JOURNAL OF EDUCATION, HEALTH AND SPORT
eISSN 2391-8306 · Open Access · Peer-reviewed
apcz.umk.pl/JEHS·Nicolaus Copernicus University in Toruń

Cite as: PARDA, Julia, BUNDYRA, Jakub, JANIK, Dominika, GAŃSKA, Oliwia Zuzanna, SOCHOCKA, Agata, ZAPART, Zuzanna, MARTYNA SZEPIETOWSKA, NOWICKA, Nina, SIKORSKA, Alicja and MIAN, Emil. Hypertrophic Cardiomyopathy in the Era of Targeted Therapy: The Role of Cardiac Myosin Inhibitors, Contemporary Sudden Cardiac Death Risk Stratification, and the Importance of Differential Diagnosis — A Narrative Review. Journal of Education, Health and Sport. 2026;94:72850. https://doi.org/10.12775/JEHS.2026.94.72850

ARTICLE TIMELINE
Received: 31.05.2026 Revised: 10.07.2026
Accepted: 12.07.2026 Published: 15.07.2026

INDEXING & EVALUATION
MEiN points: 40 Unique ID: 201159
Disciplines: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences).

The journal has been awarded 40 points in the parametric evaluation by the Polish Ministry of Higher Education and Science (Annex to the announcement of 05.01.2024, No. 32318). Unique Journal Identifier: 201159. Scientific disciplines: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences).

Punkty Ministerialne z 2019 – aktualny rok 40 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 Lp. 32318. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).

Hypertrophic Cardiomyopathy in the Era of Targeted Therapy: The Role of Cardiac Myosin Inhibitors, Contemporary Sudden Cardiac Death Risk Stratification, and the Importance of Differential Diagnosis — A Narrative Review

Julia Parda, ORCID: https://orcid.org/0009-0006-9079-5936

E-mail: parda.julka@gmail.com

Medical University of Warsaw; ul. Żwirki i Wigury 61, 02-091Warsaw, Poland

Jakub Bundyra, ORCID: https://orcid.org/0009-0008-7042-1990

E-mail: kubabundyra4@gmail.com

Medical University of Warsaw; ul. Żwirki i Wigury 61, 02-091Warsaw, Poland

Dominika Janik, ORCID: https://orcid.org/0009-0000-8527-7428

E-mail: dominika.janik121@gmail.com

Medical University of Warsaw; ul. Żwirki i Wigury 61, 02-091Warsaw, Poland

Oliwia Zuzanna Gańska, ORCID: https://orcid.org/0009-0007-9024-0209

E-mail: oliwiaganska12@gmail.com

Medical University of Warsaw; ul. Żwirki i Wigury 61, 02-091Warsaw, Poland

Agata Sochocka, ORCID: https://orcid.org/0009-0004-5384-2014

E-mail: agatasochocka@gmail.com

Medical University of Warsaw; ul. Żwirki i Wigury 61, 02-091Warsaw, Poland

Zuzanna Zapart, ORCID: https://orcid.org/0009-0007-0466-4508

E-mail: pczuzanna@gmail.com

Medical University of Warsaw; ul. Żwirki i Wigury 61, 02-091Warsaw, Poland

Martyna Szepietowska, ORCID: https://orcid.org/0009-0000-2423-4563

E-mail: mszepietovska@gmail.com

Medical University of Warsaw; ul. Żwirki i Wigury 61, 02-091Warsaw, Poland

Nina Nowicka, ORCID: https://orcid.org/0009-0004-1942-0045

E-mail: nina.en@autograf.pl

Medical University of Warsaw; ul. Żwirki i Wigury 61, 02-091Warsaw, Poland

Alicja Sikorska, ORCID: https://orcid.org/0009-0009-6274-6944

E-mail: alicja.sikorska@gmail.com

Medical University of Warsaw; ul. Żwirki i Wigury 61, 02-091Warsaw, Poland

Emil Mian, ORCID: https://orcid.org/0009-0006-1538-7190

E-mail: emilmian@icloud.com

Medical University of Warsaw; ul. Żwirki i Wigury 61, 02-091Warsaw, Poland

Corresponding Author:
Julia Parda, E-mail: parda.julka@gmail.com

Abstract (Structured)

Introduction and purpose: Hypertrophic cardiomyopathy (HCM) is a common genetic myocardial disease characterized by unexplained left ventricular hypertrophy, phenotypic heterogeneity, and a clinical course ranging from asymptomatic presentation to heart failure, atrial fibrillation, ventricular arrhythmias, and sudden cardiac death. The aim of this narrative review was to summarize knowledge on HCM in the era of targeted therapy, with particular emphasis on cardiac myosin inhibitors, sudden cardiac death risk stratification, and the importance of differential diagnosis.

Brief description of the state of knowledge: HCM should be regarded as a genetically mediated and phenotypically diverse disease rather than a single morphologic pattern. Phenotyping is essential because obstructive and non-obstructive forms differ in symptoms, prognosis, and treatment options. Cardiac myosin inhibitors, especially mavacamten and aficamten, represent mechanism-directed therapy targeting sarcomeric hypercontractility and have shown the greatest clinical benefit in symptomatic obstructive HCM. Sudden cardiac death prevention still requires individualized multivariable assessment integrating clinical markers, ambulatory rhythm evaluation, and cardiovascular magnetic resonance findings, particularly myocardial fibrosis. Differential diagnosis remains crucial because athlete's heart, hypertensive remodeling, restrictive phenotypes, and infiltrative or metabolic phenocopies may mimic HCM but require different management.

Summary (conclusions): Cardiac myosin inhibitors have become a major advance in symptomatic obstructive HCM, but their long-term role across all phenotypes remains to be defined. Contemporary management of HCM should combine precise phenotyping, substrate-

oriented sudden cardiac death risk stratification, and careful differential diagnosis to support individualized care.

Key words: hypertrophic cardiomyopathy; cardiac myosin inhibitors; mavacamten; sudden cardiac death; cardiac magnetic resonance; differential diagnosis.

1. Introduction and purpose

Hypertrophic cardiomyopathy (HCM) is one of the best-recognized inherited myocardial disorders and historically evolved from the earlier concept of idiopathic hypertrophic subaortic stenosis to the current understanding of a complex myocardial disease with variable genetic background, heterogeneous ventricular remodeling, and broad clinical expression [1-5]. Contemporary HCM is defined by otherwise unexplained left ventricular hypertrophy and may present across a wide clinical spectrum ranging from incidental imaging detection to exertional symptoms, atrial fibrillation, progressive heart failure, ventricular arrhythmias, and sudden cardiac death [2,3]. In addition, HCM remains highly relevant in sports cardiology because it continues to be considered one of the important structural causes of sudden cardiac death in young athletes, despite growing awareness that athletic remodeling and concealed myocardial disease can overlap in difficult diagnostic scenarios [8,14-16].

Current management of HCM is increasingly shaped by three interconnected domains. The first is the transition from conventional symptom-oriented therapy toward mechanism-directed pharmacological treatment, particularly through cardiac myosin inhibitors. The second is the refinement of sudden cardiac death risk stratification, which now relies not only on clinical history and rhythm monitoring, but also on phenotype-specific imaging markers and scar assessment. The third is the need for careful differential diagnosis, because increased wall thickness does not necessarily indicate sarcomeric HCM and may instead reflect athlete's heart, hypertensive remodeling, infiltrative disease, metabolic disorders, or restrictive overlap phenotypes [2-8].

These developments have major practical implications. Therapeutic decisions increasingly depend on whether the patient has obstructive or non-obstructive disease, whether fibrosis or adverse remodeling is present, and whether the observed hypertrophic phenotype actually represents true sarcomeric HCM rather than a phenocopy. Accordingly, the aim of this narrative review is to summarize the current state of knowledge on HCM in the era of targeted therapy, with particular focus on the clinical role and limitations of cardiac myosin inhibitors,

the modern approach to sudden cardiac death risk stratification, and the practical importance of differential diagnosis in contemporary clinical care [2-13].

2. Description of the state of knowledge

2.1. Hypertrophic cardiomyopathy as a genetic and phenotypically heterogeneous disease

Hypertrophic cardiomyopathy is best understood as a genetically mediated myocardial disorder rather than a uniform anatomical label, because its final phenotype reflects interactions between primary sarcomeric variants, modifier mechanisms, age-dependent penetrance, and progressive myocardial remodeling [2-7]. Classically, HCM is inherited in an autosomal dominant manner and is most commonly associated with pathogenic variants in MYH7 and MYBPC3, while additional sarcomeric genes such as TNNT2, TNNI3, MYL2, and MYL3 may contribute to genotype–phenotype diversity [3,5-7]. In modern clinical genetics, HCM is no longer interpreted exclusively as a simple monogenic disorder: in a proportion of patients, the phenotype may reflect oligogenic or polygenic influences, incomplete penetrance, and environmental modifiers, which is why family history and expert interpretation of genetic results remain essential [5-7].

From a tissue perspective, HCM is characterized by cardiomyocyte hypertrophy, myocyte disarray, and interstitial fibrosis, but these histopathological hallmarks may translate into markedly different structural and functional presentations [2,3]. Thus, the disease may manifest as classic asymmetric septal hypertrophy, apical hypertrophy, diffuse hypertrophy, obstructive physiology, non-obstructive disease, restrictive features, or adverse remodeling with systolic dysfunction. This variability explains why HCM should be regarded as a spectrum rather than a single static pattern of increased wall thickness [2-5].

2.2. Clinical phenotypes of HCM and the importance of accurate phenotyping

The clinical expression of HCM is highly variable, and accurate phenotyping has direct consequences for diagnosis, prognosis, and therapy [2,3]. In practical terms, phenotyping should not be limited to measuring maximal wall thickness. It should also define the distribution of hypertrophy, the presence or absence of left ventricular outflow tract obstruction at rest or with provocation, the degree of diastolic dysfunction, atrial remodeling, myocardial fibrosis, and special structural features such as apical aneurysm or restrictive physiology [2-5]. These variables determine whether the patient’s dominant problem is

dynamic obstruction, exertional symptoms, diastolic heart failure, arrhythmic substrate, or phenotype overlap with another cardiomyopathy.

Classical phenotypic subgroups include obstructive and non-obstructive HCM, asymmetric septal hypertrophy, apical HCM, and less common forms with midventricular obstruction or progressive adverse remodeling [2,3]. In addition, some patients demonstrate a restrictive phenotype characterized by severe diastolic dysfunction, small ventricular cavities, and marked biatrial enlargement. Such cases blur the boundary between HCM and primary restrictive cardiomyopathy and support the concept that hypertrophic and restrictive phenotypes may form part of a continuous sarcomeric spectrum [4,5].

For this reason, precise phenotyping requires multimodality assessment. Echocardiography remains the first-line imaging tool, but cardiovascular magnetic resonance is increasingly essential because it reveals concealed hypertrophy, defines the true extent and pattern of scar, identifies apical aneurysm, and helps clarify phenotype overlap or atypical remodeling [2-5]. Accurate phenotyping therefore underpins individualized care, including the choice between standard medical therapy, myosin inhibition, septal reduction strategies, family evaluation, and intensified arrhythmic surveillance.

2.3. Cardiac myosin inhibitors as mechanism-directed therapy in HCM

Cardiac myosin inhibitors represent the most important recent pharmacological advance in HCM because they directly target the central sarcomeric abnormality responsible for hypercontractility and impaired relaxation, rather than acting only through indirect negative inotropy [10-13]. This mechanism-based approach is fundamentally different from traditional treatment with beta-blockers, non-dihydropyridine calcium channel blockers, or disopyramide, which may improve symptoms but do not directly modify the molecular basis of the disease [12,13].

Mavacamten, the first-in-class allosteric inhibitor of β-cardiac myosin, reduces excessive actin–myosin cross-bridge formation and thereby improves energetic efficiency, lowers left ventricular outflow tract gradients, and improves symptoms, functional class, and exercise-related parameters in symptomatic obstructive HCM [10-13]. Narrative reviews and pooled analyses indicate that it also reduces eligibility for septal reduction therapy in selected patients referred for invasive intervention [11-13]. Aficamten appears to apply the same general principle of sarcomeric modulation, while offering a shorter half-life and potentially more predictable pharmacokinetic behavior, which may facilitate dose titration in carefully selected patients with obstructive disease [12,13].

The importance of myosin inhibitors becomes even clearer when viewed against the historical evolution of HCM therapy. Early management focused on describing the disease and relieving obstruction by invasive means, whereas later practice increasingly differentiated between surgical myectomy and alcohol septal ablation as competing strategies for symptomatic obstructive disease [1,9]. Observational analyses of alcohol septal ablation raised concern that infarct-based septal reduction might create a scar substrate associated with unwanted long-term arrhythmic consequences when compared with myectomy, reinforcing the appeal of non-invasive therapies that can improve hemodynamics without deliberately inducing septal necrosis [9].

Despite these advances, cardiac myosin inhibitors should currently be regarded primarily as a treatment option for symptomatic obstructive HCM, because evidence in non-obstructive phenotypes remains less convincing [11-13]. Their use still requires careful echocardiographic monitoring, especially because excessive reduction in contractility may lead to reversible decreases in left ventricular ejection fraction. Practical implementation also raises issues related to pharmacokinetics, dose titration, access, and long-term monitoring, with mavacamten being especially sensitive to CYP2C19-dependent variability in drug exposure [10,12,13]. Thus, myosin inhibitors are best viewed as a major step toward disease-specific therapy, but not yet as a universal solution for every HCM phenotype.

At the same time, contemporary practice should avoid simplistic enthusiasm. Myosin inhibitors do not eliminate the need for individualized decision-making, because patient age, phenotype, ventricular function, arrhythmic profile, access to expert care, and local experience with septal reduction strategies remain important determinants of management [2,3,9-13]. In this sense, the optimal role of myosin inhibitors may be as part of an integrated strategy in expert HCM care: a strategy that combines accurate diagnosis, phenotype-based selection, serial imaging, and long-term reassessment rather than a one-time prescription model. This integrated view is also consistent with the broader movement in cardiomyopathy care toward disease-specific but carefully monitored interventions.

In routine care, the emergence of myosin inhibitors should be interpreted within the broader therapeutic pathway of HCM rather than as an isolated innovation. Patients with symptomatic obstructive disease continue to require careful baseline phenotyping, optimization of standard medical therapy, evaluation of gradient severity, and assessment of whether symptoms are driven primarily by outflow tract obstruction, arrhythmia, or progressive diastolic dysfunction [2,3,10-13]. Against this background, mechanism-directed therapy may be especially attractive in individuals who remain symptomatic despite conventional pharmacotherapy and

in those for whom the choice between continued medical management and septal reduction therapy is clinically relevant. The possibility of reducing left ventricular outflow tract gradients without surgically removing tissue or intentionally creating a septal infarction represents an important conceptual and practical shift [9-13].

2.4. Contemporary sudden cardiac death risk stratification in HCM

Sudden cardiac death risk stratification remains one of the most difficult areas in HCM management because arrhythmic risk cannot be reduced to a single clinical parameter [2,3]. Instead, risk is shaped by the interaction between patient history, ventricular phenotype, electrical instability, and myocardial substrate. The markers that continue to matter in everyday practice include family history of sudden cardiac death, unexplained syncope, non-sustained ventricular tachycardia, severe left ventricular hypertrophy, and adverse remodeling with systolic dysfunction, but modern interpretation increasingly emphasizes that these variables must be integrated rather than considered in isolation [2,3].

Cardiovascular magnetic resonance has transformed this field because it allows direct characterization of fibrosis and scar. Late gadolinium enhancement, apical aneurysm, and complex remodeling patterns provide substrate-based information that extends beyond what can be inferred from wall thickness or resting gradient alone [2-5]. This is clinically important because some patients experience malignant ventricular arrhythmias despite the absence of extreme hypertrophy, whereas others with marked hypertrophy remain relatively stable. Accordingly, a fibrosis-oriented and phenotype-oriented approach is now indispensable in individualized decision-making regarding implantable cardioverter-defibrillator therapy [2-5].

Sports cardiology offers a useful parallel perspective. In athletes with ventricular arrhythmias, isolated nonischemic left ventricular scar detected by contrast-enhanced cardiac magnetic resonance has been associated with malignant events and may remain occult on echocardiography, demonstrating how arrhythmic substrate can be missed when evaluation relies on morphology alone [8]. Although such data derive from athletic populations rather than classic HCM cohorts, they reinforce a broader principle relevant to HCM care: substrate characterization matters, and apparently modest structural disease may still carry substantial arrhythmic significance.

2.5. The importance of differential diagnosis

The differential diagnosis of HCM is of central clinical importance because the finding of increased left ventricular wall thickness does not by itself establish the diagnosis of sarcomeric HCM [2-5]. Several conditions may present with a similar hypertrophic phenotype

while carrying different pathophysiological, prognostic, and therapeutic implications. These include long-standing hypertension, aortic stenosis, physiological athlete's heart, and a broad range of metabolic, infiltrative, and syndromic phenocopies such as Fabry disease, glycogen storage disorders, Danon disease, PRKAG2 syndrome, mitochondrial disease, and cardiac amyloidosis [2-7].

This challenge becomes even greater in patients with overlapping phenotypes, particularly those with restrictive physiology, severe diastolic dysfunction, marked biatrial enlargement, or atypical fibrosis patterns. In such cases, HCM may border functionally and morphologically on primary restrictive cardiomyopathy or infiltrative disease rather than represent a classic obstructive septal form [4,5]. The Padua conceptual framework is especially useful here because it emphasizes hypertrophic/restrictive phenotypes as part of a broader pathobiological continuum rather than as rigidly separated entities [5].

Athlete's heart remains one of the most important practical differential diagnoses because physiological remodeling may blur the boundary between adaptation and disease. At the same time, sports-related literature makes clear that sudden cardiac death in athletes has a broad differential diagnosis and that HCM is only one part of a larger spectrum that includes arrhythmogenic substrates, coronary anomalies, and concealed structural disease [14-16]. Furthermore, studies of athletes with ventricular arrhythmias show that clinically relevant nonischemic scar can be present despite normal echocardiography, underscoring the value of magnetic resonance imaging when physiological remodeling and pathology overlap [8].

Therefore, accurate differential diagnosis should rely on integrated clinical evaluation, family history, echocardiography, cardiovascular magnetic resonance with tissue characterization, and appropriately selected genetic testing [2-7]. This approach is essential not only for assigning the correct label, but also for choosing the correct treatment, because disease-specific management differs substantially between sarcomeric HCM, infiltrative disease, metabolic phenocopies, and physiologic adaptation.

In practical terms, several clues should prompt clinicians to move beyond a default diagnosis of sarcomeric HCM. Disproportionate extracardiac manifestations, unusually low QRS voltages in the presence of marked wall thickening, characteristic patterns of late gadolinium enhancement, low native T1 in Fabry disease, diffuse subendocardial enhancement in amyloidosis, pre-excitation or conduction disease in storage disorders, and marked biatrial enlargement with relatively modest hypertrophy are all examples of findings that may redirect the diagnostic pathway [2-8]. These features are especially important because some phenocopies are treatable through disease-specific interventions that are fundamentally

different from management focused on sarcomeric HCM or left ventricular outflow tract obstruction.

The need for rigorous differential diagnosis also extends to apparently straightforward obstructive disease. Even when symptoms and hemodynamics are compatible with HCM, appropriate etiological classification remains essential because targeted therapy with cardiac myosin inhibitors is mechanistically aligned with sarcomeric hypercontractility rather than with infiltrative or metabolic hypertrophic disease [5-7,10-13]. Thus, diagnostic precision is not merely academic; it directly determines whether a patient should receive phenotype-oriented symptomatic therapy, mechanism-directed pharmacological treatment, family cascade screening, or an alternative disease-specific pathway.

2.5.1. Practical implications of multimodal differential diagnosis

2.6. Future directions

Future progress in HCM will likely depend on moving beyond broad phenotype-based care toward more precise integration of sarcomeric biology, advanced imaging, and individualized therapeutic selection [2-7]. In the therapeutic domain, the major unanswered questions concern the long-term safety, durability of benefit, and optimal positioning of cardiac myosin inhibitors across different phenotypes, especially in non-obstructive disease and in patients with distinct pharmacokinetic backgrounds [10-13].

At the same time, sudden cardiac death prevention will likely benefit from more refined substrate-based models that combine conventional clinical markers with cardiovascular magnetic resonance, phenotype overlap classification and carefully interpreted genetic findings [2-7]. The broader goal is not simply to label HCM more accurately, but to understand which patient is most likely to benefit from disease-specific pharmacotherapy, intensified rhythm surveillance, or phenotype-tailored follow-up. In this sense, the future of HCM care is likely to be increasingly individualized, multimodal, and mechanism-aware.

To synthesize the most clinically relevant literature discussed in this review, the key studies underpinning current concepts of HCM diagnosis, targeted therapy, sudden cardiac death risk stratification, and differential diagnosis are summarized in Table 1.

Table 1. Selected key studies relevant to targeted therapy, sudden cardiac death risk stratification, and differential diagnosis in hypertrophic cardiomyopathy

Study	Type of paper / population	Main contribution	Relevance to the present review
Maron et al. [1]	JACC state-of-the-art review	Summarizes the modern diagnostic framework of HCM, including echocardiography, CMR, family screening, obstructive versus non-obstructive phenotyping, and phenocopies.	Core source for the diagnostic structure of the manuscript.
Marian and Braunwald [3]	Broad expert review	Explains the genetic basis, histopathology, sarcomeric mechanisms, fibrosis, and classical clinical expression of HCM.	Key background source for genetics, pathogenesis, and biological heterogeneity of HCM.
Vio et al. [6]	Review on overlap phenotypes	Shows that HCM may overlap with restrictive physiology and explains differentiation from primary restrictive cardiomyopathy, amyloidosis, Fabry disease, and storage disorders.	Important for the section on overlap phenotypes and phenocopies.
Corrado et al. [5]	Conceptual	Reclassifies	Supports phenotype-

	classification review	cardiomyopathies according to pathobiology and remodeling pattern and emphasizes the hypertrophic/restrictive spectrum.	based interpretation and the therapeutic implications of accurate classification.
García-Hernández et al. [6]	Contemporary genetics review	Expands the concept of HCM from simple monogenic disease toward more complex genetic architecture and clinical application of genetic results.	Supports the section on genotype–phenotype heterogeneity and future individualized care.
Wilde et al. [7]	International expert consensus	Defines the practical role of genetic testing, cascade screening, and variant interpretation in cardiac diseases including HCM.	Supports the sections on genetic testing and etiologic classification.
Zorzi et al. [8]	Observational imaging study in athletes	Shows that isolated nonischemic left ventricular scar detected by CMR may be associated with malignant arrhythmic events in athletes.	Valuable for the differential diagnosis and substrate-based risk discussion.
ten Cate et al. [9]	Observational comparison of alcohol septal	Raised concern regarding potentially unwanted long-term	Useful as historical and practical context when discussing the

	ablation and myectomy	arrhythmic consequences of infarct-based septal reduction.	appeal of non-invasive targeted therapy.
McGurk et al. [10]	Focused pharmacogenetic commentary	Highlights the effect of CYP2C19-dependent variability on mavacamten pharmacokinetics and monitoring.	Supports the individualized treatment and safety perspective.
Rangwala et al. [11]	Systematic review and meta-analysis	Demonstrates pooled clinical benefit of mavacamten and reduced eligibility for septal reduction therapy in short-term randomized data.	Provides quantitative support for the efficacy and safety subsection of targeted therapy.
Younas et al. [10]	Narrative review	Summarizes the mechanisms and clinical role of mavacamten and aficamten in HCM.	Useful synthesis for the section on cardiac myosin inhibitors.
Skibicka et al. [2]	JEHS narrative review	Summarizes the modern therapeutic role of cardiac myosin inhibitors in obstructive and non-obstructive HCM.	Important JEHS source directly aligned with the central theme of the manuscript.
Kafara et al. [14]; Słowiaczek et al. [15]; Wrzesiński et al. [16]	Review articles in sports medicine journals	Provide sports-related clinical context and emphasize the broader differential diagnosis of sudden	Support the sections on differential diagnosis and sport-related clinical relevance.

		cardiac death in athletes.	

Abbreviations: HCM, hypertrophic cardiomyopathy; CMR, cardiovascular magnetic resonance; HCM, hypertrophic cardiomyopathy.

6. Conclusions

1. Hypertrophic cardiomyopathy should be regarded as a genetically mediated and phenotypically heterogeneous myocardial disease rather than a single morphologic pattern of left ventricular hypertrophy, which is why accurate clinical and imaging-based phenotyping remains fundamental for diagnosis, prognosis, and treatment selection [1,3].
2. Cardiac myosin inhibitors represent the most important recent pharmacologic advance in symptomatic obstructive HCM because they directly target sarcomeric hypercontractility, improve symptoms and functional status, reduce left ventricular outflow tract obstruction, and may decrease the need for septal reduction therapy, although their role in non-obstructive HCM remains uncertain and careful monitoring is still required [2,9,10,20].
3. Contemporary sudden cardiac death risk stratification in HCM should be individualized and multivariable, integrating clinical history, arrhythmic burden, phenotype severity, and especially cardiovascular magnetic resonance markers of myocardial fibrosis and adverse remodeling, because no single parameter is sufficient to identify all high-risk patients [1,3,11].
4. Differential diagnosis remains a central pillar of modern HCM care because phenocopies and overlapping phenotypes—including athlete's heart, hypertensive remodeling, Fabry disease, amyloidosis, glycogen storage disease, and restrictive forms—may mimic HCM but require different prognostic interpretation, family screening strategies, and disease-specific treatment [6,7,19,20,29,30].
5. Future progress in HCM will likely depend on combining mechanism-directed therapy with more precise genotype-informed assessment, advanced substrate characterization by CMR, and broader disease-modifying strategies aimed not only at sarcomeric dysfunction but also at fibrosis, remodeling, and intercellular signaling [3,7,20,21].

Disclosure

Author's Contributions:

Conceptualization: Julia Parda

Methodology: Oliwia Gańska, Agata Sochocka

Investigation: Dominika Janik, Jakub Bundyra

Resources: Julia Parda, Dominika Janik

Data curation: Emil Mian, Nina Nowicka Oliwia Gańska

Writing—original draft preparation: Julia Parda, Agata Sochocka

Writing—review and editing: Julia Parda, Zuzanna Zaparta, Martyna Szepietowska

Visualization: Alicja Sikorska, Nina Nowicka

Supervision: Julia Parda, Jakub Bundyra

All authors have read and agreed to the published version of the manuscript.

Funding

This research received no external funding.

Institutional Review Board Statement

Not applicable.

Informed Consent Statement

Not applicable.

Data Availability Statement

Data sharing is not applicable to this article.

Acknowledgments

None.

Conflicts of Interest

The authors declare no conflicts of interest.

Declaration of the Use of Generative AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work, the authors used ChatGPT (OpenAI) for language support, structural planning of the manuscript, and assistance in improving readability. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the substantive content of the publication.

References

1. Maron BJ, Desai MY, Nishimura RA, et al. Diagnosis and evaluation of hypertrophic cardiomyopathy: JACC State-of-the-Art Review. J Am Coll Cardiol. 2022;79(4):372-389. https://doi.org/10.1016/j.jacc.2021.12.002

2. Skibicka K, Skibicki T, Wesołowska W, et al. Precision Negative Inotropy: The Rise of Cardiac Myosin Inhibitors in HCM. Journal of Education, Health and Sport. 2025;84:65626. https://doi.org/10.12775/JEHS.2025.84.65626

3. Marian AJ, Braunwald E Hypertrophic cardiomyopathy: genetics, pathogenesis, clinical manifestations, diagnosis, and therapy. Circ Res. 2017;121(7):749-770. https://doi.org/10.1161/CIRCRESAHA.117.311059

4. Maron BJ. Clinical course and management of hypertrophic cardiomyopathy. N Engl J Med. 2018;379(7):655-668. https://doi.org/10.1056/NEJMra1710575

5. Maron BJ, Maron MS. Hypertrophic cardiomyopathy. Lancet. 2013;381(9862):242-255. https://doi.org/10.1016/S0140-6736(12)60397-3

6. Vio R, Angelini A, Basso C, et al. Hypertrophic cardiomyopathy and primary restrictive cardiomyopathy: similarities, differences and phenocopies. J Clin Med. 2021;10(9):1954. https://doi.org/10.3390/jcm10091954

7. García-Hernández S, de la Higuera Romero L, et al. Emerging themes in genetics of hypertrophic cardiomyopathy: current status and clinical application. Can J Cardiol. 2024;40(5):738-752. https://doi.org/10.1016/j.cjca.2024.01.011

8. Wilde AAM, Semsarian C, Márquez MF, et al. European Heart Rhythm Association/Heart Rhythm Society/Asia Pacific Heart Rhythm Society/Latin American Heart Rhythm Society expert consensus statement on the state of genetic testing for cardiac diseases. Heart Rhythm. 2022;19(7):e1-e60.
https://doi.org/10.1093/europace/euac106

9. Rangwala HS, Fatima H, Ali M, Ahmed ST, et al. Analyzing safety and effectiveness of mavacamten in comparison with placebo for managing hypertrophic cardiomyopathy: a systemic review and meta-analysis. Egypt Heart J. 2023;75:99 https://doi.org/10.1186/s43044-023-00427-5

10. Younas A, Qadri M, Ijlal A, et al. Cardiac myosin inhibitors - a cutting-edge solution for the management of hypertrophic cardiomyopathy: a narrative review. Ann Med Surg (Lond). 2025;87:4316-4324. https://doi.org/10.1097/MS9.0000000000003436

11. Maron MS. Clinical utility of cardiovascular magnetic resonance in hypertrophic cardiomyopathy. J Cardiovasc Magn Reson. 2012;14:13. https://doi.org/10.1186/1532-429X-14-13

12. Olivotto I, Oreziak A, Barriales-Villa R, et al. Mavacamten for treatment of symptomatic obstructive hypertrophic cardiomyopathy (EXPLORER-HCM): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2020;396(10253):759-769. https://doi.org/10.1016/S0140-6736(20)31792-X

13. Desai MY, Owens A, Geske JB, et al. Myosin inhibition in patients with obstructive hypertrophic cardiomyopathy referred for septal reduction therapy. J Am Coll Cardiol. 2022;80(2):95-108.

14. Ho CY, Mealiffe ME, Bach RG, et al. Evaluation of mavacamten in symptomatic patients with nonobstructive hypertrophic cardiomyopathy. J Am Coll Cardiol. 2020;75(21):2649-2660. https://doi.org/10.1016/j.jacc.2020.03.064

15. Tian Z, Li L, Li X, et al. Effect of mavacamten on Chinese patients with symptomatic obstructive hypertrophic cardiomyopathy: the EXPLORER-CN randomized clinical trial. JAMA Cardiol. 2023;8(10):957-965. https://doi.org/10.1001/jamacardio.2023.3030

16. Maron MS, Masri A, Choudhury L et al. Phase 2 study of aficamten in patients with obstructive hypertrophic cardiomyopathy. J Am Coll Cardiol. 2023;81(1):34-45. https://doi.org/10.1080/vjbm-2025-0003

17. Hartman JJ, Hwee DT, Robert-Paganin J, et al. Aficamten is a small-molecule cardiac myosin inhibitor designed to treat hypertrophic cardiomyopathy. Nat Cardiovasc Res. 2024;3:1003-1016. https://doi.org/10.1038/s44161-024-00505-0

18. Braunwald E, Saberi S, Abraham TP, et al. Mavacamten: a first-in-class myosin inhibitor for obstructive hypertrophic cardiomyopathy. Eur Heart J. 2023;44(46):4622-4633. https://doi.org/10.1093/eurheartj/ehad637

19. Crescenzi C, Zorzi A, Migliore F, et al. Predictors of left ventricular scar using cardiac magnetic resonance in athletes with apparently idiopathic ventricular arrhythmias. J Am Heart Assoc. 2021;10(1):e018206. https://doi.org/10.1161/JAHA.120.018206

20. Zorzi A, Cipriani A, Bariani R, et al. Ventricular arrhythmias in young competitive athletes: prevalence, determinants, and underlying substrate. J Am Heart Assoc. 2018;7(12):e009171. https://doi.org/10.1161/JAHA.118.009171

21. Nicin L, Schuster A, Lippmann N, et al. A human cell atlas of the pressure-induced hypertrophic heart disease. Nat Cardiovasc Res. 2022;1:553-566. https://doi.org/10.1038/s44161-022-00019-7

22. Ommen SR, Mital S, Burke MA, et al. 2020 AHA/ACC guideline for the diagnosis and treatment of patients with hypertrophic cardiomyopathy. J Am Coll Cardiol. 2020;76(25):e159-e240. https://doi.org/10.1016/j.jacc.2020.08.045
23. Maron MS, Maron BJ, Harrigan C, et al. Hypertrophic cardiomyopathy phenotype revisited after 50 years with cardiovascular magnetic resonance. J Am Coll Cardiol. 2009;54(3):220-228. https://doi.org/10.1016/j.jacc.2009.05.006
24. Elliott PM, Anastasakis A, Borger MA, et al. 2014 ESC guidelines on diagnosis and management of hypertrophic cardiomyopathy. Eur Heart J. 2014;35(39):2733-2779. https://doi.org/10.1093/eurheartj/ehu284
25. Corrado D, Thiene G, Bauce B, et al. The "Padua classification" of cardiomyopathies: combining pathobiological basis and morpho-functional remodeling. Int J Cardiol. 2025;408:132571. https://doi.org/10.1016/j.ijcard.2024.132571
26. Wheeler MT, Olivotto I, Elliott PM, et al. Effects of mavacamten on measures of cardiopulmonary exercise testing beyond peak oxygen consumption: a secondary analysis of the EXPLORER-HCM randomized trial. JAMA Cardiol. 2023;8(3):240-247. https://doi.org/10.1001/jamacardio.2022.5099
27. Hegde SM, Lester SJ, Solomon SD, et al. Effect of mavacamten on echocardiographic features in symptomatic patients with obstructive hypertrophic cardiomyopathy. J Am Coll Cardiol. 2021;78(25):2518-2532. https://doi.org/10.1016/j.jacc.2021.09.1381
28. Desai MY, Owens A, Wolski K, et al.Mavacamten in patients with hypertrophic cardiomyopathy referred for septal reduction: week 56 results from the VALOR-HCM randomized clinical trial. JAMA Cardiol. 2023;8(10):968-977. https://doi.org/10.1001/jamacardio.2023.3342
29. Kafara Z, Jurczak D, Jonczyk A, et al. Causes of sudden cardiac death in professional athletes. Quality in Sport. 2025;39:59201. https://doi.org/10.12775/QS.2025.39.59201
30. Słowiaczek A, Matyka K, Wojnar M, et al. Sudden cardiac death in athletes – can we prevent it? Journal of Education, Health and Sport. 2023;13(5):27-32. https://doi.org/10.12775/JEHS.2023.13.05.003
31. Wrzesiński B, Piechocka E, Duda G, et al. Sudden death amongst people practicing competitive sports (review article). Journal of Education, Health and Sport. 2018;8(2):43-52. https://doi.org/10.5281/zenodo.1165406