

Deciphering the Clinical Heterogeneity and Molecular Underpinnings of Hypertrophic Cardiomyopathy: A Contemporary Synthesis of Genetic, Diagnostic, and Therapeutic Paradigms

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ABSTRACT

Hypertrophic cardiomyopathy (HCM) stands as the most prevalent heritable cardiomyopathy, characterized by a complex and heterogeneous phenotype primarily involving unexplained left ventricular hypertrophy in the absence of loading conditions sufficient to account for its magnitude. This monogenic disorder is principally attributed to pathogenic variants in sarcomeric proteins, which instigate a cascade of molecular events culminating in myocyte hypertrophy, disarray, and interstitial fibrosis. The clinical trajectory of HCM is notably variable, ranging from a lifelong asymptomatic course to profound manifestations including heart failure with preserved or reduced ejection fraction, atrial fibrillation, and sudden cardiac death, the latter often linked to ventricular arrhythmias. Contemporary management has evolved beyond a one-size-fits-all approach, now emphasizing a personalized, multimodal strategy. This encompasses sophisticated risk stratification for sudden cardiac death, the judicious application of septal reduction therapies for refractory symptomatic left ventricular outflow tract obstruction, and the nascent era of disease-modifying pharmacological agents. Recent investigations into cardiac sarcomere function and the resulting hypercontractile state have illuminated novel therapeutic targets, offering promising avenues for intervening directly in the underlying pathophysiology. This article seeks to synthesize the current understanding of HCM's genetic architecture, pathophysiological mechanisms, and the expanding armamentarium of diagnostic and therapeutic modalities, thereby providing a comprehensive overview for the modern management of this multifaceted disease.

KEYWORDS: Hypertrophic Cardiomyopathy, Sarcomeric Mutation, Left Ventricular Outflow Tract Obstruction, Sudden Cardiac Death Risk Stratification, Cardiac Magnetic Resonance, Myocardial Fibrosis, Mavacamten, Septal Myectomy.

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INTRODUCTION

Hypertrophic cardiomyopathy represents a quintessential model of a Mendelian inherited cardiac condition, yet its clinical expression reveals profound heterogeneity that continues to challenge clinicians and investigators alike. As the most common genetic cardiovascular disorder, with an estimated prevalence of 1:500 in the general population, HCM is defined by the presence of increased left ventricular

wall thickness that cannot be explained solely by abnormal loading conditions. The foundational pathophysiological derangement in HCM resides within the cardiac sarcomere, where mutations in genes encoding its constituent proteins, such as beta-myosin heavy chain and myosin-binding protein C, disrupt the delicate equilibrium of force generation and regulation. This molecular insult precipitates a state of hypercontractility and impaired myocardial relaxation,

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setting the stage for the hallmark features of the disease: asymmetric septal hypertrophy, dynamic left ventricular outflow tract obstruction, microvascular dysfunction, and diastolic impairment.^{1,2}

The histopathological landscape is invariably marked by myocyte disarray and interstitial fibrosis, which serve as the anatomical substrate for life-threatening ventricular arrhythmias. The clinical presentation of HCM is a spectrum of considerable breadth; a significant proportion of genetically affected individuals remain asymptomatic, while others experience exertional dyspnea, angina pectoris, palpitations, or syncope. The most devastating consequence, sudden cardiac death, often in young and apparently healthy individuals, has been a central focus of clinical research, leading to the development of sophisticated risk prediction models that incorporate factors such as massive left ventricular hypertrophy, unexplained syncope, non-sustained ventricular tachycardia, and the extent of late gadolinium enhancement on cardiac magnetic resonance imaging. The management paradigm has historically centered on symptom palliation using negative inotropic agents like beta-blockers and non-dihydropyridine calcium channel blockers. However, the therapeutic landscape is currently undergoing a significant transformation.^{2,3}

The refinement of septal reduction therapies—both surgical myectomy and alcohol septal ablation—has provided durable symptomatic relief for patients with obstructive physiology. Furthermore, the advent of cardiac myosin inhibitors, such as mavacamten, heralds a new era of precision medicine by directly targeting the underlying hypercontractile sarcomere function. This manuscript will delve into the intricate genetic basis and multifaceted pathophysiology of HCM, critically appraise contemporary diagnostic algorithms and risk stratification tools, and explore the expanding therapeutic horizons that are progressively shifting the management goal from symptomatic relief toward disease modification.³

Diagnosis of Hypertrophic Cardiomyopathy

The diagnostic journey for hypertrophic cardiomyopathy constitutes a multifaceted process that integrates a detailed clinical evaluation with advanced multimodality imaging and genetic testing, all aimed at establishing the presence of the disease, characterizing its phenotypic expression, and differentiating it from other pathological entities that can mimic its presentation. The cornerstone of diagnosis rests upon the echocardiographic identification of unexplained left ventricular hypertrophy, which is typically defined as a maximal wall thickness of equal to or greater than 15 millimeters in an adult, as measured in end-diastole. This morphological hallmark often presents in an asymmetric pattern, most frequently involving the basal interventricular septum, though the hypertrophy can be concentric, apical, or confined to the lateral wall, thereby underscoring the heterogeneous nature of the disease.^{3,4,5}

Critical to the echocardiographic assessment is the comprehensive Doppler evaluation to delineate the hemodynamic consequences of the hypertrophied morphology, specifically the detection and quantification of left ventricular outflow tract obstruction, both at rest and under provocation with the Valsalva maneuver or exercise. The presence of systolic anterior motion of the mitral valve apparatus, whereby the mitral valve leaflets are drawn towards the interventricular septum during systole, is a pathognomonic feature of the obstructive phenotype and is intimately associated with the generation of a dynamic outflow gradient, often accompanied by significant secondary mitral regurgitation.^{5,6}

In contemporary practice, cardiac magnetic resonance imaging has emerged as an indispensable complementary tool, providing unparalleled tissue characterization and a more comprehensive assessment of cardiac morphology. Its superior spatial resolution allows for the precise quantification of left ventricular mass and the detection of hypertrophy in segments that are often challenging to visualize with echocardiography, such as the apical variant. Perhaps its most significant contribution lies in its unique capacity to identify and quantify myocardial fibrosis through the technique of late gadolinium enhancement. The presence and extent of this replacement fibrosis are not only a marker of the underlying disease process but have also been robustly correlated with an increased propensity for ventricular arrhythmias and adverse cardiac events, thereby providing critical prognostic information beyond anatomical assessment. The diagnostic workup is incomplete without a meticulous and comprehensive family history, spanning at least three generations, to identify patterns of inheritance, unexplained sudden cardiac death, or heart failure in relatives.⁶

This familial context provides the crucial impetus for formal genetic counseling and testing. Targeted genetic analysis for pathogenic variants in sarcomere genes is now a standard component of the diagnostic algorithm, serving to confirm the diagnosis in probands, facilitate cascade screening among asymptomatic family members, and in some instances, offer insights into the potential phenotypic expression and prognosis. The integration of these diverse data streams—clinical, imaging, and genetic—allows for a confident diagnosis of HCM and forms the essential foundation upon which risk stratification and a personalized management plan are meticulously constructed.⁶

Therapeutic Management of Hypertrophic Cardiomyopathy

The management of hypertrophic cardiomyopathy has evolved into a sophisticated, multimodal endeavor aimed not only at symptom palliation but also at modifying the disease's natural history and preventing its most devastating complications. The therapeutic armamentarium now encompasses novel pharmacological agents, advanced

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interventional procedures, and sophisticated device therapy, each targeting distinct aspects of the disease's pathophysiology.⁶

Mavacamten

The advent of cardiac myosin inhibitors represents a paradigm shift in the pharmacological management of obstructive hypertrophic cardiomyopathy, moving beyond mere symptom control to directly address the underlying hypercontractile state of the sarcomere. Mavacamten, as the first-in-class agent in this category, functions by allosterically modulating the myosin head, thereby reducing its excessive actin-binding affinity and transitioning a disproportionate number of myosin heads into a super-relaxed state. This pharmacodynamic action results in a dose-dependent reduction in left ventricular contractility and a significant decrease in the left ventricular outflow tract gradient. The clinical corollary of this molecular intervention is a marked improvement in functional capacity, as evidenced by increased peak oxygen consumption on cardiopulmonary exercise testing, alongside substantial alleviation of exertional dyspnea and angina. Its use, however, necessitates rigorous and continuous monitoring due to the risk of iatrogenic systolic dysfunction, requiring serial assessment of left ventricular ejection fraction and outflow tract gradients to ensure that the therapeutic effect remains within a safe and efficacious window, thereby preventing the development of heart failure.^{7,8}

Implantable Cardioverter-Defibrillator (ICD)

The primary indication for implantable cardioverter-defibrillator therapy in hypertrophic cardiomyopathy is the primary prevention of sudden cardiac death in individuals deemed to be at high risk for malignant ventricular arrhythmias. This decision is predicated upon a comprehensive risk stratification algorithm that incorporates well-established clinical markers, including a history of unexplained syncope, massive left ventricular wall thickness, the documentation of non-sustained ventricular tachycardia on ambulatory monitoring, and an attenuated blood pressure response during exercise. Furthermore, the identification of extensive late gadolinium enhancement on cardiac magnetic resonance imaging, indicative of significant myocardial fibrosis, is increasingly recognized as an important arbiter of arrhythmic risk. The device itself functions as a sentinel, continuously monitoring the cardiac rhythm and delivering life-saving antitachycardia pacing or a defibrillatory shock in the event of ventricular tachycardia or fibrillation. While the prophylactic implantation of an ICD is a weighty clinical decision, balancing the lifelong protection it affords against the potential for device-related complications and inappropriate shocks, its role in altering the mortality profile of this disease for high-risk patients is unequivocal.^{7,8}

Septal Myectomy

Septal myectomy remains the historical gold standard and most definitive therapeutic intervention for patients with severe drug-refractory symptoms and a significant left ventricular outflow tract obstruction. This surgical procedure, typically performed through a transaortic approach, involves the meticulous and targeted resection of a portion of the hypertrophied basal interventricular septum. The objective of this mechanical intervention is the anatomical abolition of the septal bulge that underlies both the outflow tract obstruction and the systolic anterior motion of the mitral valve. The resultant hemodynamic improvement is often immediate and durable, characterized by the elimination of the pressure gradient, a reduction in left ventricular systolic pressures, and the resolution of secondary mitral regurgitation. Consequently, patients experience profound and sustained symptomatic relief. The performance of this complex operation is strongly recommended in high-volume centers with specific surgical expertise, as the proficiency of the surgeon is directly correlated with the procedural success and the minimization of complications such as iatrogenic ventricular septal defect or complete heart block.^{8,9}

Alcohol Septal Ablation

Alcohol septal ablation presents a percutaneous alternative to surgical myectomy for a carefully selected subset of patients, typically older individuals with significant comorbidities that elevate surgical risk. This catheter-based intervention induces a controlled myocardial infarction in the septal perforator artery that supplies the hypertrophied segment responsible for the outflow obstruction. Under echocardiographic and angiographic guidance, a small volume of absolute alcohol is injected into the target septal branch, resulting in localized necrosis, thinning, and scarring of the basal septum over the subsequent weeks to months. This remodeling process gradually widens the outflow tract and reduces the systolic anterior motion of the mitral valve, thereby ameliorating the dynamic gradient. While generally effective, the procedure carries specific risks, most notably the development of right bundle branch block and a non-trivial incidence of procedurally-induced complete heart block, often necessitating permanent pacemaker implantation. The long-term hemodynamic and clinical outcomes are favorable, though a higher rate of required reinterventions compared to myectomy has been observed, making careful patient selection and detailed discussion of the risks and benefits of both septal reduction strategies paramount.^{10,11}

Artificial Intelligence Algorithms in the Prediction of Sudden Cardiac Death

The integration of artificial intelligence into the risk stratification paradigm for sudden cardiac death in hypertrophic cardiomyopathy represents a frontier of significant promise, aiming to transcend the inherent limitations of conventional clinical prediction models.

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Traditional risk scores, while foundational, often operate on a dichotomous assessment of a limited number of variables, potentially overlooking the complex, non-linear interactions between multifaceted clinical, imaging, and genetic factors that culminate in an arrhythmogenic substrate. Artificial intelligence, particularly through the application of sophisticated machine learning and deep learning architectures, offers a transformative approach by harnessing high-dimensional data to identify subtle patterns and latent prognostic signatures imperceptible to conventional analysis. These algorithms are capable of processing and synthesizing a vast array of inputs, including standard clinical parameters, intricate features derived from cardiac magnetic resonance imaging such as texture analysis of myocardial tissue and the complex geometry of hypertrophy, ambulatory electrocardiographic monitoring data, and polygenic risk scores.^{12,13}

For instance, deep neural networks can be trained on raw pixel data from cardiac MRI studies to autonomously extract features associated with myocardial fibrosis and myocyte disarray, quantifying not just the presence but the spatial distribution and heterogeneity of late gadolinium enhancement, which may hold greater prognostic weight than its mere extent. Furthermore, unsupervised learning techniques can potentially deconstruct the phenotypic heterogeneity of HCM into novel sub-phenotypes with distinct arrhythmic propensities, moving beyond the current one-size-fits-all risk model. The ultimate objective of these computational efforts is the development of a highly personalized, continuously evolving risk prediction tool that can provide a more nuanced and accurate estimation of individual patient risk.^{14,15}

This would empower clinicians to make more informed and confident decisions regarding the imperative for primary prevention implantable cardioverter-defibrillator therapy. However, the clinical implementation of these algorithms necessitates rigorous validation in large, multicenter prospective cohorts to ensure generalizability and to address challenges pertaining to model interpretability, often referred to as the "black box" phenomenon, and the mitigation of algorithmic bias before they can be assimilated into mainstream clinical practice and guideline recommendations.¹⁵

CONCLUSION

In conclusion, hypertrophic cardiomyopathy persists as a profoundly complex and heterogeneous myocardial disorder, whose clinical management has progressively evolved from a generalized approach to a highly personalized and nuanced strategy. The foundational understanding of HCM as a disease of the sarcomere has been greatly enriched by advances in genetic testing, which not only facilitate definitive diagnosis in probands but also enable predictive testing in family members, thereby opening avenues for pre-

clinical care and early intervention. The contemporary diagnostic paradigm, heavily reliant on multimodality imaging, extends beyond mere anatomical characterization to provide critical insights into the underlying arrhythmogenic substrate, most notably through the detection and quantification of myocardial fibrosis via cardiac magnetic resonance. The therapeutic landscape is currently experiencing a significant transformation, moving from the historical reliance on symptomatic management with negative inotropic agents to a more targeted and interventional framework. The refinement of septal reduction therapies, both surgical myectomy and alcohol septal ablation, provides durable symptomatic relief for patients with obstructive physiology, while the emergence of novel pharmacological agents such as cardiac myosin inhibitors heralds a new era of disease-modifying therapy by directly targeting the fundamental hypercontractile state of the sarcomere. Concurrently, the sophisticated application of risk stratification models, now potentially augmented by artificial intelligence algorithms capable of deciphering complex data patterns, continues to guide the imperative decision for primary prevention implantable cardioverter-defibrillator implantation. Looking forward, the ongoing elucidation of genotype-phenotype correlations and the integration of deep phenotyping with multi-omics data hold the promise of further refining prognostic accuracy and tailoring therapeutic interventions with unprecedented precision. The future of HCM management lies in this continued synthesis of molecular insight, advanced imaging, and innovative therapeutics, all orchestrated within a comprehensive care model that addresses the multifaceted needs of the patient from diagnosis through long-term follow-up, ultimately aiming to alter the natural history of this disease and improve quality of life.

REFERENCES

- I. Lai, C., Yin, M., Kholmovski, E.G. *et al.* Multimodal AI to forecast arrhythmic death in hypertrophic cardiomyopathy. *Nat Cardiovasc Res* 4, 891–903 (2025). <https://doi.org/10.1038/s44161-025-00679-1>
- II. Wang, H., Wu, Q., Chen, W., Roevers, L., Lazzerini, P. E., & Xiao, J. (2024). Editorial: Case reports in general cardiovascular medicine: 2023. *Frontiers in Cardiovascular Medicine*, 11, 1461761. <https://doi.org/10.3389/fcvm.2024.1461761>
- III. Fishman, G. I. *et al.* Sudden cardiac death prediction and prevention: report from a National Heart, Lung, and Blood Institute and Heart Rhythm Society Workshop. *Circulation* 122, 2335–2348 (2010).
- IV. Adabag, A. S., Luepker, R. V., Roger, V. L. & Gersh, B. J. Sudden cardiac death: epidemiology and risk factors. *Nat. Rev. Cardiol.* 7, 216–225 (2010).

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- V. John, R. M. et al. Ventricular arrhythmias and sudden cardiac death. *Lancet* 380, 1520–1529 (2012).
- VI. Rea, T. D. & Page, R. L. Community approaches to improve resuscitation after out-of-hospital sudden cardiac arrest. *Circulation* 121, 1134–1140 (2010).
- VII. Estes, N. A. M. 3rd Predicting and preventing sudden cardiac death. *Circulation* 124, 651–656 (2011).
- VIII. Merchant, F. M., Levy, W. C. & Kramer, D. B. Time to shock the system: moving beyond the current paradigm for primary prevention implantable cardioverter-defibrillator use. *J. Am. Heart Assoc.* 9, e015139 (2020).
- IX. Merchant, F. M., Jones, P., Wehrenberg, S., Lloyd, M. S. & Saxon, L. A. Incidence of defibrillator shocks after elective generator exchange following uneventful first battery life. *J. Am. Heart Assoc.* 3, e001289 (2014).
- X. Semsarian, C., Ingles, J., Maron, M. S. & Maron, B. J. New perspectives on the prevalence of hypertrophic cardiomyopathy. *J. Am. Coll. Cardiol.* 65, 1249–1254 (2015).
- XI. Maron, B. J. et al. Management of hypertrophic cardiomyopathy: *JACC* state-of-the-art review. *J. Am. Coll. Cardiol.* 79, 390–414 (2022).
- XII. Maron, B. J. et al. Prevalence of hypertrophic cardiomyopathy in a general population of young adults. Echocardiographic analysis of 4111 subjects in the CARDIA study. Coronary Artery Risk Development in (Young) Adults. *Circulation* 92, 785–789 (1995).
- XIII. Ahluwalia, M., Kpodonu, J. & Agu, E. Risk stratification in hypertrophic cardiomyopathy: leveraging artificial intelligence to provide guidance in the future. *JACC Adv.* 2, 100562 (2023).
- XIV. Börjesson, E., Svennblad, B., Wisten, A., Börjesson, M. & Stattin, E.-L. Symptoms and ECG changes precede sudden cardiac death in hypertrophic cardiomyopathy—a nationwide study among the young in Sweden. *PLoS ONE* 17, e0273567 (2022).
- XV. Calò, L. et al. The value of the 12-lead electrocardiogram in the prediction of sudden cardiac death. *Eur. Heart J. Suppl.* 25, C218–C226 (2023).