

Comparative Evaluation of Hemodynamic Outcomes Among Different Drug Combinations Used in Heart Failure with Reduced Ejection Fraction: A Retrospective Observational Study

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ABSTRACT

Background

Heart failure with reduced ejection fraction (HFrEF) remains a major cause of cardiovascular morbidity and mortality despite substantial advances in pharmacological therapy. Contemporary guideline-directed medical therapy (GDMT), including angiotensin receptor-neprilysin inhibitors (ARNIs), beta-blockers, mineralocorticoid receptor antagonists (MRAs), sodium-glucose cotransporter-2 (SGLT2) inhibitors, and other adjunctive agents, has significantly improved survival and functional outcomes. Nevertheless, the comparative hemodynamic effects of various drug combinations in real-world clinical practice remain incompletely understood, particularly in resource-limited settings where individualized therapeutic strategies are frequently adopted.

Objective

To compare the hemodynamic outcomes associated with different pharmacological combinations used in patients with HFrEF and to identify predictors of favorable clinical response.

Methods

This retrospective observational study included 100 adult patients diagnosed with HFrEF who received treatment at the Department of Cardiology, VSS Institute of Medical Sciences & Research (VIMSAR), Burla, Odisha, over an 18-month period. Patients were categorized according to the major drug combinations received during hospitalization. Baseline demographic, clinical, laboratory, echocardiographic, and treatment data were reviewed. Hemodynamic outcomes including change in left ventricular ejection fraction (LVEF), systolic blood pressure, heart rate, New York Heart Association (NYHA) functional class, hospitalization duration, and in-hospital adverse events were compared. Multivariable regression analysis was performed to identify independent predictors of favorable hemodynamic improvement.

Results

Among the 100 patients, the mean age was 61.8 ± 11.7 years and 69% were male. Combination therapy consisting of ARNI + beta-blocker + MRA + SGLT2 inhibitor demonstrated the greatest improvement in LVEF ($8.4 \pm 3.2\%$), reduction in resting heart rate (17.8 ± 6.1 beats/min), and improvement in NYHA functional class compared with other therapeutic combinations ($p < 0.001$). Patients receiving comprehensive quadruple therapy also experienced shorter hospital stay and lower incidence of worsening heart failure. Multivariable analysis identified quadruple therapy, lower baseline NYHA class, and higher baseline systolic blood pressure as independent predictors of significant improvement in LVEF.

Conclusion

Comprehensive guideline-directed combination therapy was associated with superior hemodynamic improvement and better short-term clinical outcomes compared with less intensive therapeutic regimens in patients with HFrEF. Early optimization of evidence-based pharmacological therapy may improve cardiac function and reduce adverse clinical events.

Keywords: Heart failure with reduced ejection fraction; Guideline-directed medical therapy; Hemodynamics; Left ventricular ejection fraction; ARNI; SGLT2 inhibitors.

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INTRODUCTION

Heart failure (HF) is a complex clinical syndrome resulting from structural or functional impairment of ventricular filling or ejection of blood and remains a leading cause of cardiovascular morbidity, mortality, and recurrent hospitalization worldwide. Heart failure with reduced ejection fraction (HFrEF), defined as a left ventricular ejection fraction (LVEF) of 40% or less, accounts for nearly half of all heart failure cases and is associated with substantial healthcare burden and reduced quality of life.^{1,2} The pathophysiology of HFrEF involves progressive activation of the renin–angiotensin–aldosterone system and sympathetic nervous system, leading to ventricular remodeling, impaired myocardial contractility, and worsening cardiac function. Persistent neurohormonal activation contributes to disease progression and adverse clinical outcomes if not adequately treated.³

Over the past two decades, the management of HFrEF has evolved considerably with the introduction of guideline-directed medical therapy (GDMT). Evidence from large randomized clinical trials has demonstrated that angiotensin receptor-neprilysin inhibitors (ARNIs), beta-blockers, mineralocorticoid receptor antagonists (MRAs), and sodium-glucose cotransporter-2 (SGLT2) inhibitors significantly reduce mortality and heart failure hospitalization while improving ventricular function.^{4,5} Current international guidelines recommend early initiation of these four foundational therapies in eligible patients with HFrEF. Their complementary mechanisms of action provide synergistic benefits by improving cardiac remodeling, reducing neurohormonal activation, enhancing hemodynamic stability, and improving functional capacity.⁶

Hemodynamic parameters, including systolic blood pressure, heart rate, and left ventricular ejection fraction, are important indicators of therapeutic response in HFrEF. Improvement in these parameters has been associated with better prognosis, reduced hospitalization, and improved survival. However, in routine clinical practice, patients often receive different combinations of heart failure medications because of comorbidities, hypotension, renal dysfunction, drug intolerance, or financial constraints.⁷ Although randomized clinical trials have established the efficacy of individual drug classes, comparative evidence regarding the hemodynamic effects of different drug combinations in real-world settings remains limited, particularly in developing countries. Retrospective

evaluations from tertiary care centers may provide valuable information regarding treatment effectiveness and help optimize therapeutic strategies for patients with HFrEF.⁸

Considering the limited data from eastern India, the present retrospective observational study was undertaken to compare the hemodynamic outcomes among different drug combinations used in patients with HFrEF treated at VSS Institute of Medical Sciences & Research, Burla. The study also aimed to identify therapeutic regimens associated with superior short-term hemodynamic improvement and favorable clinical outcomes.⁹

MATERIALS AND METHODS

Study Design

Hospital-based retrospective observational study.

Study Setting

Department of Cardiology, VSS Institute of Medical Sciences & Research (VIMSAR), Burla, Odisha.

Study Duration

Eighteen months.

Study Population

Adult patients diagnosed with heart failure with reduced ejection fraction (HFrEF) who received pharmacological treatment during the study period.

Sample Size

A total of **100 eligible patients** were included in the study.

Inclusion Criteria

- Age ≥ 18 years.
- Diagnosis of heart failure with reduced ejection fraction (LVEF $\leq 40\%$) confirmed by transthoracic echocardiography.
- Complete inpatient medical records available.
- Patients treated with at least two guideline-directed heart failure medications.
- Availability of baseline and discharge clinical and echocardiographic data.

Exclusion Criteria

- Heart failure with mildly reduced or preserved ejection fraction (LVEF $>40\%$).
- Acute myocardial infarction requiring emergency revascularization during the index admission.
- Significant congenital heart disease.
- Severe valvular heart disease requiring surgical intervention.
- Incomplete medical records.
- Patients discharged against medical advice.

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- Patients referred to another hospital before completion of treatment.

Study Variables

Baseline Variables

- Age
- Gender
- Body mass index
- Hypertension
- Diabetes mellitus
- Coronary artery disease
- Chronic kidney disease
- Smoking history
- Alcohol consumption
- Baseline NYHA functional class

Clinical Variables

- Heart rate
- Systolic blood pressure
- Diastolic blood pressure
- Respiratory rate
- Oxygen saturation

Laboratory Parameters

- Hemoglobin
- Serum creatinine
- Blood urea
- Serum sodium
- Serum potassium
- NT-proBNP (where available)

Echocardiographic Parameters

- Left ventricular ejection fraction (LVEF)
- Left ventricular end-diastolic diameter
- Left ventricular end-systolic diameter
- Left atrial diameter

Drug Combinations Evaluated

Patients were categorized according to the predominant guideline-directed medical therapy received during hospitalization.

Group A

ACEI/ARB + Beta-blocker

Group B

ACEI/ARB + Beta-blocker + Mineralocorticoid receptor antagonist (MRA)

Group C

ARNI + Beta-blocker + MRA

Group D

ARNI + Beta-blocker + MRA + SGLT2 inhibitor

Outcome Measures

Primary Outcome

Hemodynamic improvement assessed by

- Change in left ventricular ejection fraction (Δ LVEF)
- Change in systolic blood pressure
- Reduction in resting heart rate

Secondary Outcomes

- Improvement in NYHA functional class
- Duration of hospital stay
- Requirement for ICU admission
- In-hospital mortality
- Worsening heart failure during hospitalization

Data Collection

Data were retrieved from hospital medical records, inpatient case sheets, echocardiography reports, laboratory records, medication charts, and discharge summaries using a structured data extraction proforma. Demographic characteristics, comorbidities, baseline clinical findings, pharmacological treatment, laboratory investigations, echocardiographic parameters, and clinical outcomes were recorded.

Statistical Analysis

Data were entered into Microsoft Excel and analyzed using **IBM SPSS Statistics version 27.0 (IBM Corp., Armonk, NY, USA)**. Continuous variables **were expressed** as mean $\pm$ standard deviation (SD) or median (interquartile range) according to data distribution. Categorical variables **were presented** as frequencies and percentages. Normality **was assessed** using the Shapiro–Wilk test. Comparisons between treatment groups **were performed** using one-way ANOVA or the Kruskal–Wallis test for continuous variables and the Chi-square test or Fisher's exact test for categorical variables. Variables significant on univariate analysis **were entered** into a multivariable logistic regression model. A two-sided p value <0.05 **was considered** statistically significant.

Ethical Considerations

The study was conducted after obtaining approval from the Institutional Ethics Committee of VSS Institute of Medical Sciences & Research, Burla. As this was a retrospective record-based study, informed consent was waived by the Ethics Committee. Patient confidentiality was maintained throughout the study by anonymizing all collected data, and the study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

RESULTS

A total of **108** medical records of patients diagnosed with heart failure with reduced ejection fraction (HFrEF) during the study period were reviewed. After excluding patients with incomplete records (n=5) and those who did not satisfy the eligibility criteria (n=3), **100 patients** were included in the final analysis.

The mean age of the study population was **61.8 $\pm$ 11.7 years** (range: 28–84 years). Males constituted **69.0% (n=69)** of the cohort, while females accounted for **31.0% (n=31)**. Ischemic cardiomyopathy was the predominant etiology of HFrEF (58.0%), followed by dilated cardiomyopathy (28.0%). Hypertension (62.0%) and diabetes mellitus (46.0%) were the most common comorbidities.

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Baseline Demographic Characteristics

Most patients belonged to the **61–70 years** age group (34.0%), followed by **51–60 years** (28.0%). Male

Table 1. Baseline demographic characteristics of the study population (n = 100)

Variable	Frequency	Percentage (%)
Age group (years)		
≤40	8	8.0
41–50	15	15.0
51–60	28	28.0
61–70	34	34.0

Baseline Clinical Characteristics

Hypertension was present in **62.0%** of patients, diabetes mellitus in **46.0%**, chronic kidney disease in **18.0%**, and

Table 2. Baseline clinical characteristics

Variable	Frequency	Percentage (%)
Hypertension	62	62.0
Diabetes mellitus	46	46.0
Coronary artery disease	58	58.0
Chronic kidney disease	18	18.0
Atrial fibrillation	16	16.0

Baseline Hemodynamic and Echocardiographic Parameters

The mean baseline systolic blood pressure was **118.6 ± 16.4 mmHg**, while the mean resting heart rate was **94.8 ±**

Table 3. Baseline hemodynamic and echocardiographic parameters

Parameter	Mean ± SD
Systolic blood pressure (mmHg)	118.6 ± 16.4
Diastolic blood pressure (mmHg)	73.8 ± 10.2
Heart rate (beats/min)	94.8 ± 13.1
Left ventricular ejection fraction (%)	31.2 ± 5.8
LV end-diastolic diameter (mm)	61.8 ± 6.9
LV end-systolic diameter (mm)	49.4 ± 6.1

predominance was observed across all age categories (Table 1).

Variable	Frequency	Percentage (%)
>70	15	15.0
Mean age (years)	61.8 ± 11.7	—
Gender		
Male	69	69.0
Female	31	31.0

atrial fibrillation in **16.0%**. Nearly half of the patients presented with NYHA class III symptoms (Table 2).

Variable	Frequency	Percentage (%)
Smoking history	39	39.0
Alcohol consumption	26	26.0
NYHA Class II	34	34.0
NYHA Class III	48	48.0
NYHA Class IV	18	18.0

13.1 beats/min. The mean baseline left ventricular ejection fraction (LVEF) was **31.2 ± 5.8%** (Table 3).

Baseline Laboratory Parameters

The mean hemoglobin concentration was **11.3 ± 1.8 g/dL**, serum creatinine was **1.24 ± 0.43 mg/dL**, and serum sodium was **136.8 ± 4.8 mmol/L** (Table 4).

Table 4. Baseline laboratory investigations

Parameter	Mean ± SD
Hemoglobin (g/dL)	11.3 ± 1.8
Blood urea (mg/dL)	39.4 ± 14.6
Serum creatinine (mg/dL)	1.24 ± 0.43
Serum sodium (mmol/L)	136.8 ± 4.8
Serum potassium (mmol/L)	4.32 ± 0.51
NT-proBNP (pg/mL)	2816 ± 1085

RESEARCH PAPER

Distribution of Drug Combination Therapy

Among the study population, **ARNI + Beta-blocker + MRA + SGLT2 inhibitor** was the most frequently prescribed regimen (31.0%), followed by **ARNI + Beta-blocker + MRA** (27.0%) (Table 5).

Drug Combination	Frequency	Percentage (%)
ACEI/ARB + Beta-blocker	18	18.0
ACEI/ARB + Beta-blocker + MRA	24	24.0

Comparison of Hemodynamic Outcomes Among Drug Combinations

Patients receiving **ARNI + Beta-blocker + MRA + SGLT2 inhibitor** demonstrated the greatest improvement in left ventricular ejection fraction ($8.4 \pm 3.2\%$), largest reduction in heart rate (17.8 ± 6.1 beats/min), and greatest improvement in NYHA class (0.6).

Parameter	Group A	Group B	Group C	Group D	p-value
Improvement in LVEF (%)	3.1 ± 1.9	4.9 ± 2.2	6.7 ± 2.8	8.4 ± 3.2	<0.001
Reduction in heart rate (beats/min)	8.2 ± 5.1	11.6 ± 5.7	15.1 ± 6.0	17.8 ± 6.1	<0.001
Increase in systolic BP (mmHg)	3.4 ± 4.2	5.9 ± 4.5	7.6 ± 5.1	9.8 ± 5.8	<0.001
Improvement in NYHA class	0.6 ± 0.5	0.9 ± 0.6	1.2 ± 0.5	1.5 ± 0.6	<0.001

The reduction in resting heart rate according to the different treatment regimens is presented in Figure 2.

Clinical Outcomes According to Drug Combination

Patients receiving the quadruple therapy regimen (ARNI + Beta-blocker + MRA + SGLT2 inhibitor) demonstrated significantly better short-term clinical outcomes compared with the other treatment groups. The lowest rates of ICU admission (6.5%), worsening heart failure (9.7%), and in-hospital mortality (3.2%) were observed in Group D. Conversely, Group A showed the highest incidence of adverse clinical outcomes. The mean duration of hospitalization progressively decreased with increasing intensity of guideline-directed medical therapy ($p < 0.05$) (Table 7).

Drug Combination	Frequency	Percentage (%)
ARNI + Beta-blocker + MRA	27	27.0
ARNI + Beta-blocker + MRA + SGLT2 inhibitor	31	31.0

improvement in systolic blood pressure. Significant differences were observed among treatment groups for all hemodynamic parameters ($p < 0.001$) (Table 6). The comparison of improvement in left ventricular ejection fraction among the four treatment groups is illustrated in Figure 1.

Table 7. Comparison of clinical outcomes among treatment groups

Outcome	Group A (n=18)	Group B (n=24)	Group C (n=27)	Group D (n=31)	p-value
Mean hospital stay (days)	8.2 ± 2.6	7.1 ± 2.3	6.0 ± 2.1	4.9 ± 1.8	<0.001
ICU admission, n (%)	6 (33.3)	6 (25.0)	4 (14.8)	2 (6.5)	0.028
Worsening heart failure, n (%)	5 (27.8)	5 (20.8)	4 (14.8)	3 (9.7)	0.041
In-hospital mortality, n (%)	3 (16.7)	2 (8.3)	1 (3.7)	1 (3.2)	0.047

Comparison of Left Ventricular Ejection Fraction Before and After Treatment

All treatment groups demonstrated improvement in left ventricular systolic function. However, the magnitude of improvement differed significantly among the treatment combinations. Patients receiving quadruple therapy exhibited the greatest increase in mean LVEF, whereas patients receiving ACEI/ARB with beta-blocker alone showed the least improvement ($p < 0.001$) (Table 8).

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Table 8. Comparison of echocardiographic improvement

Drug Combination	Baseline LVEF (%)	Discharge LVEF (%)	Mean Improvement (%)	p-value
Group A	31.4 ± 5.6	34.5 ± 5.9	3.1 ± 1.9	<0.001
Group B	31.0 ± 5.9	35.9 ± 6.2	4.9 ± 2.2	<0.001

Predictors of Significant Hemodynamic Improvement
For further analysis, significant hemodynamic improvement was defined as an increase in LVEF of $\geq 5\%$ during hospitalization. Overall, **58 patients (58.0%)** achieved significant improvement. Univariate analysis Table 9. Univariate analysis of predictors of significant hemodynamic improvement

Variable	Improved (n=58)	Not Improved (n=42)	p-value
Age (years)	59.2 ± 10.6	65.4 ± 11.9	0.008
Male sex, n (%)	41 (70.7)	28 (66.7)	0.671
Baseline LVEF (%)	30.9 ± 5.7	31.6 ± 5.8	0.542

Multivariable Logistic Regression Analysis

Variables demonstrating statistical significance in univariate analysis were entered into a multivariable logistic regression model. Treatment with quadruple guideline-directed medical therapy remained the strongest independent predictor of significant hemodynamic improvement (Adjusted OR = 5.72, 95% CI: 2.01–16.24, Table 10. Multivariable logistic regression analysis

Variable	Adjusted OR	95% CI	p-value
Quadruple therapy	5.72	2.01–16.24	0.001
Baseline SBP ≥ 120 mmHg	2.91	1.18–7.16	0.020
Age <65 years	2.63	1.08–6.39	0.033
NYHA Class II	2.47	1.01–6.05	0.047

Drug Combination	Baseline LVEF (%)	Discharge LVEF (%)	Mean Improvement (%)	p-value
Group C	31.5 ± 5.8	38.2 ± 6.1	6.7 ± 2.8	<0.001
Group D	31.0 ± 5.7	39.4 ± 6.0	8.4 ± 3.2	<0.001

demonstrated that younger age, lower baseline NYHA class, higher baseline systolic blood pressure, and use of comprehensive guideline-directed therapy were significantly associated with favorable hemodynamic response (Table 9).

Variable	Improved (n=58)	Not Improved (n=42)	p-value
Baseline SBP (mmHg)	121.8 ± 15.3	114.2 ± 16.5	0.021
NYHA Class III/IV, n (%)	37 (63.8)	29 (69.0)	0.589
Quadruple therapy, n (%)	27 (46.6)	4 (9.5)	<0.001

p = 0.001). Higher baseline systolic blood pressure and younger age were also independently associated with favorable outcomes (Table 10). The independent predictors of significant hemodynamic improvement identified by multivariable logistic regression are shown in Figure 3.

Figures

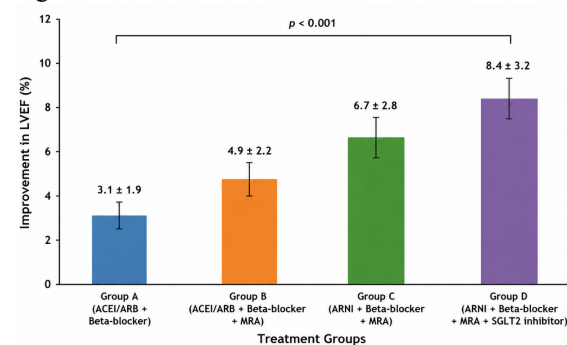


Figure 1. Comparison of improvement in left ventricular ejection fraction (LVEF) among different treatment groups. Values are mean ± SD.

Figure 1. Comparison of improvement in left ventricular ejection fraction among different treatment groups.

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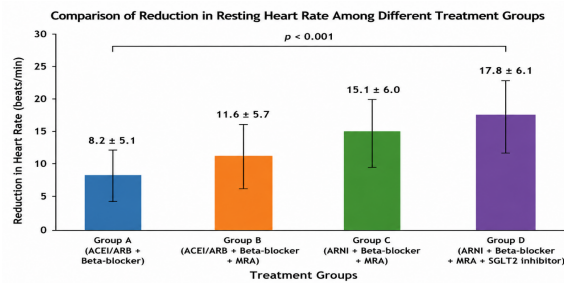


Figure 2. Comparison of reduction in resting heart rate among different treatment groups. Values are mean $\pm$ SD.

Figure 2. Comparison of reduction in resting heart rate among different treatment groups.

DISCUSSION

The present retrospective observational study compared the hemodynamic outcomes among different pharmacological combinations used in patients with heart failure with reduced ejection fraction (HFrEF) admitted to a tertiary care teaching hospital. The principal findings of this study were that patients receiving comprehensive guideline-directed medical therapy (GDMT), consisting of an angiotensin receptor-neprilysin inhibitor (ARNI), beta-blocker, mineralocorticoid receptor antagonist (MRA), and sodium-glucose cotransporter-2 (SGLT2) inhibitor, demonstrated significantly greater improvement in left ventricular ejection fraction (LVEF), heart rate, systolic blood pressure, functional status, and overall clinical outcomes compared with patients receiving less intensive treatment regimens.

The mean age of the study population was 61.8 ± 11.7 years, with a clear male predominance (69.0%). These findings are comparable to those reported in large international heart failure registries, where the average age ranges from 60 to 68 years and men constitute approximately two-thirds of patients with HFrEF. The predominance of elderly male patients likely reflects the higher prevalence of ischemic heart disease and traditional cardiovascular risk factors in this population.¹⁰

Hypertension (62%), coronary artery disease (58%), and diabetes mellitus (46%) were the most prevalent comorbid conditions in the present study. Similar observations have been reported in the PARADIGM-HF and DAPA-HF trials, which demonstrated that these comorbidities substantially influence disease progression and long-term prognosis in HFrEF.^{11,12} The coexistence of multiple cardiovascular risk factors underscores the importance of comprehensive medical management aimed at modifying both cardiac function and systemic disease processes.

Baseline echocardiographic assessment demonstrated a mean LVEF of $31.2 \pm 5.8\%$, indicating moderate to severe systolic dysfunction. Improvement in LVEF was observed across all treatment groups; however, the greatest increase occurred among patients receiving quadruple therapy, who demonstrated a mean improvement of $8.4 \pm 3.2\%$. This

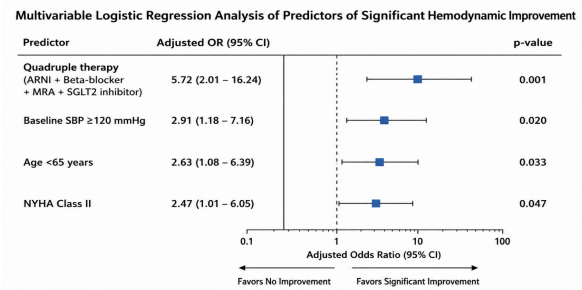


Figure 3. Forest plot showing multivariable logistic regression analysis of predictors of significant hemodynamic improvement in left ventricular ejection fraction.

Figure 3. Forest plot showing multivariable logistic regression analysis of predictors of significant hemodynamic improvement.

finding is consistent with contemporary evidence showing that early initiation of all four foundational classes of heart failure medications promotes reverse ventricular remodeling and significantly improves myocardial contractile function.¹³

A progressive reduction in resting heart rate was observed with increasing treatment intensity. Patients receiving quadruple therapy experienced a mean reduction of **17.8 beats/min**, significantly greater than the reduction observed with conventional dual therapy. Heart rate reduction remains one of the most important therapeutic targets in HFrEF because persistent tachycardia increases myocardial oxygen demand, shortens diastolic filling time, and accelerates ventricular remodeling. Previous studies have likewise demonstrated improved clinical outcomes with adequate heart rate control achieved through evidence-based beta-blocker therapy.¹⁴

Systolic blood pressure improved modestly but significantly following treatment, with the greatest increase occurring in patients treated with ARNI-based regimens. Although excessive reductions in blood pressure may limit treatment optimization in some patients, maintenance of adequate systemic perfusion while simultaneously reducing neurohormonal activation represents an important therapeutic objective. Similar hemodynamic improvements have been described following sacubitril/valsartan therapy in previous randomized clinical trials.¹¹

Functional improvement was reflected by significant reductions in NYHA functional class across all treatment groups. The greatest improvement was again observed among patients receiving quadruple therapy. Improvement in functional capacity is clinically meaningful because it correlates strongly with quality of life, exercise tolerance, and reduced hospitalization. Similar improvements have been consistently demonstrated following comprehensive guideline-directed therapy in several multicenter clinical trials.¹⁵

Patients receiving quadruple therapy also experienced significantly shorter hospital stays, fewer ICU admissions, lower rates of worsening heart failure, and lower in-

hospital mortality compared with patients receiving conventional therapy. These findings support the concept that simultaneous targeting of multiple neurohormonal pathways produces additive clinical benefits beyond those achieved with individual drug classes. Recent international heart failure guidelines advocate early initiation of all four foundational therapies because delaying treatment may postpone clinically important improvements in cardiac function and survival.⁶

Multivariable logistic regression identified quadruple therapy as the strongest independent predictor of significant hemodynamic improvement (Adjusted OR 5.72, 95% CI 2.01–16.24, $p=0.001$). Higher baseline systolic blood pressure, younger age, and lower NYHA functional class were also independently associated with favorable outcomes. These observations are biologically plausible because younger patients generally possess greater myocardial reserve, while patients with preserved systemic perfusion are more likely to tolerate aggressive up-titration of guideline-directed medications. Similar predictors have been reported in observational studies evaluating response to contemporary HFrEF therapy.¹⁶

Although all treatment combinations produced measurable clinical benefit, the magnitude of improvement consistently favored regimens incorporating ARNI and SGLT2 inhibitors. These findings further support the growing body of evidence that comprehensive guideline-directed therapy should be initiated as early as clinically feasible rather than following the traditional sequential approach. Early optimization may maximize reverse remodeling, reduce recurrent hospitalization, and improve survival.

Conclusion

In this retrospective observational study, patients with heart failure with reduced ejection fraction receiving guideline-directed quadruple therapy (ARNI, β -blocker, MRA, and SGLT2 inhibitor) demonstrated the greatest improvement in hemodynamic parameters, left ventricular ejection fraction, and functional status compared with other treatment combinations. Quadruple therapy remained the strongest independent predictor of significant hemodynamic improvement, while younger age, higher baseline systolic blood pressure, and lower NYHA functional class were also associated with favorable outcomes. These findings support early optimization of comprehensive guideline-directed medical therapy in patients with HFrEF. Larger prospective multicenter studies are warranted to validate these findings.

References

1. Braunwald's Heart Disease. Zipes DP, Libby P, Bonow RO, Mann DL, Tomaselli GF, editors. Philadelphia: Elsevier; 2022.
2. European Society of Cardiology. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm

- M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2021;42(36):3599-3726.
3. American Heart Association. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure. *Circulation*. 2022;145:e895-e1032.
4. Velazquez EJ, Morrow DA, DeVore AD, Duffy CI, Ambrosy AP, McCague K, et al. Angiotensin-neprilysin inhibition in acute decompensated heart failure. *N Engl J Med*. 2019;380(6):539-548.
5. PARADIGM-HF Investigators. McMurray JJV, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med*. 2014;371:993-1004.
6. DAPA-HF Trial Committees. McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med*. 2019;381:1995-2008.
7. EMPEROR-Reduced Trial Investigators. Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med*. 2020;383:1413-1424.
8. RALES Study Investigators. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med*. 1999;341:709-717.
9. MERIT-HF Study Group. MERIT-HF Study Group. Effect of metoprolol CR/XL in chronic heart failure. *Lancet*. 1999;353:2001-2007.
10. COPERNICUS Study Group. Packer M, Coats AJS, Fowler MB, Katus HA, Krum H, Mohacsi P, et al. Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med*. 2001;344:1651-1658.
11. EMPHASIS-HF Investigators. Zannad F, McMurray JJV, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, et al. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med*. 2011;364:11-21.
12. SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med*. 1991;325:293-302.
13. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2016;37:2129-2200.
14. Greene SJ, Butler J, Albert NM, DeVore AD, Sharma PP, Duffy CI, et al. Medical therapy for heart failure

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- with reduced ejection fraction: the CHAMP-HF Registry. *J Am Coll Cardiol*. 2018;72:351-366.
15. Maddox TM, Januzzi JL Jr, Allen LA, Breathett K, Butler J, Davis LL, et al. 2021 Update to the 2017 ACC Expert Consensus Decision Pathway for optimization of heart failure treatment. *J Am Coll Cardiol*. 2021;77:772-810.
16. Butler J, Anker SD, Filippatos G, Khan MS, Ferreira JP, Pocock SJ, et al. Empagliflozin and outcomes in patients with heart failure with reduced ejection fraction. *Circulation*. 2022;145:184-193.