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Review Article

Sarcomere protein modulation: The new frontier in cardiovascular medicine and beyond

Cristina Morelli [a,1], Gessica Ingrasciotta [a,1], Daniel Jacoby [b], Ahmad Masri [c], Iacopo Olivotto [a,*]

[a] Azienda Ospedaliera Universitaria Careggi and University of Florence, Florence, Italy
[b] Department of Internal Medicine, Section of Cardiovascular Medicine, Yale University, New Haven, CT, USA
[c] Knight Cardiovascular Institute, Oregon Health & Science University, Portland, OR, USA

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ABSTRACT

Over the past decade, the constant progress in science and technologies has provided innovative drug molecules that address specific disease mechanisms thus opening the era of drugs targeting the underlying pathophysiology of the disease. In this scenario, a new paradigm of modulation has emerged, following the development of small molecules capable of interfering with sarcomere contractile proteins. Potential applications include heart muscle disease and various forms of heart failure, although promising targets also include conditions affecting the skeletal muscle, such as degenerative neuromuscular diseases. In cardiac patients, a cardiac myosin stimulator, omecamtiv mecarbil, has shown efficacy in heart failure with reduced systolic function, lowering heart failure related events or cardiovascular death, while two inhibitors, mavacamten and aficamten, in randomized trials targeting hypertrophic cardiomyopathy, have been shown to reduce hypercontractility and left ventricular outflow obstruction improving functional capacity. Based on years of intensive basic and translational research, these agents are the prototypes of active pipelines promising to deliver an array of molecules in the near future. We here review the available evidence and future perspectives of myosin modulation in cardiovascular medicine.

In recent years, constant progress in science and technology has resulted in innovative molecules addressing core mechanisms of myocardial disease affecting millions worldwide [1]. A targeted molecular approach, well established in oncology over the last two decades, is likely to revolutionize a field, such as cardiovascular therapeutics, long dominated by agents modulating neuroendocrine systems and ion channels rather than myocardial function. The sarcomere is the fundamental unit of striated muscle contraction, containing myosin, a protein that converts chemical energy into mechanical force through its interaction with actin. This complex interaction is regulated by other proteins including troponin and tropomyosin and is critically dependent on changes in calcium concentrations [2]. In the heart, this functional unit can be altered due to mutations in the genes encoding sarcomere proteins, as in hypertrophic cardiomyopathy (HCM) [3,4] and dilated cardiomyopathy (DCM) [5,6]. However, acquired abnormalities are common and represent critical contributors to various forms of heart failure. In this context, allosteric, orally available sarcomere modulators represent a promising new therapeutic strategy [7]. Several molecules have already been tested or are currently undergoing Phase 3 clinical trials including the allosteric cardiac myosin inhibitors mavacamten [8] and aficamten [9], developed for patients with obstructive HCM (a paradigm of heart failure with preserved ejection fraction) and the cardiac myosin activator omecamtiv mecarbil [10], developed for patients with systolic dysfunction (Fig. 1).

On a broader perspective, beyond the scope of the present review, the sarcomere apparatus is emerging as a promising therapeutic target also at the skeletal muscle level, with molecules directed at neuromuscular diseases such as spinal muscular atrophy (SMA) [11] and amyotrophic lateral sclerosis (ALS) [12], respectively. Fast skeletal muscle troponin activators (FSTAs) have been shown to increase muscle force by slowing the off rate of calcium from troponin, thus increasing calcium sensitivity [13]. Tirasemtiv [14], a first-generation FSTA, in the phase III clinical trial VITALITY-ALS (Ventilatory Investigation of Tirasemtiv and Assessment of Longitudinal Indices after Treatment for a Year), failed to reach the primary endpoint of improvement in slow vital capacity (SVC) in ALS patients [15]. However, participants tolerating their intended dose exhibited a trend toward treatment benefit, promoting the development of reldesemtiv [16], a second generation FSTA with improved

* Corresponding author.
E-mail address: iacopo.olivotto@unifi.it (I. Olivotto).
[1] the two authors contributed equally to this work.

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selectivity. Reldesemtiv also failed to achieve the primary SVC endpoint in ALS patients, in the phase 2b trial FORTITUDE-ALS (Functional Outcomes in a Randomized Trial of Investigational Treatment with CK-2127107 to Understand Decline in Endpoints in ALS; Clinical.gov: NCT03160898). However, there was a statistically significant reduction in decrease of ALS Functional Rating Scale-Revised Total Scores pooling across all active dose groups compared to placebo [17]. These results supported the implementation of the ongoing phase III, double-blind, randomized, placebo-controlled clinical trial COURAGE-ALS (Clinical Outcomes Using Reldesemtiv on ALSFRS-R in a Global Evaluation in ALS) [18].

In view of these multiple, promising pipelines, the concept of sarcomere protein modulation is here to stay and physicians will need to familiarize themselves with these agents in the near future. We here review the available evidence and future perspectives of myosin modulation in cardiovascular medicine (Fig. 2).

1. Hypertrophic cardiomyopathy

HCM is the most common inherited disease of the myocardium, defined by the presence of unexplained left ventricular hypertrophy, generally caused by mutations in genes encoding proteins of the cardiac sarcomere [3,19]. Symptoms include dyspnea on exertion, angina, atypical chest pain, syncope, and palpitations. The natural history is variable; many patients have a normal life expectancy whereas others may experience disease progression with profound exercise limitation, recurrent arrhythmias and premature death [19]. The presence of dynamic left ventricular outflow tract obstruction (LVOTO) increases risk of adverse outcome and is a main determinant of symptoms [19]. When associated with drug-refractory symptoms, LVOTO represents an indication for invasive septal reduction therapies such as surgical myectomy or percutaneous alcohol septal ablation [19].

In the normal heart, myosin shifts in equilibrium between two states: an *open-headed structure*, with high ATPase activity, available for actin cross-bridge formation, and a *folded back or super-relaxed (SRX) state,* characterized by low ATPase activity and not available for the interaction with actin filaments [20]. Thus, on the one hand, the force generated by the sarcomere depends on the proportion of open-headed myosins and on the number of myosin-actin cross-bridge interactions; on the other, SRX myosins are deemed essential for long-term, sustainable performance of the heart muscle. At any given cardiac cycle, only a fraction of myosin heads are engaged in contraction: maintenance of the SRX state is an evolutionarily conserved energy-saving mechanism critical for maintaining contractile and energetic homeostasis within the cardiomyocyte, allowing a decrease in the metabolic rate during periods of myocardial stress [20,21]. In HCM hearts, SRX myosin dysregulation has been proposed as a main driver of pathophysiology, since disease-causing mutations tend to increase the number of open-headed myosins and promote exaggerated cross-bridge interactions. In a cascade of downstream maladaptive mechanisms, this phenomenon leads to the development of hypertrophy, hyper-dynamic contraction, increased energy cost of force generation and fibrosis – i.e. the full-blown HCM phenotype [1,22–24]. Recent efforts have therefore focused on identifying small molecules capable of binding to the catalytic domain of β myosin thereby favouring the SRX conformation and altering the number of myosin molecules functionally accessible for the interaction with actin. Two myosin inhibitors, mavacamten and aficamten, have been developed and successfully employed in clinical trials [25–26].

1.1. Mavacamten

Mavacamten is a first-in-class, allosteric inhibitor of cardiac β myosin ATPase, able to decrease actin-myosin affinity thus restoring a normal/quasi normal amount of myosin heads in SRX state and reducing the excessive number of actin-myosin cross bridges [8,27,28] (Fig. 2). Preclinical studies in murine models have shown that mavacamten is able to reduce hypercontractility and revert or prevent left ventricular hypertrophy, cardiomyocyte disarray and myocardial fibrosis [29,30]. In the Phase 2 PIONEER-HCM (Pilot Study Evaluating drug in Subjects With Symptomatic Hypertrophic Cardiomyopathy and Left Ventricular Outflow Tract Obstruction) study, enrolling patients with symptomatic obstructive HCM (oHCM, with resting or exercise-induced dynamic outflow gradient ≥50 mmHg), mavacamten was able to reduce post-exercise LVOTO and to improve exercise capacity and symptoms with excellent tolerability and safety profiles [31]. The study showed

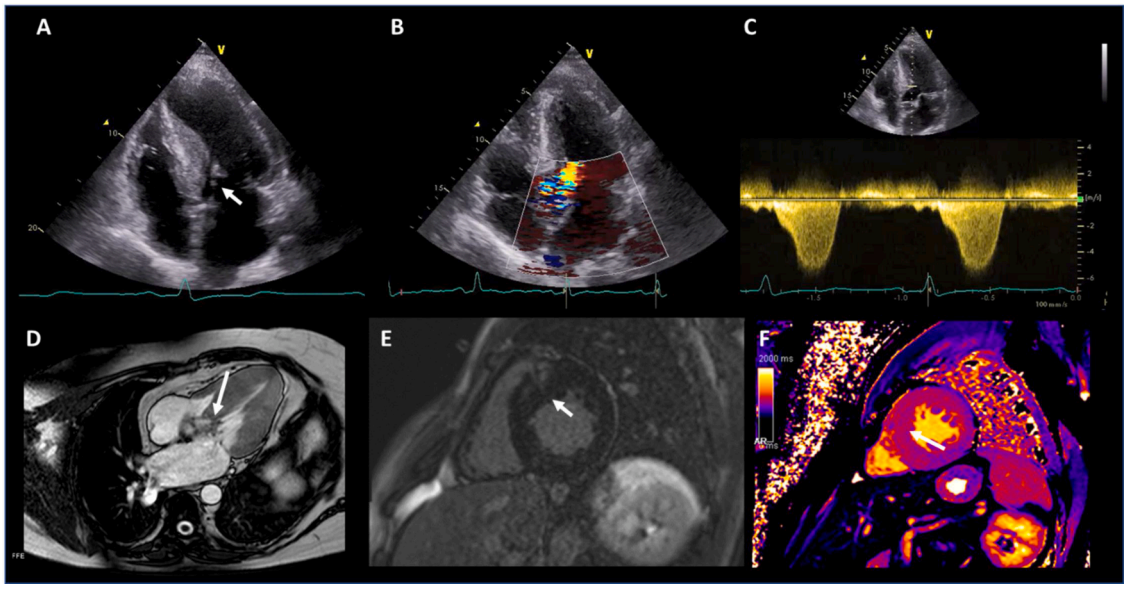

Fig. 1. 42 years old male patient with oHCM and typical imaging findings. Transthoracic echocardiogram: (A,B) asymmetric septal wall hypertrophy with turbulence in the left ventricular outflow tract and mitral leaflet elongation (arrow); (C) characteristic continuous-wave Doppler signal with a late-peaking dagger-shaped appearance. Cardiac Magnetic Resonance: (D) typical artifact due to turbulence jet across the LVOT (arrow); (E) LGE in the hypertrophied anterior septal myocardium; (F) patchy areas of prolonged T1 values in the anteroseptal segment in short-axis T1 mapping. oHCM: obstructive hypertrophic cardiomyopathy; LVOT: left ventricular outflow tract; LGE: late gadolinium enhancement.

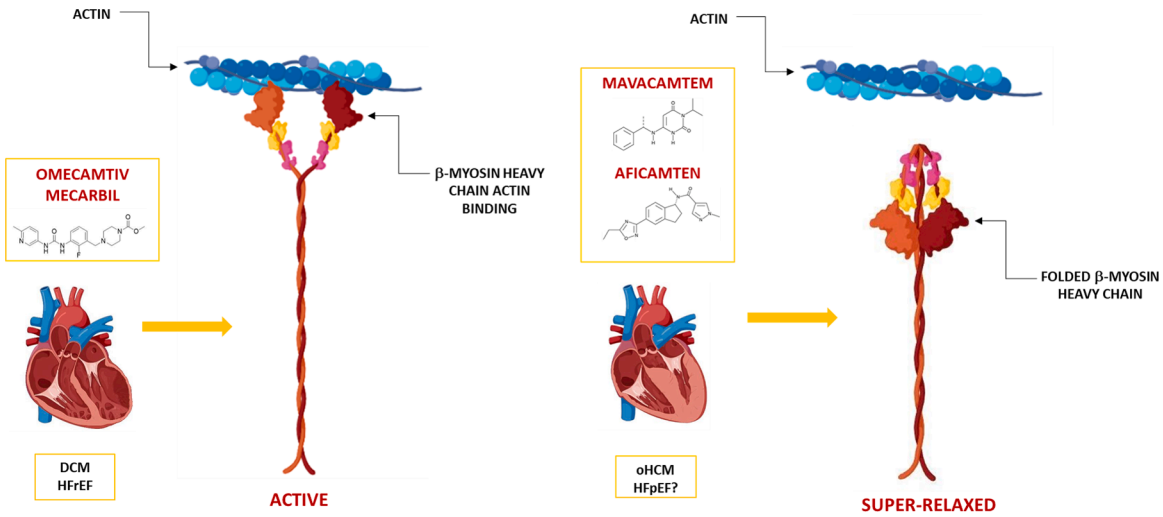

Fig. 2. Human β-cardiac myosin shifts in equilibrium between two states: an open-headed structure, or active state, available for actin cross-bridge formation and a folded back, or super-relaxed (SRX) state, not available for the interaction with actin filaments. Mavacamten and CK-274 shift this equilibrium toward the SRX state, ultimately reducing contractility, in the opposite way omecamtiv mecarbil stabilizes the active state, thereby increasing contractility. *Created with BioRender.com.*

significant improvement in circulating biomarkers, a benefit also demonstrated in nonobstructive HCM patients in the phase II MAVERICK-HCM (Mavacamten in Adults With Symptomatic Non-Obstructive Hypertrophic Cardiomyopathy) trial [32].

The phase III EXPLORER-HCM trial (Mavacamten for treatment of symptomatic obstructive hypertrophic cardiomyopathy), the largest to date in HCM, randomized 251 patients with symptomatic oHCM to mavacamten or placebo, on top of their previous medical therapy with betablockers or calcium antagonists - although disopyramide was not allowed. The primary endpoint was a composite of functional capacity evaluated by cardiopulmonary exercise testing and symptom burden expressed as New York Heart Association (NYHA) class [25]. After a 30-week treatment period, patients were considered responders if they achieved an increase in pVO2 of $\geq$ 1.5 mL/kg/min (compared to the initial assessment) with an improvement of $\geq$ 1 NYHA class or $a \geq 3.0$ mL/kg/min increase in pVO2 with no worsening of NYHA class. Patients assigned to mavacamten were more likely to reach the primary endpoint compared to placebo (37% vs 17%, $p = 0.0005$) (Fig. 3.)

Furthermore, a hierarchical assessment of predefined secondary endpoints (all with $p>0.001$) showed a consistent, significant benefit of mavacamten in terms of pVO2 increase versus baseline (1.4 vs. 0.6–2.1 mL/kg/min), NYHA functional class ($\geq$ 1 NYHA class improvement in 65% vs. 31% in the placebo arm), reduction in post-exercise LVOTO (almost 50 mmHg, compared to no change in the placebo group), symptoms status and quality of life [25]. At the end of the treatment period, the Kansas City Cardiomyopathy Questionnaire (KCCQ) had improved by 13.6 points in the mavacamten arm vs. 4.2 in the placebo. Approximately three-quarters of patients who were in NYHA class II at baseline became asymptomatic with mavacamten. Moreover, 27% of treated patients had a complete therapeutic response (defined as both an exercise-induced LVOTO less than 30 mmHg and a NYHA class I at final evaluation – equivalent to an optimal surgical result) versus 1% of those on placebo. The clinical and hemodynamic benefit was independent of age and gender and was associated by marked reduction in two predictors of long-term outcome, serum NT-proBNP and high sensitivity cardiac troponin I (hs-cTnI) [33,34]. Of note, greater clinical benefit was observed in patients with pathogenic mutation, while it was not present in genotype negative patients [25]. These effects were achieved with an average reduction of left ventricular ejection fraction (LVEF) of only 4%, with most patients remaining well above a normal threshold of systolic function. A recently published echocardiographic sub-study of EXPLORER-HCM has shown a significant cardiac remodeling effect of mavacamten in oHCM. Besides reducing LVOTO, treatment was associated with improved left ventricular diastolic function and reduced left atrial volume index compared to baseline, an effect not seen in placebo [35].

Mavacamten was generally well tolerated, and its safety profile was not different from placebo. The only patient who died – suddenly – during the study was in the placebo arm. Two patients in the mavacamten group developed stress cardiomyopathy with apical ballooning, which spontaneously recovered. Overall, seven patients on mavacamten had a transient decrease in LVEF to less than 50%; three had protocol-driven temporary treatment discontinuation during the 30-week treatment, while in four the reduction in LVEF was observed at end-of-treatment visit. Following an 8-week washout, LVEF recovered to normal values in all patients except one who experienced a procedural complication and severe LVEF drop following atrial fibrillation ablation during the washout period with partial recovery (to LVEF 50%). A long-term, open-label extension study is ongoing to assess the safety profile of mavacamten at 5 years of follow-up (MAVA-LTE; NCT03723655). A recent interim analysis based on the patients enrolled from EXPLORER-HCM (EXPLORER-LTE) has shown sustained benefit and safety of mavacamten beyond 1 year of treatment [36].

At the time of writing, mavacamten is awaiting approval from the United States Food and Drug Administration. If granted, it remains to be clarified how the drug will be included in the therapeutic algorithm for oHCM. In particular, the positive results of EXPLORER-HCM have raised expectations that mavacamten may reduce the need for invasive interventions. However, the trial was not designed to address this point, as patients enrolled were in large part mildly symptomatic (NYHA class II) and therefore not immediate operative candidates. An answer to this important issue will hopefully derive from the ongoing VALOR-HCM (A Study to Evaluate Mavacamten in Adults With Symptomatic Obstructive HCM Who Are Eligible for Septal Reduction Therapy; NCT04349072) trial, specifically designed to evaluate the effect of mavacamten in reducing or postponing the number of septal reduction therapy

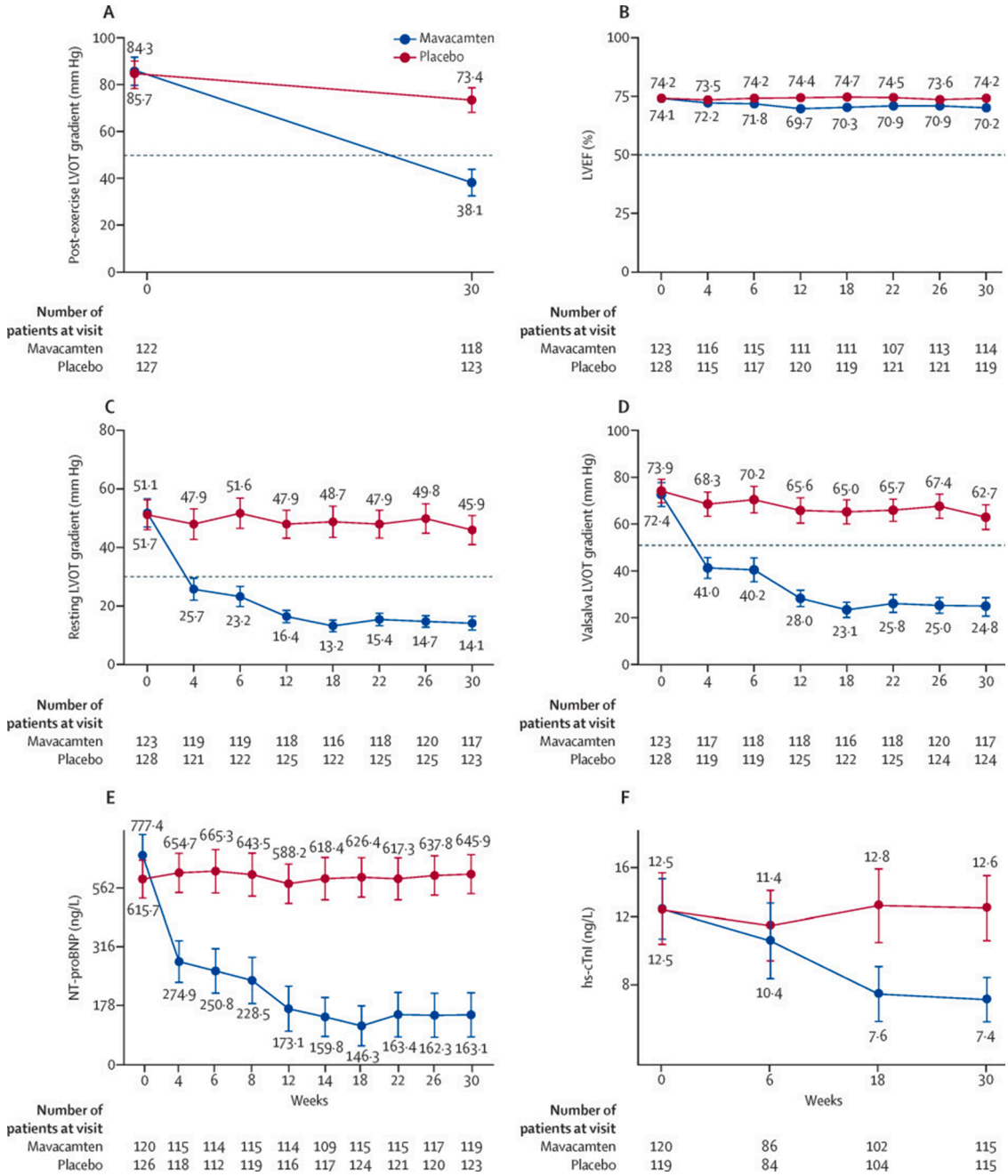

Fig. 3. LVOT gradient, LVEF and cardiac biomarkers variations in EXPLORER-HCM trial. Mean post-exercise LVOT gradient over time **(A)**, LVEF **(B)**, resting and Valsalva LVOT gradient **(C-D)**. Geometric mean over time is shown for NTproBNP (E) and hs-cTnI (F). Error bars are 95% CIs. The dashed lines represent the threshold for guideline-based invasive intervention (LVOT gradient >50 mm Hg) in A and D, the threshold for guideline-based diagnosis of obstruction (LVOT gradient <30 mm Hg) in C and the protocol threshold for temporary discontinuation (LVEF <50%) in B.
Legend: high sensitivity cardiac troponin I (hs-cTnI), left ventricular ejection fraction (LVEF), left ventricular outflow tract (LVOT), N terminal pro B-type natriuretic peptide (NT-proBNP). This figure is taken from "*Mavacamten for treatment of symptomatic obstructive hypertrophic cardiomyopathy (EXPLORER-HCM): a randomized, double-blind, placebo-controlled, phase 3 trial*, Olivotto et al. published on The Lancet, Vol 396, issue 10,253, Page 759–769, 2020.

procedures in subjects with severely symptomatic oHCM.

2. Aficamten

Aficamten is an oral cardiac myosin inhibitor with similar mechanism of action to mavacamten, although it binds to a different allosteric site and exhibits a shorter half-life (t½) [37,38] (Fig. 2). The recently completed Phase II REDWOOD-HCM (Randomized Evaluation of Dosing With CK-274 in Obstructive Outflow Disease in HCM) study [26] was a double-blind, dose-finding clinical trial which randomized 41 symptomatic oHCM patients on background medical therapy, to either aficamten 5 mg titrated up to 15 mg (Cohort 1), aficamten 10 mg titrated to 30 mg (Cohort 2), or placebo. The 2-week step titration strategy included escalation criteria of LVEF >50% and resting >30 mmHg or post-Valsalva >50 mmHg LVOTO. The primary endpoint was to determine the safety and tolerability of aficamten. After 10 weeks of treatment, both treatment cohorts showed markedly greater reductions in the average resting and post-Valsalva LVOT gradient from baseline, compared to placebo. The majority of patients on aficamten achieved a resting LVOT gradient <30 mmHg and post-Valsalva gradient <50

mmHg (78.6% in Cohort 1; 92.9% in Cohort 2; 7.7% in placebo) at the expense of only a modest decrease in average LVEF and with no dose interruptions due to LVEF reduction below 50%. Reductions in LVOTO were dose-dependent, occurred within two weeks of starting treatment, and peaked within two to six weeks of starting dose titration. In addition, both aficamten cohorts showed greater reduction in NT-proBNP levels and improvement of ≥1 NYHA class vs baseline, compared to placebo. Treatment with aficamten was well tolerated with similar incidence of adverse events between treatment arms. Subsequently, a REDWOOD-HCM Cohort 3 has been enrolled, in order to assess the effect of aficamten co-administered with disopyramide in oHCM. The results from Cohort 3, accepted for presentation at the American College of Cardiology 71 st Annual Scientific Session & Expo in Washington, DC in April, showed substantial reductions in the average resting LVOT gradient as well as the post-Valsalva LVOT gradient and improvement of NYHA class in the majority of patients. There were no patients whose LVEF fell below the prespecified safety threshold of 50% and safety and tolerability of aficamten were consistent with prior experience in REDWOOD-HCM [39]. Furthermore, REDWOOD-HCM OLE, an open-label extension clinical trial designed to evaluate the long-term safety and tolerability of aficamten in patients previously enrolled in REDWOOD-HCM, is currently underway [40]. Based on these promising results, the phase III SEQUOIA-HCM (Safety, Efficacy, and Quantitative Understanding of Obstruction Impact of aficamten in HCM), a multicentre randomized, placebo-controlled, double-blind clinical trial in patients with oHCM, is due to start enrolling soon [41]. The primary endpoint is change in peak pVO2 from baseline to week 24. Secondary endpoints include the change in patient's quality of life, by KCCQ score, in post-Valsalva LVOT gradient and in NYHA class.

3. Heart failure with reduced ejection fraction

The prevalence of heart failure with reduced ejection fraction (HFrEF) is of pandemic proportion in the western world, due to aging of the population and effective treatments, that prevent mortality but increase residual morbidity in the general population. The quest for positive inotropes for HFrEF dates back many years. Traditional positive inotropes mainly modulate calcium signaling in the myocardium (calcitropes). Despite improving cardiac output, however, these agents have generally been associated with increased mortality because of predisposition to arrhythmias, hypotension, and increased myocardial energy demand [42,43], limiting their use to the acute setting and to heart failure patients who are refractory to other therapies and are suffering the consequences of end-stage organ hypoperfusion [44]. Omecamtiv mecarbil (OM) [10] is the first cardiac myosin activator (myotrope) which was successfully investigated in multiple clinical trials [45–47]. OM directly activates cardiac myosin in a calcium-independent manner, increasing the transition rate of myosin into the actin-bound force--generating state (Fig. 2). OM action improves systolic function via increasing ejection duration without affecting the rate of contraction (dP/dt) [48], making OM an energetically efficient drug that does not lead to greater oxygen consumption [49], nor cause hypotension.

The COSMIC—HF trial (Chronic Oral Study of Myosin Activation to Increase Contractility in Heart Failure) established the superiority of pharmacokinetic dosing of OM and its safety [45]. In the phase III trial GALACTIC—HF (Global Approach to Lowering Adverse Cardiac outcomes Through Improving Contractility in Heart Failure), 8256 patients with symptomatic heart failure and a LVEF ≤ 35% were randomized to OM (pharmacokinetic-guided dosing) vs placebo. The primary outcome was a composite of a first heart-failure event (hospitalization or urgent visit for heart failure) or cardiovascular death. Over a median follow-up of 21.8 months, the primary outcome occurred in 37% of patients on OM vs 39.1% of patients on placebo (HR 0.92, 95% CI 0.86–0.99, $p = 0.03$). OM decreased NTproBNP by 10% as compared with placebo. There was no difference in the rate of cardiovascular death or patient-reported outcomes between both groups. There were no major safety issues related to OM [50].

In a subsequent pre-specified sub-group analysis of GALACTIC—HF, LVEF was the strongest modifier of treatment effect of OM (interaction $p = 0.004$). Patients with an LVEF≤22% had 17% relative risk reduction for the primary outcome (HR 0.83, 95% CI 0.73–0.95) as compared with patients with LVEF ≥33% (HR 0.99, 95% CI 0.84–1.16), interaction $p = 0.013$) [51]. In a similar fashion, OM produced a 22% reduction in NT-proBNP in patients with LVEF ≤22% as compared with a 3% reduction in patients with LVEF ≥33% ($p = 0.54$; interaction $p < 0.001$). Thus, OM showed greater therapeutic efficacy in patients with worse LVEF, consistent with its specific mechanism of action. Similarly, a post-hoc analysis showed greater efficacy of OM in patients with severe heart failure, defined as the presence of all these characteristics: NYHA functional class III/IV, LVEF of 30% or less, and hospitalization for heart failure within the previous 6 months (Fig. 4).

A further potential benefit of OM is the reduction of ischemic stroke incidence in patients with HFrEF. Recent data from GALACTIC—HF showed that, in patients on OM, the risk of first fatal or non-fatal stroke was reduced by 35% (HR 0.65; 95% CI 0.49, 0.87; $p = 0.004$), and that of fatal stroke by 44% (HR 0.56; 95% CI 0.31, 0.99; $p = 0.048$). Treatment was also associated with a reduction in new onset atrial fibrillation/flutter (no atrial fibrillation/flutter present at screening: $n = 5987$, HR 0.70, CI 0.50, 0.99; $p = 0.044$; no history of atrial fibrillation/flutter: $n = 4757$, hazard ratio 0.60, CI 0.37, 1.00; $p = 0.048$) [52]. These are intriguing findings showing that the benefit of OM might extend beyond its effect on LVEF. In the evolving and competitive world of HFrEF therapeutics, however, further understanding of which patient subsets may represent ideal responders to OM is imperative. Meanwhile, a second myosin activator, danicamtiv has been shown to be safe in a phase 2a clinical trial and led to improved left ventricular and left atrial echocardiographic parameters versus placebo with further trials in development [53].

4. Future perspectives and conclusions

As we look to the future for myomodulators, we anticipate the completion of additional phase 2 and 3 studies (i.e. REDWOOD, SEQUOIA, METEORIC, COURAGE-ALS, and VALOR-HCM), as well as the results of long-term open label extension studies (PIONEER-OLE, MAVA-LTE, REDWOOD-OLE). These data will provide much needed insights into safety and tolerability, but also critically into remodeling and disease modifying effects of these novel agents, which have been demonstrated so far only in experimental models [29]. With approval by regulatory bodies, application of myomodulators in clinical practice will provide additional observational learning opportunities.

The impact of myomodulation on disease expression is likely to be different depending both on underlying etiology, and stage of disease development. Particular interest and expectations are raised by the possibility of interfering with the development of monogenic heart disease in healthy mutation carriers or patients with early phenotypes [54]. This represent an ambitious goal, and is limited to relative uncommon conditions. However, GALACTIC—HF has taught us that myosin modulators may also be effective in conditions that are very prevalent in the general population, such as HFrEF. Many further questions and unmet needs must be confronted. In the case of OM, does this agent provide additional benefit in HFrEF patients treated with the full pharmacological armamentarium now including SGLT-2 inhibitors (little employed in GALACTIC—HF)? What role might OM have in patients with left ventricular assist device (LVAD) and the possibility of left ventricular recovery? Can it be used in patients with right ventricular failure both with and without pulmonary hypertension? Additionally, what role if any might there be for palliation of late-stage heart failure? In a mirror-like fashion, it is hard to resist the speculation that myosin inhibitors such as mavacamten may be beneficial not only in HCM, but also in certain subsets of HFpEF characterized by left ventricular hypertrophy and diastolic impairment. If so, however, a precise definition

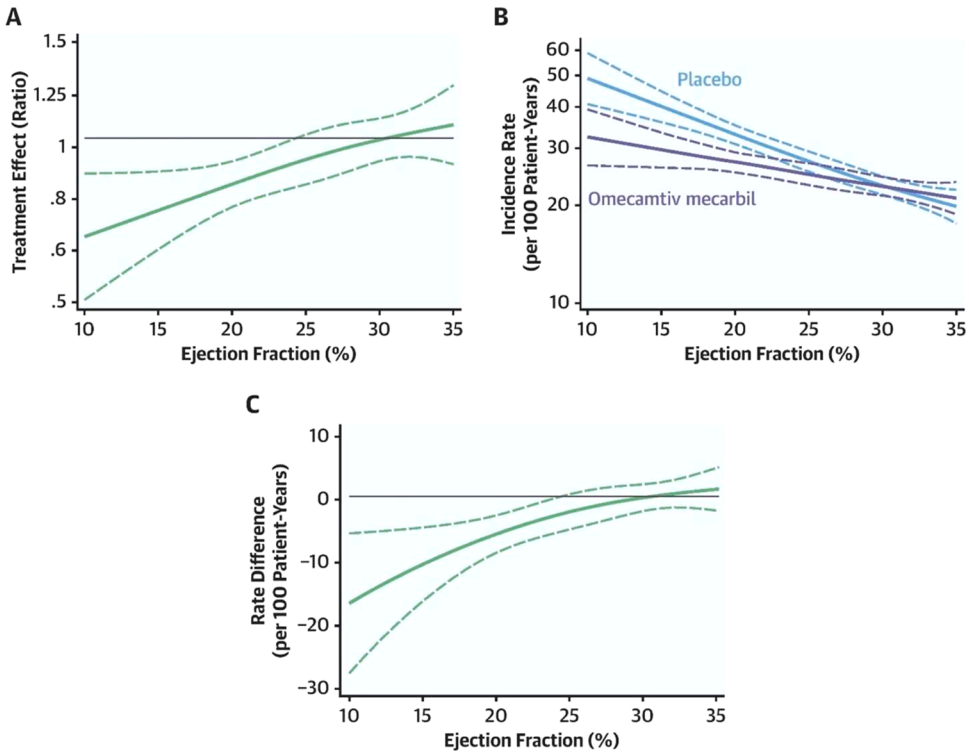

Fig. 4. Increasing beneficial effect of treatment of omecamtiv mecarbil with decreasing of LVEF. For lower values of LVEF there was a greater reduction of the primary composite endpoint (time-to-first heart failure or cardiovascular death event) with interaction $p = 0.004$ **(A)**. Incidence rates (events/100 patient-years) of primary composite endpoint decreases for higher values of LVEF in both the placebo (blue lines) and omecamtiv mecarbil groups (purple lines) **(B)**. Omecamtiv mecarbil shows an increment of the absolute rate reduction in the primary composite endpoint with a decreasing of EF **(C)**. This figure is taken from "*Effect of Ejection Fraction on Clinical Outcomes in Patients Treated With Omecamtiv mecarbil in GALACTIC—HF,* John R Teerlink et al., published on Journal Of The American College Of Cardiology, VOL. 78, N. 2, 2021.

of the potential responder, will be key.

Disclosures

IO has served as PI in the Explorer HCM trial, and is an advisor for Bristol Meier Squibb, Cytokinetics and Amicus and has received grants from Genzyme, Menarini International, Boston Scientific. DJ is a Cytokinetics employee, has received consulting fees for serving on an Advisory Board for Myocardia/BMS and Cytokinetics and he owns the patent: System and Method for Generating Biological Tissue, United States 15/883,381; owns Propria, LLC. AM has received research grants from Pfizer, Ionis, Akcea, Ultromics and the Wheeler Foundation, fees (honoraria or consulting) from Eidos, Pfizer, Ionis, Alnylam, Cytokinetics, Bristol Meier Squibb, Tenaya, and Attralus. The other authors declare they have no conflict of interest.

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Supplementary materials

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