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Efficacy of sacubitril/valsartan among patients with chronic heart failure with reduced ejection fraction

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Abstract

Objective: Chronic heart failure is one of the leading causes of hospitalization and recurrent admissions among the elderly population worldwide. This study was conducted to determine the efficacy of Sacubitril/Valsartan among heart failure cases with reduced left ventricular ejection fraction.

Methods: This prospective simple experimental study was conducted over a 6-month duration from Feb. 1st, 2023 to July 30th, 2023 at Islamabad Medical Complex after ethical approval. Adult patients (≥ 25 years of age; both genders) presenting with chronic heart failure (CHF) with LVEF ≤ 40% for ≥ 3 months duration; NYHA-II/III/ambulatory-IV, ischemic/non-ischemic cardiomyopathy cases were included by consecutive non-probability sampling. Systolic blood pressure (SBP)<100mmHg, eGFR<30mL/min/m^2, serum potassium>4.5mEq/L, known drug reactions, and congenital heart disease cases were **excluded**. After detailed clinical evaluation, baseline ejection fraction (EF), and NT Pro-BNP levels were documented. Patients were started on Sacubitril/valsartan and followed every 2 months till 6 months duration. EF, NT Pro-BNP levels re-checked at 6th month. The primary endpoint was EF improvement at 6 months. Secondary endpoints were all-cause mortality or hospitalization due to heart failure. Data was analyzed by SPSS V-25, with significant $p<0.05$.

Results: Amongst 100 cases, (63% males; 37% females), 10% patients were 29-45 years, 49% (46-60 years) and 41% (61-75 years). 13% of cases had CABG, 30% had PCI, and 55% had no previous cardiac invention. 57 patients received dose-50/day and 43 received dose-100/day. At baseline, 79 patients had NYHA-II, 17(NYHA-III) and 4(NYHA-IV). After six months, 78 patients had NYHA-II, 2(NYHA-III) and 1(NYHA-IV). 12 patients lost to follow-up, 4 expired, while therapy stopped in 4 due to raised creatinine. At baseline, 8 patients had no mitral regurgitation (MR), 4(trace MR), 48(mild MR), 25(moderate MR) and 15 had severe MR. After six months, 16 patients had no MR, 13(trace MR), 37(mild MR), 13(moderate MR) and 2 had severe MR. The statistically significant difference found in pro-BNP, creatinine, SBP, ejection fraction, E/e, E/A ratio, left ventricular end-diastolic volume (LEDV) and left ventricular end-systolic volume (LVESV) between baseline versus at six months ($p<0.05$).

Conclusion: In chronic heart failure cases with reduced ejection fraction (HFrEF), sacubitril/valsartan has proven to be significantly effective in improving NYHA class, degree of MR, cardiovascular mortality and Hospitalization.

MeSH Keywords: heart failure, Ejection fraction, Mitral regurgitation, ventricular ejection fraction.

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1. Introduction

Chronic heart failure (CHF) is a clinical syndrome characterized by shortness of breath or exertional restriction due to decreased ventricular filling, reduced ejection of blood or both. Heart failure with reduced ejection fraction (HFrEF) is a term used to describe HF in which the left ventricular ejection fraction (LVEF) is ≤ 40% and is complemented by progressive left ventricular dilatation and undesirable cardiac remodelling.1 Chronic heart failure is one of the leading causes of hospitalization and readmission among geriatrics in Pakistan as well as worldwide. According to the American Heart Association – Heart Disease and Stroke Statistics Report (2012), the approximate prevalence of CHF was 5.7 million, and one million hospital admissions were attributable to CHF.

In addition to ACE-I, ARBs, beta-blockers, SGLT2-I, anti-aldosterone and ARNi have also been included as a part of CHF treatment according to the American Heart Association. The sacubitril/valsartan drug inhibits neprilysin and blocks angiotensin II type-I receptors, increasing the levels of peptides degraded by neprilysin. Valsartan inhibits the effects of angiotensin II by blocking the angiotensin-I receptor and by inhibiting the release of angiotensin II-dependent aldosterone. A randomized control trial by McMurray et al, compared the first approved ARNi, sacubitril-valsartan, with enalapril in patients with HFrEF who were symptomatic and were tolerating an adequate dose of either ACE-I or ARB, sacubitril-

valsartan significantly reduced the rate of cardiovascular death or hospitalization due to CHF by 20% relative to enalapril. Sacubitril–valsartan was also better than enalapril in minimizing all-cause mortality (16% reduction), and restricting the progression of CHF. Therefore, in patients who remain symptomatic despite optimal treatment with ACE-I, ARBs, beta blockers and anti-aldosterone medications, sacubitril–valsartan is recommended by the 2016 European Society of Cardiology guidelines (Class I, Level B) as an alternative to ACE-I.

It was also observed in a large study conducted in a neighbouring country that there is much more improvement in EF among the ARNi group, with 58% population using the sacubitril/valsartan group showing a 5-10% improvement in EF, as compared to only 18% in the ACE-I group. The ARNI group also showed fewer hospital admissions in comparison with the ACE-I group. ARNIs have been shown by Greene et al to reduce post-discharge mortality and all-cause hospitalization as compared to angiotensin-converting enzyme inhibitor/angiotensin II receptor blockers. This study was conducted to determine the efficacy of Sacubitril/Valsartan among patients with heart failure with reduced left ventricular ejection fraction. This may provide regional data and help in improving the clinical and biochemical parameters in cases with CHF.

2. Materials & Methods

This prospective, non-randomized, simple experimental study was conducted over 6 months duration from February 1st, 2023 to July 30th, 2023, at both the outdoor and indoor of Islamabad Medical Complex, following the ethical approval. The sample size of 97 was calculated by the WHO calculator. N=pq*(1.96)2 /(0.1)2,P=0.71 and q=0.29. taking an estimated prevalence of 6.7% in South Asia, with a confidence interval of 95% and 5% precision.

One hundred patients presenting with chronic heart failure (CHF) with LVEF<40% were included by consecutive non-probability sampling. Patients >25 years of age of both genders, NYHA II, III, ambulatory IV, those already on maximum medical therapy for CHF for at least 3 months before randomization, ischemic and non-ischemic cardiomyopathy cases regardless of prior intervention status were included. The cases who were hypotensive (SBP<100mmHg), with eGFR <30mL/min/m2 (eGFR was calculated by MDRD GFR calculator) , serum potassium>4.5mEq/L, known drug reactions/ angioedema, and CHF secondary to congenital or valvular heart disease were excluded.

Chronic heart failure was defined as a clinical syndrome with symptoms and/or signs caused by a structural and/or functional cardiac abnormality and was corroborated by elevated natriuretic peptide levels and/or objective evidence of pulmonary or systemic congestion. HFrEF (Heart Failure with Reduced Ejection Fraction) was interpreted as symptomatic CHF with LVEF<40%. The drug used in the study was Sacubitril/valsartan-50 (Dose used 24mg Sacubitril/26mg Valsartan), i.e. supramolecular sodium salt complex of the neprilysin inhibitor prodrug sacubitril and angiotensin receptor blocker (ARB) valsartan.

Informed consent was obtained from all the patients fulfilling the inclusion criteria. The patient's profile along with relevant history and biochemical markers was documented on a specially designed Performa. After the detailed clinical evaluation, the baseline ejection fraction, and NT Pro-BNP levels were documented. Patients were then started on the Sacubitril/valsartan and followed every 2 months till 6 months duration. The ejection fraction and NT Pro-BNP levels were re-checked in 6th month. The primary endpoint was Ejection fraction improvement at 6 months. Secondary endpoints were the all-cause mortality in 6 months or hospitalization due to heart failure in 6 months.

Data was analyzed by statistical package for social sciences (IBM SPSS V-25). Frequencies and percentages were calculated for qualitative variables (gender, co-morbid, cardiac intervention, drug dose, NYHA class and severity of MR). Mean and standard deviation were calculated for quantitative variables (i.e., biochemical markers, and ejection fraction). Student t-test was applied to compare the EF, Pro-BNP and other bio-chemical markers before and after administering the sacubitril/valsartan. P-value <0.05 was considered to be statistically significant.

3. Results

Among the hundred cases, according to gender, 63(63%) were males and 37(37%) females. There were 10(10%) patients between 29-45 years, 49(49%) 46-60 years and 41(41%) 61-75 years. Twenty-nine (29%) patients had one risk factor, 38 (38%) patients had two risk factors, 5(5%) patients had three risk factors, 9(9%) patients had >3 risk factors and 19(19%) patients had none. Fifty fine

(55%) patients had no history of cardiac invention, 13(13%) had CABG, 30(30%) had PCI, and 01(1%) patient had PCI-CABG and post-ICD respectively (Table 4). As per the administered dose, 57(57%) patients received the Sacubitril/valsartan-50 (24mg Sacubitril/26mg Valsartan) once a day and 43(43%) patients received it twice a day (Table 1).

Table 1: Presenting the qualitative variables including demographic data, risk factors, and cardiac intervention categories of study participants (n=100)

Variables		n (%), n=100
Gender	Male	**63(63%)**
	Female	**37(37%)**
Age (years)	29 – 45	**10(10%)**
	46 – 60	**49(49%)**
	61 – 75	**41(41%)**
Risk factors (co-morbid conditions)	1	**29(29%)**
	2	**38(38%)**
	3	**05(5%)**
	3	**09(9%)**
	No co-morbid conditions	**19(19%)**
Cardiac intervention	None	**55(55%)**
	CABG	**13(13%)**
	PCI	**30(30%)**
	PCI CABG	**01(1%)**
	Post ICD	**01(1%)**
Dose/day	50 (24mg Sacubitril/26mg Valsartan) once a day	**57(57%)**
	100 (24mg Sacubitril/26mg Valsartan) twice a day	**43(43%)**
Outcome	Completed the study duration	**80(80%)**
	Lost to follow-up	**12 12%)**
	Death before completion	**04 (4%)**
	Discontinued due to raised creatinine	**04 (4%)**

Table 2: Comparison of the severity of NYHA class and Mitral regurgitation (MR) at the baseline Vs. at 6 months after administering the sacubitril/valsartan (n=100)

Variables		Baseline (n=100)	After six months (n=81)	P-value
NYHA CLASS	**II**	79 (79%)	78(78%)	***0.0027***
	III	17 (17%)	02(02%)	
	IV	04 (04%)	01(01%)	
MR SEVERITY	**No MR**	08 (08%)	16(16%)	***0.0003***
	Trace	04 (04%)	13(13%)	
	Mild	48 (48%)	37(37%)	
	Moderate	25 (25%)	13(13%)	
	Severe	15 (15%)	02 (02%)	

(Student t-test; significant p<0.05)

According to the NYHA class, 79(79%) patients had NYHA class II, 17(17%) had class III, and 4(4%) had class IV in the baseline group. While after six months group, 78(78%) patients had NYHA class II, 2(2%) had class III and one had class IV. During the study duration, 12(12%) patients were lost to follow-up, 4(4%) patients expired before completion and 4(4%) patients were discontinued due to raised creatinine (Table 2).

Regarding the MR severity, 8(8%) patients had no MR, 4(4%) had trace MR, 48(48%) had mild, 25(25%) had moderate and 15(15%) had severe MR at baseline. While after six months, 16(16%) patients had no MR, 13(13%) had trace, 37(37%) had mild, 13(13%) patients had moderate and 2(2%) had severe MR (Table 2).

While comparing the pro-BNP, creatinine, SBP, ejection fraction, E/e, E/A ratio, LVEDV and LVESV at baseline versus after six months of therapeutic intervention, there was a statistically significant difference ($p<0.05$; Table 3).

Table 3: Comparison of pro-BNP, creatinine, SBP, Ejection fraction, E/e, E/A ratio, LVDEV and LVESV in both groups (n=100)

Variables	Baseline (n=100)	After six months (n=81)	*P-value*
Pro-BNP	680.56±243.21	252.26±370.72	0.001
Creatinine	1.06±0.34	0.96±0.27	0.054
SBP	123.20±14.50	118.27±12.43	0.016
Ejection fraction	34.49±7.08	37.43±5.53	0.005
E/e	12.56±16.11	7.73±2.80	0.008
E/A ratio	0.83±0.31	0.72±0.19	0.007
LVEDV	165.29±49.08	150.46±39.73	0.029
LVESV	104.23±54.33	91.05±28.94	0.051

4. Discussion

It has been demonstrated in the current study that sacubitril/valsartan is effective in improving outcomes for patients with reduced ejection fraction (HFrEF) in chronic heart failure. Sacubitril/valsartan was found to be more effective than enalapril in lowering the risk of heart failure-associated hospitalization and cardiovascular death in patients with HFrEF, according to a PARADIGM-HF trial in 2014. For patients who required emergency hospitalization due to acute heart failure (AHF), the gender of the patient was an independent predictor of their outcome. In this study, 90% of patients were between 46-75 years of age, and 63% of cases were males. The female patients had valvular disease, de novo HF, and maintained LVEF. Most of the cases were elderly. Specifically, poor outcomes were linked to advanced age in female AHF patients.[6] The effectiveness of vericiguat was not affected by concurrent use of sacubitril and valsartan for at least three months, and both study arms reported equal levels of safety and tolerability. Those randomized to

receive placebo versus vericiguat were more likely to start using sacubitril/valsartan.

It is noteworthy that as medical knowledge advances, additional research may be carried out to evaluate the long-term safety and effectiveness of sacubitril/valsartan or to compare it with alternative treatments. This variation in the use of the sacubitril/valsartan pattern started early in the follow-up period and got wider over time. Comparable percentages of patients in both treatment groups were administered valsartan/sacubitril either before or following their initial hospital stay. This variation in the usage pattern of sacubitril/valsartan started smaller during the follow-up period and got wider over some time. Similar numbers of patients in both treatment arms received sacubitril/valsartan before or after the first hospitalization. Comparably, the pattern of cardiac-related serious adverse events (SAEs) is closer to the time of drop-in and marginally more frequent. We suggest careful monitoring of cases receiving sacubitril/valsartan by individualization of therapy, dose adjustment and monitoring.

When sacubitril/valsartan was prescribed at discharge for patients hospitalized for HFrEF, it was found to be independently linked to lower post-discharge mortality when compared with the angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker. This also reduced mortality and all-cause hospitalization. These results validate the usual US clinical practice of using sacubitril/valsartan to enhance post-discharge outcomes for geriatric patients hospitalized for HFrEF. Several trials (CHAMP-HF, PARADIGM-HF, PIONEER-HF) showed their significance in chronic heart failure patients where multiple drugs interact and patient handling gets difficult along with polypharmacy and complex therapeutic regimes. Vitale G et al found that Sacubitril/valsartan was associated with a significant improvement in exercise tolerance, peak oxygen consumption, and ventilatory efficiency at 6.2 months follow-up. Compared with ACE inhibitors or ARBs, sacubitril-valsartan significantly decreased the risk of death from all causes or cardiovascular causes and hospitalization for CHF in patients with HFrEF but failed to improve all-cause mortality and cardiovascular mortality in heart failure with preserved ejection fraction (HFpEF) cohorts.

We observed a significant decline in the SBP from a mean of 123 mmHg to 118 mmHg (p=0.016) after administering the Sacubitril-valsartan, however, this was well tolerated by patients in this study. Studies have demonstrated that Sacubitril-valsartan increased the risk of symptomatic hypotension but slowed the decline in kidney function and elevation in serum potassium concentration compared with ACE inhibitors or ARBs. In our cases the mean creatine reduced from 1.06 to 0.96 post 6 months of therapy with Sacubitril-valsartan, however, the difference wasn't significant (p=0.054). There is a possibility that if this study had been extended for a longer duration, we might have observed wider differentiation in certain parameters. In four of our study participants, therapy was stopped due to a significant elevation of serum creatinine. Based on this observation, we recommend that renal functions be monitored in all the cases at baseline as well as at specified intervals, along with necessary action if deterioration is observed.

Studies have demonstrated that one of the side effects of Sacubitril-valsartan is angioedema. However, literature shows that angio-edema occurs less frequently in the sacubitril-valsartan group. We haven't observed angio-edema in any of the study participants, reason could be the careful selection of cases and excluding the ones with a history of pre-existing drug allergies or reactions.

Four of the study participants unfortunately expired during the six-month duration. In Japanese patients with HFrEF, there was no difference in reduction in the risk of CV death or CHF hospitalization between sacubitril/valsartan and enalapril, and sacubitril/valsartan was safe and well tolerated. As shown by the PARADIGM-HF study sacubitril/valsartan, a first-in-class ARNi, provides a novel oral therapy for heart failure and lowers mortality in patients with HFrEF. It is a promising therapeutic approach for cardiovascular illnesses because of its unusual dual action, which enhances the natriuretic peptide system and blocks the renin-angiotensin system. Acknowledged in the most recent guidelines from the ESC and AHA/ACC, sacubitril/valsartan is superior to ACE inhibitors and beta-blockers in terms of symptom relief, especially when paired with diuretic medication. No difference in the energetic efficiency of cardiac work between ARNI and valsartan-only groups in HFrEF patients. However, ARNI reduces the systemic blood pressure, LV mechanical workload, myocardial perfusion, and LV oxygen demands over run-in period valsartan alone.

In this study, regarding the severity of MR, only 8% of patients had no MR at baseline while the rest of them had various degrees of MR severity. After six months, 16% of patients had no MR and a significant reduction

in MR severity was observed overall. Hence, we may conclude that Sacubitril-valsartan does have significant efficacy in reducing the severity of MR in CHF cases. Similarly, the EF significantly improved from 34.49% to 37.45% post-therapy (p=0.005). The rest of the echocardiography-based parameters including the E/e, E/A ratio, LVEDV and LVESV also significantly improved post-therapy (p<0.05).

The Pro-BNP levels in our study participants improved from 680 pg/mL to 252 pg/mL post-therapy. This improvement is quite significant with a p-value of 0.001. This lab parameter has approx. 97% sensitivity and 84% specificity. However, this strong and independent prognostic parameter is underutilized in patients with heart failure. We recommend that pro-BNP levels be obtained to quantify the course of CHF in cases irrespective of the overall symptoms of CHF.

Studies have demonstrated that after 12 weeks of treatment, there was no significant benefit of sacubitril/valsartan on either a six-minute walking test (6MWT) or daytime physical activity measured by actigraphy compared with enalapril. Contrary to this our patients demonstrated significant improvement in symptoms. This was assessed by the NYHA class, i.e., the New York Heart Association (NYHA) functional class. This helps to classify congestive heart failure patients based on their symptoms. We haven't performed the 6MWT though, but based on NYHA we did observe significant improvement in the functional capacity of CHF cases.

The current study is unique because it adds to regional data with extensive analysis based on clinical, echocardiographic and biochemical evaluation of the CHF cases intervened by sacubitril/valsartan. It's recommended that a case-control study with randomization may further extend the verification of the study and bring clarity to the results. Hence, a consensus can be made for the management of CHF cases in our population based on the safety and efficacy of sacubitril/valsartan.

5. Conclusion

In chronic heart failure cases with reduced ejection fraction (HFrEF), sacubitril/valsartan has proven to be significantly safe and effective in improving NYHA class, degree of MR, cardiovascular mortality and Hospitalization. In the CHF patients receiving sacubitril/valsartan, the close monitoring of renal functions, individualization of therapy and careful monitoring are recommended. We may conclude that sacubitril/valsartan improves the functional class, cardiac echocardiographic and biochemical markers in CHF cases.

INSTITUTIONAL REVIEW BOARD

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Contributions:

M.M - Conception of study
M.M - Experimentation/Study Conduction
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S.B.A, A.S - Manuscript Writing
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References

1. Murphy SP, Ibrahim NE, Januzzi JL Jr. Heart Failure with Reduced Ejection Fraction: A Review. JAMA. 2020; 324(5):488-504. doi:10.1001/jama.2020.10262.
2. Mueed A, Raza SH, Shiekh SA, Mumtaz Z, Khanzada F, Tun HN. Factors participating in readmission of heart failure patient, and hospital burden in Karachi, Pakistan. Euro J Cardiovascular Med. 2020; 5(6):591-4. doi: 10.5083ejcm20424884.168
3. Roger VL, Go AS, Lloyd-Jones DM. heart disease and stroke statistics--2012 update: a report from the American Heart Association. 2012 Jun 5;125(22):e1002]. Circulation. 2012;125(1):e2-e220. doi:10.1161/CIR.0b013e31823ac046.
4. McMurray JJ, Packer M, Desai AS. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med. 2014;371(11):993-1004. doi:10.1056/NEJMoa1409077.
5. Ponikowski P, Voors AA, Anker SD.ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016;37(27):2129-2200. doi:10.1093/eurheartj/ehw128.
6. Jariwala P, Punjani A, Boorugu H, Madhawar DB. A clinical experience of Indian patients with heart failure with reduced left ventricular ejection fraction using an angiotensin receptor-neprilysin inhibitor [ARNI] on an outpatient basis. Indian Heart J. 2021;73(2):211-13. doi: 10.1016/j.ihj.2021.01.002.
7. Greene SJ, Choi S, Lippmann SJ, et al. Clinical Effectiveness of Sacubitril/Valsartan Among Patients Hospitalized for Heart Failure With Reduced Ejection Fraction. J Am Heart Assoc. 2021;10(16):e021459. doi:10.1161/JAHA.121.021459.

8. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. American Journal of Kidney Diseases: The Official Journal of the National Kidney Foundation. 2002;39 (2 Suppl 1):266.
9. Nozaki A, Shirakabe A, Hata N, Kobayashi N, Okazaki H, Matsushita M, et al. The prognostic impact of gender in patients with acute heart failure–An evaluation of the age of female patients with severely decompensated acute heart failure. Journal of cardiology;2017 Sep 1;70(3):255-62. http://dx.doi.org/10.1016/j.jjcc.2016.11.015.
10. Senni M, Alemayehu WG, Sim D. Efficacy and safety of vericiguat in patients with heart failure with reduced ejection fraction treated with sacubitril/valsartan: insights from the VICTORIA trial. Eur J Heart Fail. 2022;24(9):1614-22. doi:10.1002/ejhf.2608.
11. Greene SJ, Choi S, Lippmann SJ,Clinical Effectiveness of Sacubitril/Valsartan Among Patients Hospitalized for Heart Failure with Reduced Ejection Fraction. J Am Heart Assoc. 2021;10(16):e021459. doi:10.1161/JAHA.121.021459.
12. Vardeny O, Claggett B, Packer M, Efficacy of sacubitril/valsartan vs. enalapril at lower than target doses in heart failure with reduced ejection fraction: the PARADIGM-HF trial. Eur J Heart Fail. 2016;18(10):1228-1234. doi:10.1002/ejhf.580.
13. Vitale G, Romano G, Di Franco A. Early Effects of Sacubitril/Valsartan on Exercise Tolerance in Patients with Heart Failure with Reduced Ejection Fraction. J Clin Med. 2019;8(2):262. doi:10.3390/jcm8020262.
14. Zhang H, Huang T, Shen W. Efficacy and safety of sacubitril-valsartan in heart failure: a meta-analysis of randomized controlled trials. ESC Heart Fail. 2020;7(6):3841-3850. doi:10.1002/ehf2.12974.
15. Tsutsui H, Momomura SI, Saito Y. Efficacy and Safety of Sacubitril/Valsartan in Japanese Patients with Chronic Heart Failure and Reduced Ejection Fraction- Results From the PARALLEL-HF Study. Circ J. 2021;85(5):584-94. doi:10.1253/circj.CJ-20-0854.
16. Dargad RR, Prajapati MR, Dargad RR, Parekh JD. Sacubitril/valsartan: A novel angiotensin receptor-neprilysin inhibitor. Indian Heart J. 2018;70 Suppl 1(Suppl 1):S102-S110. doi:10.1016/j.ihj.2018.01.002.
17. Nesterov SV, Räty J, Nammas W. Short-term effects of sacubitril/valsartan therapy on myocardial oxygen consumption and energetic efficiency of cardiac work in heart failure with reduced ejection fraction: A randomized controlled study. Eur J Heart Fail. 2024;26(1):117-126. doi:10.1002/ejhf.3072
18. Piepoli MF, Hussain RI, Comin-Colet J. Outstep-Hf: randomized controlled trial comparing short-term effects of sacubitril/valsartan versus enalapril on daily physical activity in patients with chronic heart failure with reduced ejection fraction. Eur J Heart Fail. 2021;23(1):127-135. doi:10.1002/ejhf.2076.