

Managing drug–drug interactions with mavacamten: A focus on combined use of antiarrhythmic drugs and anticoagulants

Fabrizio Ricci, MD, PhD, MSc,^{1,2,3,4} Lorenzo V. Molinari, MD,¹ Davide Mansour, MD,¹ Kristian Galanti, MD,¹ Fabio Vagnarelli, MD, PhD,⁵ Giulia Renda, MD, PhD,^{1,2} Sabina Gallina, MD,^{1,2} Anjali Owens, MD,⁹ Jasmine A. Luzum, PharmD, PhD,⁶ Iacopo Olivotto, MD,^{7,8} Mohammed Y. Khanji, MBBCh, PhD, MRCP,^{9,10,11} Anwar A. Chahal, MBChB, PhD, MRCP^{9,12,13,14}

ABSTRACT

Mavacamten is a selective, allosteric, and reversible cardiac myosin inhibitor, representing the first disease-specific treatment for obstructive hypertrophic cardiomyopathy (HCM) that targets the core pathophysiological mechanism of this condition. Clinical evidence supports its efficacy in improving symptoms, cardiac function, and remodeling, thereby supplementing established treatment regimens. However, mavacamten is extensively metabolized by hepatic cytochromes, and its half-life is contingent upon CYP2C19 phenotype. Consequently, coadministered medications that inhibit or induce these enzymes may significantly alter mavacamten pharmacokinetics, potentially leading to reversible systolic dysfunction or diminished therapeutic efficacy. This paper provides a comprehensive analysis of mavacamten pharmacokinetics and its potential interactions with antithrombotic and antiarrhythmic agents, which are the cornerstones of atrial fibrillation management in HCM population. Our aim is to offer clinicians practical guidance on safely administering mavacamten in conjunction with these medications, discuss the role of pharmacogenomics, and outline rigorous patient safety monitoring strategies to ensure effective and individualized treatment.

KEYWORDS Antiarrhythmic drugs; Anticoagulants; Drug–drug interaction; Hypertrophic cardiomyopathy; Mavacamten; Pharmacogenomics; Pharmacokinetics

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Introduction

Hypertrophic cardiomyopathy (HCM) refers to a complex and heterogeneous disease, both from a phenotypic and genetic standpoint, defined by a hypertrophic myocardium not explained by abnormal loading conditions, with an estimated prevalence of 1 in 500.^{1,2} HCM spectrum encompasses sarcomeric, nonsarcomeric, and syndromic subtypes. Pathogenetic variants in *MYBPC3* and *MYH7* genes are the most frequent genetic causes of sarcomeric HCM and have been associated

with variable onset of disease and prognosis.^{3,4} Depending on complex interaction of genetic and environmental variables, disease course can be complicated by dynamic left ventricular outflow tract (LVOT) obstruction and heart failure (HF) through progressive stages of adverse left ventricular remodeling and overt left ventricular (LV) dysfunction. In addition, HCM is burdened by increased risk of arrhythmias and thromboembolic stroke. Although ventricular arrhythmias and sudden cardiac death are the most severe consequences

From the ¹Department of Neuroscience, Imaging and Clinical Sciences, G D'Annunzio University of Chieti-Pescara, Chieti, Italy, ²University Cardiology Division, Heart Department, Policlinico SS Annunziata, Chieti, Italy, ³Department of Clinical Sciences, Lund University, Malmö, Sweden, ⁴Institute for Advanced Biomedical Technologies, G D'Annunzio University of Chieti-Pescara, Chieti, Italy, ⁵Department of Cardiology, Lancisi Cardiovascular Center, Marche University Hospital, Ancona, Italy, ⁶Department of Clinical Pharmacy, University of Michigan College of Pharmacy, Ann Arbor, Michigan, USA, ⁷Meyer Children's Hospital IRCCS, Florence, Italy, ⁸Cardiomyopathy Unit, Careggi University Hospital, Florence, Italy, ⁹Barts Heart Centre, Barts Health NHS Trust, London, UK, ¹⁰NIHR Barts Biomedical Research Centre, William Harvey Research Institute, Queen Mary University of London, London, UK, ¹¹Newham University Hospital, Barts Health NHS Trust, London, UK, ¹²Center for Inherited Cardiovascular Diseases, WellSpan Health, Lancaster, Pennsylvania, USA, ¹³Division of Cardiovascular Diseases, Mayo Clinic, Rochester, Minnesota, USA, and ¹⁴Center for Inherited Cardiovascular Disease, University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania, USA.

<https://doi.org/10.1016/j.hrthm.2024.11.041>

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of HCM, these occur in only 2% of all patients with HCM. The most frequent supraventricular arrhythmia in HCM is atrial fibrillation (AF), affecting approximately 20% of patients, with prevalence as high as 40% in those older than 70 years of age.^{5,6} Patients affected by HCM and AF can suffer from highly debilitating symptoms, as the loss of atrial contribution to ventricular filling is associated with progression of HF. As AF is often poorly tolerated in patients with HCM, rhythm-control strategies are key for successful treatment and often dramatically improve symptoms.⁷ Patients with HCM and AF have a sufficiently increased risk of stroke⁸; therefore, direct oral anticoagulants (DOACs) should be considered the lifelong default treatment recommendation irrespective of the CHA₂DS₂-VASc score.^{9,10} The mechanisms of AF and increased thromboembolic risk in HCM are likely multifactorial and linked to atrial myopathy.^{11,12}

For the purposes of management, HCM is classified into obstructive (oHCM) and nonobstructive (noHCM) phenotypes. oHCM is identified when a resting or provokable peak instantaneous Doppler LVOT gradient of ≥ 30 mm Hg is detected. A distinctive feature of oHCM is the reversibility of HF symptoms when LVOT obstruction is relieved or abolished. This condition is highly amenable to effective treatment options in most patients and has a much more favorable prognosis compared with HF in nonobstructive HCM and nonsarcomeric HCM diseases.¹³ In patients with gradients below 50 mm Hg, treatment generally follows the guidelines established for noHCM. Conversely, septal reduction therapy is recommended for symptomatic patients when the gradient ≥ 50 mm Hg,¹⁴ as these individuals are more likely to benefit from invasive interventions.

Management of symptomatic LVOT obstruction in HCM is an evolving field and includes a combination of lifestyle modifications, pharmacologic interventions, and septal reduction therapies. First-line treatment of oHCM includes beta blockers, nondihydropyridine calcium channel blockers, and disopyramide. These conventional agents are exploited for their negative inotropic actions reducing the risk for dynamic LVOT obstruction. This approach is defined as nonselective because it does not target the primary mechanisms of the disease, but it acts on the consequences of the hypertrophic myocardium.¹⁴ Although there is no evidence that conventional drugs are able to prevent progression of disease, they aim to manage symptoms, improve cardiac function, and reduce the risk of complications. In patients refractory to medical therapy, septal reduction therapies—including surgical myectomy and less invasive transcatheter approaches—are recommended to improve symptoms and quality of life.^{15–19} When mitral regurgitation is caused by morphologic alterations of the valve apparatus, myectomy can be combined with mitral valve interventions.²⁰ In patients with history of AF undergoing septal myectomy, the addition of ablation surgery and left atrial appendage ligation has been shown to reduce the risk of AF recurrences²¹ and the rate of thromboembolic and hemorrhagic events,¹¹ respectively.

Recent advancements in the understanding of the pathophysiological mechanisms and molecular underpinnings of

the disease have paved the way for the development of myosin inhibitors, an innovative drug class holding the potential not only to alleviate symptoms but also to modify progression of disease by directly targeting the hypercontractility and altered energetics of the cardiac muscle. These compounds operate by reversibly inhibiting the interaction between beta-cardiac myosin and actin, thereby diminishing sarcomere force output to reduce myocardial contractility and improve ventricular compliance. Two cardiac myosin inhibitors—mavacamten and aficamten—have demonstrated clinically relevant results by achieving sustained improvements of LVOT gradient, exercise capacity, quality of life, and symptom burden in patients with oHCM.²² As these drugs are gradually entering in our treatment tools, given their hepatic metabolism, it is essential to clarify its real-world applications. Notably, although international guidelines provide comprehensive recommendations on the use of mavacamten for oHCM, they offer limited guidance on managing AF and other supraventricular arrhythmias in this context. The scope of this paper is to equip clinicians with practical guidance on the use of mavacamten, particularly in navigating drug–drug interactions with antiarrhythmic medications and anticoagulants. It aims to provide a detailed framework for safely managing arrhythmias and prevention of stroke in patients receiving myosin inhibitor therapy.

Mavacamten: First-in-Class Cardiac Myosin Inhibitor

Mavacamten is a selective, allosteric, and reversible small-molecule cardiac myosin inhibitor, representing the first disease-specific treatment for oHCM that targets the core pathophysiological mechanism of the condition and has the ability to shift the overall myosin population toward an energy-sparing, recruitable, super-relaxed state, reducing the excessive myocardial force of contraction and consumption of adenosine triphosphate (ATP) by myosin.²³

Mavacamten is the first-in-class oral inhibitor of cardiac myosin approved for the treatment of symptomatic oHCM. It is available in capsules containing 2.5 (light purple cap), 5 (yellow cap), 10 (pink cap), or 15 (gray cap) mg. The Food and Drug Administration (FDA) and the European Medicines Agency (EMA) approved mavacamten for the treatment of symptomatic oHCM (New York Heart Association [NYHA] class II or III) in adult patients in 2022 and 2023, respectively.²⁴ In 2023, the National Institute for Health and Clinical Excellence (NICE) and the Medicines and Healthcare Products Regulatory Agency granted mavacamten a marketing license in England, Wales, and Northern Ireland, and the Scottish Medicines Consortium recommendation echoes that of NICE in April 2024. Importantly, mavacamten is recommended only if it is an add-on to individually optimized standard care including beta blockers, nondihydropyridine calcium channel blockers, or disopyramide, unless these are contraindicated.²⁵

In clinical trials,^{26,27} mavacamten yielded a sustained reduction in LVOT gradients, improved exercise capacity and ventilatory efficiency, and was associated with a

marked improvement in NYHA functional class and Kansas City Cardiomyopathy Questionnaire.²⁷ In addition, it lessened the need for stereotactic radiation therapy (SRT), decreased levels of N-terminal pro-B-type-natriuretic peptide (NT-proBNP) and hs-cTnI and was associated with reduction in left ventricular mass index,²⁸ improved indices of diastolic function,²⁹ and long-term favorable cardiac remodeling.²² Although mavacamten can lower left ventricular ejection fraction (LVEF), raising the risk of systolic dysfunction, the EXPLORER-HCM (Mavacamten for Treatment of Symptomatic Obstructive Hypertrophic Cardiomyopathy) study observed this effect to be rare, generally not associated with occurrence of cardiac events, and fully reversible. At baseline, the average resting LVEF was 74% in both the mavacamten and placebo groups. Over 30 weeks, the mavacamten group experienced an average LVEF reduction of 4% (95% confidence interval [CI] -5.3 to -2.5), whereas the placebo group saw no change (95% CI -1.2 to 1.0). By week 38, after mavacamten was paused for 8 weeks, the average LVEF in both groups had returned to baseline levels. Long-term extension studies³⁰⁻³² evaluating the long-term efficacy and safety of mavacamten showed clinically important and durable improvements in LVOT gradients, with no new safety signals observed.

Notably, in MAVA-LTE (A Long-Term Safety Extension Study of Mavacamten in Adults Who Have Completed EXPLORER-HCM) study, more than 739 patient-years of exposure, 20 patients (8.7%) experienced 22 transient reductions in LVEF to below 50%, with an exposure-adjusted incidence of 2.77 per 100 patient-years. These LVEF reductions led to temporary treatment interruptions, but all patients recovered LVEF to $\geq 50\%$. Of the total cohort, 5 patients (2.2%) died during the study, but none of these deaths was considered to be related to treatment with mavacamten.³³

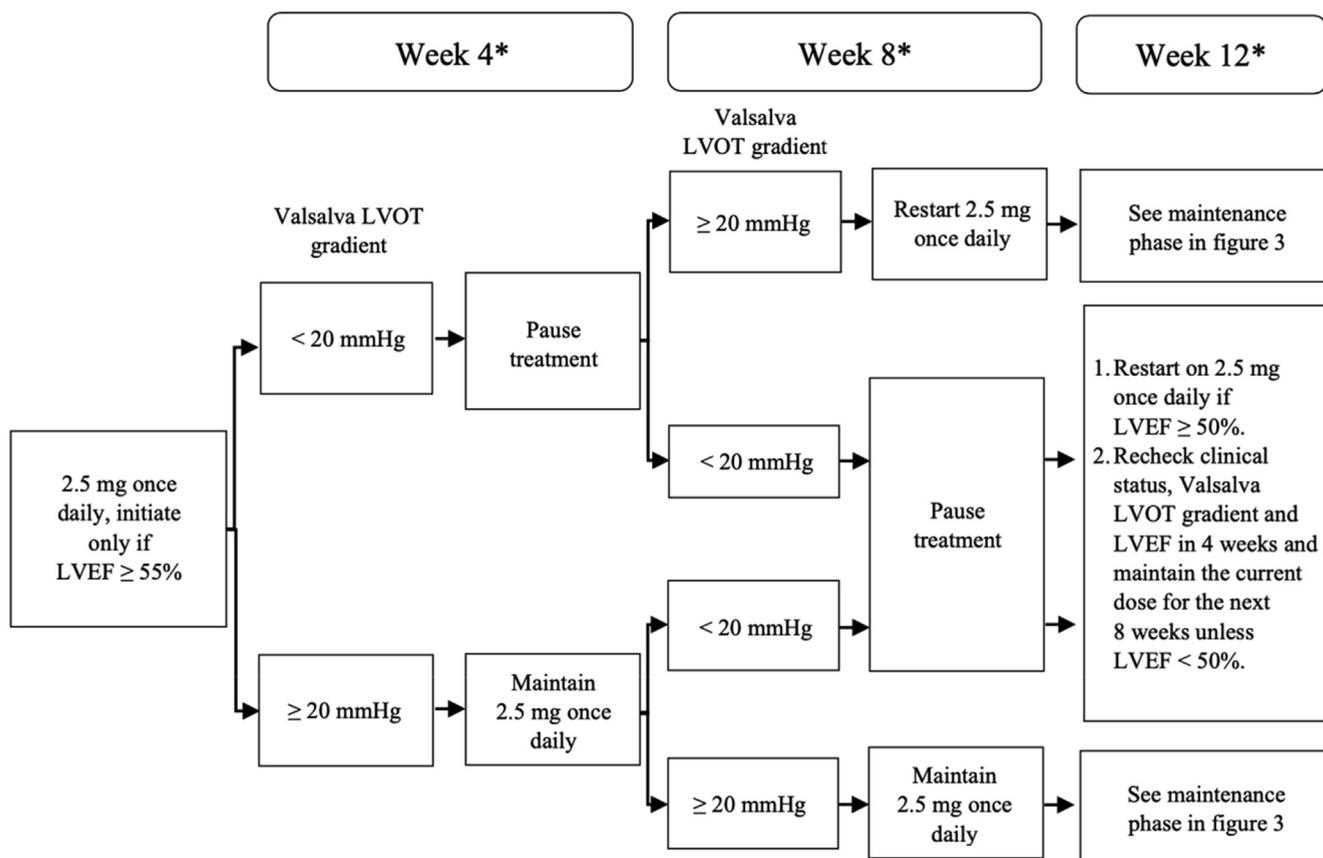
The 2023 European Society of Cardiology (ESC) guidelines for the management of cardiomyopathies recommend mavacamten (titrated to maximum tolerated dose under echocardiographic surveillance of LVEF) as an add-on therapy to beta blockers or calcium channel blockers (CCBs) in patients with symptomatic oHCM (Class IIa, Level A).³⁴ It is also recommended as monotherapy in patients who are intolerant or have contraindications to beta blockers, CCBs, or disopyramide (Class IIa, Level B), with the goal of improving symptoms in those unresponsive to first-line therapies.

The 2024 AHA/ACC/AMSSM/HRS/PACES/SCMR guideline for the management of HCM similarly recommend mavacamten for symptomatic patients with oHCM and left ventricular outflow tract obstruction (LVOTO) despite beta blocker or CCB treatment as a Class I, Level B indication.³⁵ In this document, mavacamten is one of several class I treatment options, along with disopyramide or septal reduction therapy, offering a more flexible approach to treatment escalation. However, neither set of guidelines offers clear, detailed guidance on managing AF in patients receiving myosin inhibitors, an increasingly relevant issue as these therapies become more common in clinical practice.

EMA Assessment and REMS Program

The EMA Committee for Medicinal Products for Human Use (CHMP) issued a positive opinion on April 26, 2023, this being the first European Union (EU) approval of a cardiac myosin inhibitor.²⁴ Mavacamten appeared to be generally well tolerated, with dizziness and dyspnea as most common reported adverse events. Although based on the clinical trial data, the current safety profile of mavacamten does not suggest any safety concerns, a detrimental effect on cardiovascular function or safety could not be excluded and therefore remains of concern. Mavacamten is contraindicated during pregnancy, and women of childbearing age must use effective contraception during treatment with mavacamten and for 6 months (5 half-lives in CYP2C19 poor metabolizers) following discontinuation. Clinical data on mavacamten overdose are scant, but it is known to precipitate systolic dysfunction and, in severe cases, cardiogenic shock. Management includes stopping mavacamten, supportive medical measures to maintain hemodynamic stability, monitoring vital signs and LVEF, and considering activated charcoal early to reduce absorption, despite specific studies on its effectiveness remains to be established.

Notably, as mavacamten is mainly metabolized by CYP2C19, and elimination half-life strongly depends on the CYP2C19 phenotype, this is the first cardiovascular medicinal product for which the European summary of product characteristics states that patients should be CYP genotyped to determine the appropriate dose. Given the associated risk of HF because of systolic dysfunction, echocardiographic evaluation of LVEF is mandatory before and during treatment with mavacamten, with algorithms for initiation and maintenance for appropriate dosing and rigorous safety monitoring (Figures 1, 2, and 3). The initiation of mavacamten in individuals with an LVEF below 55% is not advised. Should the LVEF fall below 50% during any assessment, or should the patient demonstrate symptoms of heart failure or a deteriorating clinical condition, administration of mavacamten should be paused (Figure 4). Furthermore, concurrent use of mavacamten with certain cytochrome P450 inhibitors, or the discontinuation of specific cytochrome P450 inducers, increases the risk of systolic dysfunction. Therefore, mavacamten is contraindicated in conjunction with moderate to strong CYP2C19 inhibitors or potent CYP3A4 inhibitors, as well as with moderate to robust CYP2C19 or CYP3A4 inducers (Table 1). Managing antiarrhythmic drugs (AADs) and oral anticoagulation warrant special attention in patients with oHCM on mavacamten (Figures 5 and 6).⁶⁻¹⁰ The implementation of CYP2C19 testing will likely progress in tandem with reimbursement pathways. In many EU countries, mavacamten is already available and reimbursed for patients with oHCM, promoting the adoption of genotyping practices. However, in regions in which reimbursement is still pending, this process may take longer. Until these frameworks are in place, compassionate-use programs can provide access to patients with precise indications, ensuring treatment continuity.



* Interrupt treatment if LVEF is < 50% at any clinical visit; restart treatment after 4 weeks if LVEF ≥ 50% (see figure 4).

LVEF = left ventricular ejection fraction; LVOT = left ventricular outflow tract

Figure 1

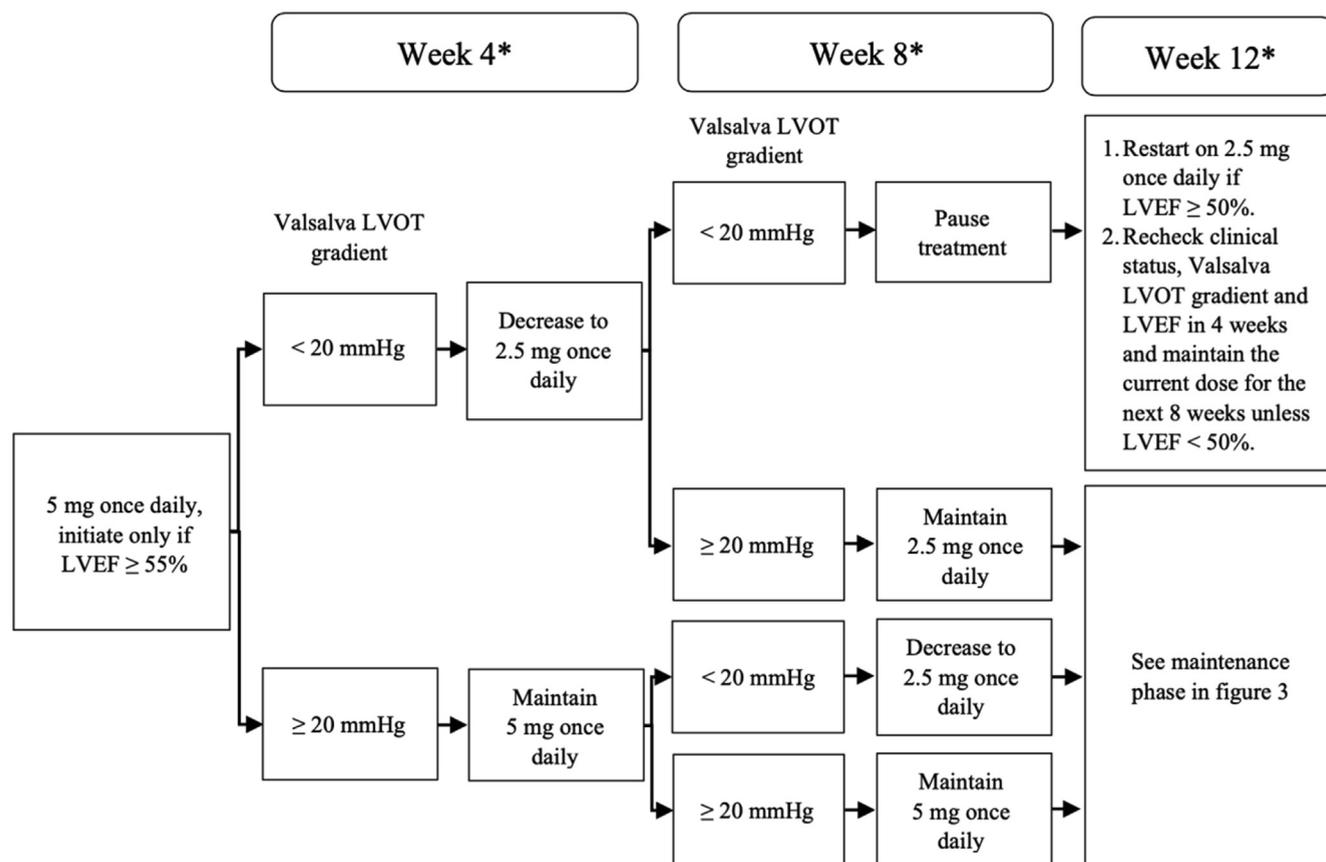
Treatment initiation of mavacamten in CYP2C19 poor metabolizer phenotype in European Medicines Agency prescribing information.³⁶

In the United States, mavacamten is currently supplied through the Risk Evaluation and Mitigation Strategy (REMS) program, which is designed to monitor patients periodically with echocardiograms for early detection of systolic dysfunction and to screen for drug interactions before each prescription fill, with no need for CYP genotyping.²² REMS requires the health care provider and pharmacist to undergo educational programs, including counseling patients on the risk of HF, assessing the patient's cardiovascular status, and obtaining echocardiograms at specific times after starting the drug. It also provides a guide for patients who should be screened for potential drug–drug interactions and undergo an echocardiogram before enrolling in the REMS program. As mavacamten may cause profound decreases in LVEF, regular monitoring for clinical symptoms of HF and systolic dysfunction is recommended, including echocardiographic assessments at 4, 8, and 12 weeks (initiation phase, Figure 2) after initiating mavacamten treatment and every 12 weeks thereafter (maintenance phase, Figure 3). For patients with LVEF < 50% at any time during mavacamten treatment, temporary or permanent treatment discontinuation is warranted (Figure 4).

Pharmacokinetics of Mavacamten

Human cytochrome P450 enzymes (CYP450) possess an exceptionally broad substrate specificity, enabling them to metabolize a vast array of chemically diverse compounds.³⁹ This capacity is often facilitated by their ability to bind multiple substrate molecules simultaneously. CYP3A4 is particularly notable in this regard, as it metabolizes more than 40% of drugs currently on the market, making it a critical site for drug–drug interactions. These interactions, which can either inhibit or activate metabolic processes, are essential considerations in clinical pharmacology because they may provoke significant physiological responses, sometimes even dangerous ones.³⁹ At present, the literature reports 472 documented interactions, primarily involving antibiotics, antifungal medications, and neurologic drugs as well as well-known inducers and inhibitors of common cytochromes.

In management of HCM, understanding and managing these interactions is crucial because of their potential impact on treatment efficacy and patient safety. The complexity increases as patients with HCM often require concomitant medication regimens, including anticoagulants and AADs, which elevates the risk of adverse drug interactions. These



* Interrupt treatment if LVEF is $< 50\%$ at any clinical visit; restart treatment after 4 weeks if LVEF $\geq 50\%$ (see figure 4).

LVEF = left ventricular ejection fraction; LVOT = left ventricular outflow tract

Figure 2

Treatment initiation of mavacamten in CYP2C19 intermediate, normal, rapid and ultrarapid metabolizer phenotype in prescribing information.³⁶

interactions can lead to diminished therapeutic efficacy, heightened toxicity, or new adverse effects, all of which demand vigilant management to safeguard patient outcomes.

Mavacamten is extensively metabolized in the liver by cytochrome P450 enzymes, predominantly CYP2C19 (74%), CYP3A4 (18%), and—to a lesser extent—CYP2C9 (8%).³⁸ At therapeutic levels, mavacamten does not inhibit key enzymes such as CYP2D6, CYP2C9, CYP2C19, or CYP3A4 in vitro, yet it acts as an inducer for CYP2B6. The terminal half-life of mavacamten is contingent upon the CYP2C19 metabolic phenotype, spanning from 6 to 23 days. Accordingly, coadministered medications that either inhibit or induce these enzymes significantly influence mavacamten pharmacokinetics, thereby altering its systemic exposure.²⁴

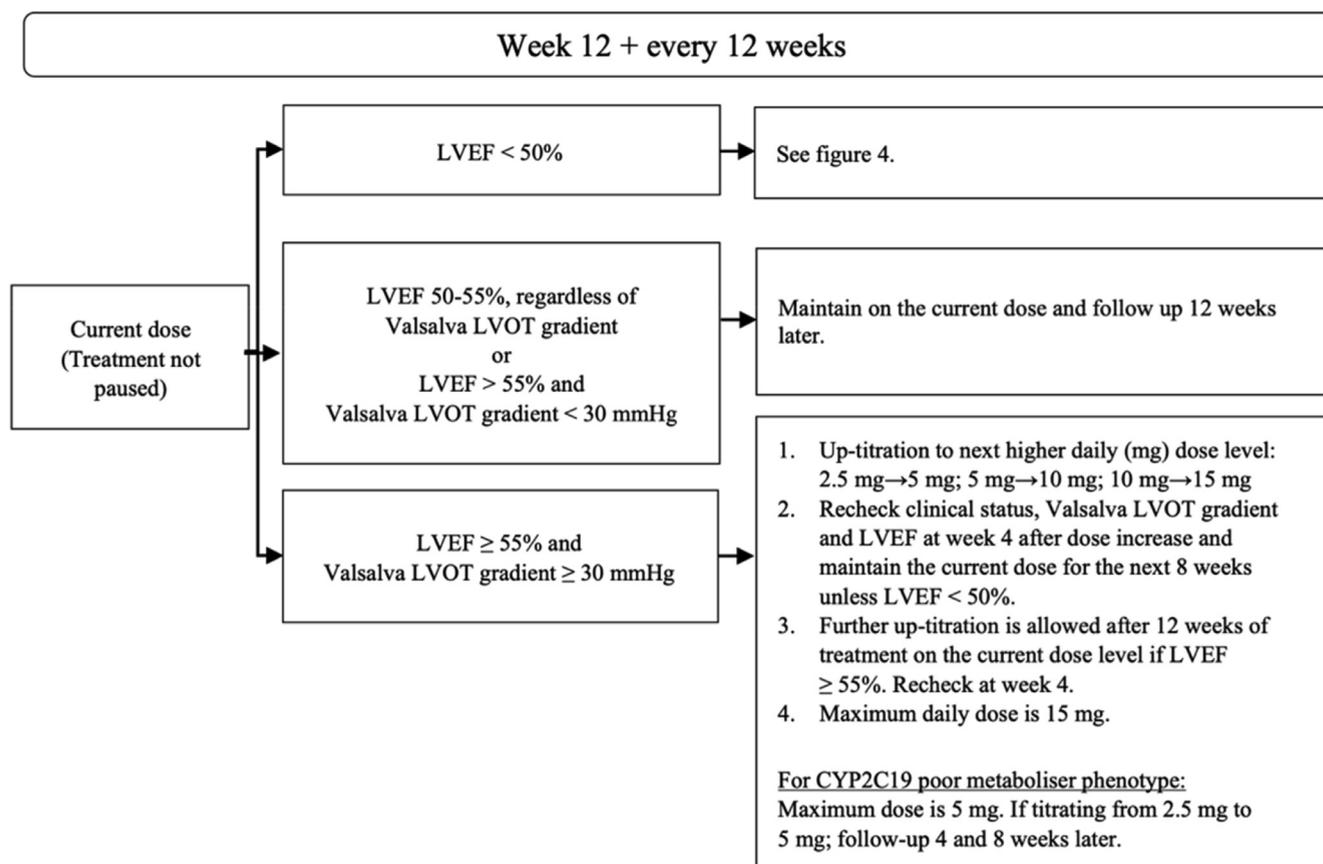
Given these characteristics, dose adjustments, and careful monitoring are paramount when mavacamten is used with cytochrome P450 modulators. For example, coadministration with strong CYP2C19 inhibitors, such as fluvoxamine, ketocazole or omeprazole, necessitates vigilance because of increased mavacamten plasma levels that may elevate the risk of HF from systolic dysfunction.²² Conversely,

concomitant use of inducers such as rifampin—a CYP2C19 and CYP3A4 inducer—could accelerate mavacamten metabolism, potentially leading to subtherapeutic effects.

In light of this, the CYP2C19 genotype plays a critical role in determining the starting dose of mavacamten, especially in populations with a high prevalence of poor metabolizers, such as those of Oceanian and Asian descent⁴⁰ (Figure 7). Patients with 2 loss-of-function alleles (eg, $*2/*2$, $*2/*3$, $*3/*3$) exhibit a poor metabolizer phenotype, necessitating a starting dose adjustment to 2.5 mg with a cap of 5 mg to mitigate heightened exposure. For patients with unknown phenotype awaiting genotyping, uptitration above 5 mg can only be done once the genotyping results have ruled out the poor metabolizer phenotype. Starting dose is 5 mg for the other phenotypes.²⁴

Phenoconversion

It is important for prescribers to be well versed in the concept of phenoconversion, an overlooked phenomenon that occurs when a patient's genetically predicted drug metabolism does not align with their actual capacity.⁴¹ Studies have shown that



LVEF = left ventricular ejection fraction; LVOT = left ventricular outflow tract

Figure 3

Mavacamten maintenance phase in European Medicines Agency prescribing information.³⁶

only 40% of patients exhibit concordance between their CYP2C19 genotype and phenotype, indicating that, in most cases, genetic testing alone is insufficient to accurately predict drug metabolism. Phenoconversion is frequently triggered by drug–drug interactions, but it can also result from various clinical factors such as liver disease, diabetes, cancer, advanced age, and systemic inflammation. Therefore, even though patients' pharmacogenetic test results indicate that they are CYP2C19 normal metabolizers, their CYP2C19 phenotype may actually be an intermediate or poor CYP2C19 metabolizer. In the context of mavacamten therapy, phenoconversion can lead to elevated drug exposure and an increased risk of adverse outcomes, such as systolic dysfunction. This underscores the necessity for personalized dosing adjustments and vigilant patient monitoring. Given that phenoconversion may occur in up to 60% of patients,⁴² clinicians must account for both pharmacogenetic testing and clinical factors to optimize treatment safety and efficacy.

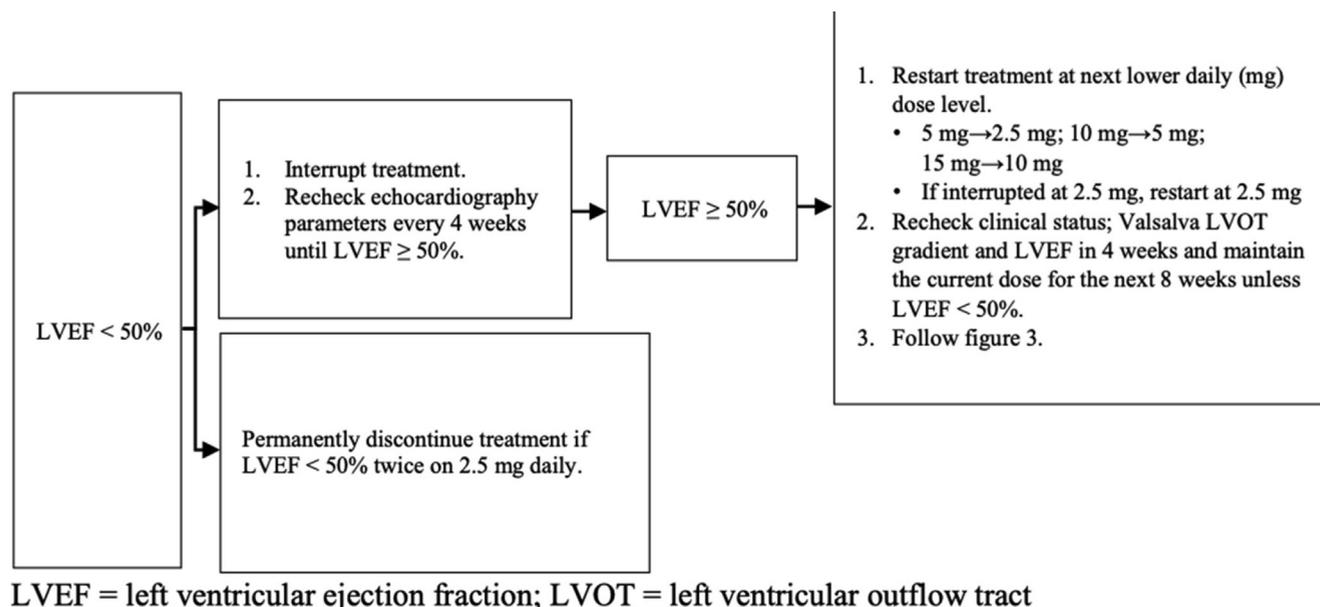
Drug–Drug Interactions

The coadministration of mavacamten with moderate to strong CYP3A4 inhibitors requires caution because of potential increases in drug exposure. For patients on such treatments, including verapamil and diltiazem, dose adjustments and

enhanced monitoring of LVEF and other clinical parameters are essential. Although mavacamten concentration can be therefore modified by inducers or inhibitors of CYP3A4 and CYP2C19, current data indicate that mavacamten is not able to indirectly modify the concentrations of currently available antiarrhythmic drugs or anticoagulants (Figures 5 and 6).

Mavacamten is an inducer of CYP3A4, CYP2C9, and CYP2C19, so its potential to modulate the effect of other drugs metabolized by these pathways must be considered in clinical practice. US FDA label recommended closer monitoring when mavacamten is used in combination with CYP3A4, CYP2C19, and CYP2C9 substrates. This is the case for midazolam and hormonal contraceptives, which are both CYP3A4 substrates, leading to a decrease in drug exposure and activity. Patients should therefore be advised to use alternative contraceptive methods that are not affected by CYP450 enzyme induction (eg, intrauterine system) or add nonhormonal contraception during concomitant use and for 4 months after the last dose of mavacamten.

In this context, the use of mavacamten exemplifies the critical intersection of pharmacokinetics and personalized medicine, in which therapeutic efficacy and patient safety are closely interlinked with the genetic and metabolic profile of the individual. Table 2 and Table 3 offer guidance for adjusting mavacamten dosing in response to interactions

**Figure 4**

Mavacamten treatment interruption at any clinic visit if LVEF < 50% in European Medicines Agency³⁶ and US³⁷ prescribing information. Dose modification with concomitant drugs. For concomitant treatment with inhibitors and inducers of CYP2C19 or CYP3A4, follow the steps in Tables 2 and 3.

with drugs affecting CYP2C19 or CYP3A4 enzymes based on the patient's CYP2C19 phenotype. They outline how to modify doses or enhance monitoring when starting, stopping, or changing doses of these drugs, ensuring personalized and safe management of mavacamten therapy. The EMA and FDA labels for mavacamten have somewhat different recommendations for managing drug-drug and drug-gene interactions with mavacamten, and thus the application of these recommendations will depend on the prescribers' location.

Notably, EMA gives different recommendations when dealing with strong CYP2C19 inhibitors than FDA. Although FDA contraindicates their use, EMA supports genotyping and eventually decreasing the dose of mavacamten. The effect of moderate and strong CYP2C19 inhibitor on the pharmacokinetics of mavacamten has never been investigated in a clinical drug-drug interaction study. The effect of a strong CYP2C19 inhibitor should be similar to the effect of the CYP2C19 poor metabolizing status. From literature, coadministration of mavacamten with a weak CYP2C19 inhibitor

Table 1 Summary of established and potentially significant drug-drug interactions with mavacamten in FDA prescribing information³⁷

Moderate to strong CYP2C19 inhibitors or strong CYP3A4 inhibitors	
Clinical impact	Concomitant use with a moderate to strong CYP2C19 or a strong CYP3A4 inhibitor increases mavacamten exposure, which may increase the risk of heart failure caused by systolic dysfunction.
Prevention or management	Concomitant use with a moderate to strong CYP2C19 inhibitor or a strong CYP3A4 inhibitor is contraindicated.
Moderate to strong CYP2C19 inducers or moderate to strong CYP3A4 inducers	
Clinical impact	Concomitant use with a moderate to strong CYP2C19 inducer or a moderate to strong CYP3A4 inducer decreases mavacamten exposure, which may reduce mavacamten efficacy. The risk of heart failure caused by systolic dysfunction may increase after discontinuation of these inducers as the levels of the induced enzyme normalizes.
Prevention or management	Concomitant use of a moderate to strong CYP2C19 inducer or a moderate to strong CYP3A4 inducer is contraindicated.
Weak CYP2C19 inhibitors or moderate CYP3A4 inhibitors	
Clinical impact	Concomitant use with a weak CYP2C19 inhibitor or a moderate CYP3A4 inhibitor increases mavacamten exposure, which may increase the risk of adverse drug reactions.
Prevention or management	Initiate mavacamten at the recommended starting dosage of 5 mg orally once daily in patients who are on stable therapy with a weak CYP2C19 inhibitor or a moderate CYP3A4 inhibitor. Reduce dose of mavacamten by 1 level (ie. 15 to 10 mg, 10 to 5 mg, or 5 to 2.5 mg) in patients who are on mavacamten treatment and intend to initiate a weak CYP2C19 inhibitor or a moderate CYP3A4 inhibitor. Avoid initiation of concomitant weak CYP2C19 and moderate CYP3A4 inhibitors in patients who are on stable treatment with 2.5 mg of mavacamten because a lower dose is not available.

ANTI-ARRHYTHMIC DRUGS	CLASS IA	CLASS IB	CLASS IC**
<p>MAVACAMTEN is metabolized by CYP2C19 and CYP3A4</p> <p>Any CYP3A4 or CYP2C19 inhibitor can increase the risk of heart failure due to systolic dysfunction</p> <p>Any CYP3A4 or CYP2C19 inducer can cause a loss in therapeutic effect of mavacamten</p>	<p>Disopyramide* Hepatic metabolism via CYP3A4</p> <p>Procainamide Hepatic and renal metabolism via N-acetylprocainamide acetylation</p> <p>Quinidine Hepatic metabolism (90%) via CYP3A4 and renal (10%)</p>	<p>Mexiletine Hepatic metabolism via CYP2D6 and CYP1A2</p> <p>Lidocaine Hepatic via CYP3A4</p>	<p>Flecainide Hepatic metabolism via CYP2D6</p> <p>Propafenone Hepatic metabolism via CYP3A4, CYP1A2, CYP2D6</p>
	Monitor QTc Active surveillance	Considered safe	Monitor QRS duration Consider therapy modification
CLASS ID	CLASS II	CLASS III	CLASS IV
<p>Ranolazine* 95% is metabolized by CYP3A4 enzymes and by CYP2D6 5% is excreted renally unchanged</p> <p>Weak inhibitor of CYP3A4</p>	<p>Metoprolol Hepatic metabolism via CYP2D6</p> <p>Propranolol Hepatic metabolism via CYP2D6</p> <p>Esmolol Metabolized by RBCs esterases</p> <p>Nadolol No hepatic metabolism: renal excretion without modifications</p>	<p>Amiodarone Hepatic metabolism via CYP1A2, CYP2C9, CYP2D6, CYP3A4 Moderate inhibitor of CYP3A4, CYP2D6</p> <p>Dronedarone Hepatic metabolism via CYP3A4 Moderate inhibitor of CYP3A4, CYP2D6 Potent inhibitor of P-glycoprotein</p> <p>Sotalol Renal metabolism (90%)</p> <p>Ibutilide and Dofetilide Hepatic metabolism</p>	<p>Verapamil* Hepatic metabolism via CYP3A4, CYP3A5, CYP2C8</p> <p>Diltiazem* Hepatic metabolism via CYP3A4</p> <p>Moderate CYP3A4 inhibitors</p>
Monitor QTc Active surveillance	Considered safe	Monitor QTc Active surveillance	Active surveillance

Figure 5

Antiarrhythmic drugs. Drug interactions identified. Routine monitoring is recommended, but no specific precautions are needed. Green: Medications are considered safe for use with mavacamten, with no significant drug–drug interactions identified. Routine monitoring is recommended, but no specific precautions are needed. Orange: Medications require caution and active monitoring because of potential interactions with mavacamten. Dose adjustments or therapy modifications may be necessary based on individual patient response. For these drugs, European and American regulatory agencies provide varying recommendations, meaning that clinical judgment and evolving evidence are essential when determining the appropriate approach. Red: Medications carry a high risk of serious interactions with mavacamten, potentially leading to serious adverse effects. Close monitoring and frequent reassessment of cardiac conduction are required. In many cases, alternative treatments or significant therapy modifications may be necessary. *Patients on background dual treatment with beta blocker and calcium channel blocker treatment or disopyramide or ranolazine were excluded from the EXPLORER-HCM trial but included in the VALOR-HCM trial. The Food and Drug Administration (FDA) and European Medicines Agency (EMA) provide different guidance on the concomitant use of mavacamten with disopyramide, ranolazine, verapamil with a beta blocker, or diltiazem with a beta blocker. The EMA notes that the safety of using mavacamten in combination with disopyramide, ranolazine, verapamil with a beta blocker, or diltiazem with a beta blocker has not been established. Although it does not prohibit the combination, it emphasizes the need for close monitoring when these medications are used together because of potential safety concerns, particularly related to their combined negative inotropic effects. The FDA takes a more cautious approach, recommending preferably avoiding the use of mavacamten with disopyramide, ranolazine, verapamil with a beta blocker, or diltiazem with a beta blocker. The FDA highlights the additive negative inotropic effects, which increase the risk of left ventricular systolic dysfunction and worsening heart failure symptoms. Because of these risks and limited clinical experience with this combination, the FDA advises against using them together. **Flecainide or propafenone are not generally recommended in the absence of an implantable cardioverter defibrillator because of concerns with proarrhythmic effects and hemodynamic deterioration and conversion to atrial fibrillation/flutter with rapid ventricular conduction.³⁸

resulted in a 48% increase in mavacamten area under the curve (AUC)_{inf} with no effect on C_{max} in CYP2C19 normal metabolisers (see Table 2 for further indications).

Mavacamten and AADs

Mavacamten works by inhibiting the activity of myosin, a protein involved in muscle contraction. When considering the interactions of mavacamten with AADs, it is important to note that, based on scattered data present in the literature, mavacamten does not have significant interactions with several drugs commonly used in the treatment of arrhythmias. Figure 5 summarizes essential pharmacokinetics

aspects and drug–drug interaction of AADs in patients treated with mavacamten. In the text, for the purposes of flow, we summarize the literature with Class II and Class IV agents, as these are first-line agents in oHCM, followed by Class I and Class III agents, selected specifically for maintaining sinus rhythm.

Class II

Beta blockers remain first-line agents for managing oHCM. There are no reported metabolic interactions between mavacamten and beta blockers. Caution is advised in those with sinus bradycardia or conduction system disease.

ANTICOAGULANTS	PARENTERAL ANTICOAGULANTS	VKA	DIRECT FACTOR XIa INHIBITORS
<p>MAVACAMTEN is metabolized by CYP2C19 and CYP3A4</p> <ul style="list-style-type: none"> Any CYP3A4 or CYP2C19 inhibitor can increase the risk of heart failure due to systolic dysfunction Any CYP3A4 or CYP2C19 inducer can cause a loss in therapeutic effect of mavacamten <p>Available literature shows no CYP-related interactions with parenteral and oral anticoagulants</p> <p>Evidence is lacking for some drugs</p>	<p>LMWH Metabolized by desulfation and depolymerization Half-Life: 3-6 hrs</p> <p>UFH Metabolized by desulfation and depolymerization Half-Life: 30-150 minutes</p> <p>Fondaparinux Renally excreted unmodified Half-Life: 17-21 hrs</p> <p>Bivalirudine Metabolized by proteolytic cleavage Half-Life: 25 minutes</p> <p>Argatroban* Metabolized by CYP3A4, CYP3A5 Half-Life: 45 minutes</p> <p>Lepirudine Renal metabolism Half-Life: 10 minutes</p>	<p>Warfarin Metabolized by CYP2C9, CYP1A2, CYP3A4 Half Life: 36-42 hrs</p> <p>Acenocoumarol Metabolized by CYP2C9, CYP2C19, CYP3A4 Half-Life: 8-11 hrs</p>	<p>Asundexian Metabolized via carboxylesterase 1 and via CYP3A4</p> <p>Milvexian Metabolized by CYP3A4, and CYP3A5</p>
	Considered safe	Considered safe*	Active surveillance
APIXABAN	EDOXYBAN	RIVAROXABAN	DABIGATRAN
<p>Target: factor Xa</p> <p>Metabolized by CYP3A4, CYP2J2</p> <p>Drug interaction with strong CYP3A4 inhibitor</p> <p>Drug interaction with inducer and strong inhibitor of P-glycoprotein</p> <p>Half-Life: 9-14 hrs</p>	<p>Target: factor Xa</p> <p>Metabolized by CYP3A4</p> <p>Drug interaction with strong CYP3A4 inhibitor</p> <p>Drug interaction with inducer and strong inhibitor of P-glycoprotein</p> <p>Half-Life: 9-11 hrs</p>	<p>Target: factor Xa</p> <p>Metabolized by CYP3A4, CYP2J2</p> <p>Drug interaction with strong CYP3A4 inhibitor</p> <p>Drug interaction with inducer and strong inhibitor of P-glycoprotein</p> <p>Half-Life: 5-13 hrs</p>	<p>Target: factor IIa</p> <p>Metabolized by conjugation with P-glycoprotein</p> <p>Dabigatran etexilate, a precursor, is metabolized by cytochrome oxidase P450</p> <p>Drug interaction with strong inhibitor/inducer of P-glycoprotein</p> <p>Half-Life: 12-17 hrs</p>
Considered safe*	Considered safe*	Considered safe*	Considered safe

Figure 6

Parenteral and oral anticoagulants. Green: Medications are considered safe for use with mavacamten, with no significant drug–drug interactions identified. Routine monitoring is recommended, but no specific precautions are needed. Regulatory agencies may provide varying recommendations, meaning that clinical judgment and evolving evidence are essential when determining the appropriate approach. Orange: Medications require caution and active monitoring because of potential interactions with mavacamten. Dose adjustments or therapy modifications may be necessary based on individual patient response. Red: Medications carry a high risk of serious interactions with mavacamten, potentially leading to serious adverse effects. Close monitoring and frequent reassessment of cardiac conduction are required. In many cases, alternative treatments or significant therapy modifications may be necessary. *European and American regulatory agencies provide varying recommendations, meaning that clinical judgment and evolving evidence are essential when determining the appropriate approach. The FDA and EMA have differing perspectives on the interaction between mavacamten and CYP3A4 substrates such as apixaban, rivaroxaban, and edoxaban. The FDA highlights that mavacamten can induce the metabolism of CYP3A4, CYP2C19, or CYP2C9 substrates, potentially lowering their plasma concentrations, which may reduce their effectiveness. As a result, the FDA recommends close monitoring when these drugs are used together to ensure therapeutic efficacy is maintained. The EMA, however, considers the interaction less significant, noting only a modest reduction in concentrations of CYP3A4 substrates, such as midazolam, which they do not see as clinically significant, and thus does not emphasize monitoring.

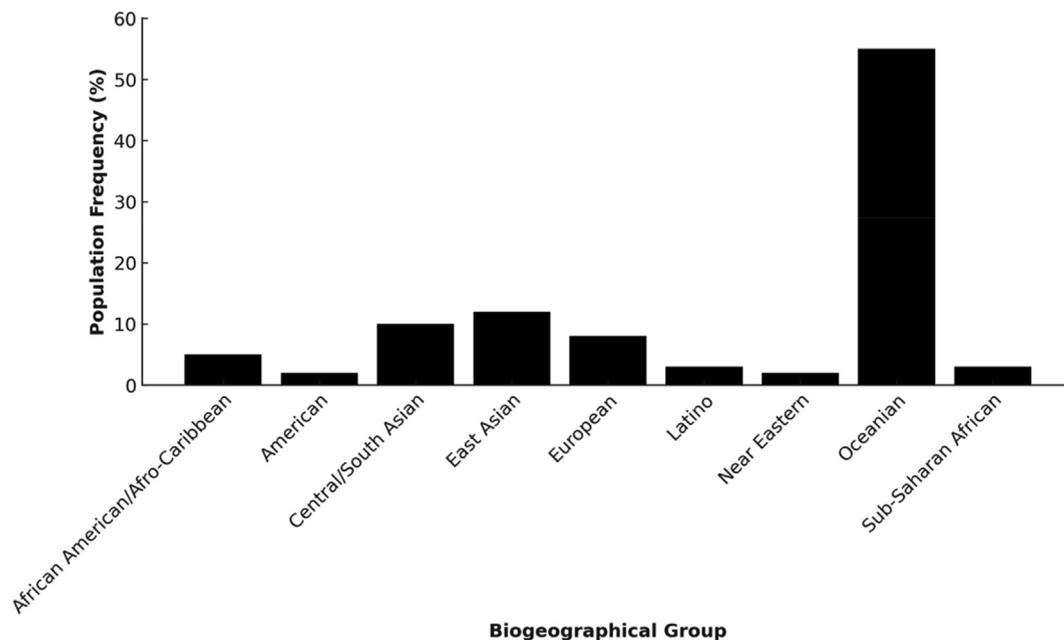
Class IV

Verapamil, a moderate inhibitor of CYP3A4 and CYP2C19, can increase the plasma levels of drugs metabolized by these pathways, including mavacamten. In a phase 1 study,⁴³ participants were randomized to receive either mavacamten alone or mavacamten with verapamil to assess pharmacokinetic interactions. Mavacamten was generally well tolerated in both groups, with only mild adverse events reported, except for 1 moderate case of presyncope in the combination group. No serious adverse events or laboratory abnormalities were noted. The findings confirmed that CYP3A4 plays a minor role in mavacamten metabolism, suggesting a low likelihood of significant drug–drug interactions between mavacamten and verapamil. However, because of individual variability in CYP2C19 activity, dose adjustments of mavacamten may be required when coadministered

with CYP3A4 inhibitors. In addition, caution is advised when combining mavacamten with beta blockers or nondihydropyridine calcium channel blockers, especially in older patients or those with conduction system disease, because of the increased risk of bradycardia, heart block, or hypotension.

Class I

Disopyramide (Class IA) and mavacamten should be used with caution because of the potential for additive effects on the QT interval. Class IB drugs, such as mexiletine and lidocaine, are considered safe. Class IC AADs can be considered safe because there are no reported metabolic interactions between mavacamten and these drugs. However, flecainide and propafenone are generally avoided because of concerns with proarrhythmic effects and hemodynamic deterioration

**Figure 7**

Frequencies of CYP2C19 poor metabolizer and likely poor metabolizer phenotypes in different biogeographical groups.

because of conversion to AF or atrial flutter with rapid ventricular conduction.⁴⁴ Ranolazine was developed as an antianginal agent and used to treat microvascular obstruction, but experimental and clinical studies have shown that it also has antiarrhythmic properties based on the frequency-dependent blockade of peak sodium channel current and rapidly activating delayed rectifier potassium current in the atria and blockade of late phase of the inward sodium current in the ventricles. For this reason, ranolazine is currently classified as a Class ID AAD.⁴⁵ In a small prospective trial, ranolazine reduced the arrhythmic burden and improved biomarker profile in patients with HCM.⁴⁶ Ranolazine is extensively metabolized by CYP3A enzymes and, to a lesser extent, by CYP2D6, with approximately 5% excreted renally unchanged. Ranolazine is a weak inhibitor of CYP3A4⁴⁷ and generally does not require dose adjustment of mavacamten.

Class III

Class III AADs such as amiodarone and dronedarone should be used with caution, as these are both moderate inhibitors of the CYP3A4 enzyme. The concurrent administration of amiodarone and mavacamten for managing AF in patients with oHCM could lead to increase in mavacamten half-life and effect on myocardial function, potentially exacerbating hypotension and depression of myocardial contractility. Amiodarone-related hypotension is caused by both vasodilation and myocardial depression, possibly induced by molecules used to dilute the drug in standard preparations.⁴⁸

It is therefore advised to reduce the dose of mavacamten if starting with amiodarone (Figure 5 and Tables 1 and 2). Health care professionals should review a patient's medication history thoroughly, assess potential interactions, and consider individual patient factors before initiating or adjusting drug

therapy. Regular monitoring and communication with patients are essential to ensure the safety and efficacy of the prescribed medications. Dofetilide and ibutilide are 2 similar drugs used to treat AF and atrial flutter. Their metabolism is primarily hepatic, with no known interactions with CYP metabolism of mavacamten. Sotalol is a particular drug that combines beta-blocker properties with Class III channel blocker properties. Its metabolism is mostly renal (90%). Active surveillance on QTc is warranted. Overall, limited data exist to inform the safety and efficacy of using sotalol or dofetilide in patients with HCM.⁴⁹

Mavacamten and Anticoagulants

Vitamin K antagonists (VKAs) such as warfarin and acenocoumarol undergo hepatic metabolism predominantly through CYP2C9, complemented by CYP1A2 and CYP3A4 pathways. Warfarin metabolism renders it susceptible to interactions with drugs that modulate these cytochromes, which can significantly affect therapeutic efficacy and safety profiles. Acenocoumarol, similarly metabolized with additional involvement of CYP2C19, shares this susceptibility.

In the absence of specific data on mavacamten drug–drug interactions, particularly with VKAs, clinicians are advised to exercise rigorous surveillance. This is imperative, especially when concurrent therapy with CYP modulators is required. Given the profound consequences of altered anticoagulation states, health care professionals must remain vigilant for any indications of bleeding, such as spontaneous bruising, hematuria, or gastrointestinal bleeding, which could signify an excessive anticoagulant effect.

The ESC guidelines recommend universal oral anticoagulation for all patients with HCM and AF because of their consistently high stroke risk, regardless of the CHA₂DS₂-VA

Table 2 EMA guidance on mavacamten dose modifications/contraindications with concomitant drugs that are inhibitors of CYP2C19 or CYP3A4 or inducers of CYP2C19 or CYP3A4, based on patient's CYP2C19 phenotype status⁴⁴

Concomitant medicinal product	CYP2C19 poor metabolizer phenotype*	CYP2C19 intermediate, normal, rapid and ultra-rapid phenotype
Inhibitors		
Combined use of a strong CYP2C19 inhibitor and a strong CYP3A4 inhibitor	Contraindicated	Contraindicated
Strong CYP2C19 inhibitor (eg, fluvoxamine, ticlopidine, chloramphenicol, delavirdine, gemfibrozil, stiripentol, fluoxetine, imipramine, clomipramine, lansoprazole, isoniazide, zarflukast, tioconazole, miconazole)	No dose adjustment. If CYP2C19 phenotype has not yet been determined: no adjustment of the starting dose of 2.5 mg is needed. The dose should be reduced from 5 mg to 2.5 mg or pause treatment if on 2.5 mg.	Initiate mavacamten at a dose of 2.5 mg. The dose should be reduced from 15 mg to 5 mg and from 10 mg and 5 mg to 2.5 mg or pause treatment if on 2.5 mg.
Strong CYP3A4 inhibitor (eg, clarithromycin, itraconazole, posaconazole, ritonavir, darunavir, lopinavir, saquinavir, variconazole, loperamide, efavirenz)	Contraindicated	No dose adjustment
Moderate CYP2C19 inhibitor (eg, sertraline, efavirenz, armodafinil, cisapride, eslicarbazepine acetate, abiraterone)	No dose adjustment If CYP2C19 phenotype has not yet been determined: No adjustment of the starting dose of 2.5 mg is needed. The dose should be reduced from 5 mg to 2.5 mg or pause treatment if on 2.5 mg.	No adjustment of the starting dose of 5 mg is needed. The dose should be reduced by 1 dose level or pause treatment if on 2.5 mg.
Moderate CYP3A4 inhibitor (eg, erythromycin, fluconazole, miconazole, delavirdine, amprenavir, fosamprenavir, conivaptan) or Weak CYP3A4 inhibitor (eg, amlodipine, ranolazine, fluoxetine, dexamethasone acetate, tacrolimus, cimetidine, quinidine, citalopram, propofol, lomitapide, ticagrelor)	No adjustment of the starting dose of 2.5 mg is needed; if patients are receiving a 5-mg dose of mavacamten, their dose should be reduced to 2.5 mg	No dose adjustment
Inducers		
Discontinuing or decreasing the dose of strong CYP2C19 inducer and strong CYP3A4 inducer	The dose should be reduced from 5 mg to 2.5 mg or pause treatment if on 2.5 mg.	The dose should be reduced by 1 dose level when on doses 5 mg or higher when discontinuing or decreasing the dose of strong inducers while on mavacamten. No dose adjustment when on 2.5 mg.
Discontinuing or decreasing the dose of moderate or weak CYP3A4 inducer	Decrease mavacamten dose to 2.5 mg or pause treatment if on 2.5 mg.	No dose adjustment.

The table outlines how to adjust mavacamten doses or identify contraindications based on enzyme interactions, ensuring safe and effective treatment.

*Includes patients for whom the CYP2C19 phenotype has not yet been determined.

score.⁵⁰ On the other hand, the AHA/ACC guidelines similarly advise anticoagulation for all patients with HCM and AF but specifically recommend DOACs over VKAs, irrespective of the CHA₂DS₂-VASc score.⁹

DOACs are favored because of their comparable or reduced thromboembolic and bleeding risks compared with VKAs.⁵¹ These agents are substrates for both CYP3A4 and P-glycoprotein (P-gp)^{52,53}; thus, their coadministration with inducers of these proteins may decrease plasma concentrations, which warrants consideration of alternative treatments or enhanced monitoring for potential interactions.

In clinical practice, it is often necessary to coadminister mavacamten with parenteral or oral anticoagulants because of comorbid conditions such as AF.⁵⁴ Although mavacamten itself lacks anticoagulant properties, interactions with strong inducers and inhibitors of hepatic CYP3A4 and P-gp may influence the pharmacokinetics of the anticoagulants and alter their pharmacologic effect. Current literature shows no CYP-

related drug–drug interactions with mavacamten; however, active surveillance is advised, especially when concurrent treatment with CYP modulators is required.

Notably, mavacamten has no known interactions with DOACs, VKAs, or heparin, suggesting a lower risk for drug–drug interactions.⁵⁵ However, the FDA has issued a warning regarding the potential for increased concentrations of CYP3A4 substrates when used concurrently with mavacamten. The FDA and EMA differ in their views on the interaction between mavacamten and CYP3A4 substrates⁵⁶ including apixaban, rivaroxaban, and edoxaban. The FDA emphasizes that mavacamten can induce the metabolism of CYP3A4 substrates, potentially reducing their plasma concentrations and effectiveness, leading to the recommendation for close monitoring. In contrast, the EMA considers the interaction less significant, noting only a modest reduction in concentrations of CYP3A4 substrates such as midazolam, which they do not deem clinically significant, and thus they do not

Table 3 EMA guidance for dose modification or additional monitoring of patients initiating or discontinuing treatment with—or changing the dose of—concomitant drugs that are inhibitors of CYP2C19 or CYP3A4 or inducers of CYP2C19 or CYP3A4, based on patient's CYP2C19 phenotype status^a

Concomitant drugs	CYP2C19 poor metabolizer phenotype*	CYP2C19 intermediate, normal, rapid and ultra-rapid metabolizer phenotype
Inhibitors		
Combined use of a strong CYP2C19 inhibitor and a strong CYP3A4 inhibitor	Contraindicated	Contraindicated
Strong CYP2C19 inhibitors (eg, fluvoxamine, ticlopidine, chloramphenicol, delavirdine, gemfibrozil, stiripentol, fluoxetine, imipramine, clomipramine, lansoprazole, isionazide, zarfilukast, tioconazole, miconazole)	No dose adjustment. Monitor LVEF 4 weeks later, and then resume the patient's monitoring and titration schedule If CYP2C19 phenotype has not yet been determined: No adjustment of the starting dose of 2.5 mg is needed. The dose should be reduced from 5 mg to 2.5 mg or pause treatment if on 2.5 mg. Monitor LVEF 4 weeks later, and then resume the patient's monitoring and titration schedule.	Initiate mavacamten at a dose of 2.5 mg. The dose should be reduced from 15 mg to 5 mg and from 10 mg and 5 mg to 2.5 mg or pause treatment if on 2.5 mg. Monitor LVEF 4 weeks later and then resume the patient's monitoring and titration schedule.
Strong CYP3A4 inhibitors (eg, clarithromycin, itraconazole, posaconazole, ritonavir, darunavir, lopinavir, saquinavir, variconazole, loperamide, efavirenz)	Contraindicated	No dose adjustment Monitor LVEF 4 weeks later, and then resume the patient's monitoring and titration schedule.
Moderate CYP2C19 inhibitors (eg, sertraline, efavirenz, armodafinil, cisapride, eslicarbazepine acetate, abiraterone)	No dose adjustment. Monitor LVEF 4 weeks later, and then resume the patient's monitoring and titration schedule. Adjust mavacamten dose based on clinical assessment. If CYP2C19 phenotype has not yet been determined: No adjustment of the starting dose of 2.5 mg is needed. The dose should be reduced from 5 mg to 2.5 mg or pause treatment if on 2.5 mg. Monitor LVEF 4 weeks later, and then resume the patient's monitoring and titration schedule. Adjust mavacamten dose based on clinical assessment.	No adjustment of the starting dose of 5 mg is needed. Initiating or increasing the dose of a moderate inhibitor while on mavacamten treatment: Dose should be reduced by 1 dose level or pause treatment if on 2.5 mg. Monitor LVEF 4 weeks later, and then resume the patient's monitoring and titration schedule.
Moderate CYP3A4 inhibitors (eg, verapamil, diltiazem, erythromycin, fluconazole, miconazole, delavirdine, amprenavir, fosamprenavir, conivaptan)	If on medication when starting mavacamten, no adjustment of the starting dose of 2.5 mg is needed Initiating or increasing the dose of a moderate inhibitor while on mavacamten treatment: If patients are receiving a 5 mg dose of mavacamten, their dose should be reduced to 2.5 mg or if on 2.5 mg pause treatment for 4 weeks. Monitor LVEF 4 weeks later, and then resume the patient's monitoring and titration schedule.	No dose adjustment. Monitor LVEF 4 weeks later, and then resume the patient's monitoring and titration schedule.
Weak CYP2C19 inhibitors (eg, manidipine, artenimol, lopinavir, omeprazole, voriconazole, esomeprazole, pantoprazole, rucaparib, dovitinib, oritavancin, bortezonib, ethanol, sildenafil, citalopram, ethambutol)	No dose adjustment. Monitor LVEF 4 weeks later, and then resume the patient's monitoring and titration schedule. Adjust mavacamten dose based on clinical assessment.	Initiating or increasing the dose of a weak inhibitor while on mavacamten treatment: Monitor LVEF 4 weeks later, and subsequently resume the patient's monitoring and titration schedule. Adjust mavacamten dose based on clinical assessment.

Table 3 Continued

Concomitant drugs	CYP2C19 poor metabolizer phenotype*	CYP2C19 intermediate, normal, rapid and ultra-rapid metabolizer phenotype
Inhibitors		
Weak CYP3A4 inhibitors (eg, amlodipine, ranolazine, fluoxetine, dexamethasone acetate, tacrolimus, cimetidine, quinidine, citalopram, propofol, lomitapide, ticagrelor)	If on medication when starting mavacamten, no adjustment of the starting dose of 2.5 mg is needed. Initiating or increasing the dose of weak inhibitor while on mavacamten treatment: If patients are receiving a 5 mg dose of mavacamten, their dose should be reduced to 2.5 mg or if on 2.5 mg pause treatment for 4 weeks. Monitor LVEF 4 weeks later, and then resume the patient's monitoring and titration schedule.	Initiating or increasing the dose of a weak inhibitor while on mavacamten treatment: No dose adjustment. Monitor LVEF 4 weeks later, and then resume the patient's monitoring and titration schedule. Adjust mavacamten dose based on clinical assessment.
Inducers		
Strong CYP2C19 inducers (eg, rifampicin, apalutamide, rifamycin, rifaximin, rifapentine) or Strong CYP3A4 inducers (eg, carbamazepine, phenobarbital, phenytoin, rifampin)	Initiating or increasing the dose of strong inducer while on mavacamten treatment: Monitor LVOT gradient and LVEF 4 weeks later. Adjust mavacamten dose based on clinical assessment and then resume the patient's monitoring and titration schedule. The maximum dose is 5 mg. Discontinuing or decreasing the dose of strong inducer while on mavacamten treatment: Decrease mavacamten dose from 5 mg to 2.5 mg or pause treatment if on 2.5 mg. Monitor LVEF 4 weeks later, and then resume the patient's monitoring and titration schedule.	Initiating or increasing the dose of strong inducer while on mavacamten treatment: Monitor LVOT gradient and LVEF 4 weeks later. Adjust mavacamten dose based on clinical assessment and then resume the patient's monitoring and titration schedule. Discontinuing or decreasing the dose of strong inducer while on mavacamten treatment: Decrease mavacamten by 1 dose level when on doses 5 mg or higher. Maintain mavacamten dose when on 2.5 mg. Monitor LVEF 4 weeks later, and then resume the patient's monitoring and titration schedule.
Moderate CYP2C19 inducers (eg, carbamazepine, rifabutin, letermovir, rifampicin, phenytoin) or Weak CYP2C19 inducers (eg, common valerian)	No dose adjustment Monitor LVEF 4 weeks later, and then resume the patient's monitoring and titration schedule; adjust mavacamten dose based on clinical assessment	Initiating the dose of moderate or weak inducer while on mavacamten treatment: Monitor LVOT gradient and LVEF 4 weeks later. Adjust mavacamten dose based on clinical assessment and then resume the patient's monitoring and titration schedule. Discontinuing a moderate or weak inducer while on mavacamten treatment: Decrease mavacamten by 1 dose level when on doses 5 mg or higher. Maintain mavacamten dose when on 2.5 mg. Monitor LVEF 4 weeks later, and then resume the patient's monitoring and titration schedule. Adjust dose based on clinical assessment.
Moderate CYP3A4 inducer (eg, bosentan, modafinil, etravirin, nafcillin, bexarotene, dexamethasone) or Weak CYP3A4 inducers (eg, armodafinil, rufinamide, rifabutin, felbamate, tocilizumab, pyridostigmine, delafloxacin)	Initiating or increasing the dose of moderate or weak inducer while on mavacamten treatment: Monitor LVOT gradient and LVEF 4 weeks later. Adjust mavacamten dose based on clinical assessment and then resume the patient's monitoring and titration schedule. Discontinuing or decreasing the dose of moderate or weak inducer while on mavacamten treatment: Decrease mavacamten dose to 2.5 mg or pause treatment if on 2.5 mg. Monitor LVEF 4 weeks later, and then resume the patient's monitoring and titration schedule.	No dose adjustment. Monitor LVEF 4 weeks later, and then resume the patient's monitoring and titration schedule. Adjust mavacamten dose based on clinical assessment.

The table offers strategies for modifying mavacamten doses and enhancing monitoring practices when changes in concomitant drug use could alter mavacamten metabolism.

LVEF = left ventricular ejection fraction; LVOT = left ventricular outflow tract.

*Includes patients for whom the CYP2C19 phenotype has not yet been determined.

emphasize the need for close monitoring. Recent advancements in anticoagulation therapy, such as Factor Xla inhibitors asundexian and milvexian, introduce promising options, although data on their interactions with mavacamten remain limited. [Figure 6](#) provides an overview of the pharmacokinetics and potential drug–drug interactions of oral and parenteral anticoagulants.

Future Directions

Pharmacogenomics is pivotal in delineating the interactions among mavacamten, anticoagulants, and AADs, especially concerning the CYP450 enzyme system. By investigating the genetic variations in enzymes such as CYP2C9, which is implicated in mavacamten metabolism, clinicians can anticipate individual variances in drug processing and the consequent therapeutic responses. Genetic polymorphisms within these enzymes have the capacity to modulate metabolism of mavacamten, affecting its interactions with other medications and potentially altering its efficacy and safety profile. The application of pharmacogenomic testing identifies individuals who may exhibit atypical drug responses, thus enabling bespoke dosing regimens and a reduction in adverse effects. With the integration of pharmacogenomic information into clinical practice, personalized treatment plans can be developed. These plans may involve dose adjustments or the selection of alternative therapies with a diminished likelihood of interaction. Such a tailored approach not only augments therapeutic outcomes but also diminishes the incidence of negative drug reactions. Employing pharmacogenomic data in clinical decision-making processes aids in mitigating the risks associated with drug–drug interactions of mavacamten, thereby optimizing its efficacy for patients concurrently undergoing anticoagulant⁵⁷ or antiarrhythmic treatment.⁵⁸ Given that CYP2C19 gene is frequently included in different pharmacogenomic panels tested in clinical practice because of its involvement in the metabolism of a myriad of frequently prescribed medications,⁵⁹ such as antiplatelets, antidepressants and proton pump inhibitors, there is a growing need for regulatory strategies to manage and reuse genotyping data, ensuring pharmacogenetic data are accessible and applicable in various prescribing scenarios.

Long-term phase IV surveillance studies are crucial for comprehensively evaluating the implications of mavacamten use in patients with HCM, particularly concerning management of arrhythmias. These studies provide invaluable insights into the safety and efficacy of mavacamten over extended periods, shedding light on its potential impact on arrhythmic events. Understanding the long-term effects of mavacamten in real-world clinical settings is essential for optimizing patient care and guiding clinicians in navigating arrhythmia-management strategies. By emphasizing the importance of ongoing surveillance studies, health care providers can further refine treatment protocols and ensure the optimal use of mavacamten in patients with HCM, ultimately improving outcomes and enhancing patient safety. The DISCOVER-HCM registry for mavacamten (NCT05489705) is expected to enroll ~1500 patients with oHCM and will assess the real-world safety and

effectiveness of mavacamten in the United States. [ClinicalTrials.gov](https://clinicaltrials.gov) lists trials on adult patients with oHCM in China (NCT05174416) and Japan (NCT05414175). The EMBARK-HFpEF trial (NCT04766892) will examine its role in heart failure with preserved ejection fraction and the ODYSSEY-HCM trial (NCT05582395) in oHCM. As the results from these trials become available, it will be possible to develop more precise clinical indications for mavacamten.

Aficamten, the next-in-class cardiac myosin inhibitor, reduces LV contractility by decreasing active actin–myosin cross-bridges. Its refined pharmacokinetic profile, featuring a shorter half-life and a shallow dose-response relationship, allows for dose adjustments every 2 weeks. Metabolism through multiple CYP pathways reduces drug–drug interaction concerns and may simplify its clinical application. The SEQUOIA-HCM trial demonstrated that aficamten (5 mg–20 mg daily) significantly improved exercise capacity over 24 weeks in patients with symptomatic HCM, most of whom were on background therapy.⁶⁰ Notable improvements were observed in LVOT gradient, quality of life, and angina. Reductions in NT-proBNP and hs-cTnI levels highlighted enhancements in cardiac function and structure beyond LVOT gradient improvement. These benefits were consistent among patients on beta blockers and those with pathogenic sarcomeric variants. Although LVEF showed a modest decrease, it remained within the normal range. Head-to-head comparisons and cost-effectiveness analyses will be crucial to establish the role of aficamten in the management of HCM.

Conclusion

Mavacamten represents a paradigm shift in the management of oHCM, directly targeting the underlying pathophysiology of the disease. Clinical trials have consistently demonstrated its capacity to alleviate HF symptoms and enhance quality of life. The management of concomitant AF in patients treated with myosin inhibitors remains a challenge, but with careful monitoring, it can be managed safely. Genetic polymorphisms affecting hepatic cytochromes have the potential to influence metabolism of mavacamten, which in turn may affect its interactions with antithrombotic and antiarrhythmic agents and ultimately its safety and efficacy. Although the evidence to date is reassuring, the need for real-world data remains critical, particularly to determine whether a genotype-guided therapeutic approach provides superior outcomes compared with existing strategies. Ongoing research and long-term surveillance will be essential to fully define the long-term safety profile and therapeutic impact of mavacamten. Its integration into clinical practice should remain firmly grounded in evolving evidence, ensuring that treatment remains both evidence based and patient centered.

Funding Sources: Dr Ricci was supported by the European Union - Next Generation EU, under the National Recovery and Resilience Plan (NRPP), Mission 4 Component 2-MC42, Investment 1.5-Call No. 3277 of 30.12.2021 - The Italian Ministry of University and Research (MUR), Award Number:

ECS00000041, project title: 'Innovation, digitalisation and sustainability for the diffused economy in Central Italy', Concession Degree No. 1057 of 23.06.2022 adopted by the Italian Ministry of University and Research (MUR). CUP: D73C22000840006. Dr Chahal was supported by WellSpan Health Philanthropy.

Disclosures: Dr Luzum is a consultant for Ariel Precision Medicine. Dr Owens has consulted for Alexion, BMS, Cyto-kinetics, Pfizer, Lexeo, Edgewise, BioMarin, Tenaya, Imbria, and Stealth Therapeutics. Dr Vagnarelli has received speaker and advisor fees from BMS. Dr Olivotto has received consulting fees and has served on advisory boards for BMS, Cyto-genetics, Amicus, Genzyme, Takeda, Chiesi, Rocket Pharma, Lexeo, and Tenaya. Dr Renda has received research grants and contracts from Bayer and Janssen/BMS and speaker honoraria from Bayer, Boehringer Ingelheim, and Daiichi-Sankyo. The other authors have no conflicts of interest to disclose.

Address reprint requests and correspondence: Dr C. Anwar A. Chahal, Center for Inherited Cardiovascular Diseases, Well-Span Health, 140 North Pointe Boulevard, Lancaster, PA 17601, USA. E-mail address: cchahal@wellspan.org; chahal.anwar@mayo.edu

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