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The Effect of Sacubitril/Valsartan on Functional Capacity of Patients Diagnosed With Heart Failure With Reduced Ejection Fraction Assessed by Six Minute Walk Test

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Abstract: Background: Heart failure (HF) constitutes a leading cause of morbidity and mortality worldwide and is associated with severe impairment in functional capacity. In patients with chronic HF and reduced ejection fraction (HFrEF), the PARADIGM-HF (Prospective Comparison of ARNI with an ACE-Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial showed that sacubitril/valsartan reduced the risk of the composite of cardiovascular (CV) death or first hospitalization for heart failure (HF) by 20% compared to enalapril during a median follow-up of 27 months. Remarkably, the trial showed also an early beneficial effect of sacubitril/valsartan by reducing the risk of 30-day readmission for any cause and HF by 26% and 38%, respectively. However, there is limited data on the short-term effect of sacubitril/valsartan on patient's functional performance. **Objective:** To evaluate if there is any short term effect of Sacubitril/Valarstan drug on the functional capacity of stable HF patients with reduced ejection fraction, which is measured by the simple non-invasive six minute walk test, in only 30 days period. **Methods:** This is a prospectively studied a cohort of patients with chronic HF, visited outpatients clinics in Ain Shams University Hospital and 6TH October University Hospital From November 1, 2018 to June 1, 2019. The inclusion criteria were: a) left ventricular systolic dysfunction ≤ 40%, b) stable New York Heart Association (NYHA) functional class ≥II, and c) prior treatment with angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB). In eligible patients, according to current guidelines, treatment with ACEI or ARB was replaced by sacubitril/valsartan. All patients provided informed consent and the protocol was approved by the research ethics committee in Ain Shams University. **Results:** Mean age of the studied patients was 55.07 ± 10.16 years, 83.3% males, 83.3% with ischemic cardiomyopathy, and 66.7% on NYHA functional class III. The mean (SD) of LVEF, 6-MWT, systolic blood pressure and estimated glomerular filtration rate were 30.00 ± 3.12 %, 279.33 ± 45.78 m, 114.33 ± 6.12 mm Hg and 64.83 ± 4.62 ml/min/1.73 m^2, respectively. The starting dos sacubitril/valsartan was 49/51 mg. Compared with baseline, the 6-MWT distance increased significantly at 30 days (+Δ = 92 m (40 – 150); p ≤ 0.001. In this observational study, treatment onset with sacubitril/valsartan was associated with 30-day improvement in the distance walked in 6-MWT. Further controlled studies are needed to confirm our results. **Conclusion:** In this observational study, treatment onset with sacubitril/valsartan was associated with 30-day improvement in the distance walked in 6-MWT.

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Keywords: Sacubitril/Valsartan; Six Minute Walk Test; Ejection Fraction

1. Introduction

Heart failure (HF) is a chronic, progressive, highly debilitating and life-threatening condition in which the heart cannot pump enough blood around the body because the muscles of the heart become too weak or too stiff to work properly ***(Mosterd et al., 2007).*** Heart failure (HF) is a major public health concern that affects as many as 23 million people worldwide ***(Bui et al., 2011)***. Furthermore, hospitalization rate and costs of care for HF are enormous. There has been substantial progress in the management of chronic HF with the availability of drugs such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), beta-blockers, and mineralocorticoid receptor antagonist (MRA). Because of high morbidity and mortality, there is an overwhelming need for new therapies that are safe and that can improve outcomes in patients with HF.

Heart failure (HF) is a complex clinical syndrome characterized by abnormalities in cardiac structure and function, dynamic remodelling, and

disturbances of the neurohormonal axis ***(McMurray et al., 2005).*** Neurohormonal regulatory mechanisms contribute to and modulate key pathways leading to HF, acting through three main systems: 1-The autonomic nervous system (ANS) ***(Ieda et al., 2009)***. 2-The rennin-angiotensin-aldosterone system (RAAS). Excess activity may contribute to pathological clinical alterations in HF, such as volume retention, peripheral vasoconstriction, and myocyte hypertrophy. 3-The natriuretic peptide system (NPS) which is a system composed of three.

Structurally related hormones: atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP), and C-type natriuretic peptide (CNP). ANP and BNP are secreted from the cardiac atria and ventricles, respectively, All natriuretic peptides (NPs) have varying effects on endocrine function, cardiac and kidney homeostasis, and blood volume control ***(Volpe et al., 2016; Potter et al., 2009).***

Different pharmacological approaches have been used to treat the neuroendocrine dysregulation in HF, including angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptors blockers (ARBs), mineralocorticoid receptor antagonists (MRAs), and beta-blockers (BBs). Conventional drug development in HF has focused on the attenuation of sympathetic nervous system (SNS) and RAAS, as pathways responsible for long-term ventricular remodelling ***(Vaduganathan et al., 2015)*** via the inhibition of the SNS with BBs and of the RAAS axis with ACEI/ARBs and MRAs.

Sacubitril/valsartan (previously known as LCZ696) is a first-in-class approved angiotensin receptor-neprilysin inhibitor (ARNI). LCZ696 combines a neprilysin inhibitor (sacubitril) and an ARB (valsartan). Neprilysin is a zinc-dependent neutral endopeptidase that is responsible for the degradation of several vasoactive peptides such as NPs, bradykinin, and adrenomedullin and contributes to the breakdown of angiotensin II ***(Daniels et al., 2007)***. Neprilysin inhibition and blockade of the Ang II type I receptor result in increasing the concentration of endogenous vasoactive peptides. In this way, the adaptive mechanisms of heart failure are stimulated with the final result in vasodilatation, the reduction of progression in myocardial fibrosis, the reduction of salt retention and the reduction of excessive neurohormonal activation.

Neuromodulation with ARNI simultaneously influences the RAAS and NPS pathways, and thus represents a successful and innovative approach in HF drug development ***(Senni et al., 2016).*** Indeed, Sacubitril/Valsartan promotes neurohormonal balance, leading to early relief of HF signs and symptoms, and long-term improvement in left ventricular remodelling. In July 2015, the FDA approved Sacubitril/ Valsartan for use in patients who have chronic and stable but symptomatic HF and who have a left ventricular ejection fraction (LVEF) of less than 40%.

Evidence from the prospective comparison of ARNI with ACEI to determine impact on global mortality and morbidity in HF (PARADIGM- HF) clinical trial; it was conducted on 8,399 patients who had NYHA class II–IV HF and an LVEF of not more than 40% and who were randomly assigned to LCZ696 (200 mg twice a day) or Enalapril (10 mg twice a day). The trial was stopped early because of an overwhelming benefit with LCZ696 therapy demonstrated that Sacubitril/ Valsartan reduced the risk of cardiovascular death by 20% [13.3% vs. 16.5%; hazard ratio (HR) 0.80; P <0.001] and HF-related hospitalization by 21% (12.8% vs. 15.6%; HR 0.79; P <0.001) compared with Enalapril in patients with HF with reduced ejection fraction. Sacubitril/Valsartan was also found to be associated with a reduction in 30-day readmissions following HF hospitalizations by 38% and for any cause by 26% ***(McMurray et al., 2014)***. Furthermore, those patients who received LCZ696 had lower levels of the biomarkers NT-proBNP and troponin compared with those receiving Enalapril. These differences were apparent within 4 weeks of treatment and were maintained when patients were assessed again 8 months later. This trial provided strong evidence for superiority of the ARNI in patients with HF with reduced ejection fraction (HFrEF).

These findings led to an American College of Cardiology (ACC)/ American Heart Association (AHA)/ Heart Failure Society of America (HFSA) Focused update on new pharmacological therapy for HF in May 2016 which recommends an ARNI as part of an evidence-based regimen to replace an ACEI or ARB in patients with chronic HF and reduced ejection fraction ***(Yancy et al 2016).*** Also, the 2016 contemporary guidelines of European Society of Cardiology suggest replacement of ACE inhibitors (ARBs in patients intolerant to ACE inhibitors) with ARNI as a possible therapeutic procedure. European recommendations differ from those of American guidelines regarding introduction of ARNI in later phases of the therapeutic algorithm, after previous standard ACE inhibitor therapy (ARBs in patients intolerant to ACE inhibitors), beta blockers and antagonists of mineral corticoid receptors.

The severity of congestive heart failure is usually graded according to patients reported symptoms, and in particular to the amount of physical activity that is associated with dyspnoea or fatigue. There is a simple practical test, the measurement of the distance walked in six minutes which is considered more realistic test of exercise capacity in patients with congestive heart

failure. The 6MWT is highly reproducible in patients with symptoms of HF. It is somewhat correlated to NYHA-FC and quality of life. It is a simple and inexpensive exercise originally designed to assess functional capacity in patients with chronic pulmonary disease. The test has been used in a number of randomized clinical HF trials to assess drug efficacy because of its prognostic value ***(Roul et al., 1998)***. The potential advantage of the 6MWT over other tests like symptom-limited cardiopulmonary exercise testing is that it is inexpensive and does not require specialized equipment. In addition, the Studies of Left Ventricular Dysfunction (SOLVD) Registry demonstrated the safety of this simple tool in 833 patients and found that the distance was predictive of the mortality and hospitalization rates for HF. With the 6MWT, a distance <350 m is associated with increased mortality in patients with HF, and change in walking distance >50 m is considered clinically relevant ***(Lipkin et al., 1986; Du et al., 2017).***

Aim of the Work

The study aims to evaluate if there is any short term effect of Sacubitril/ Valarstan drug on the functional capacity of stable HF patients with reduced ejection fraction, which is measured by the simple non-invasive six minute walk test, in only 30 days period.

2. Patients and Methods

From November 1, 2018 to June 1, 2019, we prospectively studied a cohort of patients with chronic HF, visited outpatients clinics in Ain Shams University Hospital and 6TH October University Hospital. The inclusion criteria were: a) left ventricular systolic dysfunction ≤ 40%, b) stable New York Heart Association (NYHA) functional class ≥II, and c) prior treatment with angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB). In eligible patients, according to current guidelines, treatment with ACEI or ARB was replaced by sacubitril/valsartan. All patients provided informed consent and the protocol was approved by the research ethics committee in Ain Shams University.

6-MWTwas performed at two time points (baseline assessment and after 30-day initiation of sacubitril/valsartan). Patients were instructed to cover the maximum distance possible in 6min, pausing to rest when needed in a 30 meter flat corridor. In each visit we registered demographic information, medical history, vital signs, 12 lead electrocardiogram, 6-MWT, standard laboratory data and pharmacological treatments. Doses of sacubitril/valsartan were prescribed according to established recommendations. The recommended starting dose was 49/51 mg twice-daily. By protocol, no treatment changes occurred between the two visits.

Sampling size: 30 patients with stable heart failure with reduced ejection fraction.

An informed consent was obtained from all the patients, approval of the Ain Shams university ethical committee was obtained according to the ethical guidelines of the 1975 declaration of Helsiniki as revised in 2008.

Methodology:

All the patients were subjected to: **History taking with special stress on;** *Smoking, hypertension, diabetes mellitus, family history of IHD, dyslipidemia,* history of angina, Currently used medications. **Full clinical examination**: it will be done twice; before giving the drug and 30 days after.

1. Twelve leads surface ECG:

It will be done to all patients before giving the drug and upon the request of the physician at any time if the patient condition necessitates so.

2. Routine investigations:

Full labs; will be carried for all patients before giving the drug and follow up 30 days after with special emphasis on renal profile (Serum creatinine, urea, sodium, potassium) and complete blood count. Estimated GFR will only be calculated using the following formula ***(Stevens et al., 2006)*:**

Estimated GFR (mL/min/1.73 m2) = 175 × (standardized SCr in mg/dL)-1.154 × (age in years)-0.203 ×(0.742 if female) × (1.212 if black), where SCr is the standardized serum creatinine value.

3. Conventional 2D Echocardiography:

Echocardiographic assessment will be done before giving the drug Sacubitril/Valsartan and after a period of 30 days from the intake of the medication to each patient to assess ejection fraction, LV dimensions, and valvular abnormalities, pulmonary artery pressure will be measured from a continuous wave Doppler regurgitate tricuspid jet signal if present. Using Philips affinity 50 w by S4-2 probe with frequency ranging from 1 to 4 MHz. Patients were examined in left lateral decubitus position, the left ventricular ejection fraction (LVEF) was calculated according to the according to the American Society of Echocardiography by using modified Simpson's method in this way the left endocardium was traced in four apical and two chambers views at end diastole and end systole to obtain left ventricular end diastolic and end systolic volumes as well as LVEF according to the American Society of Echocardiography.

Normal reference value for mean LVEF is (62 ± 5 %).

4. Therapies:

- Patients will be treated according to the current American Heart Association, the American College of

Cardiology, the European Society of Cardiology, and the Heart Failure Society of America (HFSA) guidelines. The standard HF drugs include diuretics, Beta-blockers, Mineralocorticoid antagonist (MRA). The only medication that will be added is our drug of interest (Sacubitril/Valsartan) instead of ACE-I or ARBS with 36 hours interval before the shift from ACEI.

Doses of Sacubitril/valsartan were prescribed according to established recommendations. The recommended starting dose was 49/51 mg twice-daily. By protocol, no treatment changes occurred between the two visits ***(Ponikowski, 2016).***

5. The six minute walk test: it was done twice before starting the Sacubitril/valsartan and a 30 day after.

Statistical Analysis

Data were collected, revised, coded and entered to the Statistical Package for Social Science (IBM SPSS) version 23. The quantitative data were presented as mean, standard deviations and ranges when parametric. Also qualitative variables were presented as number and percentages. The comparison between groups regarding qualitative data was done by using ***Chi-square test*** and/or ***Fisher exact test*** when the expected count in any cell found less than 5. The comparison between two paired groups regarding quantitative data and parametric distribution was done by using ***Paired t-. Spearman correlation coefficients*** were used to assess the correlation between two quantitative parameters in the same group.

3. Results

The previous table shows that most of our patients were males and have ICM representing 83.3% for both, meanwhile female and DCM patients represented only 16.7%. DM, smoking, dyslipidemia were the major risk factors with 66.7 % while 50% of our patients were hypertensive. 63.3 % of patients had positive family history of IHD.

Table (1): Descriptive data regarding Demographic data

		Total no. = 30
Age	Mean ± SD	55.07 ± 10.16
	Range	36 – 75
Gender	Female	5 (16.7%)
	Male	25 (83.3%)
DM	No	10 (33.3%)
	Yes	20 (66.7%)
HTN	No	15 (50.0%)
	Yes	15 (50.0%)
Smoking	No	10 (33.3%)
	Yes	20 (66.7%)
Dyslipedemia	No	10 (33.3%)
	Yes	20 (66.7%)
Family history of IHD	No	11 (36.7%)
	Yes	19 (63.3%)
Type of cardiomyopathy	ICM	25 (83.3%)
	DCM	5 (16.7%)

Table (2): Comparison between: Before and after introducing the drug Sacubtril/Valsartan regarding NYHA class, LVEF, BP, eGFR and serum potassium

		Pre	**Post**	**Paired t-test**		
				t	**P-value**	**Sig.**
NYHA class	1	0 (0%)	26 (86.7%)	48.571	0.000	HS
	2	10 (33.3%)	4 (13.3%)			
	3	20 (66.7%)	0 (0%)			
LVEF	Mean ± SD	30.00 ± 3.12	30.90 ± 2.78	-4.506	0.000	HS
	Range	25 – 35	25 – 35			
SBP	Mean ± SD	114.33 ± 6.12	108.67 ± 5.71	7.215	0.000	HS
	Range	105 – 130	100 – 120			
DBP	Mean ± SD	71.50 ± 5.28	68.83 ± 6.78	5.113	0.000	HS
	Range	60 – 80	60 – 80			
e GFR (ml/m2/min)	Mean ± SD	64.83 ± 4.62	64.13 ± 4.11	3.252	0.003	HS
	Range	56 – 74	56 – 70			
Serum K	Mean ± SD	4.14 ± 0.36	3.98 ± 0.23	4.127	0.000	HS
	Range	3.5 – 4.8	3.4 – 4.4			

P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant

Table (3): Treatment used by patients including ACEi/ARBS, beta blockers, MRA and diuretics before introducing Sacubitril/Vlasrtan.

Pre treatment		**No. (%)**
Torisamide	No	8 (26.7%)
	Yes	22 (73.3%)
Torisamide dose	Mean ± SD	16.36 ± 4.92
	Range	10 – 20
Furisamide	No	23 (76.7%)
	Yes	7 (23.3%)
Furisamide dose	Mean ± SD	40.00 ± 0.00
	Range	40 – 40
Capotopril	No	26 (86.7%)
	Yes	4 (13.3%)
Capotopril dose	Mean ± SD	100.00 ± 40.83
	Range	50 – 150
Candsartan	No	28 (93.3%)
	Yes	2 (6.7%)
Candsartan dose	Mean ± SD	12.00 ± 5.66
	Range	8 – 16
Irbisartan	No	29 (96.7%)
	Yes	1 (3.3%)
Irbisartan dose	Mean ± SD	150.00 ± 0.00
	Range	150 – 150
Ramipril	No	12 (40.0%)
	Yes	18 (60.0%)
Ramipril dose	Mean ± SD	2.71 ± 0.88
	Range	1.3 – 5
Valsartan	No	25 (83.3%)
	Yes	5 (16.7%)
Valsartan dose	Mean ± SD	96.00 ± 60.66
	Range	40 – 160
Spironolactone	No	0 (0.0%)
	Yes	30 (100.0%)
Spironolactone dose	Mean ± SD	61.67 ± 24.33
	Range	25 – 100
Bisoprolol	No	0 (0.0%)
	Yes	30 (100.0%)
Bisoprolol dose	Mean ± SD	4.00 ± 1.25
	Range	2.5 – 5

Table (4): Treatment used by patients after introducing Sacubitril/Vlasrtan instead of ACEi and ARBS. Beta blockers, MRAs and diuretics doses were the same with no change.

Post treatment		**No. (%)**
SACUBITRIL-VALSARTAN	No	0 (0.0%)
	Yes	30 (100.0%)
SACUBITRIL-VALSARTAN dose	Mean ± SD	146.67 ± 50.74
	Range	100 – 200
Torisamide	No	8 (26.7%)
	Yes	22 (73.3%)
Torisamide dose	Mean ± SD	16.36 ± 4.92
	Range	10 – 20
Furisamide	No	22 (73.3%)
	Yes	8 (26.7%)
Furisamide dose	Mean ± SD	40.00 ± 0.00
	Range	40 – 40
Spironolactone	No	0 (0.0%)
	Yes	30 (100.0%)
Spironolactone dose	Mean ± SD	61.67 ± 24.33
	Range	25 – 100
Bisoprolol	No	0 (0.0%)
	Yes	30 (100.0%)
Bisoprolol dose	Mean ± SD	4.00 ± 1.25
	Range	2.5 – 5

Table (5): 6MWT before and after treatment with sacubitril/valsartan

6MWT	**Pre**	**Post**	**Paired t-test**		
			t	**P-value**	**Sig.**
Mean ± SD	279.33 ± 45.78	372.00 ± 41.31	-19.942	0.000	HS
Range	220 – 380	280 – 470			

P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant

The table shows highly significant increase in the distance walked assessed by 6MWT. Before treatment with Sacubitril/valsartan; 6MWT was (**279.33 ± 45.78**) and after treatment, it reached (**372.00 ± 41.31**).

Table (5): The table shows the distance and the percentage of distance improved after treatment with Sacuibitril/Valsartan reaching 34.51 ± 11.89 %.

		Total no. = 30
Distance Improved	Mean ± SD	92.67 ± 25.45
	Range	40 – 150
Percentage of distance improved	Mean ± SD	34.51 ± 11.89
	Range	10.81 – 56.52

Table (6): The table shows the percentage of distance improved in correlation with patient age and Sacuibtril/valsartan dose. There were highly significant correlation between the dose and percentage of improvement in the 6 MWT

	Percentage of distance improved	
	r	**P-value**
Age	0.292	0.117
SACUBITRIL-VALSARTAN dose	**0.842****	**0.000**

P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant

Table (7): The table shows different demographic data relation to the percentage of distanced improved. There were non-significant relation to gender, DM, HTN, Smoking, Dyslipidemia and family history of IHD. On the other hand, there was significant relation to the type of cardiomyopathy as patient with ICM showed better improvement in the percentage of distance walked assessed by 6MWT

		Percentage of distance improved		Independent t-test		
		Mean ± SD	**Range**	**t**	**P-value**	**Sig.**
Gender	Female	37.97 ± 16.25	20 – 56.52	0.707	0.486	NS
	Male	33.82 ± 11.13	10.81 – 55.56			
DM	No	32.66 ± 11.92	10.81 – 52.17	-0.595	0.556	NS
	Yes	35.43 ± 12.07	13.16 – 56.52			
HTN	No	31.57 ± 12.29	10.81 – 56.52	-1.375	0.180	NS
	Yes	37.45 ± 11.1	20 – 55.56			
Smoking	No	36.21 ± 12.56	20 – 56.52	0.547	0.589	NS
	Yes	33.66 ± 11.78	10.81 – 55.56			
Dyslipedemia	No	32.75 ± 8.6	23.53 – 52.17	-0.566	0.576	NS
	Yes	35.39 ± 13.35	10.81 – 56.52			
Family history of IHD	No	33.65 ± 10.66	20 – 53.85	-0.297	0.769	NS
	Yes	35.01 ± 12.8	10.81 – 56.52			
Type of cardiomyopathy	ICM	36.53 ± 11.33	13.16 – 56.52	2.219	0.035	S
	DCM	24.4 ± 10.09	10.81 – 37.5			

P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant

4. Discussion

The present study was a prospective observational study that included 30 patients diagnosed with heart failure with reduced ejection fraction (HFrEF) with LVEF <40 % and NYHA-FC II-III symptoms. Most of our patients have ICM (83.3%). In the present study, the mean age of the included patients was 55.07 ± 10.16 years and the vast majority of the patients were males (83.3%). The study aimed to evaluate if there is any short term effect of Sacubitril/Valarstan drug on the functional capacity of stable HF patients with reduced ejection fraction, which is measured by the simple non-invasive six minute walk test, in only 30 days period.

This study showing sacubitril/valsartan is associated with short-term improvement of submaximal exercise capacity (measured as distance walked in 6-MWT). Compared with baseline, the 6-MWT distance increased significantly at 30 days (+Δ = 92.67m ± 25.45; p b 0.001) these findings are in agreement with prior findings suggesting a short-term clinical beneficial effect of sacubitril/valsartan by reducing the risk of early hospitalizations in the PARADIGM-HF trial ***(Burchfield et al., 2013)***.

Similar to our findings, **Bittner and colleagues (2019)** studied the short term effect of sacubtril/vlasratan on functional capacity in patients with HFrEF**,** From November 1, 2016 to February 1, 2017, a total of 58 stable symptomatic patients with HFrEF were eligible for sacubitril/valsartan and underwent 6-MWT before and 30 days after initiation of sacubitril/valsartan therapy. A mixed-effects model for repeated-measures was used to analyze the changes. Mean age was 70±11 years. 72.4% males, 46.6%with ischemic heart disease, and 51.7% on NYHA functional class III were included. The mean (SD) values of baseline LVEF and 6MWTwere 30±7%, and 300±89m, respectively. Compared with baseline, the 6-MWT distance increased significantly at 30 days by 13.9% (+Δ = 41.8 m (33.4–50.2); p b 0.001**).**

In this study, more than half of our patients failed to reach the target dose of the sacubitril/valstan (79/103 bid) due the short term of the study. Although the best improvement in the 6MWT was shown with that dose, the other dose (49/51 bid) showed also significant improvement in the functional capacity.

Similarly, **Cittadini and colleagues (2012),** utilized data from PARADIGM-HF to test the hypothesis that participants who exhibited any dose reduction during the trial would have similar benefits from lower doses of sacubitril/valsartan relative to lower doses of enalapril. In a post-hoc analysis from PARADIGM-HF, they characterized patients by whether they received the maximal dose (200 mg sacubitril/valsartan or 10 mg enalapril twice daily) throughout the trial or had any dose reduction to lower doses (100/50/0 mg sacubitril/valsartan or 5/2.5/0 mg enalapril twice daily). The treatment effect for the primary outcome was estimated. The treatment benefit

of sacubitril/valsartan over enalapril following a dose reduction was similar (HR 0.80, 95% CI 0.70–0.93, $P < 0.001$) to that observed in patients who had not experienced any dose reduction (HR 0.79, 95% CI 0.71–0.88, $P < 0.001$). The magnitude of benefit for patients on lower doses of sacubitril/valsartan relative to those on lower doses of enalapril was similar to that of patients who remained on target doses of both drugs.

The mechanisms by which sacubitril/valsartan might improve exercise capacity early in HFrEF remains unclear. We guess neprilysin inhibition mediated by sacubitril would acutely amplify hemodynamic effects of natriuretic peptides (natriuresis, vasodilation), resulting in a reduction in cardiac and pulmonary pressures and improvement in exertional symptoms at short-term. However, beyond the effects on natriuretic peptides, it is also remarkable that neprilysin inhibition could modify the biological activity of N50 endogenous peptides by inhibiting their metabolism. Among others, neprilysin inhibition could increase the half-life of adrenomedullin, bradykinin and substance P, all of them substrates of neprilysin that promotes peripheral vasodilation ***(D'Elia et al., 2017)***.

The current available evidence shows that the incidence of congestive heart failure increases significantly with age as the elderly constituting up to 80% of patients suffering from this disease ***(Go et al., 2013).*** On the other hand, despite the fact that the cumulative incidence of HF is similar between both genders, women are approximately 65% less likely to develop heart failure with reduced ejection fraction (HFrEF) (LVEF ≤40%) than men, particularly in their younger years ***(Kenchaiah et al., 2015).*** In the present study, the mean age of the included patients was 55.07 ± 10. 16 years and the vast majority of the patients were males (83.3 %).

The relative contribution of various risk factors to the development of heart failure remains controversial and has seldom been investigated in population-based studies ***(Cheng et al., 2009).***

Data from the National Health and Nutrition Epidemiologic Survey (NHANES) suggested that coronary heart disease had the largest impact on the development of heart failure, and may be responsible for more than 60% of cases. In the present study, the major risk factors were smoking, diabetes and dyslipidemia representing 66.7% for each; while half of the patients were hypertensive. it worth mentioning that the main type of cardiomyopathy in the present study was ICM representing about 83.3% and this is in consistent with our major risk factors.

Similarly, ***Emdin and colleagues (2015)*** conducted a Population-Based Case-Control study on the relative contribution of risk factors to the development of heart failure, between 1979 and 2002, on 962 incident heart failure cases. They found that hypertension was the most common (66%), followed by smoking (51%). The risk of heart failure was particularly high for coronary disease and diabetes with odds ratios (95% confidence intervals) of 3.05 (2.36–3.95) and 2.65 (1.98–3.54), respectively. The coronary disease accounted for the greatest proportion of cases in men (PAR 23%) ***(Shannon et al., 2009).***

In this study, the patients with ischemic etiology of HFrEF showed better improvement in the functional capacity assessed by 6MWT. However, PARADIGM-HF, the most common HFrEF etiology was ischemic heart disease (in 60% of participants). Of the non-ischemic etiologies reported, the largest category was idiopathic (47% of non-ischemic cases) and another 29% of patients were ascribed a hypertensive etiology. When adjusted for other prognostic variables, including natriuretic peptides, outcomes were similar across etiologic categories. The benefit of sacubitril/valsartan over enalapril was not modified by etiology ***(Bittner et al., 2019).***

Although the physiological mechanisms of action of Sacubitril/ Valsartan are well described, its effects on left ventricular remodeling and left ventricular ejection fraction (LVEF) have not been well studied. Left ventricular remodeling is a major mechanism underlying disease progression in patients with HFrEF ***(Vasan et al., 1996)***. Even though we did not expect any short term improvement in LV ejection fraction, in our study, we found that LVEF was improved to reach (30.90 ± 2.78). The pre study LVEF was (30.00 ± 3.12).

5. Conclusion

In this observational study, treatment onset with sacubitril/valsartan was associated with 30-day improvement in the distance walked in 6-MWT.

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