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REVIEW

Cardiac Myosin Activators in Heart Failure: Experimental Advances Amid Clinical Uncertainty

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Abstract: Heart failure remains a leading cause of morbidity and mortality despite advances in neurohormonal and device-based therapies, and conventional inotropes are constrained by pro-arrhythmic and energetically costly mechanisms. Cardiac myosin activators (CMAs) offer a conceptually distinct approach by directly modulating the actin–myosin cross-bridge cycle within the sarcomere, but their clinical trajectory has been more nuanced than initially anticipated. Omecamtiv mecarbil(OM) and danicamtiv are the most advanced CMAs to enter human trials; both show reproducible, dose-dependent improvements in systolic function and chamber mechanics in preclinical and early-phase studies, yet a narrow exposure window, signals of diastolic and energetic trade-offs at higher doses, and largely modest or heterogeneous effects on clinical outcomes have tempered expectations and no agent has yet achieved regulatory approval. In this review, we critically appraise the mechanistic rationale, translational evidence and pivotal clinical trials of these agents, integrating emerging work on myocardial energetics and diastolic function. We also compare myosin activation with myosin inhibition and outline future research priorities—including optimisation of dosing strategies, phenotype-guided patient selection, rigorous evaluation of long-term safety and exploration of next-generation myosin-targeting strategies—that must be addressed before CMAs can be credibly positioned within routine heart-failure management.

Keywords: cardiac myosin activator, heart failure, omecamtiv mecarbil, danicamtiv, dilated cardiomyopathy

Introduction

Heart failure (HF) remains one of the most pressing global health challenges, affecting tens of millions of individuals worldwide and accounting for substantial morbidity, mortality and healthcare expenditure despite advances in guideline-directed medical and device-based therapies.[1] The therapeutic ceiling of current neurohormonal and vasodilatory strategies appears to be approaching, underscoring the unmet need for mechanistically novel interventions.

Traditional positive inotropes, such as digoxin or catecholamines, have sought to enhance cardiac contractility but are limited by increased myocardial oxygen consumption, arrhythmogenicity, and adverse long-term outcomes.[2] Against this background, the concept of directly targeting sarcomere function has emerged as a compelling alternative. By modulating the activity of cardiac myosin—the molecular motor driving contractile force through actin–myosin cross-bridge cycling—myotropes represent a fundamentally different class of agents aimed at augmenting systolic performance without the energetic and electrophysiological liabilities of earlier drugs.[3]

Unlike conventional inotropes, cardiac myosin activators (CMAs) enhance contractile force by recruiting a greater proportion of myosin heads into strongly bound, force-generating states for a given level of calcium cycling, rather than increasing intracellular calcium as the primary driver of inotropy.[4–6] This novel mechanism has led to the conceptualization of CMAs as a new class of agents - "myotropes"-that modulate contractility independently of neurohormonal or calcium-driven pathways.[4] Conceptually, this activator strategy complements the emerging paradigm of myosin inhibition in hypertrophic cardiomyopathy (for example with Mavacamten), underscoring that both up- and down-titration of sarcomeric force can be therapeutically exploited in different disease states.[3]

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Graphical Abstract

Cardiac myosin activators (Omecamtiv Mecarbil and Danicamtiv) enhance systolic performance byprolonging cross-bridge duty cycle, yet translation into improved survival and quality of life remains uncertain

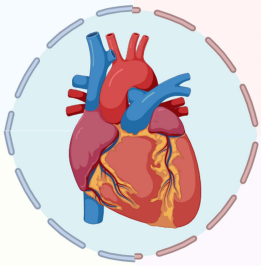
Mechanism

increasing the "duty ratio"—the proportion of time that myosin heads remain strongly bound to actin during the contractile cycle—thereby prolonging systolic ejection time (SET), enhancing stroke volume, and improving cardiac output

Clinical Trials

Omecamtiv Mecarbil:
ATOMIC-AHF→IV dosing in acute Hf, primary endpoint (dyspnea) not met, high-dose signal, no↑O_2demand
COSMIC-HF → ↑SET, ↓LVESD, ↓NT-ProBNP
GALACTIC-HF→ modest ↓CV death/HF hospitalization, greatest effect in very low LVEF
METEORIC-HF → no VO, improvement

Danicamtiv:
Phase 1/2a→↑LVEF, ↑GLS, ↓LV volumes, no excess arrhythmias
No Phase 3 outcomes yet



Real-World Evidence /Translational Insights

GALACTIC-HF subgroup signals:
AF/flutter - efficacy preserved
Sex differences - women slightly greater benefit
Hospitalized patients → larger absolute benefit

Safety: no major arrhythmia signals, theoretical energetic cost still debated

Translation gap: surrogate imaging gains ≠ functional improvement

Challenges / Future Directions

1. No mortality/survival benefit yet proven
2. limited data for Danicamtiv, lack of Phase 3 outcomes
3. Energetic efficiency and diastolic trade-offs remain concerns
4. Need phenotype-guided trials (strain, imaging, genetics)
5. Potential in combination therapy with SGLT2i or others

Conclusion:From surrogate gains to survival: cardiac myosin activators must prove durable benefit in phenotype-guided,outcome-driven trials.

Two leading CMAs have entered clinical development: Omecamtiv mecarbil(OM), the most extensively studied, and Danicamtiv, a newer agent with distinct structural and functional characteristics. Both agents share a common target—cardiac myosin—but differ in their molecular binding modes, impact on diastolic function, and stage of clinical evaluation.

However, despite their compelling mechanistic rationale, the available clinical data remain mixed and insufficient to establish therapeutic benefit. In GALACTIC-HF, Omecamtiv mecarbil produced a statistically significant but clinically modest reduction in the composite outcome, and regulatory review (the US FDA and EMA) ultimately judged the evidence insufficient for approval. Danicamtiv has demonstrated favorable effects on systolic and atrial function in early-phase studies, but no Phase III efficacy data are available, and no cardiac myosin activator has yet achieved regulatory approval for heart failure. These preliminary and often mixed findings highlight a core uncertainty: although myotropes consistently improve surrogate markers such as ejection fraction, systolic ejection time, and global longitudinal strain, it remains unclear whether these physiological signals meaningfully translate into symptomatic, functional, or survival benefits. Against this background, the present review synthesises current preclinical and clinical evidence on cardiac myosin activators, with a particular focus on OM and danicamtiv, and provides a critical appraisal of their pharmacology, efficacy, safety and translational outlook.

Pharmacomechanical Coupling via Myosin Modulation: The Activator Strategy

Cardiac myosin activators (CMAs) represent a distinct pharmacological class designed to enhance myocardial contractility by directly modulating sarcomeric function, without elevating intracellular calcium concentrations. This approach marks a departure from traditional inotropes such as dobutamine or milrinone, which augment contractility via cyclic AMP signaling at the cost of increased cytosolic calcium and proarrhythmic risk.[2] By targeting the actin-myosin cross-bridge cycle itself, CMAs aim to deliver inotropic support through a mechanism that is both energetically more favorable and less arrhythmogenic.[7,8]

Recent mechanokinetic modeling suggests that OM's hallmark effects—slowed actin-activated ATPase and reduced shortening velocity with preserved isometric force—can be reproduced by a smaller pre/post–power-stroke free-energy gap and a higher activation barrier for the lever-arm swing, which provides a parameter-level explanation for the macroscopic phenomenon of prolonging systole without substantially increasing myocardial oxygen demand.[9]

The central pharmacological mechanism involves increasing the "duty ratio"—the proportion of time that myosin heads remain strongly bound to actin during the contractile cycle—thereby prolonging systolic ejection time (SET), enhancing stroke volume, and improving cardiac output.[7,8] This concept is illustrated in Figure 1, which contrasts the conventional cross-bridge cycle with the proposed modulatory effects of Omecamtiv mecarbil and Danicamtiv on key transitional states. Rather than simply increasing the number of cross-bridges formed, CMAs enhance the quality and persistence of force-generating interactions. Consistent with this concept, single-molecule and skinned-fiber experiments show that Danicamtiv increases myosin attachment rates and enhances thin-filament activation, indicating molecule-specific kinetic signatures within the CMA class.[10] Recent single-molecule experiments further demonstrated that Danicamtiv reduces the amplitude of the myosin working stroke while accelerating actomyosin attachment, thereby enhancing thin-filament activation at submaximal calcium.[11]

Recent structural and biophysical insights have refined our understanding of how CMAs influence this process. Cryo-electron microscopy and X-ray crystallography studies reveal that these agents stabilize specific transitional conformations of the myosin head, particularly the pre-power-stroke state, through interaction with hydrophobic pockets near the converter domain.[12] Integrative evidence indicates that stabilizing pre-power-stroke conformers prolongs actin-bound time without perturbing intracellular Ca^{2+} handling, aligning structural biology with the observed systolic benefits.[13] While the precise binding kinetics differ between molecules, the unifying theme is modulation of cross-bridge mechanics without perturbing calcium flux.[12,14,15]

Energetic considerations also play a pivotal role. OM has been shown to increase ATP turnover modestly in preclinical models, raising questions about the energetic cost of sustained systolic tension and whether the additional

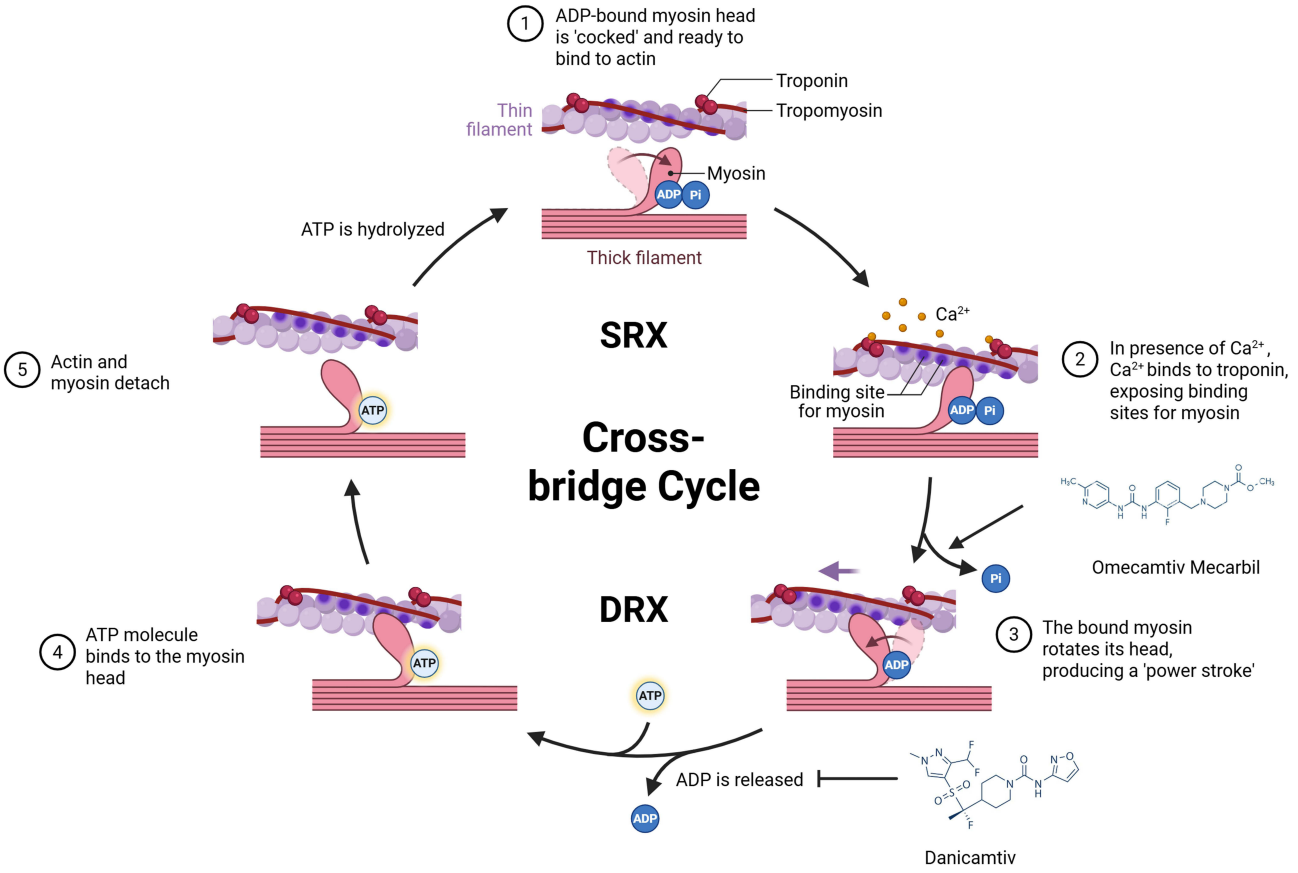


Figure 1 Cardiac myosin cross-bridge cycle and sites of action of Omecamtiv mecarbil and danicamtiv.The diagram illustrates the actin–myosin cross-bridge cycle from the super-relaxed (SRX) pool of myosin heads to the force-generating disordered-relaxed (DRX) states: (1) ATP is hydrolysed and the myosin head is cocked in a pre-power-stroke (PPS) conformation; (2) Ca^{2+} binding to troponin moves tropomyosin on the thin filament, exposing actin-binding sites; (3) strong actin binding and phosphate release trigger the power stroke, followed by ADP release and ATP rebinding, which detach myosin and reset the cycle (4–5). Omecamtiv mecarbil binds to the S1 region of cardiac myosin and stabilises the PPS, strongly bound state, thereby prolonging the time myosin spends in force-generating cross-bridges during systole. Danicamtiv, acting at a distinct allosteric pocket, increases the recruitment and attachment rate of myosin heads and enhances thin-filament activation, augmenting systolic force with comparatively less diastolic penalty.

contractile force justifies the higher ATP consumption.[16,17] Danicamtiv, in contrast, may confer a more balanced energetic profile with chamber-specific effects, modulating atrial and ventricular cross-bridge kinetics differentially.[14] At supra-therapeutic exposure, OM increased the open probability of cardiac ryanodine receptor (RyR2) channels in canine sarcoplasmic reticulum preparations.[18] Importantly, these effects were observed at concentrations well above those achieved in clinical use, and have not been associated with major changes in whole-cell Ca^{2+} transients or SR Ca^{2+} load at therapeutically relevant exposures.

In contrast to activators, cardiac myosin inhibitors such as Mavacamten and aficamten adopt a diametrically opposed strategy—stabilizing the super-relaxed state (SRX), thus reducing the number of myosin heads available for actin engagement. This mechanism is particularly useful in diseases of hypercontractility such as hypertrophic cardiomyopathy (HCM).[5] Although the conceptual dichotomy between activation and inhibition appears straightforward, it is important to note that both classes ultimately modulate the same key biophysical variables—duty ratio and cross-bridge cycling rate—but in opposite directions.

Taken together, myosin-targeted therapies underscore the potential of sarcomeric proteins as viable drug targets in heart failure. However, the mechanistic elegance of these strategies must be evaluated alongside physiological complexity, chamber-specific responses, and energetic cost. Future development of CMAs will depend not only on optimizing binding kinetics, but also on defining clear translational frameworks that link biophysical modulation to clinical efficacy.

Omecamtiv Mecarbil as a Pioneer in Myotropic Therapy

Omecamtiv mecarbil (OM), originally designated CK-1827452, represents the first-in-class, small-molecule cardiac myosin activator to progress into late-phase clinical evaluation. Jointly developed by Cytokinetics and Amgen, OM was identified through high-throughput screening strategies aimed at discovering compounds capable of selectively enhancing cardiac myosin ATPase activity.[19,20] This discovery strategy intentionally sought to bypass the limitations of conventional inotropes such as dobutamine and milrinone, whose mechanisms—by increasing intracellular calcium—are associated with elevated myocardial oxygen demand, heightened arrhythmogenic risk, and adverse long-term outcomes.[19,20]

Mechanism of Action and Pharmacological Profile

Preclinical studies provided early validation of OM's unique pharmacodynamic profile. In isolated cardiac muscle preparations, intact animal models, and engineered human myocardium, OM improved contractile force generation without major changes in global Ca^{2+} transients at clinically relevant exposures,[3,20] However, in a post-ischaemic pig model, Bakkehaug et alreported that OM increased myocardial oxygen consumption and reduced cardiac mechanical efficiency,[16] highlighting a potential energetic trade-off under certain experimental conditions. The compound achieves this by binding selectively to the myosin S1 domain, stabilizing the pre-power-stroke conformation, and prolonging the strongly bound actin–myosin cross-bridge state during systole.[3,14] This prolongation of systolic ejection time (SET) increases stroke volume and cardiac output without appreciable increases in heart rate. Structural elucidation by cryo-electron microscopy (Halder et al[12]) demonstrated that OM occupies a hydrophobic pocket near the converter domain of myosin, thereby stabilizing myosin heads in a force-generating conformation.

Pharmacokinetic investigations have characterized OM as exhibiting linear, dose-dependent plasma exposure with predictable interindividual variability.[19] This facilitates consistent pharmacodynamic effects, a property not typically seen with traditional inotropes. According to Malik et al.[4] OM's pharmacological distinction lies in augmenting contractility without perturbing diastolic calcium kinetics, thus avoiding calcium overload-mediated arrhythmia.

Clinical Development and Evidence from Key Trials

Following promising early-phase safety and pharmacokinetic data, OM advanced into a structured clinical trial program spanning both acute and chronic heart failure populations. Notably, the earliest Phase 2 infusion study already demonstrated concentration-dependent increases in systolic ejection time and stroke volume, alongside reductions in ventricular volumes.[21]

The Phase II COSMIC-HF trial (Chronic Oral Study of Myosin Activation to Increase Contractility in Heart Failure) enrolled 448 ambulatory patients with chronic heart failure with reduced ejection fraction (HFrEF).[7] Patients were randomized to two different oral OM dosing regimens or placebo for 20 weeks. COSMIC-HF demonstrated significant, dose-dependent improvements in systolic performance metrics, including increased SET, stroke volume, and reductions in left ventricular end-systolic dimension (LVESD) compared with placebo. Importantly, NT-proBNP levels declined significantly, consistent with reduced wall stress. Additional echocardiographic substudies from COSMIC-HF have shown that OM also improved right ventricular (RV) structure and function, including increases in RV fractional area change and tricuspid annular plane systolic excursion (TAPSE), suggesting a potential benefit on biventricular performance.[22] Moreover, global longitudinal strain (GLS) analysis demonstrated significant improvement, reinforcing OM's capacity to enhance myocardial deformation beyond traditional volumetric indices.[23] Early concerns regarding prolonged SET leading to increased myocardial oxygen demand were addressed by metabolic substudy findings, which showed no significant rise in oxygen consumption.[7]

In the ATOMIC-AHF trial (Acute Treatment with Omecamtiv mecarbil to Increase Contractility in Acute Heart Failure),[8] intravenous OM was tested in 613 patients hospitalized with acute decompensated HFrEF. While the trial met its mechanistic objectives—demonstrating improved left ventricular systolic function—the primary clinical endpoint of dyspnea relief did not reach statistical significance. There was also no significant reduction in short-term rehospitalization rates. These findings, echoed by Teerlink et al,[4,8] suggested that OM's benefits may be more pronounced in chronic rather than acute decompensated settings.

The pivotal Phase III GALACTIC-HF trial enrolled 8256 patients across 35 countries, evaluating OM versus placebo on a composite primary endpoint of time to cardiovascular death or first heart failure event.[24] The trial population included a broad spectrum of HFrEF patients, with a median left ventricular ejection fraction (LVEF) of 26%. GALACTIC-HF met its primary endpoint, showing an 8% relative risk reduction in the composite outcome, driven largely by reductions in hospitalization for worsening heart failure.[24–26] Notably, Felker et al reported that patients with baseline LVEF <28% experienced the greatest relative benefit, suggesting a potential role for OM in advanced systolic dysfunction.[24,26] However, subgroup analyses also indicated attenuated benefit in patients with elevated baseline troponin, possibly reflecting vulnerability to myocardial stress under prolonged systolic activation.[26,27]

Pre-specified subgroup analyses focusing on patients with atrial fibrillation or atrial flutter indicated that OM maintained its efficacy in reducing the composite endpoint, despite the altered atrial contribution to ventricular filling in these patients. The relative risk reduction was consistent with the overall trial population, and no excess safety signal was observed.[28] Additional analyses also explored sex-based differences, revealing that women derived comparable or slightly greater benefit in terms of reducing heart failure hospitalizations, with no new safety concerns identified.[29] These subgroup findings are consistent with mechanistic interpretations from subsequent reviews, which emphasized OM's ability to prolong systolic ejection and enhance contractile performance without increasing myocardial oxygen demand, potentially explaining the sustained benefit in diverse patient phenotypes.[30] When enrollment occurred during HF hospitalization, the relative benefit of OM was maintained, yet the absolute benefit was larger than in outpatients because event rates were higher.[31]

Although GALACTIC-HF is the only large, event-driven phase III trial of a cardiac myosin activator and did demonstrate a statistically significant reduction in the primary composite endpoint, the absolute effect size was modest, the mortality benefit uncertain,[24–26] and regulatory agencies did not consider these data sufficient to establish a favourable benefit–risk profile.

The METEORIC-HF trial (Multicenter Exercise Tolerance Evaluation of Omecamtiv mecarbil in Heart Failure with Reduced Ejection Fraction),[32] designed to evaluate functional capacity, enrolled 276 stable HFrEF patients and assessed peak oxygen uptake (VO_2) via cardiopulmonary exercise testing over 20 weeks. Despite improvements in echocardiographic parameters, OM did not significantly improve peak VO_2 or other exercise tolerance endpoints. This highlighted a potential dissociation between surrogate hemodynamic improvements and patient-centered functional outcomes—a recurring challenge in the development of cardiac myosin activators.

A summary of the major clinical trials evaluating Omecamtiv mecarbil is provided in Table 1.

Safety, Tolerability, and Clinical Implications

Across trials, OM has generally demonstrated a favorable safety profile. Alqatati et al, in a systematic review, concluded that OM was not associated with increased arrhythmia risk or adverse hemodynamic effects in HFrEF populations.[35] Greenberg further evaluated OM's safety in high-risk ischemic cardiomyopathy patients undergoing exercise stress testing, finding no significant increase in ischemic burden, supporting its tolerability under stress.[36]

Nevertheless, mechanistic concerns persist. Preclinical studies by Bakkehaug et al suggested that prolonged cross-bridge engagement might elevate myocardial ATP utilization, potentially compromising mechanical (myocardial) efficiency—here understood as external cardiac work per unit myocardial oxygen consumption—at higher doses or with prolonged exposure durations.[16,17] Although this theoretical risk has not translated into overt clinical harm, it underscores the importance of careful dosing and long-term monitoring in future studies.

Current Limitations and Future Perspectives

While OM represents a mechanistically novel approach to heart failure therapy, its clinical trajectory underscores several limitations. Chief among these is the lack of consistent improvement in exercise capacity or quality-of-life endpoints, as demonstrated in METEORIC-HF.[32] This raises questions about the reliance on echocardiographic surrogates in drug development for HFrEF. Furthermore, comparisons with other myosin activators—such as Danicamtiv—should be interpreted cautiously; although preliminary studies suggest potentially less diastolic impairment and more favorable

Table 1 Summary of Key Clinical Trials and Preclinical Studies of Cardiac Myosin Activators (Omecamtiv Mecarbil and Danicamtiv)

Agent	Study/Acronym	Dose	Objectives & Primary Endpoints	Key Results (selected)	Publication (Year)
Omecamtiv mecarbil	Conscious dog HF model[33]	Intravenous 0.25 mg/kg loading + 0.25 mg/kg/h for 24 h	To investigate PK/PD, safety, and effects on LV systolic ejection time(SET) and systolic function in two canine heart failure models: MI-sHF and LVH-sHF.	Significantly prolonged SET, increased stroke volume and cardiac output, decreased heart rate and LVEDP, unchanged MVO_2 → improved cardiac efficiency, and no desensitization within 72 h.	2010
	Porcine post-ischaemic dysfunction and ex vivo hearts[16]	Near-supratherapeutic exposure (0.75 mg/kg bolus + 0.5 mg/kg/h infusion in pigs; ~400 ng/mL ex vivo) titrated to achieve a 15–20% increase in systolic ejection time.	To assess the effect of Omecamtiv mecarbil on myocardial energetics in post-ischemic dysfunctional hearts.	At these high exposures, OM increased systolic performance but disproportionately raised MVO_2, shifting the work–MVO_2 relation upward and reducing overall cardiac efficiency.	2015
	Canine RyR2 activation study[18]	High-concentration OM (1–10 μM)	To determine whether OM directly modulates cardiac RyR2 activity and compare effects on cardiac vs skeletal muscle ryanodine receptors.	At high concentrations (1–10 μM), OM selectively activated cardiac RyR2 without affecting skeletal RyR1. The study did not assess therapeutic doses. This supratherapeutic RyR2 activation may help explain the increased O_2 consumption seen in Bakkehaug 2015.	2017
	First-in-human dose-ranging[19]	0.005–1.0 mg/kg/h for 6 hours in sequential dose-escalating cohorts.	Establish PK/PD, safety/tolerability; effects on systolic ejection time (SET) and systolic function in stable HF	Dose-related ↑SET and improvements in LV systolic indices; PK–PD characterized; no excess arrhythmias	2011
	ATOMIC-AHF[8]	A 24–48 mg/h IV loading infusion for 2 h followed by 6–11 mg/h for 18 h.	IV OM (~48 h) in acute decompensated HF; primary endpoint: dyspnea relief; prespecified exposure–response	Primary endpoint not met overall; high-dose cohort showed dyspnea signal; ↑SET, ↓LVESD; safety comparable to placebo	2016
	COSMIC-HF[7]	Oral modified-release OM was given as 25 mg twice daily or 25 mg twice daily uptitrated to 50 mg twice daily in the PK-titration group based on trough levels.	20-week oral OM in chronic HFrEF; PK-guided vs fixed-dose vs placebo; primary: exposure; key secondary: SET, SV, LV dimensions, NT-proBNP	PK-guided arm achieved target exposure; ↑SET, ↑SV, ↓LVESD, ↓NT-proBNP vs placebo	2016
	GALACTIC-HF[24-26]	Started at 25 mg twice daily, then blindly titrated at week 4 to 25, 37.5, or 50 mg twice daily according to week-2 trough concentrations (target 200–1000 ng/mL).	Phase 3, event-driven RCT in symptomatic HFrEF; primary: time to first HF event or CV death	Primary composite reduced (modest effect size); greater benefit at very low LVEF; overall safety acceptable	2021-2024
	METEORIC-HF[32]	Oral OM 25, 37.5, or 50 mg twice daily for 20 weeks, with the dose chosen to achieve prespecified target plasma levels using the same PK-guided scheme as GALACTIC-HF.	Phase 3, CPET-based functional trial; primary: change in peak VO_2 over ~20 weeks	No significant improvement in peak VO_2 vs placebo despite favorable systolic indices	2022
Danicamtiv	Phase I SAD/MAD in healthy volunteers[14]	Response curve from 0.1 to 10.6 μM was constructed (EC50 ≈ 1 μM, maximally effective at 10.6 μM)	Characterize safety and PK (including relative bioavailability/food effect)	Acceptable tolerability; predictable PK; no dose-limiting arrhythmias reported	2023–2024
	Phase 2a in HFrEF[34]	50, 75 or 100 mg twice daily for 7 days (plus a 75 mg BID fasting cohort A),	Randomized, double-blind, multiple-dose (7–14 days); echocardiographic endpoints (LVEF, GLS, LA strain/volume); safety	Dose-dependent ↑LVEF (~3–5%) and GLS; ↓LV volumes; LA indices improved; no excess ventricular arrhythmias on continuous ECG	2020
Omecamtiv mecarbil and Danicamtiv	Differential effects in human myocardium	OM 0.5 μM; DN 2 μM	Assess how OM and DN alter steady-state and dynamic contractile mechanics in nonfailing vs failing human myocardium.	Failing myocardium was more sensitive to myosin activation; OM caused greater slowing of cross-bridge kinetics and shortening velocity than DN; both increased Ca^{2+} sensitivity more in failing tissue.	2025

Notes: Upward (↑) and downward (↓) arrows denote increases or decreases in the corresponding parameter relative to baseline or control.

Abbreviations: OM, Omecamtiv mecarbil; DN, danicamtiv; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; MI-sHF, myocardial infarction–induced systolic heart failure; LVH-sHF, left ventricular hypertrophy–associated systolic heart failure; LV, left ventricle; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVEDP, left ventricular end-diastolic pressure; SV, stroke volume; SET, systolic ejection time; MVO_2, myocardial oxygen consumption; VO_2, oxygen consumption; CPET, cardiopulmonary exercise testing; PK, pharmacokinetics; PD, pharmacodynamics; SAD, single ascending dose; MAD, multiple ascending dose; BID, twice daily; LA, left atrium; GLS, global longitudinal strain; CV, cardiovascular.

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energetic profiles with Danicamtiv,[4] definitive head-to-head trials are lacking, and detailed discussion of these agents is reserved for later sections of this review.

In summary, OM is the pioneering agent in the myosin activation class, supported by a robust body of preclinical and clinical evidence. Its development has yielded critical mechanistic and translational insights, but also highlighted the challenges of aligning surrogate hemodynamic benefits with meaningful functional outcomes. GALACTIC-HF provides a statistically significant but modest signal on composite outcomes, and its favourable effects on surrogate markers and certain high-risk subgroups are better regarded as hypothesis-generating than as proof of established clinical benefit. Ongoing work should focus on patient selection, combination strategies, and long-term energetic safety to maximize the clinical potential of this first-generation myotrope.

Danicamtiv: Innovation or Iteration?

Following the clinical validation of Omecamtiv mecarbil (OM), Danicamtiv emerged as the second clinically relevant cardiac myosin activator to progress into human studies. Discovered by Cytokinetics in 2016 through a high-throughput small-molecule screening program designed to refine the pharmacodynamic profile of earlier myotropic agents,[6,37] Danicamtiv was explicitly developed to address specific mechanistic and tolerability limitations observed during OM's clinical trajectory. These included concerns over diastolic function impairment, the overall myocardial energetic burden of prolonged systolic activation, and the need for more predictable pharmacokinetics.[7,16] The overarching question remains whether Danicamtiv represents a genuine pharmacological advance or simply an incremental refinement of the myotrope class.

Mechanistic Distinctions Compared to Omecamtiv Mecarbil

Danicamtiv shares the core myotropic principle of directly enhancing systolic performance by prolonging the actin–myosin cross-bridge interaction.[6,38] However, structural and biophysical studies have revealed molecular distinctions that may be clinically relevant. In preclinical investigations, Choi et al[3] demonstrated that Danicamtiv binds to cardiac myosin at a distinct allosteric site compared with OM, modulating the myosin ATPase cycle in a way that increases the proportion of myosin heads in a force-generating state during systole. This interaction appears to optimize cross-bridge recruitment without a proportional rise in myocardial oxygen demand, potentially improving contractile efficiency—here referring to the amount of force or shortening generated per unit ATP hydrolyzed at the myofilament level.[6,15]

Studies using engineered human cardiac tissues and isolated myocardium preparations, as reported by Malik et al,[4,14] indicated that Danicamtiv prolongs the cross-bridge duty cycle similarly to OM but with less pronounced slowing of diastolic relaxation. These findings, supported by kinetic modeling, suggest a more favorable balance between systolic augmentation and diastolic preservation. Recent work-loop studies further suggest that Danicamtiv can enhance mechanical efficiency by increasing external work more than heat, with minimal effect on the energetic cost of Ca^{2+} cycling, although these findings remain confined to preclinical models.[39] While these mechanistic advantages are encouraging, we should not be overly optimistic until they are confirmed by reliable clinical trials and a larger body of physiological studies.

Preclinical Validation and Early-Phase Clinical Studies

Extensive preclinical pharmacokinetic/pharmacodynamic (PK/PD) profiling established that Danicamtiv exhibits linear pharmacokinetics, predictable dose–plasma concentration relationships, and high cardiac target engagement across species.[14,37] In murine heart failure models induced by transverse aortic constriction, Danicamtiv improved stroke volume, left ventricular ejection fraction (LVEF), and myocardial strain without significant changes in heart rate or systemic vascular resistance.[33,40] In canine models of pacing-induced cardiomyopathy, similar benefits were observed, with improved systolic indices sustained over repeated dosing, indicating minimal tachyphylaxis.

First-in-human Phase I trials, initiated in 2020, enrolled healthy volunteers and patients with stable heart failure with reduced ejection fraction (HFrEF) to assess tolerability, dose proportionality, and early safety.[4,34] In these studies, single and multiple ascending doses up to the maximum tolerated range were well tolerated, with no clinically significant

arrhythmias detected by continuous ECG monitoring. Blood pressure remained stable, and no dose-limiting adverse events occurred. Plasma half-life was compatible with once- or twice-daily dosing, supporting feasibility for chronic use.

The pivotal Phase IIa trial, as reported by Malik et al[34] enrolled patients with stable HFrEF (mean baseline LVEF ~28%, NYHA class II–III) across multiple centers. Over a 14-day treatment period, participants were randomized to receive escalating oral doses of Danicamtiv or placebo, with echocardiographic parameters assessed at baseline and end of treatment. Danicamtiv produced dose-dependent improvements in LVEF, with the highest dose cohort achieving mean absolute increases of 4–5 percentage points. Global longitudinal strain improved by an average of 1.5–2%, and reductions in left ventricular end-systolic and end-diastolic volumes were consistent with reverse remodeling effects.

Subgroup analysis indicated that patients with baseline LVEF ≤30% experienced the greatest relative improvement, a population that typically responds poorly to conventional inotropes. Importantly, no significant increase in ventricular ectopy or sustained arrhythmias was observed, and NT-proBNP levels trended downward, suggesting possible hemodynamic unloading.[34] However, the trial was not powered for clinical outcomes, and the short treatment duration precluded conclusions on long-term safety or sustained efficacy. Table 1 provides an overview of the key official clinical trials of Danicamtiv.

These Phase I–IIa findings are encouraging from a mechanistic and haemodynamic standpoint but remain strictly exploratory; no phase III or outcomes-driven data are available, and danicamtiv should therefore be considered an early-stage, hypothesis-generating candidate rather than a clinically validated therapy.

Clinical Limitations and Remaining Uncertainties

Despite promising mechanistic and early-phase efficacy signals, Danicamtiv's development is constrained by the absence of large-scale outcome trials analogous to OM's GALACTIC-HF. As noted in contemporary reviews,[4,34] no published phase III program has yet demonstrated reductions in heart failure hospitalizations, cardiovascular mortality, or other hard endpoints. Without such evidence, enthusiasm remains tempered, and regulatory approval pathways remain speculative.

Mechanistic uncertainties also persist. Although preclinical studies suggest a lesser impact on diastolic function compared with OM, subtle prolongation of relaxation times has been observed at higher doses in both animal and early human studies.[4,14,40] Moreover, the long-term energetic implications of prolonged systolic activation remain incompletely understood; theoretical concerns include increased ATP turnover and a potential compromise of myocardial efficiency—classically defined as external mechanical work per unit myocardial oxygen consumption—under chronic use.[16]

Another unresolved question is the degree to which Danicamtiv's molecular refinements translate into tangible clinical advantages. Cytokinetics investigators have acknowledged that while the drug offers distinct allosteric binding and a potentially more favorable diastolic profile, these attributes may not yield substantial differentiation in real-world patient outcomes.[14,38] Malik et al[4] have emphasized that precision medicine approaches—such as targeting patients with advanced systolic dysfunction but preserved diastolic reserve—may be essential to realizing clinical benefit.

From a translational perspective, the development of Danicamtiv highlights the broader challenge facing the myotrope class: the need to demonstrate that improvements in surrogate echocardiographic markers correspond to meaningful gains in symptoms, exercise capacity, and survival. The absence of functional improvement data, such as peak VO_2 or six-minute walk distance, further limits interpretation. Future trials will need to incorporate such endpoints alongside robust safety surveillance, particularly for arrhythmia risk and long-term myocardial energetics.

In summary, Danicamtiv introduces meaningful molecular distinctions from OM and has demonstrated a favorable early safety and efficacy profile in preclinical and phase I–IIa clinical settings. But without confirmatory outcome trials its clinical utility and net benefit–risk profile remain entirely speculative. The lack of definitive outcome data and persistent mechanistic concerns necessitate cautious interpretation. Whether Danicamtiv represents a substantive therapeutic advance or a carefully optimized iteration will depend on the results of future adequately powered trials assessing hard clinical endpoints, functional capacity, and long-term safety.

Discussion

Cardiac myosin activators represent a paradigm shift in the pharmacological management of systolic heart failure, offering a mechanism of action distinct from conventional inotropes by directly enhancing sarcomeric contractility without proportionally increasing intracellular calcium levels or myocardial oxygen consumption.[6,37] Omecamtiv mecarbil (OM) and Danicamtiv have emerged as the leading representatives of this class, each advancing through early-phase clinical evaluation with promising yet nuanced results. However, translating their molecular innovations into robust clinical benefit remains challenging, and the field must address persistent uncertainties before these agents can be firmly positioned in heart failure therapy.

The experience with OM provides both a foundation and a cautionary framework for interpreting Danicamtiv's development. OM's trajectory—from early pharmacodynamic validation[3,19] to the large-scale GALACTIC-HF trial—demonstrated the feasibility of myosin activation in improving surrogate measures such as ejection fraction and cardiac output, but also revealed limitations. While GALACTIC-HF met its primary composite endpoint, the magnitude of benefit on hard outcomes such as cardiovascular mortality was modest, and safety concerns regarding diastolic function and myocardial energetics persisted.[4,19,20] Danicamtiv's preclinical profile suggests possible advantages in diastolic preservation[4,14] and allosteric binding differences,[3,6] yet it remains uncertain whether these molecular refinements will yield a clinically meaningful advantage, particularly in long-term outcomes. The major official clinical trials evaluating cardiac myosin activators, including Omecamtiv mecarbil and Danicamtiv, are summarized in Table 1.

A broader comparative lens—including insights from myosin inhibitors such as Mavacamten—can inform activator strategies. While Mavacamten has shown transformative effects in obstructive hypertrophic cardiomyopathy,[41] its opposite mechanism (ATPase inhibition reducing hypercontractility) highlights the bidirectional potential of sarcomeric targeting. Thus, "myosin modulation" is a spectrum rather than a single inotropic tactic. Activators are likely best positioned as precision therapies for subgroups with pronounced systolic impairment, such as those with markedly reduced baseline LVEF.[33,34]

For Danicamtiv, the priority is robust phase III evidence on mortality and hospitalization. Current data are limited to early-phase trials,[34] which show dose-dependent echocardiographic improvements but are underpowered for clinical events. Larger trials should include longer follow-up, comprehensive arrhythmia surveillance, and detailed hemodynamic profiling; lessons from OM suggest that imaging biomarkers, strain analysis, and genetic profiling could sharpen patient selection.[4,19]

A growing body of preclinical work has already quantified how cardiac myosin modulators reshape the energetic efficiency of contraction. In a porcine post-ischaemic heart failure model, Bakkehaug et al showed that near-supratherapeutic concentrations of Omecamtiv mecarbil shift the relation between external cardiac work and myocardial oxygen consumption upward, such that each unit of stroke work requires more oxygen, consistent with reduced global cardiac efficiency driven in part by activation of resting myosin ATPase.[16] In contrast, Obata et al, using isolated rat hearts, reported that intermediate OM concentrations can actually improve the oxygen cost of pressure–volume area, indicating better contractile (work) efficiency within a narrow dose window, whereas higher doses again increase the VO_2 cost of Ca^{2+} handling and attenuate this benefit.[42] Complementing these OM data, recent work-loop experiments in intact rodent myocardium have demonstrated that Danicamtiv increases external work more than heat production and has little effect on the energetic cost of Ca^{2+} cycling, thereby enhancing mechanical efficiency at the muscle level.[39] Taken together, these studies highlight that "efficiency" under myosin modulation is highly context- and dose-dependent—varying with species, preparation, disease state, and exposure—and underscore the need for future clinical programmes to incorporate direct or surrogate indices of work per unit oxygen consumption when defining the true energetic profile of these drugs.

Another underexplored avenue lies in combination strategies. Given the multifactorial nature of HFrEF, studies should assess whether myosin activators synergize with guideline neurohormonal antagonists or metabolic modulators. Preclinical evidence suggests additive benefits when sarcomeric activation is coupled with agents that improve myocardial energetics, such as sodium-glucose cotransporter 2 (SGLT2) inhibitors.[33,40] Carefully designed mechanistic trials could clarify whether such combinations improve systolic function while also achieving a more favorable balance between external cardiac work and energetic cost (eg ATP or oxygen consumption per unit stroke work), thereby mitigating potential diastolic trade-offs.[16]

From a translational science perspective, next-generation design may expand beyond actin–myosin cross-bridge modulation. Structural biology and high-throughput screening nominate titin, myosin light chain, and regulatory troponin subunits as druggable nodes.[6,41] Selectively tuning these elements could allow for more precise control over contractility, relaxation, and compliance, potentially overcoming the intrinsic limitations observed with current agents. Data from other tissues show that

moving myosin head-state occupancy—from the disordered-relaxed (DRX) state to the super-relaxed (SRX) state—may confer energetic and functional benefits beyond the heart.[43] Paired with neuromuscular observations that OM can shift fiber-level Ca^{2+} sensitivity,[44] this points to shared sarcomeric levers—but isoform differences and energetic costs still limit direct extrapolation.

From an evidentiary standpoint, the story of cardiac myosin activation is still dominated by preclinical experiments and early-phase surrogate-endpoint trials. Omecamtiv mecarbil remains the only agent tested in a large, event-driven phase III trial, and although GALACTIC-HF met its composite primary endpoint, the absolute risk reduction was modest and the impact on mortality uncertain.[24–26] Subsequent systematic reviews and meta-analyses have reinforced this picture, showing consistent improvements in ejection fraction, natriuretic peptides and symptom scores, but no clear reduction in all-cause or cardiovascular mortality, and only small effects on heart failure hospitalisations.[35]

The clinical necessity of another "contractility booster" remains questionable if such agents merely reshuffle hemodynamics without improving substantive outcomes. If myosin modulators ultimately earn a place, it should be by doing more with less—delivering greater external work for a given energetic cost and preserving contractile reserve in the sickest patients. Regulatory assessments have been concordant with this cautious interpretation. The US FDA issued a complete response letter requesting an additional outcomes trial to establish substantial evidence of effectiveness and an acceptable benefit–risk balance,[45] and the EMA application for Omecamtiv mecarbil (Kinharto) was subsequently withdrawn after feedback that GALACTIC-HF alone was insufficient to demonstrate that benefits outweigh risks.[46] No cardiac myosin activator is currently approved for heart failure, and danicamtiv has not progressed beyond phase IIa. In this context, the mechanistic and surrogate-endpoint data reviewed in this article should be viewed as hypothesis-generating rather than confirmatory, underscoring the need for adequately powered, outcome-driven trials before myotropes can be considered established components of guideline-directed therapy.

Beyond OM and danicamtiv, several early-stage approaches are extending the concept of sarcomere-directed therapy to other contractile and cytoskeletal targets. Preclinical studies and conceptual reviews have described small molecules that tune titin-based passive stiffness, agents that shift thick- and thin-filament regulatory states, and hybrid "myotropes" that combine modest effects on myosin with actions on Ca^{2+} handling or myocardial energetics.[2,4,43] None of these strategies has progressed to late-phase clinical development, but together they illustrate how experience with cardiac myosin activators is beginning to inform a broader family of sarcomere-focused interventions and may ultimately expand the palette of contractility-modifying therapies beyond OM and Danicamtiv.

Conclusion

Cardiac myosin activators such as Omecamtiv mecarbil and danicamtiv have established sarcomeric myosin as a tractable drug target in human heart failure, with reproducible improvements in systolic performance, chamber mechanics and selected biomarkers across preclinical and early-phase studies. At the same time, the available clinical signals are heterogeneous and, where positive, generally modest in magnitude; functional capacity outcomes have been neutral, phase III outcome data for danicamtiv are still lacking, and no cardiac myosin activator has yet received regulatory approval, so these agents are best regarded at present as experimental therapies with an as-yet incompletely defined benefit–risk profile. The next phase of development will require rigorously powered, outcome-driven trials that integrate myocardial energetics and diastolic function into their design and use phenotype-guided enrolment strategies to link biophysical modulation to meaningful gains in survival and quality of life.[4,19,34] If such studies can demonstrate durable improvements in symptoms, functional capacity and survival, myosin activation could justify a narrowly defined role alongside guideline-directed therapy for selected patients with advanced systolic dysfunction.

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Disclosure

The author(s) report no conflicts of interest in this work.

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