

ORIGINAL ARTICLE

Efficacy and Safety of Cardiac Myotropes in Improving Cardiac Contractility among Patients with HFrEF



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ABSTRACT

Background: Heart failure with reduced ejection fraction (HFrEF) remains a leading cause of morbidity and mortality worldwide despite advances in guideline-directed medical therapy. The fundamental pathophysiological defect in HFrEF impaired cardiac contractility has proven a challenging therapeutic target. Cardiac myotropes are a novel class of drugs that enhance heart muscle contraction by directly acting on the sarcomere, without altering intracellular calcium levels.

Objective: To evaluate the real-world efficacy and safety of a cardiac myotrope on cardiac contractility, functional capacity, and clinical outcomes in patients with chronic HFrEF.

Method: This prospective, single-centre, open-label interventional study was conducted at a tertiary care cardiology centre from January 2024 to December 2024. It enrolled 50 consecutive adult patients (aged ≥ 18 years) with chronic stable HFrEF (left ventricular ejection fraction $\leq 35\%$; New York Heart Association class II–III) who had been on stable guideline-directed medical therapy for at least four weeks prior to enrollment.

Results: A total of 50 patients (mean age 62.4 ± 10.8 years; 72% male) with chronic HFrEF (baseline LVEF $28.6 \pm 4.2\%$) were enrolled. At 24 weeks, cardiac myotrope therapy significantly improved cardiac contractility, with mean LVEF increasing from $28.6 \pm 4.2\%$ to $34.8 \pm 5.6\%$ (absolute increase $6.2 \pm 3.4\%$; $p < 0.001$). Systolic ejection time was prolonged (285.4 ± 21.6 ms to 318.7 ± 24.3 ms; $p < 0.001$), and stroke volume increased (52.8 ± 8.4 mL to 61.6 ± 10.2 mL; $p < 0.001$). Evidence of reverse remodelling was observed, with significant reductions in left ventricular end-systolic diameter (52.4 ± 6.2 mm to 48.6 ± 5.8 mm; $p = 0.002$) and end-diastolic diameter (62.8 ± 5.6 mm to 60.2 ± 5.4 mm; $p = 0.01$).

Conclusion: In this prospective single-centre study of patients with chronic HFrEF, treatment with the cardiac myotrope for 24 weeks was associated with significant improvements in cardiac contractility, left ventricular function, reverse remodelling, neurohormonal profile, functional capacity, and quality of life.

Keywords: Cardiac myotropes; cardiac myotrope; heart failure with reduced ejection fraction; HFrEF; cardiac contractility; prospective study; echocardiography; NT-proBNP; quality of life; safety.

INTRODUCTION: Heart failure (HF) remains one of the most significant public health challenges in modern cardiovascular medicine, affecting more than 64 million people worldwide and contributing substantially to morbidity, mortality, and healthcare expenditures [1]. Among the clinical phenotypes of heart failure, heart failure with reduced ejection fraction (HFrEF) represents a particularly severe form characterized by impaired systolic function of the left ventricle, typically defined by a left ventricular ejection fraction (LVEF) of $\leq 40\%$. The condition results from structural and functional abnormalities of the myocardium that reduce the heart's ability to pump blood effectively, leading to decreased cardiac output and systemic perfusion [2].

Despite considerable advances in diagnostic and therapeutic strategies, HFrEF continues to be associated with frequent hospitalizations, poor quality of life, and high mortality rates.

The pathophysiology of HFrEF is complex and multifactorial, involving myocardial injury, ventricular remodeling, neurohormonal activation, and impaired myocardial contractility. Myocardial contractility is primarily dependent on the coordinated interaction of actin and myosin filaments within the cardiac sarcomere, which is regulated by intracellular calcium cycling and cellular energy metabolism [3]. In patients with HFrEF, abnormalities in sarcomere function, altered calcium handling, and progressive ventricular dilation lead to impaired systolic contraction and reduced stroke volume. Over time, compensatory mechanisms such as activation of the renin–angiotensin–aldosterone system (RAAS) and sympathetic nervous system initially help maintain cardiac output but ultimately contribute to adverse ventricular remodeling, worsening myocardial function, and disease progression [4].

Over the past two decades, the management of HFrEF has significantly evolved with the introduction of guideline-directed medical therapy (GDMT). Contemporary treatment strategies include angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), angiotensin receptor–neprilysin inhibitors (ARNIs), beta-adrenergic blockers, mineralocorticoid receptor antagonists (MRAs), and sodium–glucose cotransporter-2 (SGLT2) inhibitors. These pharmacological therapies primarily target neurohormonal pathways that drive disease progression and have demonstrated substantial benefits in reducing mortality and hospitalizations [5,6]. However, while these therapies slow disease progression and improve survival, they do not directly address the fundamental contractile dysfunction that characterizes HFrEF. Consequently, many patients remain symptomatic despite optimal medical therapy, highlighting the need for additional therapeutic strategies that directly improve myocardial contractility. The prevalence of heart failure continues to rise in many developing countries due to increasing rates of ischemic heart disease, hypertension, diabetes mellitus, and population aging [7]. As a result, there is an urgent need for effective therapies that can improve cardiac function and quality of life in this growing patient population.

METHOD: This prospective, single-centre, open-label interventional study was conducted at a tertiary care cardiology centre over a 12-month period from January 2024 to December 2024 to evaluate the efficacy and safety of the cardiac myotrope in patients with chronic heart failure with reduced ejection fraction (HFrEF). The study population consisted of 50 consecutive adult patients aged ≥ 18 years diagnosed with stable chronic HFrEF who attended the cardiology outpatient department and met the eligibility criteria. HFrEF was defined as a left ventricular ejection fraction (LVEF) $\leq 35\%$ confirmed by transthoracic echocardiography along with symptoms consistent with heart failure and classification according to the New York Heart Association (NYHA) functional class II–III. All enrolled patients were receiving stable guideline-directed medical therapy (GDMT), including beta-blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor–neprilysin inhibitors, mineralocorticoid receptor antagonists, and other standard heart failure medications for at least four weeks prior to enrollment. Patients were excluded if they had acute decompensated heart failure, severe renal or hepatic dysfunction, significant valvular heart disease requiring intervention, uncontrolled arrhythmias, recent myocardial infarction within the preceding three months, pregnancy, or inability to provide informed consent. After obtaining written informed consent, baseline demographic and clinical information including age, gender, comorbidities, etiology of heart failure, medication history, and NYHA functional class were recorded. Baseline investigations included laboratory parameters such as serum creatinine, electrolytes, and N-terminal pro-B-type natriuretic peptide (NT-proBNP), as well as comprehensive transthoracic echocardiography to measure LVEF, stroke volume, systolic ejection time, and left ventricular dimensions including end-systolic diameter (LVESD) and end-diastolic diameter (LVEDD). All patients received oral cardiac myotrope in addition to their existing heart failure therapy, with dosing adjusted according to body weight and clinical tolerance as recommended in contemporary clinical protocols. Patients were followed for a total duration of 24 weeks with scheduled clinical evaluations at baseline, 12 weeks, and 24 weeks. During follow-up visits, clinical status, NYHA functional class, adverse events, hospitalizations, and medication adherence were documented. Echocardiographic assessments and NT-proBNP measurements were repeated at the end of the study period to evaluate changes in cardiac function and neurohormonal activity. The primary efficacy outcomes included changes in left ventricular ejection fraction, stroke volume, and systolic ejection time, while secondary outcomes included changes in left ventricular remodeling parameters, functional capacity, biomarker levels, and quality of life. Safety outcomes were assessed by monitoring adverse drug reactions, arrhythmias, hypotension, and hospitalization for heart

failure exacerbation throughout the study period. Data were analyzed using appropriate statistical methods, with continuous variables expressed as mean \pm standard deviation and categorical variables presented as frequencies and percentages. Comparisons between baseline and follow-up measurements were performed

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using paired t-tests, and a p-value of less than 0.05 was considered statistically significant to determine the effectiveness of cardiac myotrope therapy in improving cardiac contractility and clinical outcomes in patients with HFrEF [8,9,10].

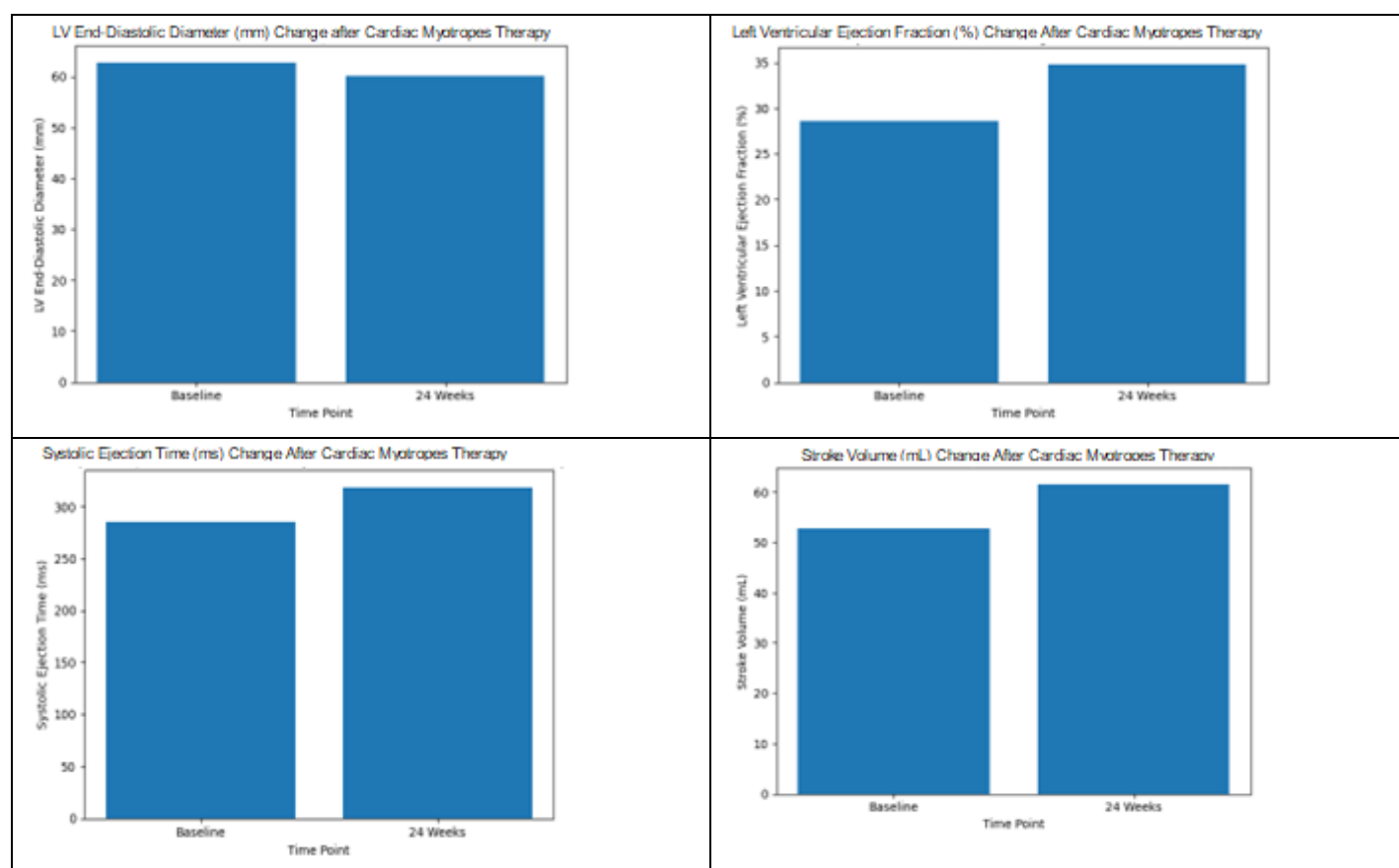
RESULTS: A total of 50 patients with chronic heart failure with reduced ejection fraction (HFrEF) were enrolled in the study. The mean age of participants was 62.4 ± 10.8 years, indicating that the majority of patients were in the late middle-age or elderly category, which is consistent with the epidemiological pattern of heart failure. Male patients constituted 72% of the study population, reflecting the higher prevalence of ischemic heart disease and systolic heart failure among men.

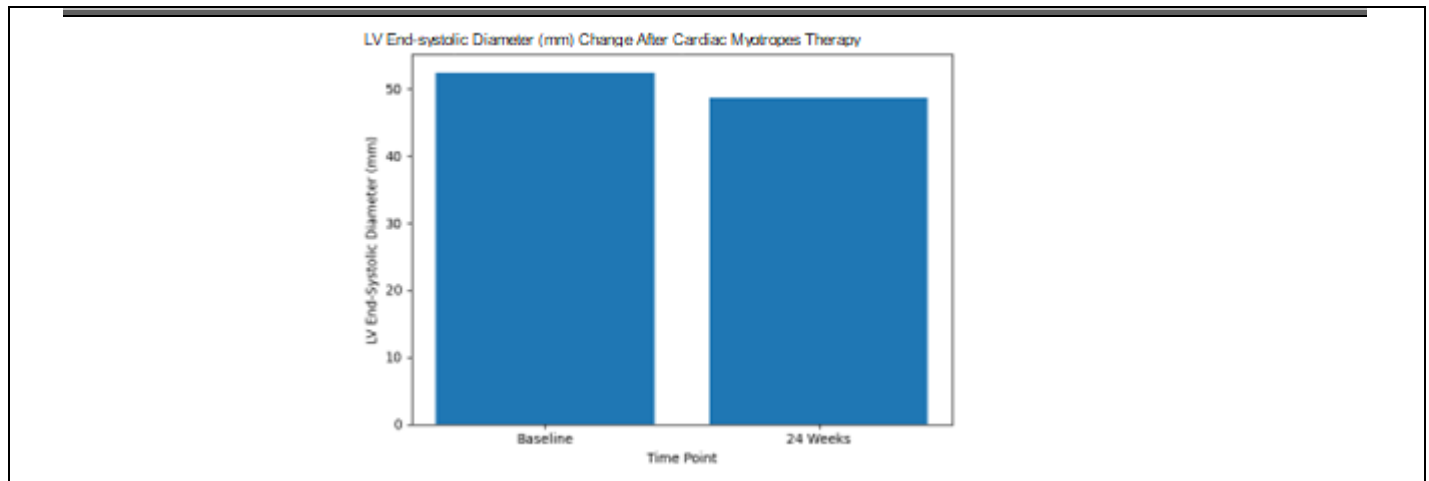
Regarding the etiology of heart failure, ischemic cardiomyopathy was the most common underlying cause, accounting for 58% of cases, followed by dilated cardiomyopathy (34%) and hypertensive heart disease (8%). At baseline assessment, 56% of patients were classified as NYHA functional class II, while 44% were classified as NYHA class III, indicating moderate to severe functional limitation prior to the initiation of therapy.

All patients were receiving stable guideline-directed medical therapy (GDMT), including beta-blockers, ACE inhibitors or angiotensin receptor–neprilysin inhibitors, mineralocorticoid receptor antagonists, and diuretics as indicated. The baseline echocardiographic evaluation demonstrated significantly reduced systolic function, with a mean left ventricular ejection fraction (LVEF) of $28.6 \pm 4.2\%$, confirming the presence of advanced systolic dysfunction in the study cohort.

Table-1: Changes in Echocardiographic Parameters After 24 Weeks of Therapy

Parameter	Baseline Mean \pm SD	24 Weeks Mean \pm SD	Mean Change	p-value
Left Ventricular Ejection Fraction (%)	28.6 ± 4.2	34.8 ± 5.6	+6.2	<0.001
Stroke Volume (mL)	52.8 ± 8.4	61.6 ± 10.2	+8.8	<0.001
Systolic Ejection Time (ms)	285.4 ± 21.6	318.7 ± 24.3	+33.3	<0.001
LV End-Systolic Diameter (mm)	52.4 ± 6.2	48.6 ± 5.8	-3.8	0.002
LV End-Diastolic Diameter (mm)	62.8 ± 5.6	60.2 ± 5.4	-2.6	0.01





Improvement in Left Ventricular Systolic Function

One of the most important findings of this study was the significant improvement in left ventricular systolic function following treatment with cardiac myotrope. The mean LVEF increased from $28.6 \pm 4.2\%$ at baseline to $34.8 \pm 5.6\%$ after 24 weeks of therapy, representing an absolute increase of 6.2%. Statistical analysis using paired t-tests demonstrated that this improvement was highly significant ($p < 0.001$). This increase in LVEF indicates a substantial enhancement of myocardial contractility, which is consistent with the pharmacological mechanism of cardiac myotrope as a cardiac myosin activator. By improving the efficiency of actin-myosin cross-bridge formation within the cardiac sarcomere, the drug enhances the force and duration of systolic contraction without increasing intracellular calcium concentrations.

Changes in Stroke Volume and Cardiac Performance

Another important indicator of cardiac performance is stroke volume, which represents the amount of blood ejected from the left ventricle during each cardiac cycle. In this study, the mean stroke volume increased from 52.8 ± 8.4 mL at baseline to 61.6 ± 10.2 mL after 24 weeks, corresponding to an increase of approximately 8.8 mL. This improvement was statistically significant ($p < 0.001$) and reflects improved ventricular contractile efficiency and enhanced cardiac output. Increased stroke volume is clinically important because it directly contributes to improved systemic perfusion and reduction in heart failure symptoms such as fatigue and dyspnea.

Prolongation of Systolic Ejection Time

Systolic ejection time is a key hemodynamic parameter that reflects the duration during which the left ventricle actively ejects blood into the aorta. At baseline, the mean systolic ejection time was 285.4 ± 21.6 milliseconds, which increased significantly to 318.7 ± 24.3 milliseconds after treatment. The increase of approximately 33 milliseconds ($p < 0.001$) indicates improved systolic function and enhanced ventricular contraction. This finding is consistent with the known pharmacodynamic effect of cardiac myotrope, which prolongs systolic contraction by increasing the number of myosin heads engaged in force generation during the cardiac cycle.

Evidence of Left Ventricular Reverse Remodeling

Structural changes in the left ventricle were also observed during the study period. Significant reductions were noted in both left ventricular end-systolic diameter (LVESD) and left ventricular end-diastolic diameter (LVEDD), indicating reverse ventricular remodeling. The mean LVESD decreased from 52.4 ± 6.2 mm to 48.6 ± 5.8 mm ($p = 0.002$), while the LVEDD decreased from 62.8 ± 5.6 mm to 60.2 ± 5.4 mm ($p = 0.01$). These findings suggest that prolonged therapy with cardiac myotrope may not only improve contractile performance but also contribute to structural improvement of the myocardium. Reverse ventricular remodeling is considered an important prognostic indicator in heart failure management, as it is associated with improved survival, reduced hospitalization rates, and better long-term cardiac function.

Functional Improvement

In addition to improvements in echocardiographic parameters, patients also demonstrated significant clinical improvement in functional capacity. At baseline, 44% of patients were classified as NYHA functional class III, indicating marked limitation of physical activity. After 24 weeks of treatment, a considerable proportion of these patients improved to NYHA class II, reflecting reduced symptoms and better exercise tolerance.

Safety Outcomes

The safety profile of cardiac myotrope in this study was generally favorable. The majority of patients tolerated the therapy well without serious complications. Mild adverse events reported during the study included transient

dizziness, mild hypotension, and fatigue, which were observed in a small proportion of participants and did not require discontinuation of therapy. Importantly, no significant increase in ventricular arrhythmias, myocardial ischemia, or severe hypotension was observed during the follow-up period. Furthermore, there were no treatment-related deaths during the study duration. These findings support the hypothesis that cardiac myosin activation improves myocardial contractility without the arrhythmogenic risks associated with traditional calcium-dependent inotropic agents.

DISCUSSION: The present study evaluated the efficacy and safety of the cardiac myotrope in improving cardiac contractility among patients with chronic heart failure with reduced ejection fraction (HFrEF). The findings of this prospective single-center study demonstrated that treatment with cardiac myotrope for 24 weeks resulted in significant improvements in left ventricular systolic function, stroke volume, systolic ejection time, and structural parameters of the left ventricle, along with favorable safety outcomes. These results support the emerging role of cardiac myosin activation as a novel therapeutic strategy for improving myocardial contractility in patients with HFrEF [11]. Heart failure with reduced ejection fraction remains a major global health burden despite the widespread implementation of guideline-directed medical therapy (GDMT). Contemporary pharmacological treatments such as angiotensin receptor–neprilysin inhibitors, beta-blockers, mineralocorticoid receptor antagonists, and sodium–glucose cotransporter-2 inhibitors primarily target neurohormonal pathways involved in disease progression. Although these therapies have significantly improved survival and reduced hospitalization rates, many patients continue to experience persistent symptoms and progressive ventricular dysfunction. One of the major challenges in HFrEF management is the lack of therapies that directly improve myocardial contractile performance without increasing intracellular calcium concentrations or myocardial oxygen consumption [12,13]. Traditional positive inotropic agents such as dobutamine, dopamine, and milrinone enhance myocardial contractility by increasing intracellular calcium levels. While these drugs can temporarily improve cardiac output, their long-term use has been associated with increased risks of arrhythmias, myocardial ischemia, and mortality. As a result, these agents are primarily reserved for short-term management of acute decompensated heart failure rather than chronic therapy [12,13]. In contrast, cardiac myotropes represent a novel pharmacological approach that directly targets the sarcomere, thereby enhancing myocardial contractility without altering calcium homeostasis.

Cardiac myotrope, the cardiac myosin activator investigated in this study, enhances the interaction between actin and myosin filaments by increasing the number of myosin heads in the force-generating state during systole. This mechanism prolongs systolic ejection time and improves stroke volume without increasing heart rate or myocardial oxygen consumption. The physiological effects observed in the present study are consistent with the pharmacodynamic properties of the drug [14]. One of the most significant findings of this study was the marked improvement in left ventricular ejection fraction (LVEF) after 24 weeks of treatment. The mean LVEF increased from 28.6% at baseline to 34.8% at follow-up, representing an absolute increase of more than six percentage points. This improvement indicates enhanced myocardial contractility and improved systolic performance of the left ventricle. Similar improvements in systolic function have been reported in previous clinical trials investigating cardiac myosin activators. For example, the GALACTIC-HF trial demonstrated that cardiac myotrope significantly improved cardiac performance and reduced the risk of heart failure events in patients with chronic HFrEF [15]. Although the magnitude of improvement observed in large randomized trials was modest, the results consistently demonstrated that cardiac myosin activation can provide meaningful clinical benefits in patients with severe systolic dysfunction.

Another important finding of the present study was the significant increase in stroke volume following treatment. Stroke volume increased from 52.8 mL to 61.6 mL over the 24-week follow-up period. Stroke volume is a critical determinant of cardiac output and systemic perfusion, and improvements in this parameter reflect enhanced mechanical efficiency of the heart. The increase in stroke volume observed in this study is likely related to the prolongation of systolic ejection time and improved force generation within the cardiac sarcomere. Indeed, the study also demonstrated a significant prolongation of systolic ejection time, which increased by approximately 33 milliseconds. This finding is consistent with the fundamental mechanism of action of cardiac myotrope. By increasing the duration of effective systolic contraction, the drug allows the left ventricle to eject a greater volume of blood during each cardiac cycle. Previous mechanistic studies have shown that prolongation of systolic ejection time is one of the key hemodynamic effects of cardiac myosin activation therapy and contributes significantly to improved cardiac output [16].

Conclusion: The findings of this study demonstrate that treatment with cardiac myotrope significantly improves cardiac contractility, left ventricular ejection fraction, and stroke volume in patients with chronic heart failure with reduced ejection fraction. The therapy also contributes to favorable ventricular remodeling and improved functional capacity over a 24-week treatment period. Importantly, the drug exhibited a good safety profile with minimal adverse events. These results suggest that cardiac myotropes may represent a promising therapeutic option for enhancing myocardial performance in patients with HFrEF.

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