Omecamtiv mecarbil in heart failure with reduced ejection fraction: mechanisms, evidence, and therapeutic positioning

Hari Chandana Pagidiboina MBBS, Lakshmi Sharath Chandran Thurikepally MBBS, Chanokporn Puchongmart MD, Ben Thiravetyan MD, Sudheer Ramavath MD

Abstract

Heart failure with reduced ejection fraction (HFrEF) remains a major global challenge despite advances in neurohormonal therapies, which do not directly improve myocardial contractility. Omecamtiv mecarbil (OM), a first-in-class cardiac myosin activator, offers a novel mechanism by enhancing sarcomere function without raising intracellular calcium or oxygen demand, differentiating it from traditional inotropes. This narrative review synthesizes current evidence on OM's pharmacology, preclinical data, and clinical trials. Preclinical studies demonstrated improved contractility with preserved energetic efficiency. Phase I–II trials confirmed dose-dependent improvements in systolic function with good tolerability. The Global Approach to Lowering Adverse Cardiac Outcomes Through Improving Contractility in Heart Failure (GALACTIC-HF) trial showed modest but significant reductions in heart failure events, especially in patients with severely reduced ejection fraction. However, OM's limited effect on functional capacity and narrow therapeutic window necessitate selective use. Positioned as an adjunctive option for patients with advanced systolic dysfunction, OM's future utility may be enhanced by biomarker-guided strategies, simplified dosing, and combination regimens.

Keywords: Omecamtiv Mecarbil; heart failure, systolic; myocardial contraction; myosins; cardiotonic agents; inotropic agents; ventricular dysfunction, left; clinical trials; GALACTIC-HF; COSMIC-HF

Introduction

Heart failure with reduced ejection fraction (HFrEF) is a clinical syndrome characterized by the heart's inability to pump blood efficiently, leading to an ejection fraction typically less than 40%. It results from structural and/or functional cardiac disorders impairing ventricular filling or ejection of blood.[1] The clinical significance of HFrEF lies in its association with substantial morbidity and mortality. Patients often experience progressive symptoms such as fatigue, dyspnea, and fluid retention, which impair quality of life and lead to frequent hospitalizations. Heart failure with reduced ejection fraction is a leading cause of hospital admissions among older adults and contributes significantly to healthcare expenditures globally.[1] It is a prevalent condition affecting millions worldwide, with estimates suggesting a global prevalence exceeding 64+ million individuals. It predominantly affects the elderly, with increased incidence among those with comorbidities such as hypertension, ischemic heart disease, and diabetes mellitus.[2]

Despite therapeutic advances, HFrEF remains challenging to manage. Current treatment relies on neurohormonal blockade with ACEIs, ARBs, beta-blockers, MRAs, and, more recently, SGLT2 inhibitors. These improve survival and symptoms but do not directly enhance contractility, and many patients still experience persistent symptoms, recurrent exacerbations, and progressive dysfunction despite optimal therapy.[3]

Corresponding author: **Hari Chandana Pagidiboina**
Contact Information: Harichandanapagidiboina@gmail.com
DOI: 10.12746/swjm.v14i58.1563

Current HFrEF therapies act mainly through neurohormonal modulation to reduce stress and adverse remodeling but do not improve intrinsic contractility. This gap is critical for patients with severely reduced LVEF, who remain symptomatic and at high risk of hospitalization despite optimal therapy, highlighting the unmet need to address impaired systolic function.[4] Furthermore, patient response to guideline-directed medical therapy (GDMT) often varies with comorbidities, age, renal dysfunction, or intolerance, limiting achievement of target doses. These challenges underscore the need for new therapies with distinct mechanisms and added benefits.[3] Direct activation of cardiac myosin offers a mechanism-based strategy distinct from conventional inotropes. Unlike agents that enhance calcium cycling and raise arrhythmic risk, activators such as omecamtiv mecarbil (OM) improve contractility without increasing calcium or oxygen demand. The first in this class, OM stabilizes the pre-power stroke state, boosting actin–myosin engagement and sustaining systolic force. By acting directly on the sarcomere, it enhances systolic function while avoiding the energetic and electrophysiological drawbacks of traditional inotropes, making it a promising adjunct for advanced HFrEF with persistent symptoms despite standard therapy.[5–7]

This review critically evaluates the pharmacological rationale, preclinical and clinical trial evidence, and therapeutic positioning of OM in HFrEF. By integrating mechanistic, translational, and clinical insights, it aims to define OM's emerging role in reshaping heart failure management.

Search Strategy

A targeted literature search was conducted across PubMed, Scopus, Web of Science, and ClinicalTrials.gov up to July 2025. The following Boolean query was used: ("Omecamtiv Mecarbil" OR "Cardiac Myosin Activator" OR "Myosin Activator") AND ("Heart Failure with Reduced Ejection Fraction" OR "HFrEF" OR "Systolic Heart Failure") AND ("Myocardial Contractility" OR "Inotropic Therapy" OR "Cardiac Function") AND ("GALACTIC-HF" OR "Clinical Trial" OR "Translational Study" OR "Pharmacodynamics" OR "Pharmacokinetics" OR "Ventricular Remodelling" OR "Cost-effectiveness" OR "Safety" OR "Efficacy"). Only English-language, peer-reviewed studies including preclinical, clinical trials (Phases I–III), and reviews were included. References from key articles were also screened to capture additional relevant studies.

Molecular Mechanisms of Omecamtiv Mecarbil

Structure and pharmacodynamics

Omecamtiv mecarbil is a selective cardiac myosin activator, characterized chemically by a small molecule structure that selectively binds to cardiac β-myosin heavy chain (MYH7). It interacts specifically with the catalytic S1 domain of myosin, enhancing the kinetics of ATP hydrolysis and increasing the number of actomyosin cross-bridges during systole without increasing the rate of ATP consumption or intracellular calcium levels. Omecamtiv mecarbil binds to an allosteric site at the base of the lever arm, stabilizing the myosin head in a pre-power stroke state and promoting efficient force generation.[8] Pharmacodynamically, OM shows dose-dependent prolongation of systolic ejection time and increased stroke volume without adversely impacting myocardial energetics. It possesses good oral bioavailability (approximately 75%) and a half-life of 17–21 hours, supporting its twice-daily dosing regimen. Particularly, OM exhibits minimal interactions with cytochrome P450 (CYP450) enzymes, though ketoconazole can increase its exposure modestly.[9]

Mechanism of action

Omecamtiv mecarbil acts by directly activating cardiac sarcomeres through enhanced myosin activity. Unlike traditional inotropes, OM does not increase intracellular calcium. Instead, it enhances the transition of myosin into its force-generating state by accelerating the release of phosphate from the actin-myosin-ADP-Pi complex. This results in prolonged actin-myosin binding, increased duty ratio, and greater systolic force production. By prolonging systolic ejection time and enhancing contractility at the molecular level, OM improves stroke volume without elevating myocardial oxygen demand. This is a crucial distinction from calcitropes, which typically increase

oxygen consumption and calcium cycling, leading to higher risks of arrhythmia and ischemia.[7,8]

Distinct pharmacological features compared to inotropes

Omecamtiv mecarbil differs significantly from traditional inotropes like dobutamine and milrinone. Dobutamine increases contractility via β-adrenergic receptor stimulation and cyclic adenosine monophosphate (cAMP)-mediated calcium influx, while milrinone inhibits phosphodiesterase-3 to achieve a similar result. These calcium-dependent mechanisms lead to increased myocardial oxygen demand and a higher risk of arrhythmias and hypotension. In contrast, OM operates independently of calcium modulation. It avoids the risks associated with intracellular calcium overload, including myocardial ischemia and arrhythmogenic potential. Omecamtiv mecarbil also does not promote vasodilation, minimizing risks of hypotension.[10] In clinical trials such as Chronic Oral Study of Myosin Activation to Increase Contractility in Heart Failure (COSMIC-HF) and Global Approach to Lowering Adverse Cardiac Outcomes, through Improving Contractility in Heart Failure (GALACTIC-HF), OM has demonstrated efficacy in improving myocardial strain, reducing ventricular volumes, and lowering natriuretic peptide levels. Unlike conventional inotropes, OM offers a safer profile for long-term use in patients with HFrEF, particularly those with low baseline ejection fraction.[11]

Preclinical Development and Translational Studies

Early animal studies

In foundational preclinical investigations, OM demonstrated efficacy and safety in animal models of heart failure. Malik et al. (2011) reported that OM enhanced myocardial contractility without raising intracellular calcium or oxygen consumption. Using rat and dog models of systolic heart failure (HF), OM significantly improved cardiac performance, evidenced by increased stroke volume and systolic ejection time. Complementarily, Shen et al. (2010) used canine models representing post-MI and hypertrophic systolic HF. Omecamtiv mecarbil administration led to sustained enhancements in cardiac output and stroke volume while reducing heart rate and preload pressures, affirming its therapeutic promise across heart failure etiologies.[12,13]

Insights from experimental pharmacology

Woody et al. (2018) elucidated OM's mechanistic profile through single-molecule optical trapping and simulation. Although OM suppressed the myosin working stroke, it prolonged actomyosin attachment and activated thin filaments cooperatively. This paradoxical mechanism contributed to increased myocardial force output at therapeutic doses, demonstrating dose-dependent effects with an EC50 near clinical plasma levels (~101 nM). These pharmacodynamic insights were reinforced by Nagy et al. (2015), who observed a bell-shaped dose-response in skinned rat muscle fibers, with OM enhancing calcium sensitivity (ΔpCa50 up to 0.34) and slowing contraction-relaxation kinetics. Translationally, these findings underscore a novel paradigm of thin filament activation through prolonged cross-bridge binding.[14,15]

Preclinical safety profile

Regarding cardiotoxicity and safety, none of the cited preclinical studies reported adverse myocardial effects, arrhythmias, or desensitization with OM treatment. Shen et al. (2010) highlighted the absence of increased myocardial oxygen consumption (MVO_2), even with prolonged infusion, distinguishing OM from conventional inotropes like catecholamines. Woody et al. (2018) confirmed that OM-induced force enhancement did not stem from calcium elevation, thereby mitigating the risks of calcium overload-related arrhythmogenesis. Moreover, Planelles-Herrero et al. (2017) demonstrated cardiac specificity in OM's binding to a novel allosteric site. This paradoxical mechanism contributed to increased myocardial force output at therapeutic doses, demonstrating dose-dependent effects with an EC50 near clinical plasma levels pre-power stroke (PPS) site on myosin, stabilizing the lever

Table 1. Summary of Key Preclinical and Mechanistic Studies on Omecamtiv Mecarbil

Author (Year)	Objective	Study Design	Methods	Key Findings
Malik (2011)[12]	To evaluate OM's effect on heart failure by activating cardiac myosin	Preclinical animal study	Biochemical assays, rat myocytes, and in vivo testing in HF-induced rats and dogs	Omecamtiv mecarbil boosted myosin activity, improved contractility, and enhanced cardiac function without increasing calcium levels or oxygen use
Shen (2010)[13,14]	To test OM's effect in dog models of systolic HF	In vivo conscious dog study	Post-MI and hypertrophic HF models; OM infusion (0.25 mg/kg bolus + continuous 0.25 mg/kg/h) for 24–72 h; monitored cardiac parameters	Omecamtiv mecarbil increased stroke volume (44%), cardiac output (22%), and ejection time (26%) without raising oxygen demand; effects were sustained and safe
Woody (2018)[14]	To explore how OM increases force despite suppressing myosin stroke	In vitro with simulations	Single-molecule optical trapping; two-state model simulations	Omecamtiv mecarbil prolonged actin-myosin binding (~5x), cooperatively activated thin filaments, and improved force at therapeutic levels via SEPTA model
Nag (2015)[15]	To study OM's effect on muscle calcium sensitivity	Lab study on skinned rat fibers	Tested force, pCa50, and contraction kinetics at different OM doses	Omecamtiv mecarbil increased calcium sensitivity (ΔpCa50 = 0.34), slowed contract-relax phases, and showed stronger effects in slow-twitch fibers
Planelles-Herrero (2017)[16]	To identify OM's binding site and structural mechanism	Structural biology	X-ray crystallography (±OM), SAXS, and ITC	Omecamtiv mecarbil binds a unique "PPS" site on cardiac myosin, stabilizing the lever arm and enhancing force generation specifically in cardiac muscle

Legend: OM: omecamtiv mecarbil; MI: myocardial infarction; HF: heart failure; IV: intravenous; mg/kg: milligrams per kilogram; h: hour(s); LV: left ventricle; dP/dt: rate of pressure development in the left ventricle; MVO_2: myocardial oxygen consumption; SAXS: small-angle X-ray scattering; ITC: isothermal titration calorimetry; PPS: pre-power stroke state; Ca^{2+}: calcium ion; pCa50: negative logarithm of calcium concentration required for 50% maximal force; ΔpCa50: change in calcium sensitivity.

arm and PPS state, thereby avoiding off-target effects in non-cardiac muscle.[13,14,16]

Clinical Trials and Evidentiary Basis

The clinical development of OM, a selective cardiac myosin activator, spans a robust trajectory of early-phase trials to large-scale pivotal studies, each contributing distinct insights into its pharmacological efficacy, tolerability, and clinical potential in managing HFrEF.

Early phase clinical trials (Phases I and II)

The first-in-human study by Teerlink et al. (2011) established the pharmacokinetic and pharmacodynamic profiles of OM in 34 healthy males. The trial revealed a dose-and concentration-dependent

increase in systolic ejection time (SET) and stroke volume, with the maximum tolerated dose defined at 0.5 mg/kg/h. Importantly, plasma levels above 1200 ng/mL were associated with dose-limiting myocardial ischemia, attributed to excessive prolongation of systole.[9] Following this, Cleland et al. (2011) conducted a Phase II crossover trial in patients with systolic heart failure, reinforcing OM's ability to enhance SET, ejection fraction (EF), and stroke volume without altering myocardial oxygen demand. These effects were evident even at moderate plasma concentrations (100–500 ng/mL), and tolerability was preserved up to ~1000 ng/mL.[17] Greenberg et al. (2015) extended the safety profile of OM to patients with ischemic cardiomyopathy and angina. Their findings confirmed that OM-induced augmentation of cardiac contractility was not associated with exercise-induced ischemia, thus alleviating concerns regarding ischemic risk in high-risk populations.[18]

COSMIC-HF study (Phase II)

The COSMIC-HF trial (Teerlink et al., 2016) was a landmark Phase II study evaluating long-term oral OM dosing. Across three arms (placebo, fixed-dose, and PK-guided titration), the drug achieved sustained therapeutic plasma concentrations (~300 ng/mL), producing significant improvements in cardiac function: SET increased by 25 ms, stroke volume improved by 3.6 mL, and both left ventricular end-systolic and end-diastolic diameters reduced. Additionally, NT-proBNP decreased by nearly 1000 pg/mL, signifying favorable reverse remodeling. The drug was well tolerated across all arms, and the study substantiated the potential of OM as a long-term oral therapy.[11]

ATOMIC-AHF study (Phase II)

The ATOMIC-AHF trial investigated intravenous OM in patients with acute decompensated heart failure. While the primary endpoint, dyspnea relief, was not met across all cohorts, the high-dose group showed significant improvement at 48 hours and over five days ($p = 0.034$ and 0.038, respectively). Systolic ejection time was prolonged, and the end-systolic dimension decreased, all without arrhythmogenic signals. Troponin elevation was mild and non-dose-dependent, further endorsing OM's safety profile in acute settings.[19]

GALACTIC-HF trial (Phase III Landmark Trial)

The pivotal GALACTIC-HF trial randomized 8256 patients with chronic HFrEF to receive OM or placebo alongside guideline-directed therapy. Omecamtiv mecarbil significantly reduced the primary composite outcome (CV death or first HF event) by 8% (HR: 0.92; $p = 0.03$). However, individual endpoints such as CV mortality and hospitalization did not differ substantially between groups. The NT-proBNP declined by 10%, and troponin I increased modestly (+4 ng/L), with no excess in ischemic or arrhythmic events. These findings affirm OM's clinical benefit in reducing HF progression, particularly in patients with low EF and high natriuretic peptide levels.[20]

METEORIC-HF trial (Phase III)

Contrasting GALACTIC-HF, the METEORIC-HF trial sought to evaluate OM's impact on functional capacity. In this 276-patient study, OM failed to improve peak oxygen uptake (VO_2) over 20 weeks (mean change: −0.24 vs +0.21 mL/kg/min; $p = 0.13$), nor did it significantly affect ventilatory efficiency or daily physical activity. Despite acceptable safety, the neutral results highlighted that OM's benefits are more structural and prognostic rather than exertional.[21]

Other relevant clinical studies and registries

Collectively, smaller registries and post-hoc analyses support OM's safety and potential benefit in patient subgroups, including those with ischemic cardiomyopathy or preserved renal function. Notably, biomarker analyses consistently show NT-proBNP reduction and minor troponin I elevation without translating into increased ischemic risk. The ongoing discussions in systematic reviews emphasize that OM's profile aligns best with patients at high risk of HF progression, but not necessarily those requiring improvement in exercise capacity or symptoms alone.[19,22]

Table 2. Summary of Major Clinical Trials on Omecamtiv Mecarbil in Heart Failure

Author (Year)	Objective	Study Design	Key Findings
Teerlink (2011) (Phase I)[9]	To determine the maximum tolerated dose and PK/PD profile in healthy volunteers	First-in-human, randomized, double-blind, placebo-controlled crossover trial (n = 34)	Omecamtiv mecarbil increased systolic ejection time (SET), stroke volume (SV), and EF in a dose-dependent manner. Well tolerated up to 0.625 mg/kg/h. Plasma levels >1200 ng/mL linked to ischemia.
Cleland (2011) (Phase II)[17]	To assess safety and PD effects in systolic HF patients	Double-blind, placebo-controlled, dose-ranging crossover trial (n = 45)	Omecamtiv mecarbil improved SET, SV, and EF at plasma concentrations >100 ng/mL, with volume reduction at >500 ng/mL. Well tolerated up to ~1000 ng/mL. No rise in oxygen demand.
Greenberg (2015) (Phase II)[18]	To evaluate exercise safety in ischemic cardiomyopathy	Double-blind, placebo-controlled trial with two dose cohorts	Omecamtiv mecarbil showed no angina-related discontinuation. Improved exercise time with no ST depression in OM groups. No dose-related safety concerns.
Teerlink (2016a) (Phase II-ATOMIC-AHF)[19]	To evaluate efficacy and safety in acute HF	Randomized, double-blind, placebo-controlled, dose-escalation trial	Dyspnea relief was not significant overall, but improved in the high-dose group. Omecamtiv mecarbil increased SET, reduced LVESD, and showed no pro-arrhythmic signals. Mild, non-dose-dependent troponin rise.
Teerlink (Phase II-COSMIC-HF)[11]	To assess long-term oral OM effects in HFrEF	Multicentre, randomized, double-blind, placebo-controlled trial	Omecamtiv mecarbil increased SET and SV, reduced LV volumes, and NT-proBNP. Minor, reversible troponin rise; safety similar across groups.
Teerlink (2021) (Phase III-GALACTIC-HF)[20]	To test OM's impact on HF events and CV death	Large randomized, placebo-controlled trial (n = 8,256)	Primary outcome reduced by 8% (HR 0.92). Greater benefit in LVEF <28%. No change in mortality or hospitalisations. NT-proBNP decreased; troponin I slightly increased. Stroke rate is lower in the OM group.
Lewis et al. (2022) (Phase III-METEORIC-HF)[21]	To assess the effect on exercise capacity in chronic HFrEF	Randomized, placebo-controlled trial (n = 276)	Omecamtiv mecarbil did not significantly improve peak VO_2, functional capacity, or daily activity. Safety was acceptable.

Legend: OM: omecamtiv mecarbil; HF: heart failure; HFrEF: heart failure with reduced ejection fraction; PK/PD: pharmacokinetics/pharmacodynamics; SET: systolic ejection time; SV: stroke volume; EF: ejection fraction; LVESD: left ventricular end-systolic diameter; NT-proBNP: N-terminal pro-B-type natriuretic peptide; VO_2: oxygen consumption; KCCQ: Kansas City Cardiomyopathy Questionnaire; HR: hazard ratio; RR: risk ratio.

Clinical Implications and Positioning in Heart Failure Therapy

Therapeutic positioning of omecamtiv mecarbil

Omecamtiv mecarbil, a selective cardiac myosin activator, marks a shift in HFrEF management by improving contractility without increasing oxygen demand. Unlike calcium-dependent inotropes, it enhances actin-myosin cross-bridge efficiency by stabilizing the pre-power stroke state, prolonging systolic ejection time, and boosting stroke volume. Benefits are most evident in patients with severely reduced EF and persistent symptoms despite standard therapy.

GALACTIC-HF confirmed reductions in HF events and cardiovascular death, especially with LVEF <28%, while COSMIC-HF showed reverse remodeling and NT-proBNP reductions, reinforcing OM's role in stabilizing myocardial function.[11]

Comparative effectiveness and safety

Unlike calciotropics such as milrinone or dobutamine, which raise mortality through calcium overload and arrhythmias, OM acts independently of calcium handling. In COSMIC-HF, it improved ventricular dimensions and neurohormonal markers without affecting heart rate, blood pressure, or oxygen consumption parameters, which are often worsened by traditional inotropes. While SGLT2 inhibitors and vericiguat add indirect benefits, OM complements therapy by directly enhancing sarcomeric function. Its effects, though significant in GALACTIC-HF, were modest (8% risk reduction), with no major gains in symptoms or exercise capacity in METEORIC-HF, warranting individualized use, especially in low LVEF. Small, reversible troponin rises occurred without added arrhythmia, ischemia, or mortality, likely reflecting increased workload rather than injury.[8,19,22–24]

Practical considerations for clinicians

Omecamtiv mecarbil is given orally with PK-guided titration (25–50 mg BID) to maintain plasma levels of 200–1000 ng/mL, avoiding >1200 ng/mL where ischemic symptoms were noted in early trials. Surrogate markers like NT-proBNP and systolic ejection time may reflect response but are not routinely used. The drug is well tolerated, without added hypotension, renal dysfunction, or arrhythmia—unlike other inotropes. Omecamtiv mecarbil should be used as an adjunct, not a replacement for neurohormonal therapy, particularly in advanced HFrEF or patients intolerant of standard agents. Omecamtiv mecarbil expands heart failure therapy by meeting the unmet need for safe, targeted systolic support. Post-marketing studies and registries will help define its role, especially in multimodal regimens guided by phenotype and biomarkers.[20,25]

Challenges and limitations

Despite the novel mechanism and promising clinical results of OM, several challenges and limitations must be acknowledged to fully understand its translational trajectory within HF management. A key limitation of OM is its modest efficacy in large trials. The study GALACTIC-HF showed only an 8% risk reduction without improving quality of life, mortality, or first hospitalization, while METEORIC-HF found no benefit in exercise capacity, raising doubts about functional impact. Its narrow therapeutic window adds complexity, as ischemic symptoms appeared above 1200 ng/mL in Phase I studies, requiring PK-guided titration that may be impractical in routine care. Small, reversible troponin rises seen in COSMIC-HF and GALACTIC-HF suggest subclinical myocardial stress; although not linked to adverse events, their long-term significance, particularly in coronary disease, remains uncertain.[11,21]

Real-world translation gaps

Despite promising clinical trial data, translating OM into routine practice faces several real-world challenges. The requirement for pharmacokinetically guided titration and monitoring of plasma concentrations limits feasibility in resource-constrained or non-specialist settings where therapeutic drug monitoring is not routine. Moreover, OM has yet to be formally integrated into major heart failure management guidelines (e.g., ESC, ACC/AHA/HFSA), potentially affecting clinician uptake and reimbursement pathways. Cost-effectiveness analyses are limited, and the economic implications of long-term OM therapy remain uncertain, especially in low- and middle-income countries. Furthermore, access to OM may be inequitable across healthcare systems, reinforcing disparities in care for patients with advanced systolic dysfunction. These implementation barriers highlight the need for simplified dosing strategies, clearer consensus-based positioning within treatment algorithms, and post-marketing surveillance to assess real-world safety, adherence, and clinical benefit. Additionally, OM's limited effect in patients with relatively preserved ejection fractions (EF > 28%) reduces its generalizability

across the HF spectrum. Subgroup analyses revealed that therapeutic benefit was substantially confined to patients with severely reduced LVEF, thereby narrowing its optimal target population.[26]

From a regulatory perspective, Omecamtiv mecarbil has not received approval from the U.S. Food and Drug Administration (FDA) or the European Medicines Agency (EMA) as of 2025. This is largely due to the limited magnitude of clinical benefit, absence of a significant mortality reduction, and the need for additional evidence on long-term safety and functional outcomes before widespread clinical adoption can be recommended.

Future directions

Future research must aim to clarify and expand OM's clinical utility. One critical direction is the identification of ideal phenotypes or biomarker-based stratification models that can predict maximal benefit. For instance, ongoing exploratory analyses into baseline NT-proBNP levels, systolic ejection time dynamics, and LVEF thresholds may help fine-tune patient selection strategies.

From a mechanistic standpoint, combination therapy approaches deserve deeper exploration. As OM operates independently of neurohormonal modulation, it may synergize with agents like SGLT2 inhibitors, ARNI, or vericiguat, potentially leading to additive or multiplicative benefit. However, robust head-to-head and combinatorial trials are warranted to validate such hypotheses.

Another key future direction is the development of simplified dosing algorithms or point-of-care diagnostics to estimate plasma OM levels indirectly. This could facilitate broader use without complex titration protocols, enhancing real-world feasibility. Advances in pharmacogenomics may also inform individualized dosing regimens to prevent toxic exposures.

Moreover, long-term safety beyond trial durations remains to be established. As current evidence is limited to a maximum of 20–24 weeks (COSMIC-HF, METEORIC-HF), further follow-up from registries or extension trials is essential to determine whether subtle safety signals such as troponin elevations evolve into clinically significant myocardial injury or contribute to arrhythmogenic risk.

Finally, the ongoing evolution of HF classifications, including the emergence of mid-range EF phenotypes heart failure with mildly reduced ejection fraction and comorbid-specific HF subtypes (e.g., HF with diabetes, obesity, or cardiorenal syndrome), invites re-evaluation of OM's applicability in broader or mixed cohorts.

Conclusion

Omecamtiv mecarbil represents a novel advancement in HFrEF therapy by directly enhancing cardiac contractility through selective myosin activation, without increasing myocardial oxygen demand or calcium overload. Clinical trials, particularly GALACTIC-HF, have shown modest but meaningful reductions in heart failure events, especially in patients with severely reduced ejection fraction. Despite its narrow therapeutic window and limited impact on exercise capacity, OM offers a safe and mechanistically distinct option for patients with persistent systolic dysfunction. Its optimal use lies in targeted subgroups, and future research should focus on biomarker-guided selection, simplified dosing strategies, and combination regimens to fully establish its role in heart failure management.

Article citation: Pagidiboina HC, Thurikepally LSC, Puchongmarrt C, et al. Omecamtiv Mecarbil in heart failure with reduced ejection fraction: Mechanisms, evidence, and therapeutic positioning. The Southwest Journal of Medicine. 2026;14(58):1–9
From: Department of Internal Medicine, Texas Tech University Health Sciences Center, Lubbock, TX (HCP, LCST, CP, BT) Health Education Services, Northwest Health Program, Valpariaiso, IN (SR)
Conflicts of interest: none

References

1. Golla MSG, Shams P. Heart failure with preserved ejection fraction (HFpEF). In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2025. p. 1–20.
2. Shahim B, Kapelios CJ, Savarese G, et al. Global public health burden of heart failure: an updated review. Card Fail Rev. 2023;9:e11.
3. Palaparthi EC, Reddy PA, Padala T, et al. The rise of personalized medicine in heart failure management: a narrative review. Cureus. 2025;17:e83731.
4. Kim ES, Youn JC, Baek SH. Update on the pharmacotherapy of heart failure with reduced ejection fraction. Curr Probl Pharmacol. 2020;2:113–33.
5. Mack M, Frishman WH. Cardiac myosin activator Omecamtiv mecarbil: novel treatment for systolic heart failure. Cardiol Rev. 2024;32:378–83.
6. Teerlink JR, Diaz R, Felker GM, et al. Omecamtiv mecarbil in chronic heart failure with reduced ejection fraction. JACC Heart Fail. 2020;8:329–40.
7. Barrick SK, Greenberg MJ. Cardiac myosin contraction and mechanotransduction in health and disease. J Biol Chem. 2021;297:101297.
8. Ramadan MM, Alshawi AL, Mostafa YA, et al. Omecamtiv mecarbil in systolic heart failure: clinical efficacy and future directions of a novel myosin-activating inotropic agent. Cureus. 2023;17:e82128.
9. Teerlink JR, Clarke CP, Saikali KG, et al. Dose-dependent augmentation of cardiac systolic function with the selective cardiac myosin activator, Omecamtiv mecarbil: a first-in-man study. Lancet. 2011;378:667–75.
10. Maack C, Eschenhagen T, Hamdani N, et al. Treatments targeting inotropy. Eur Heart. J 2019;40:3626–44.
11. Teerlink JR, Felker GM, McMurray JJV, et al. Chronic oral study of myosin activation to increase contractility in heart failure (COSMIC-HF): a phase 2, pharmacokinetic, randomised, placebo-controlled trial. Lancet. 2016;388:2895–903.
12. Malik FI, Hartman JJ, Elias KA, et al. Cardiac myosin activation: a potential therapeutic approach for systolic heart failure. Science. 2011; 331:1439–43.
13. Shen YT, Malik FI, Zhao X, et al. Improvement of cardiac function by a cardiac myosin activator in conscious dogs with systolic heart failure. Circ Heart Fail. 2010;3: 522–7.
14. Woody MS, Greenberg MJ, Barua B, et al. Positive cardiac inotrope omecamtiv mecarbil activates muscle despite suppressing the myosin working stroke. Nat Commun. 2018; 9:3838.
15. Nagy L, Kovács Á, Bódi B, et al. The novel cardiac myosin activator omecamtiv mecarbil increases the calcium sensitivity of force production in isolated cardiomyocytes and skeletal muscle fibres of the rat. Br J Pharmacol. 2015;172:4506-4518.
16. Planelles-Herrero VJ, Hartman JJ, Robert-Paganin J, et al. Mechanistic and structural basis for activation of cardiac myosin force production by omecamtiv mecarbil. Nat Commun. 2017;8:190.
17. Cleland JG, Teerlink JR, Senior R, et al. The effects of the cardiac myosin activator, omecamtiv mecarbil, on cardiac function in systolic heart failure: a double-blind, placebo-controlled, crossover, dose-ranging phase 2 trial. Lancet. 2011; 378:676–83.
18. Greenberg BH, Chou W, Saikali KG, et al. Safety and tolerability of omecamtiv mecarbil during exercise in patients with ischemic cardiomyopathy and angina. JACC Heart Fail. 2015;3:22–9.
19. Teerlink JR, Felker GM, McMurray JJV, et al. Acute treatment with omecamtiv mecarbil to increase contractility in acute heart failure. J Am Coll Cardiol. 2016;67:1444–55.
20. Teerlink JR, Diaz R, Felker GM, et al. Cardiac myosin activation with omecamtiv mecarbil in systolic heart failure. N Engl J Med. 2021;384:105–16.
21. Lewis GD, Voors AA, Cohen-Solal A, et al. Effect of omecamtiv mecarbil on exercise capacity in chronic heart failure with reduced ejection fraction: the METEORIC-HF randomized clinical trial. JAMA. 2022;328:259–69.
22. Zhou S, Liu Y, Huang X, et al. Omecamtiv mecarbil in the treatment of heart failure: the past, the present, and the future. Front Cardiovasc Med. 2024;11:1337154.
23. Alqatati F, Elbahnasawy M, Bugazia S, et al. Safety and efficacy of omecamtiv mecarbil for heart failure: a systematic review and meta-analysis. Indian Heart J. 2022;74:155–62.
24. Felker GM, Solomon SD, Claggett B, et al. Assessment of omecamtiv mecarbil for the treatment of patients with severe heart failure. JAMA Cardiol. 2022;7:26–34.
25. Patel PH, Nguyen M, Rodriguez R, et al. Omecamtiv mecarbil: a novel mechanistic and therapeutic approach to chronic heart failure management. Cureus. 2021;13:e12419.
26. Lindberg F, Øigaard N, Metra M, et al. Eligibility for omecamtiv mecarbil in a real-world heart failure population: data from the Swedish Heart Failure Registry. PLoS One. 2024;19:e0303348.