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Original Research Article

A randomized controlled trial comparing sacubitril/valsartan and telmisartan in patients with HFrEF: efficacy and safety evaluation

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ABSTRACT

Background: Heart failure with reduced ejection fraction (HFrEF) is a progressive condition associated with high morbidity, mortality, and healthcare costs. Sacubitril/valsartan, an angiotensin receptor-neprilysin inhibitor (ARNI), has demonstrated superior efficacy over traditional angiotensin receptor blockers (ARBs) in improving outcomes. This study compared the safety and efficacy of sacubitril/valsartan with telmisartan monotherapy in HFrEF patients.
Methods: A randomized, prospective, open-label, interventional study was conducted at a tertiary care center over six months. A total of 81 patients with HFrEF (EF ≤40%) were randomized into group A (telmisartan 40 mg daily) and group B (sacubitril/valsartan 200 mg twice daily). Outcomes assessed included NYHA class, left ventricular ejection fraction (LVEF), and serum BNP levels at baseline, 3 months, and 6 months. Safety was evaluated through adverse events and laboratory monitoring. Statistical analysis was conducted using SPSS, with significance set at $p<0.05$.
Results: Both groups showed significant improvement in LVEF and BNP levels. Sacubitril/valsartan demonstrated superior efficacy in reducing BNP levels (583.2±324.2 pg/ml versus 957.5±305.2 pg/ml, $p<0.0001$) and improving NYHA class ($p=0.005$). LVEF improved significantly in both groups, with no intergroup difference ($p=0.130$). No hospitalizations or mortality occurred during the study. One case of non-serious angioedema was reported in the sacubitril/valsartan group. Hematological and biochemical parameters remained stable, confirming comparable safety profiles.
Conclusions: Sacubitril/valsartan is more effective than telmisartan in improving NYHA class and reducing BNP levels in HFrEF patients, with a comparable safety profile. It should be considered a preferred treatment option in HFrEF management, particularly in patients with NYHA class II/III symptoms, as per ACC/AHA guidelines.

Keywords: BNP, Heart failure therapy, HFrEF, LVEF, NYHA class, Sacubitril/valsartan

INTRODUCTION

Heart failure (HF) is a chronic, progressive, and debilitating clinical syndrome that has reached epidemic proportions globally, including in India. Characterized by structural or functional impairment of ventricular filling or ejection, HF manifests with cardinal symptoms such as dyspnea, fatigue, and fluid retention, leading to significant morbidity and mortality. The prevalence of HF exceeds 37.7 million worldwide and is projected to increase by 25% by 2030, reflecting a growing public health challenge. In India, HF is a leading cause of hospitalizations, accounting for 1-5% of total admissions, with in-hospital mortality rates ranging from 2-17%. Despite advancements in medical care, the prognosis for HF remains dire, with a 5-year mortality rate of approximately 50%, surpassing that of several common cancers.[1-6] The increasing burden of HF is closely linked to the rise in comorbidities such as ischemic heart disease, hypertension, diabetes mellitus, atrial fibrillation, and

chronic kidney disease. The lifetime risk of developing HF is 33% for men and 28.5% for women at 55 years of age, with the prevalence escalating with age. The clinical and economic implications of HF necessitate early and accurate diagnosis, which hinges on a combination of clinical evaluation and advanced diagnostic tools, including echocardiography and biomarkers like BNP and NT-pro-BNP. These biomarkers play a pivotal role in ruling out HF, with high negative predictive value, and assist in stratifying the disease severity.[7-11]

Heart failure is classified based on ejection fraction (EF), symptomatology, and disease progression, with reduced ejection fraction (HFrEF) representing a subset characterized by significant systolic dysfunction. Standard therapeutic strategies have evolved to include guideline-directed medical therapies (GDMT), which encompass angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), beta-blockers, and, more recently, angiotensin receptor-neprilysin inhibitors (ARNIs). Sacubitril/valsartan, the first ARNI approved for HFrEF, has demonstrated superior efficacy over enalapril in reducing cardiovascular mortality and HF-related hospitalizations. By combining the AT1 receptor blockade of valsartan with the neprilysin inhibition of sacubitril, this dual agent enhances natriuretic peptide activity while mitigating the adverse effects of angiotensin II.[12-16] Telmisartan, an ARB, remains a widely used therapy for HF due to its potent AT1 receptor antagonism, favorable pharmacokinetics, and tolerability. However, comparative evidence on the safety and efficacy of sacubitril/valsartan versus telmisartan monotherapy in HFrEF patients is limited, particularly in the Indian population, where lower body weight, socioeconomic factors, and differing comorbid profiles may influence treatment outcomes.[15-19] This study aimed to address this gap by evaluating the relative safety and efficacy of sacubitril/valsartan versus telmisartan monotherapy on a background of standard care in patients with HFrEF. The findings are anticipated to generate critical evidence for optimizing HF management, with the goal of improving survival, reducing hospitalizations, and enhancing the quality of life in this high-risk population.

METHODS

Study design and setting

This randomized, prospective, open-label, comparative interventional study was conducted in the department of cardiology and the department of pharmacology at Dr. RPGMC, Kangra at Tanda, a 700-bedded multispecialty tertiary healthcare center situated in the Kangra Valley, Himachal Pradesh, India. The study aimed to compare the safety and efficacy of sacubitril/valsartan with telmisartan monotherapy in two groups of patients with heart failure with reduced ejection fraction (HFrEF). The study spanned six months, with an enrolment period of one year. Patients were screened for eligibility based on clinical signs and symptoms, 2D echocardiographic findings, and other relevant investigations, following informed consent.

Sample size calculation

The sample size was calculated using the formula for finite populations:

$N= z^2 \times p\ (1-p) / \epsilon^2$

Where: z = Z-score, ϵ\epsilonϵ = Margin of error, N = population size, p: population proportion.

Inclusion criteria

Patients with chronic heart failure with reduced ejection fraction (HFrEF, EF≤40%). Adult patients of either sex, consenting to participate in the study. BNP≥150 pg/ml for patients without heart failure hospitalization in the prior year. BNP≥100 pg/ml for patients with a history of heart failure hospitalization in the prior year.

Exclusion criteria

Patients unwilling to participate. Pregnant females. Serum potassium >5.2 mmol/l. Symptomatic hypotensive patients. Systolic blood pressure (SBP) <100 mmHg at screening or <95 mmHg at randomization. History of angioedema. Patients on medications that interact with ARNI/ARBs. Patients with congenital heart disease. History of unacceptable side effects with ACE inhibitors or ARBs.

Randomization and study protocol

Eligible patients were enrolled after obtaining written informed consent. They were randomized into two groups (group A and group B) using a block randomization technique with computer-generated random numbers, stratified by age and sex. Detailed patient histories were recorded, and clinical examinations were conducted. Baseline investigations, including fasting blood sugar (FBS), lipid profile, liver function tests (LFTs), renal function tests (RFTs), serum electrolytes, complete hemogram, electrocardiography (ECG), and 2D echocardiography, were performed. Serum BNP levels were measured at enrolment and after completion of the study.

Treatment strategy

Group A received telmisartan monotherapy at a maximum dose of 40 mg once daily, taken before breakfast. Group B received sacubitril/valsartan at a maximum dose of 200 mg twice daily, taken before meals. Patients were contacted telephonically the day after starting the medication to monitor for discomfort and adverse reactions. Follow-up visits were scheduled at 12 weeks and 24 weeks, during which clinical assessments, repeat investigations, and therapeutic outcomes were evaluated.

Outcome measures

The outcomes were assessed at the end of six months of intervention and included:

Efficacy outcomes

Improvement in New York Heart Association (NYHA) functional classification. Improvement in ejection fraction on echocardiography. Reduction in serum BNP levels.

Safety outcomes

Reports of adverse events during the study. Changes in hematological or biochemical parameters, including FBS, LFTs, and RFTs.

Statistical analysis

Data were entered into Microsoft® Excel and analyzed using SPSS Version 21 (IBM, USA). Categorical variables were expressed as frequencies and percentages, and comparisons between the two groups were performed using the chi-square test. Quantitative variables were expressed as mean ± standard deviation (SD), and independent t-tests were used for between-group comparisons. Within-group comparisons at different time points were analyzed using paired t-tests. A p value of <0.05 was considered statistically significant.

Ethical considerations

The study was conducted in compliance with ethical guidelines outlined by the Indian Council of Medical Research (1994) and the Declaration of Helsinki (2000). Approval was obtained from the Protocol Review Committee (PRC) and the Institutional Ethics Committee (IEC), and the study was registered with the Clinical Trial Registry of India (CTRI). Written informed consent was obtained from all participants, and their privacy and confidentiality were maintained. No unnecessary financial burden was placed on the patients, and data collected were used solely for academic purposes. Approval details are- PRC approval: HFW(DRPGMC)/PROTOCOL/2018/44 (01/12/2018). IEC approval: IEC/2019-158 (10/01/2019). CTRI registration: CTRI/2019/05/019284 (registered on 23/05/2019).

Figure 1 shows the CONSORT diagram for the study.

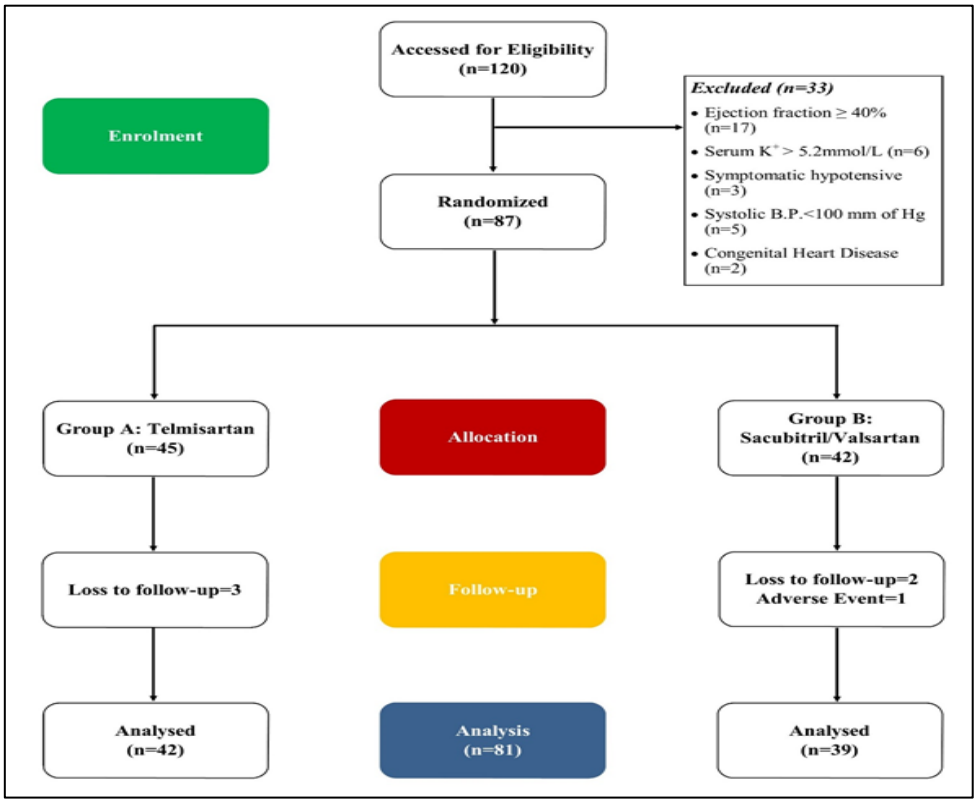

Figure 1: CONSORT flow diagram.

RESULTS

The baseline demographics and sociocultural characteristics of the study population, as summarized in Table 1 were comparable across both groups. Group A (telmisartan) included 42 patients, while group B (sacubitril/valsartan) had 39 patients. The mean age was similar between the groups (61.1±10.6 years in group A versus 59.7±11.5 years in group B, p=0.577), and a male predominance was observed in both groups (54.8% in group A versus 64.1% in group B, p=0.393). The mean BMI was also comparable (24.8±3.9 kg/m^2 in group A

versus 25.1±4.7 kg/m^2 in group B, p=0.777). Family history of cardiovascular disease was reported by 16.7% in group A and 15.4% in group B (p=1.000), while smoking (33.3% in group A versus 30.8% in group B, p=0.805) and alcohol use (38.1% in group A versus 28.2% in group B, p=0.345) were similarly distributed.

Overall, both groups were well-balanced in terms of baseline characteristics, ensuring the validity of comparisons in subsequent analyses. The clinical characteristics and co-morbidities of the study population, as shown in Table 2, were evenly distributed between the groups. Coronary artery disease (CAD) was the most prevalent condition, affecting 66.7% of patients in group A and 53.8% in group B (p=0.231). Dyslipidemia was present in 23.8% of group A patients and 33.3% of group B patients (p=0.499), while osteoarthritis (OA) was reported by 21.4% and 30.8% of patients in groups A and B, respectively (p=0.482). Hypertension affected a similar proportion in both groups (21.4% in group A versus 20.5% in group B, p=0.797), as did diabetes mellitus (19.0% in Group A versus 20.5% in Group B, p = 1.000). Chronic kidney disease (7.1% in Group A vs. 10.3% in Group B, p=0.699) and chronic obstructive pulmonary disease (4.8% in Group A versus 7.7% in group B, p=0.649) were infrequent but comparably distributed. Hypothyroidism, anemia, and atrial fibrillation were rare across both groups, with no statistically significant differences observed. These results indicate that the two groups were well-matched in terms of co-morbid conditions, ensuring a balanced baseline for the study.

Table 3 summarizes the hemodynamic parameters, including heart rate and blood pressure, at baseline, 3 months, and 6 months. Heart rate was comparable between the groups at all time points, with baseline values of 73.1±12.6 bpm in group A (telmisartan) and 72.4±12.1 bpm in group B (sacubitril/valsartan, p=0.799), remaining consistent at 3 months (72±12.3 bpm versus 71.5±11.7 bpm, p=0.852) and 6 months (72.5±11.9 bpm versus 72±11.8 bpm, p=0.850). Similarly, systolic blood pressure (SBP) was stable across both groups, with baseline values of 126±16 mmHg in group A and 128±15 mmHg in group B (p=0.564), and showed no significant differences at 3 months (124±17 mmHg versus 126±19 mmHg, p=0.618) or 6 months (126±16 mmHg versus 127±16 mmHg, p=0.779).

Diastolic blood pressure (DBP) was also comparable at baseline (72±12 mmHg versus 74±12 mmHg, p=0.455), 3 months (74±11 mmHg versus 73±11 mmHg, p=0.683), and 6 months (72±12 mmHg versus 74±11 mmHg, p=0.437). These findings demonstrate stable and comparable hemodynamic profiles in both treatment groups throughout the study. Table 4 presents the efficacy outcomes, including NYHA class, left ventricular ejection fraction (LVEF), and BNP levels, which showed significant improvement in both groups, with better results in group B (sacubitril/valsartan). At baseline, the majority of patients were in NYHA class II (71.4% in group A versus 61.5% in group B, p=0.156), but by 6 months, a greater proportion of patients in group B transitioned to class I (17.9% versus 4.8%, p=0.005). LVEF improved significantly (Figure 2) in both groups over time, increasing from 24.7±4.5% to 32.4±8.3% in group A and from 23.5±6.8% to 35.2±7.7% in group B, though intergroup differences were not statistically significant (p=0.130 at 6 months).

BNP levels showed a marked reduction in both groups (Figure 3) but were significantly lower in group B at 3 months (1010.3±307.2 pg/ml versus 1203.6±325.1 pg/ml, p=0.007) and 6 months (583.2±324.2 pg/ml versus 957.5±305.2 pg/ml, p<0.0001). These findings highlight superior improvement in clinical and biochemical outcomes with sacubitril/valsartan compared to telmisartan.

Table 5 highlights the hematological parameters, including hemoglobin levels, total leukocyte count (TLC), and platelet count, which were comparable across both groups at all time points. Hemoglobin levels were stable but slightly declined in group A over time, from 12±2.3 gm/dl at baseline to 11.7±2.9 gm/dl at 6 months, while group B maintained a steady level (12.5±2.4 gm/dl at baseline and 6 months, p=0.179). TLC remained consistent between the groups at baseline (8.9 ± 2.8 × 10^3/mm^3 in Group A versus 8.8±2.5 × 10^3/mm^3 in group B, p=0.750) and over 6 months, with no significant differences (p=0.541 at 6 months). Platelet counts were similar across both groups throughout the study, starting at 157.3±49.6 × 10^3 in group A and 154.7±51.2 × 10^3 in group B (p=0.816 at baseline) and remaining comparable at 6 months (p=0.586). These findings indicate no significant hematological changes or adverse effects related to either treatment.

Table 6 details the biochemistry parameters, including fasting blood sugar (FBS), blood urea nitrogen (BUN), creatinine, cholesterol, total bilirubin, direct bilirubin, serum HDL, serum LDL, and triglycerides, measured at baseline, 3 months, and 6 months. FBS remained stable across groups, with no significant differences over time (p=0.812 at 6 months). BUN and creatinine levels increased slightly in both groups, with comparable values at 6 months (BUN: 27.7±6.3 mg/dl in group A versus 29±6.6 mg/dl in group B, p=0.357; creatinine: 1.2±0.3 mg/dl in both groups, p=0.476).

Total bilirubin decreased marginally over the study period but was comparable between groups (0.39±0.11 mg/dl in group A versus 0.39±0.15 mg/dl in group B at 6 months, p=0.919). Similarly, direct bilirubin levels showed no significant intergroup differences (p=0.898 at 6 months). Cholesterol, serum HDL, serum LDL, and triglyceride levels were stable throughout the study and did not differ significantly between groups at any time point (e.g., cholesterol at 6 months: 188.6±23.3 mg/dl in group A versus 183.3±28.8 mg/dl in group B, p=0.676). These findings confirm the biochemical stability and tolerability of both treatments. Table 7 summarizes the adverse events and safety parameters monitored during the study,

including liver function tests (SGOT, SGPT, ALP), electrolytes (serum sodium and potassium), and adverse events. Adverse events were minimal, with only one instance of non-serious angioedema reported in group B (2.6%) after the first dose, leading to withdrawal of the participant. No adverse events were observed in group A. SGOT and SGPT levels showed marginal increases in both groups over 6 months but remained comparable (SGOT at 6 months: 44.3±31 IU/l in group A versus 42.3±28.2 IU/l in group B, p=0.764; SGPT at 6 months: 50.6±31.7 IU/l in group A versus 42.6±31 IU/l in group B, p=0.255).

ALP levels were stable and similar between groups throughout the study (p=0.639 at 6 months). Serum sodium and potassium levels remained within normal ranges in both groups with no significant intergroup differences (serum sodium at 6 months: 151.6±21.7 mEq/l in group A versus 150.5±23.7 mEq/l in group B, p=0.878; serum potassium at 6 months: 4.7±0.46 mEq/l in group A versus 4.6±0.38 mEq/l in group B, p=0.307). These findings demonstrate that both treatments were well-tolerated and safe over the study duration.

Table 1: Baseline demographics and sociodemographic characteristics.

Parameters	Group A (telmisartan)	Group B (sacubitril/valsartan)	P value
Number of patients	42 (100%)	39 (100%)	N/A
Mean age (years)	61.1±10.6	59.7±11.5	0.577
Gender (%)			0.393
Male	23 (54.8)	25 (64.1)	
Female	19 (45.2)	14 (35.9)	
Body mass index (BMI, kg/m^2)	24.8±3.9	25.1±4.7	0.777
Family history of CVD (%)			1.000
Present	7 (16.7)	6 (15.4)	
Absent	35 (83.3)	33 (84.6)	
Smoking history (%)			0.805
Present	14 (33.3)	12 (30.8)	
Absent	28 (66.7)	27 (69.2)	
Alcohol use history (%)			0.345
Present	16 (38.1)	11 (28.2)	
Absent	26 (61.9)	28 (71.8)	

Table 2: Clinical characteristics and co-morbidities.

Co-morbidity	Group A (telmisartan) (%)	Group B (sacubitril/valsartan) (%)	P value
Coronary artery disease (CAD)	28 (66.7)	21 (53.8)	0.231
Dyslipidemia	10 (23.8)	13 (33.3)	0.499
Osteoarthritis (OA)	9 (21.4)	12 (30.8)	0.482
Hypertension	9 (21.4)	8 (20.5)	0.797
Diabetes mellitus	8 (19.0)	8 (20.5)	1.000
Chronic kidney disease (CKD)	3 (7.1)	4 (10.3)	0.699
Chronic obstructive pulmonary disease (COPD)	2 (4.8)	3 (7.7)	0.649
Hypothyroidism	2 (4.8)	2 (5.1)	1.000
Anemia	1 (2.4)	2 (5.1)	0.560
Atrial fibrillation (AF)	2 (4.8)	0 (0)	0.154

Table 3: Hemodynamic parameters (heart rate and blood pressure).

Parameters	Time point	Group A (telmisartan)	Group B (sacubitril/valsartan)	P value
Heart Rate (bpm)	Baseline	73.1±12.6	72.4±12.1	0.799
	3 Months	72±12.3	71.5±11.7	0.852
	6 Months	72.5±11.9	72±11.8	0.850
Systolic BP (mmHg)	Baseline	126±16	128±15	0.564
	3 Months	124±17	126±19	0.618
	6 Months	126±16	127±16	0.779
Diastolic BP (mmHg)	Baseline	72±12	74±12	0.455
	3 Months	74±11	73±11	0.683
	6 Months	72±12	74±11	0.437

Table 4: Efficacy outcomes (NYHA class, LVEF, and BNP).

Parameters	Time point	Group A (telmisartan)	Group B (sacubitril/valsartan)	P value
NYHA class (%)	Baseline	Class I: 0, II: 71.4, III: 21.4, IV: 7.2	Class I: 0, II: 61.5, III: 33.3, IV: 5.2	0.156
	6 months	Class I: 4.8, II: 69.0, III: 26.2, IV: 0	Class I: 17.9, II: 69.2, III: 12.9, IV: 0	0.005
LVEF (%)	Baseline	24.7±4.5	23.5±6.8	0.339
	3 months	27.5±5.1	27.9±7.4	0.778
	6 months	32.4±8.3	35.2±7.7	0.130
BNP (pg/ml)	Baseline	1527.3±435.4	1604.7±487.3	0.452
	3 months	1203.6±325.1	1010.3±307.2	0.007
	6 months	957.5±305.2	583.2±324.2	<0.0001

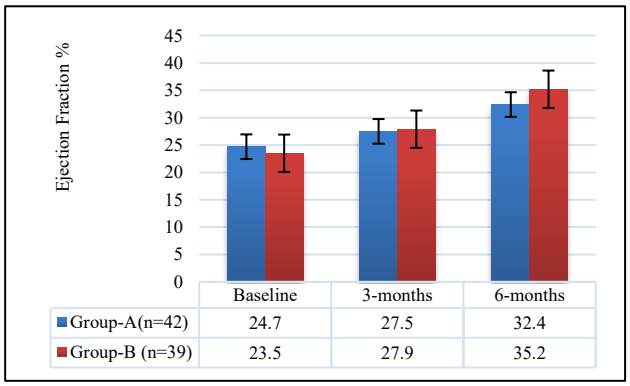

Figure 2: Bar graph showing comparison of ejection fraction improvement in both the groups.

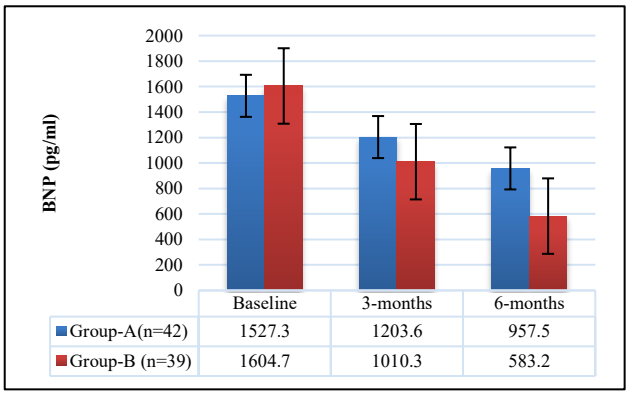

Figure 3: Bar graph showing comparison of fall in serum BNP levels in both the groups.

Table 5: Hematological parameters.

Parameter	Time point	Group A (telmisartan)	Group B (sacubitril/valsartan)	P value
Hemoglobin (gm/dl)	Baseline	12±2.3	12.5±2.4	0.368
	3 Months	12±2.3	12.4±2.3	0.360
	6 Months	11.7±2.9	12.5±2.3	0.179
TLC ($\times 10^3/mm^3$)	Baseline	8.9±2.8	8.8±2.5	0.750
	3 Months	9±2.8	8.7±2.5	0.724
	6 Months	9±2.8	8.6±2.7	0.541
Platelets ($\times 10^3$)	Baseline	157.3±49.6	154.7±51.2	0.816
	3 Months	158.5±49.2	151.7±49.7	0.541
	6 Months	158.7±52.1	152.5±49.3	0.586

Table 6: Biochemistry parameters.

Parameters	Time point	Group A (telmisartan)	Group B (sacubitril/valsartan)	P value
FBS (mg/dl)	Baseline	120.4±3.5	119.9±5.2	0.604
	3 months	121.7±13.2	119.6±14.7	0.213
	6 months	120.1±9.6	118.7±9.2	0.812
BUN (mg/dl)	Baseline	21.7±4.7	23.8±5.9	0.081
	3 months	26.6±5.5	27.9±7.1	0.347
	6 months	27.7±6.3	29±6.6	0.357
Creatinine (mg/dl)	Baseline	1±0.2	1±0.2	0.812
	3 months	1.1±0.3	1.1±0.3	0.969
	6 months	1.2±0.3	1.2±0.2	0.476
Cholesterol (mg/dl)	Baseline	196.6±28.5	202.1±30.6	0.410
	3 months	190.5±23.9	192.5±34.1	0.769

Parameters	Time point	Group A (telmisartan)	Group B (sacubitril/valsartan)	P value
	6 months	188.6±23.3	183.3±28.8	0.676
Total bilirubin (mg/dl)	Baseline	0.48±0.22	0.52±0.22	0.374
	3 months	0.41±0.13	0.42±0.19	0.711
	6 months	0.39±0.11	0.39±0.15	0.919
Direct bilirubin (mg/dl)	Baseline	0.24±0.11	0.26±0.11	0.374
	3 months	0.24±0.07	0.25±0.09	0.732
	6 months	0.24±0.06	0.24±0.07	0.898
Serum HDL (mg/dl)	Baseline	50.7±9.6	53.6±9	0.166
	3 months	51.3±10.2	54±8.6	0.198
	6 months	50.7±9.9	54.7±10.1	0.078
Serum LDL (mg/dl)	Baseline	134.2±16.3	138.4±19	0.283
	3 months	135.9±17.6	139.7±20.6	0.382
	6 months	136.5±18.1	140.8±18.4	0.296
Triglycerides (mg/dl)	Baseline	186±62.9	185±55.9	0.943
	3 months	188±64	185.6±57.7	0.857
	6 months	189±64.1	186.7±58	0.870

Table 7: Adverse events and safety parameters.

Parameters	Time point	Group A (telmisartan)	Group B (sacubitril/valsartan)	P value
Adverse events	Baseline	0 (0%)	1 (2.6%)	N/A
	3 months	0 (0%)	0 (0%)	
	6 months	0 (0%)	0 (0%)	
SGOT (IU/l)	Baseline	41.4±28.6	42.6±31.6	0.864
	3 months	46.2 34.7	43.5±34.8	0.731
	6 months	44.3±31	42.3±28.2	0.764
SGPT (IU/l)	Baseline	48.8±34	42.7±34.8	0.427
	3 months	50.8±39.8	44±35.5	0.424
	6 months	50.6±31.7	42.6±31	0.255
ALP (IU/l)	Baseline	122.6±56.8	132.3±67	0.487
	3 months	127.6±70.2	133±67.1	0.725
	6 months	125.9±66.1	132.7±64.8	0.639
Serum sodium (mEq/l)	Baseline	154.8±17.3	157.9±14.5	0.314
	3 months	155.4±17.8	152.2±13.7	0.621
	6 months	151.6±21.7	150.5±23.7	0.878
Serum potassium (mEq/l)	Baseline	4.2±0.67	4.2±0.39	0.902
	3 months	4.5±0.50	4.4±0.46	0.155
	6 months	4.7±0.46	4.6±0.38	0.307

DISCUSSION

Heart failure (HF) remains a significant global health challenge, with a prevalence of 5.8 million in the USA and approximately 15 million in Europe.[20,21] The condition not only imposes a substantial burden on individual patients due to its symptoms and frequent hospitalizations but also places immense pressure on healthcare systems due to high resource utilization.[22-24] Despite advances in pharmacotherapy, the prognosis of HF remains dismal, with 5-year survival rates of only 50%- a figure worse than advanced cancers or stroke.[25]

The primary goals of HF management are to improve clinical symptoms and quality of life (QoL), reduce hospital readmissions, and lower mortality. Regulatory and clinical success of newer drugs is often contingent on their ability to demonstrate mortality reduction, the most critical outcome in HF.[26] Current pharmacotherapies for HF with reduced ejection fraction (HFrEF) are categorized into two groups: those that modify the disease process and prolong survival and those that alleviate symptoms. The first group, recognized as guideline-directed medical therapy (GDMT), includes RAAS blockers (ACE inhibitors, ARBs, and MRAs), beta-blockers, angiotensin receptor-neprilysin inhibitors (ARNI), and hydralazine with isosorbide dinitrate in specific populations.[26] Sacubitril/valsartan, the first-in-class ARNI, has emerged as a game-changer by combining neprilysin inhibition with AT1 receptor blockade. It demonstrated superior efficacy over enalapril in reducing morbidity and mortality in the PARADIGM-HF trial.[27]

The present study aimed to compare the safety and efficacy of sacubitril/valsartan with telmisartan monotherapy in patients with HFrEF on a background of standard care. Randomization ensured a well-matched distribution of demographic and clinical variables such as age, gender, BMI, comorbidities, and lifestyle factors across both groups. The study population had a mean age of 60 years, similar to the PARADIGM-HF trial (mean age: 64 years), with 41% female representation, exceeding the typical inclusion of women in HF trials such as PARADIGM-HF (21%).[27,28]

Comorbidities in the study cohort were consistent with HF populations, with CAD/IHD being the most prevalent (60.4%), followed by dyslipidemia (28.3%), osteoarthritis (25.9%), hypertension (20.9%), and diabetes (19.7%). Clinical parameters such as heart rate and blood pressure remained comparable and stable across groups throughout the study, suggesting no significant impact of either drug on these measures.

Clinical improvement was observed in both groups, with no hospital readmissions or mortality during the 6-month study period. Notably, sacubitril/valsartan demonstrated superior efficacy in alleviating HF symptoms, as evidenced by significant improvement in NYHA class ($p=0.005$) compared to telmisartan. Both interventions significantly improved left ventricular ejection fraction (LVEF) from baseline to 6 months within their respective cohorts. However, intergroup analysis showed no significant difference in LVEF improvement between the two groups ($p=0.130$), indicating that sacubitril/valsartan was not inferior to telmisartan in enhancing LVEF.

The reduction in serum BNP levels, a key marker of HF prognosis and therapy effectiveness, was significant in both groups.[29] However, sacubitril/valsartan showed a greater reduction in BNP levels compared to telmisartan, with a highly significant intergroup difference at 6 months ($p<0.0001$). This underscores the superior efficacy of sacubitril/valsartan in reducing HF-related morbidity.

Safety was assessed through adverse events and serial monitoring of laboratory parameters. Only one patient in the sacubitril/valsartan group developed non-serious angioedema after the first dose, which resolved with oral cetirizine. Laboratory parameters, including hematologic, liver, renal, lipid, and electrolyte profiles, remained stable and comparable between groups, confirming that both drugs were well-tolerated.

This study had several limitations. The sample size, though adequate for pilot findings, could have been larger to enhance statistical power. Functional assessments such as the 6-minute walk test (6MWT), a reliable predictor of HF outcomes, were not included but could have provided additional insights. Additionally, NT-proBNP testing, recommended for patients on ARNI therapy due to its reliability unaffected by neprilysin inhibition, was not available at our institution. The choice of telmisartan as a comparator instead of valsartan, the ARB component of sacubitril/valsartan, limited the ability to isolate the effect of neprilysin inhibition.

The COVID-19 pandemic posed significant logistical challenges, impacting study operations. Despite these limitations, the study provides meaningful insights into the comparative safety and efficacy of sacubitril/valsartan and telmisartan in HFrEF management.

CONCLUSION

The study concludes that both telmisartan and sacubitril/valsartan demonstrated comparable safety profiles, with no significant adverse effects observed during the trial period. Both drugs showed significant efficacy in improving left ventricular ejection fraction (LVEF) and reducing serum BNP levels within their respective cohorts. However, sacubitril/valsartan demonstrated a superior reduction in serum BNP levels, highlighting its greater efficacy in addressing the underlying pathophysiology of HFrEF. Aligning with ACC/AHA guidelines, which recommend the initiation of ARNI therapy for patients with HFrEF ($EF \leq 40\%$) and NYHA class II or III symptoms, sacubitril/valsartan emerges as the preferred treatment option for this patient population. These findings underscore the importance of prioritizing sacubitril/valsartan therapy as a key strategy in optimizing outcomes for patients with HFrEF.

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