow-up standard echocardiographic parameters applying the Wilcoxon Signed Rank for continuous variables (paired samples) or the McNemar for categorical variables (paired samples).

Echocardiographic Evaluation	Baseline	Follow-up	p Value
LVEF (%)	30 (25-34)	37 (30-43)	<0,0001
LVEDDi (mm/m^2)	32 (29-35)	31 (27-34)	0,02
LVEDVi (mL/m^2)	90 (75-110)	74 (57-92)	<0,0001
LAESVi (mL/m^2)	46 (40-59)	43 (33-50)	0,001
MR, no. %			
-none	7 (11)	17 (26)	
-mild	27 (41)	32 (49)	
-mild to moderate	15 (23)	7 (10)	<0,0001 for all subgroups
-moderate	14 (21)	10 (15)	
-severe	3 (4)	0 (0)	
Diastolic dysfunction, no(%)			
-0	0 (0)	2 (3)	
-1	27 (40)	31 (50)	0,05
-2	7 (11)	6 (9)	
-3	10 (15,2)	7 (11)	
TAPSE (mm)	18 (13-20)	18 (15-22)	0,114
sPAP (mmHg)	37 (28-49)	31 (26-37)	0,005
TAPSE/sPAP ratio	0,43 (0,29-0,71)	0,55 (0,44-0,77)	0,004
NYHA class	2 (2-3)	2 (2-2)	0,0001
NT-proBNP (ng/ml)	1520 (630-3200)	938 (353-2052)	0,005

LVEDDi, LV internal diameter at end-diastole indexed by body surface area; LVEDVi, LV end-diastolic volume indexed by body surface area; LVESVi, LV end-systolic volume indexed by body surface area. MR, mitral regurgitation degree.

Table2. Comparison between clinical and echocardiographic parameters in patients with and without LVRR using the Mann-Whitney U test for continuous variable (independent samples) and the Chi-square test for categorical variables.

	LVRR (N =19)	No LVRR (N =43)	p Value
Age (years)	64 (54-71)	74 (66-80)	0,007
Time since first diagnosis of HF(mths)	7 (2-26)	23 (9-44)	0,009
Non ischaemic etiology, no.%	15 (79)	14 (33)	0,003
LVEF baseline %	30 (20-34)	30 (27-35)	0,495
LVEF follow-up %	45 (42-51)	32.5 (28-38)	<0,0001
LVEDDi baseline (cm/m^2)	32 (29-35)	32 (30-38)	0,265
LVEDDi follow-up	27 (25-30)	33 (29-36)	<0,0001
LAESVi baseline (mL/m^2)	41 (39-48)	48 (44-65)	0,012
LAESVi follow-up	31 (22-38)	47 (41-56)	0,0001
sPAP baseline (mmHg)	43 (26-56)	36 (28-45)	0,410
sPAP follow-up	26 (23-31)	32 (27-38)	0,038
TAPSE baseline (mm)	17,5 (16-20)	18 (14-20)	0,549
TAPSE follow-up	22 (17-23)	17 (14-20)	0,020
TAPSE/sPAP baseline	0,33 (0,28-0,62)	0,43 (0,30-0,73)	0,476
TAPSE/sPAP follow up	0,65 (0,59-0,96)	0,47 (0,41-0,75)	0,014

LVEDDi, LV internal diameter at end-diastole indexed by body surface area; LVEDVi, LV end-diastolic volume indexed by body surface area.