JACC: HEART FAILURE VOL. 13, NO. 11, 2025

STATE-OF-THE-ART REVIEW

Pathophysiology and Therapeutic Needs in Nonobstructive Hypertrophic Cardiomyopathy

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HIGHLIGHTS

- Nonobstructive HCM is a condition associated with substantial morbidity, mortality, and patient burden.
- Compared with obstructive HCM, the treatment options in nonobstructive HCM are limited.
- Targeted treatments for nonobstructive HCM that address the underlying pathophysiology are needed.
- The number of clinical studies in patients with nonobstructive HCM has steadily increased recently.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received March 21, 2025; revised manuscript received July 6, 2025, accepted July 16, 2025.

ISSN 2213-1779 https://doi.org/10.1016/j.jchf.2025.102658

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

ATP = adenosine triphosphate

CMR = cardiac magnetic resonance

DCM = dilated cardiomyopathy

GWAS = genome-wide association study

HCM = hypertrophic cardiomyopathy

KCCQ-CSS = Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score

LV = left ventricular

LVEF = left ventricular ejection fraction

LVOT = left ventricular outflow tract

pFOX = partial fatty acid oxidation

pVo_2 = peak oxygen consumption

SGLT2 = sodium-glucose cotransporter 2

ABSTRACT

Hypertrophic cardiomyopathy (HCM) affects individuals worldwide with an estimated prevalence of over 1 in 500 individuals. Nonobstructive HCM accounts for approximately 30% to 70% of cases, is extremely heterogeneous, and is associated with a notable degree of morbidity, including daily life limitations, ventricular tachyarrhythmias, progression to heart failure, and atrial fibrillation. No approved pharmaceutical therapies target the pathophysiology of nonobstructive HCM, although several clinical trials are underway. This narrative review provides a comprehensive overview of nonobstructive HCM, focusing on epidemiology, natural history, genetics, pathophysiology, clinical manifestations, diagnosis, burden of disease, and current treatments and ongoing clinical trials. (JACC Heart Fail. 2025;13:102658)

Hypertrophic cardiomyopathy (HCM) is a common heart condition for which diagnosis and treatment strategies have advanced significantly over the last decade.[1] It is clinically and hemodynamically diverse and can present in individuals of all ages.[2] Many people (approximately 46%) with HCM will experience a relatively benign clinical course, whereas the remaining 54% may experience severe symptoms and major complications, such as atrial fibrillation (AF), stroke, heart failure, or sudden cardiac death.[2,3]

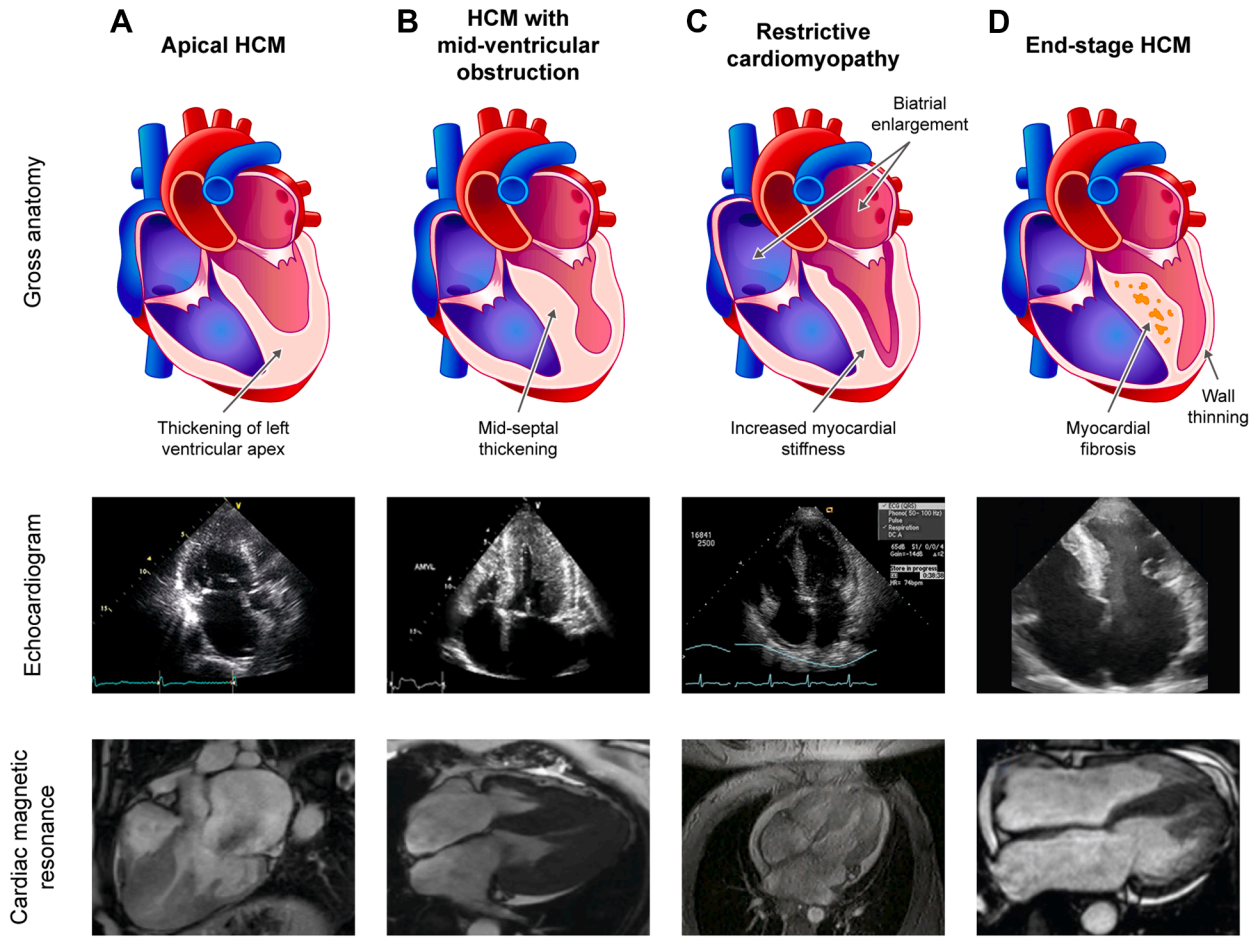
Most symptomatic patients (previously reported to be ~70%) have resting or provocable left ventricular outflow tract (LVOT) obstruction caused by hypercontractility and systolic anterior motion of the mitral valve leaflets.[4] Patients with nonobstructive disease present with similar symptoms, caused by systolic and diastolic left ventricular (LV) dysfunction and myocardial ischemia.[5,6] Autonomic dysfunction, characterized by impaired heart rate and blood pressure recovery after exercise, chronotropic incompetence, and abnormal vasodilation, is also common in HCM.[7,8] The spectrum of nonobstructive HCM is broad (**Figure 1**) and includes apical HCM, in which hypertrophy predominantly affects the LV apex; midventricular obstruction, in which midseptal hypertrophy results in impaired flow at the middle of the left ventricle, sometimes associated with apical aneurysm formation; and a predominantly restrictive phenotype with normal or reduced left ventricular ejection fraction (LVEF).[9-11] Other nonobstructive phenotypes occur in patients who may have been obstructive in the early phase of disease but have since developed progressive systolic impairment after relief of LVOT obstruction by surgery or alcohol septal ablation.[12]

Although natural history studies include patients with obstructive and nonobstructive HCM, few have focused specifically on nonobstructive disease alone.[6] Moreover, in comparison with obstructive HCM, approved treatments that target underlying disease mechanisms are lacking. In the last few years, several targeted therapies have been developed that show promise in alleviating symptoms and potentially modifying nonobstructive HCM phenotypes (**Central Illustration**). These are discussed in this review.

EPIDEMIOLOGY

The comparative epidemiology of obstructive and nonobstructive HCM is not well reported, but extrapolating from observational cohort, registry, and meta-analysis data, it is reasonable to assume that 30% to 70% of all patients with HCM have the nonobstructive phenotype.[4,13-17] Estimates for the frequency of obstructive and nonobstructive HCM depend on the sample population and screening methods.[18] In particular, prevalence estimates based on patients with overt disease are necessarily lower than those in asymptomatic patients with preclinical disease; similarly, studies of otherwise healthy individuals probably overestimate the true prevalence of HCM because of confounding comorbidities such as obesity and hypertension.[18] Variation in diagnostic criteria may also influence prevalence estimates, such as in the case of apical HCM. Fixed diagnostic thresholds for ventricular wall thickness (15-mm cutoff)[8,19] on cardiac magnetic resonance (CMR) may be insufficient for apical HCM because the apex is thinner than the basal septum, predominantly affected in other HCM subtypes.[20] Using anatomical segmental thresholds for hypertrophy in these cases may increase

FIGURE 1 Anatomical and Imaging Features of Nonobstructive HCM Subtypes



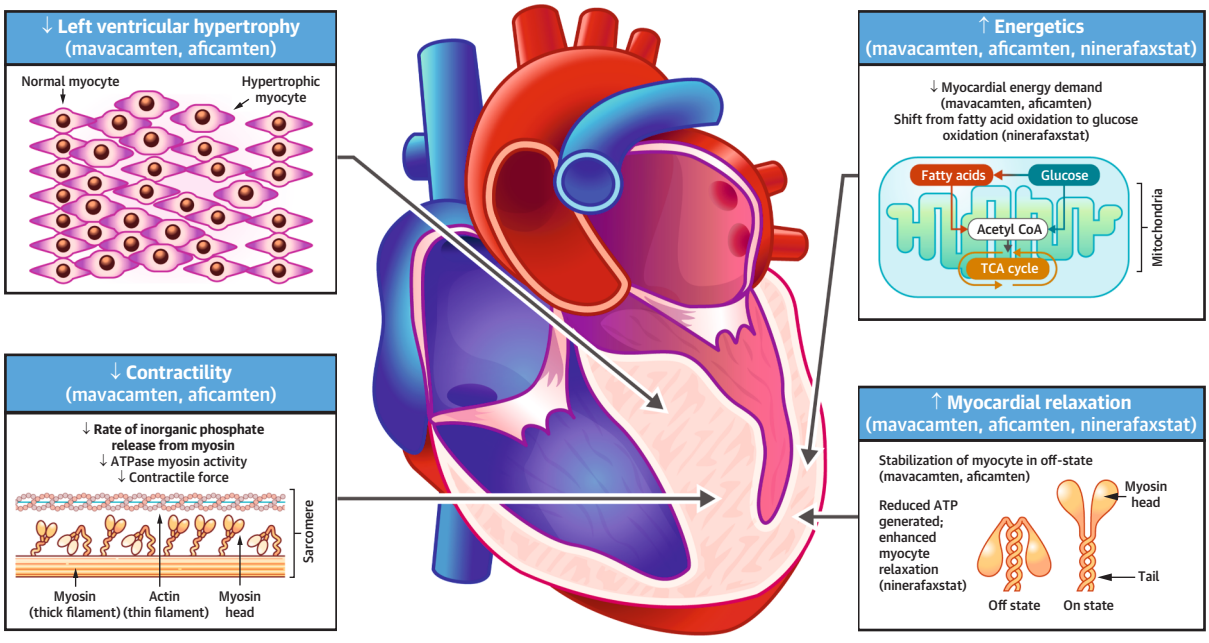
(A) Apical HCM: 3-chamber echocardiographic view and 3-chamber cine CMR view showing apical HCM in a 45-year-old man. (B) HCM with midventricular obstruction: 4-chamber echocardiographic view with provocation and 4-chamber cine CMR in a 54-year-old man with concentric LV hypertrophy and midventricular obstruction. (C) Restrictive cardiomyopathy: 4-chamber echocardiographic view suggesting normal left ventricle size with dilated left atrium and 4-chamber cine CMR in a 58-year-old woman with restrictive cardiomyopathy. (D) End-stage HCM: 4-chamber echocardiographic view and 4-chamber CMR in a 67-year-old man with end-stage HCM. CMR = cardiac magnetic resonance; HCM = hypertrophic cardiomyopathy; LV = left ventricular.

diagnostic yield for apical HCM where hypertrophy falls beneath established thresholds.[20] Similarly, diagnostic thresholds do not account for normal variation in LV wall thickness that exists between individuals.

Recently, a seminal work by Shiwani et al[21] showed how age, sex and body surface area might influence normal maximal LV wall thickness. Using CMR and a validated artificial intelligence algorithm, it was found that a fixed ≥15-mm threshold for LV hypertrophy may bias confirmation of LV hypertrophy in cohorts of individuals with comorbidities and HCM. A demographic-adjusted approach led to improved confirmation of LV hypertrophy and diagnostic accuracy. Additional studies are required for external validation of the approach.[21] Finally, systemic or phenocopy conditions such as amyloidosis or Fabry disease can cause LV maximal wall thickness ≥12 mm and as such could be misdiagnosed as HCM.[8,18,22,23] Nevertheless, the large range in estimated prevalence of HCM suggests that underdiagnosis, as well as misdiagnosis, may be common.

The highest prevalence estimates for HCM in the general population are from imaging studies using echocardiography or CMR in healthy individuals, suggesting around 1 in 500 of the general population have HCM.[18,24-27] A much lower prevalence of ~2.3 per 10,000 is reported from studies using data from

CENTRAL ILLUSTRATION **Mechanisms of Action of Investigational Therapies on Pathophysiology of Nonobstructive HCM**



Desai MY, et al. JACC Heart Fail. 2025;13(11):102658.

ATP = adenosine triphosphate; CoA = coenzyme A; HCM = hypertrophic cardiomyopathy; TCA = tricarboxylic acid.

electronic health records.[18,28,29] A constant in most studies is a male predominance, which may be explained by failure to adjust LV wall thickness measurements to sex or body size, lower disease penetrance in women, and delayed disease onset related to other genetic and endocrine factors.[30]

Because HCM is often a heritable trait caused by sarcomeric pathogenic variants, genetic screening studies provide an alternative approach in estimating disease prevalence, but these too are also subject to biases relating to methodology.[18,31] For example, UK Biobank studies report a prevalence of sarcomere variants ranging from 1:149 to 1:407.[18,32-34] Variant carriers are more likely to experience cardiomyopathy, heart failure, and ventricular arrhythmias than variant-negative control subjects, but overall disease penetrance is low (<3%).[33] This emphasizes the caution required when extrapolating prevalence from genotype alone.[33]

NATURAL HISTORY

By reason of its complex and evolving pathophysiology and broad etiologic spectrum, clinical profiles in nonobstructive HCM range from asymptomatic with minimal risk of disease-associated complications to a more malignant course associated with sudden cardiac death, progressive heart failure, or stroke. For example, in a prospective study of 249 patients with nonobstructive HCM, 5- and 10-year survival rates were 99% and 97%, respectively. This was similar to all-cause mortality in an age- and sex-matched U.S. general population and similar to patients with obstructive HCM, although fewer patients with nonobstructive HCM experienced AF (19% nonobstructive HCM vs 33% and 23% for resting and provocable obstruction, respectively) and progression to advanced heart failure symptoms (1.6% per year for nonobstructive HCM vs 7.4% and 3.2% per year for resting and provocable obstruction, respectively) than those with obstructive HCM.[14] Sudden death, resuscitated out-of-hospital cardiac arrest, and appropriate implantable cardioverter-defibrillator interventions occurred in similar rates between patients with nonobstructive and obstructive disease (0.9% per year for nonobstructive vs 0.6% and 0.8% for resting and provocable obstruction, respectively).[14]

Other studies have reported a higher frequency of ventricular arrhythmia in patients with nonobstructive HCM.[13,15] Lu et al[13] reported ventricular arrhythmias in 37% of patients with nonobstructive HCM compared with 18% of patients with labile-obstructive HCM and 13% of patients with obstructive HCM. Pozios et al[15] reported almost 3 times as many ventricular arrhythmia events in patients with nonobstructive as in patients with obstructive HCM and 5 times as many as patients with labile-obstructive HCM. Studies detailing development and use of risk prediction models for ventricular arrhythmias in young adults reported a greater risk of sudden death in those with LVOT obstruction, whereas the pediatric study reported an inverse association.[35-37] Patchy fibrosis and microvascular ischemia ultimately leading to LV wall thinning and systolic dysfunction can occur in patients with nonobstructive HCM.[15,38,39]

Although the exact mechanisms have not yet been clearly identified, these might be the results of altered energetics and myocardial relaxation.[40] LV remodeling is a clinically relevant feature to identify because it is known to increase the risk of sudden cardiac death and precede the "burned out" or overt dysfunction HCM phase (discussed later).[38,39,41] Similarly, LV apical aneurysms, characterized by thin-walled, scarred, dyskinetic/akinetic tissue at the apex, were also strongly associated with sudden death and adverse cardiac events, as well as thromboembolic events secondary to thrombus formation.[42,43]

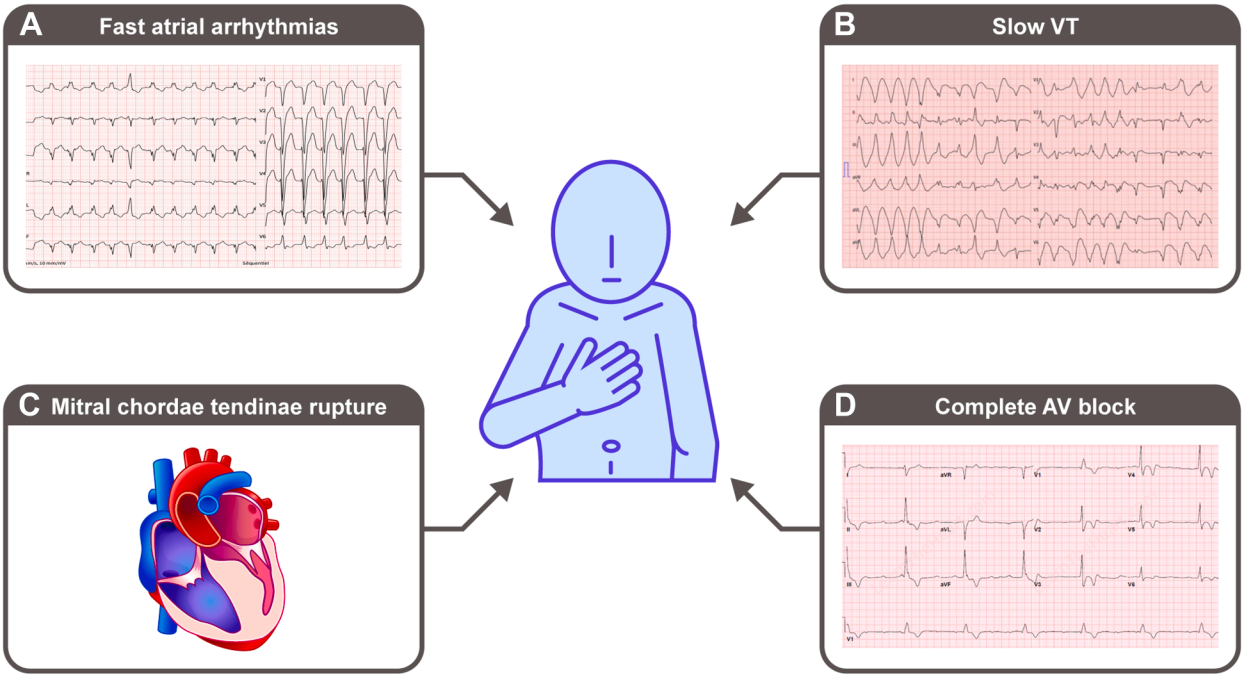
A meta-analysis by Pelliccia et al[16] shed light on long-term outcomes associated with the 2 HCM subtypes. Twenty studies were included in the analysis in which 5,058 patients had nonobstructive HCM (65%) and 2,673 (35%) had obstructive HCM. It should be noted that the proportion of patients considered to have nonobstructive HCM in that study was a potential overestimation because cases of latent obstruction were not adequately identified in the individual studies included in the analysis. Nevertheless, a lower proportion of patients with nonobstructive HCM had NYHA functional class III-IV disease than those with obstructive HCM (8% vs 16%; $P = 0.0001$). Additionally, in patients with nonobstructive HCM, maximal LV wall thickness and left atrial dimensions were significantly smaller than in patients with obstructive HCM, and mitral regurgitation was also less common. Interestingly, a higher proportion of patients with nonobstructive HCM had a family history of sudden cardiac death (26% vs 16%; $P = 0.0001$) and nonsustained ventricular tachycardia (19% vs 14%; $P = 0.0001$). Annual mortality related to HCM was not significantly different between patients with nonobstructive and obstructive HCM (1.55% and 1.77%, respectively; relative risk: 0.87 [95% CI: 0.66-1.14]).[16] A subanalysis in patients with apical HCM, which included 14 studies with 1,417 patients, reported an annual disease-related mortality of 0.81%, sudden cardiac death-related mortality in 2.5% of patients, and heart failure-related death in 0.8% of patients.[16]

The proportion of patients with nonobstructive HCM progressing to heart failure differs across studies, with recent publications reporting that 8% to 30% of patients progress to NYHA functional class III-IV.[13,14,16,44] Diastolic dysfunction is the primary mechanism responsible for heart failure symptoms in patients with nonobstructive HCM (**Figure 2**). Some patients may develop dilated-hypokinetic evolution of HCM, also known as "end-stage" or "burned out" HCM.[38] Patients with end-stage HCM have a variable clinical course, but many go on to develop advanced heart failure, requiring transplantation, and mortality is around 2% to 7% per year.[38,45,46] Genotype, a family history of end-stage HCM, myocardial scar burden, and the presence of AF are associated with the risk of end-stage HCM.[45]

Although most patients with end-stage nonobstructive HCM develop systolic dysfunction (defined as LVEF <50%), a small proportion may present with preserved systolic function (LVEF ≥50%) and restrictive physiology.[8,19,47,48] Patients with restrictive HCM and preserved LVEF are more likely to be female, to be symptomatic at presentation, to have AF, and to have a greater maximal LV wall thickness and a smaller LV end-diastolic diameter.[47] Regardless of LVEF, clinical outcomes are typically very poor, with a 5-year mortality of approximately 40% to 50% in patients with restrictive physiology.[48,49]

As with patients suffering from obstructive HCM, cardiometabolic comorbidities are also reported in patients with nonobstructive HCM. In the aforementioned study by Lu et al,[13] a lower proportion of patients with nonobstructive HCM compared with obstructive HCM had hypertension (39% vs 55%, respectively) and dyslipidemia (40% vs 55%, respectively). A similar proportion of patients with nonobstructive HCM and obstructive HCM had diabetes (10% and 8%, respectively). Across the published reports, the incidences of cardiometabolic comorbidities in nonobstructive HCM range from 31% to 44% for hypertension, 40% to 47% for dyslipidemia, and 6% to 12% for diabetes.[13,44,50]

FIGURE 2 Examples of Acute Heart Failure Patterns in Patients With Nonobstructive HCM



(A) Fast atrial arrhythmias on electrocardiogram (ECG). (B) Slow VT on ECG. (C) Mitral chordae tendinae rupture resulting in mitral regurgitation. (D) Complete AV block on ECG in a patient with apical HCM. ECG readouts courtesy of Dr Maurizi. AV = atrioventricular; VT = ventricular tachycardia; other abbreviations as in Figure 1.

GENETICS

In most cases with an identifiable etiology, HCM (obstructive and nonobstructive) is a Mendelian autosomal trait usually caused by variants in 1 of 8 sarcomere genes, the most frequent of which are myosin heavy chain beta (*MYH7*) and myosin-binding protein C3 (*MYBPC3*), together accounting for around 40% to 60% of genotype-positive cases.[18,19,51,52] A recent systematic reappraisal of gene classifications for HCM and associated syndromic conditions, including recuration of genes previously reported by the ClinGen Hereditary Cardiovascular Disorders Gene Curation Expert Panel in 2019, has reported 29 genes with definitive, strong ,or moderate evidence of disease causation. This includes 9 sarcomere genes, with *MYBPC3*, *MYH7*, *TPM1*, *TNNI3*, *ACTC1*, *MYL2*, *MYL3*, *TNNT2*, and *TNNC1* now considered definitive evidence genes. In addition, a number of genes with sarcomere-associated roles, such as *FHOD3*, *KLHL24*, *TRIM63*, *CSRP3*, and *ALPK3*, were included.[52] Between 5% and 10% of adults with a hypertrophic phenotype have disease caused by rare and nonsarcomeric variants, including those that cause inherited neuromuscular and metabolic diseases.[53,54] Other patients have acquired disorders (eg, wild-type amyloidosis) or have a polygenic predisposition to disease, with arterial hypertension considered an important nongenetic modifier.[18,55,56]

The genetic architecture of nonobstructive HCM specifically is not well studied. In general, genotype-phenotype relationships can vary, even within families harboring the same pathogenic variants.[57] Some individuals may never develop symptoms; however, numerous studies have shown that patients with HCM (obstructive and nonobstructive) harboring a disease-causing variant have worse outcomes than those without an identified pathogenic variant, including increased risk of sudden cardiac death.[58-61] Data from SHaRe (Sarcomeric Human Cardiomyopathy Registry), which included patients with obstructive or nonobstructive HCM, demonstrated that patients with sarcomeric pathogenic or likely pathogenic variants have a 2-fold greater risk of complications than those without pathogenic variants.[17] A study from the Hypertrophic Cardiomyopathy Registry reported a relationship between genotype and ventricular

structure.[62] Of the 2,636 patients with available genetic data, 35.8% carried a sarcomeric variant. Patients who carried a sarcomeric variant were less likely to have resting LVOT obstruction and more likely to have reverse septal curvature morphology. Additionally, patients carrying a sarcomeric variant were much more likely to have late gadolinium enhancement on CMR. Fewer patients carrying a sarcomeric variant had apical, concentric, or other types of LV hypertrophy, and midcavitary obstruction affected similar proportions of patients with or without a sarcomeric variant.[62] Overall, this suggests a potential relationship between presence of sarcomeric pathogenic variants, morphology, and the nonobstructive phenotype.

COMMON GENETIC VARIANTS. Genome-wide association studies (GWASs) have identified that common variants may contribute to the risk of developing HCM.[56,63,64] The largest and most recent GWAS analyzed over 9 million variants in 5,900 patients with HCM and 68,359 healthy volunteers.[64] The study identified 70 susceptibility loci (50 novel) significantly associated with HCM and 62 loci (32 novel) associated with LV volume, LV mass, and LV contractility (supporting their roles in structural traits of both obstructive and nonobstructive HCM). After a GWAS to analyze the causal association of LV contractility, a substantially shared genetic basis between obstructive and nonobstructive HCM was found. A novel disease-causing gene, supervillin (*SVIL*), was also identified among common variant loci in HCM, conferring a 10-fold increased risk of HCM (obstructive and nonobstructive).[64] A recent study using data from 184,511 individuals in the UK Biobank investigated the contributions of rare and common genetic variants to the risk of developing HCM (subtype not specified). Individuals with pathogenic or likely pathogenic variants in 14 "core" HCM genes (as designated by the ACMG [American College of Medical Genetics and Genomics]) were associated with 55-fold higher odds of developing HCM compared with those without these variants.[55]

Common genetic variants were also found to contribute substantially to HCM risk in the general population. Using a common variant or polygenic risk predictor, Biddinger et al[55] reported that a high polygenic risk score was associated with HCM among individuals who do not carry rare pathogenic variants (an increase of 1 SD in polygenic risk score was associated with 1.6- and 1.4-fold increased odds of HCM in the UK Biobank and MGB [Mass General Brigham] Biobank, respectively). Similarly, a recent study from Zheng et al[65] indicated that a high polygenic score significantly increases the risk of HCM in the general population, particularly among those with pathogenic variants. Polygenic risk scores can also explain a substantial proportion of phenotypic variability in patients with HCM (obstructive or nonobstructive), shedding light on mechanisms that might be used for pharmacologic interventions.[63]

PATHOPHYSIOLOGY OF NONOBSTRUCTIVE HCM

DISEASE MECHANISMS. Obstructive and nonobstructive HCM have been shown to have a similar genetic background specific to LV contractility.[64] However, the effects of pathogenic genetic variants are still not fully understood, but it is likely that different variants affect protein function, stability, interacting myosin head motifs, and motor function in varying degrees. For example, it has been reported that pathogenic variants in the converter region of the beta-cardiac myosin may cause HCM by altering the intrinsic force produced by individual myosin heads, whereas pathogenic variants in both the actin-binding site and converter regions of the myosin head may result in HCM by increasing the number of active myosin heads available for force production.[66] Hypercontractility, a hallmark of HCM pathophysiology, is believed to result from excessive actin-myosin cross-bridging.[67] As such, reduction in hypercontractility through inhibition of ATPase activity in cardiac myosin heavy chain is a promising therapeutic target and is supported by extensive clinical trial data showing that HCM can be effectively treated.[68-83]

Clinical genetics and basic science published reports have shed further light on the potential mechanisms by which HCM might arise. Sarcomeric variants affect contractile force generation by altering calcium-dependent myofilament tension generation, with opposing effects observed experimentally in HCM and dilated cardiomyopathy (DCM). ERK1/2 signaling resulting from myofilament tension may activate myocyte thickening, as seen in HCM, whereas ERK1/2 inhibition may result in dilated growth, as observed in DCM.[84] This is supported by data from a large GWAS that showed shared genetic loci between HCM and DCM. However, the alleles showed opposing effects on the LV traits.[63] RNA sequencing of HCM (obstruction status not assessed) and DCM hearts in mice found perturbation of metabolic pathways in cardiomyocyte cells and enrichment of profibrotic and inflammatory pathways in nonmyocyte cells (ie, cardiac fibroblasts) in both cardiomyopathy subtypes.[85] Furthermore, single nucleus RNA sequencing analysis of human left

ventricle samples from patients with HCM (obstruction status not assessed) and DCM revealed the presence of an activated fibroblast population that was near absent in healthy left ventricle samples. Chaffin et al[86] reported that the differential expression of known activated fibroblast markers in HCM and DCM hearts was almost absent in healthy hearts, which may suggest a role in cardiac fibrosis observed in these diseases.

Abnormal cardiac energy metabolism is believed to play a role in how pathogenic variants in sarcomere genes affect the disease course in HCM. Patients with HCM have a substantially reduced phosphocreatine-to-ATP ratio compared with healthy individuals, suggesting that myocardial energy deficiency may contribute to disease.[87,88] This hypothesis was supported by a proof-of-concept study of perhexiline (a carnitine palmitoyl transferase-1 inhibitor) in patients with nonobstructive HCM. The results of the study indicated that the reduced phosphocreatine-to-ATP ratio improved after a mean duration of 4.6 months of perhexiline treatment. This was associated with an improvement in reduced phosphocreatine-to-ATP ratio, exercise capacity, diastolic function, and NYHA functional class status.[89] However, a randomized, placebo-controlled clinical trial of trimetazidine (a beta-oxidation inhibitor) in patients with nonobstructive HCM failed to reach its primary endpoint of peak oxygen consumption (pVo_2) during upright bicycle ergometry after 3 months of treatment. Secondary endpoints of exercise capacity and symptom status were also not met. It was hypothesized that this may be due to weaker fatty acid oxidation with beta-oxidation inhibition compared with carnitine palmitoyl transferase-1 inhibition (ie, perhexiline) or insufficient duration of therapy.[90]

DIAGNOSTIC CONSIDERATIONS

A diagnosis of HCM is often made after a cardiac event or after a routine examination that arouses clinical suspicion.[8,19] Symptoms can be caused by systolic and diastolic LV dysfunction and myocardial ischemia.[5,6] Autonomic dysfunction, which can also be iatrogenic and linked to beta-blocker therapy, is also common and may present as impaired heart rate and blood pressure recovery after exertion, chronotropic incompetence, and abnormal vasodilation.[7,8] Physical signs in nonobstructive HCM are often more subtle than in obstructive HCM and are limited to features that reflect the hyperdynamic contraction (rapid upstroke pulse) and reduced compliance of the right ventricle (prominent a wave in jugular venous pressure) and left ventricle (S_4 gallop, double-apex beat).

The ESC (European Society of Cardiology), AHA (American Heart Association)/ACC (American College of Cardiology), and JCS (The Japanese Circulation Society)/JHFS (Japanese Heart Failure Society) guidelines recommend a comprehensive medical history and physical examination, a 12-lead electrocardiogram, and a transthoracic echocardiogram for diagnosis (ESC: Class of Recommendation [COR] 1, Level of Evidence [LOE] B and C; AHA/ACC: COR 1, LOE B; JCS/JHFS: COR 1, LOE B [relates to echocardiogram only]).[8,19,91] CMR is also recommended, particularly when echocardiography is inconclusive, because it allows tissue characterization (edema and myocardial fibrosis) and visualization of areas not well defined on echocardiography (eg, LV apex) and aids in differentiation of HCM from phenocopies such as amyloidosis or storage disease (ESC: COR 1, LOE B; AHA/ACC: COR 1, LOE B; JCS/JHFS: COR 1, LOE A and B).[8,19,91-93] HCM phenocopies (**Table 1**) may pose diagnostic challenges and have therapeutic consequences. These phenocopies should be suspected based on several red flags associated with the syndromic phenotype and ruled out by targeted genetic testing, which the EHRA (European Heart Rhythm Association)/HRS (Heart Rhythm Society)/APHRS (Asia Pacific Heart Rhythm Society)/LAHRS (Latin American Heart Rhythm Society) recommends to consist of genes with definitive or strong evidence of pathogenicity.[8,18,94,95] When HCM is established, society guidelines (ESC, AHA/ACC, JCS/JHFS, and EHRA/HRS/APHRS/LAHRS) recommend pedigree analysis and family screening when appropriate.[8,19,91,95] Further details on clinical manifestations and recommendations for diagnosis of HCM can be found in the ESC, AHA/ACC, JCS/JHFS, and EHRA/HRS/APHRS/LAHRS guidelines.[8,19,91,95]

BURDEN OF DISEASE

A few studies have assessed the clinical and economic burdens of nonobstructive HCM in patients living with the condition. A conceptual model was developed to identify the most relevant symptoms and the impact of HCM from patients' perspectives.[96] The model was generated using a web-based patient survey (444 responses), a targeted review of published reports, one-to-one interviews with 3 clinical experts, and one-to-one elicitation interviews with 27 patients. The model identified that patients with HCM most frequently experience dyspnea, palpitations, fatigue, dizziness, and chest pain. These had a

TABLE 1 HCM Phenocopy Conditions[8,18,92,137]

	Clinical Features	Electrocardiogram	Imaging	Genetics
Cardiac amyloidosis	Adult onset; broad multisystemic involvement including cardiac, musculoskeletal, ophthalmologic, peripheral, and autonomic nervous systems, liver	Low-voltage QRS complexes, pseudo-infarct Q waves and conduction abnormalities	LV and RV hypertrophy with valve thickening, atrial dilatation, apical-sparing strain pattern, diastolic dysfunction, global subendocardial or transmural LGE, increase in myocardial T1 and ECV	Patients with hereditary TTR amyloidosis have pathogenic variants in *TTR*; wild-type TTR amyloidosis and light-chain amyloidosis are not hereditary
RASopathies	Pediatric onset; facial dysmorphism, dermatologic abnormalities, other systemic involvement	Right axis deviation, bundle branch block, prolonged QT interval	LV and RV hypertrophy, papillary muscle abnormalities, congenital defects	Pathogenic variants in Ras/MAPK pathway
Mitochondrial cytopathies	Neonatal to adult onset; broad multisystemic involvement including central nervous system, cardiac, and musculoskeletal systems	Ventricular pre-excitation, increased LV voltages, conduction disorders	Asymmetrical or concentric LV hypertrophy, systolic dysfunction, LGE, increase in myocardial T1 and ECV	Pathogenic variants in maternally inherited mitochondrial genome or nuclear DNA
Glycogen storage diseases				
Danon disease	Adolescent/young adult onset; liver and muscle involvement	Ventricular pre-excitation, increased LV voltages	LV hypertrophy, asymmetrical septal hypertrophy, LV systolic dysfunction, apical-sparing strain pattern, patchy midwall LGE, increase in myocardial T1 and ECV	Pathogenic variants in *LAMP2*
PRKAG2 cardiomyopathy	Adolescent/young adult onset; muscle weakness	Ventricular pre-excitation, increased LV voltages, conduction disorders	Variable, asymmetric LV hypertrophy, patchy midwall LGE, increase in myocardial T1 and ECV	Pathogenic variants in *PRKAG2*
Pompe disease	Neonatal to adult onset; liver and muscle involvement	Increased LV voltages, short PR interval with ventricular pre-excitation or conduction block	Prominent LV hypertrophy, patchy midwall LGE, increase in myocardial T1 and ECV	Pathogenic variants in *GAA*
Cori/Forbes disease	Neonatal to adult onset; liver and muscle involvement	Increased LV voltages	Concentric LV hypertrophy, patchy midwall LGE, increase in myocardial T1 and ECV	Pathogenic variants in *AGL*
Lysosomal storage diseases				
Anderson-Fabry disease	Adulthood onset; broad multisystemic involvement including neurological, cardiac, renal, and gastrointestinal systems	Increased LV voltages, short PR interval, bradycardia, chronotropic incompetence, atrioventricular block	Concentric LV hypertrophy, RV hypertrophy, diastolic and systolic dysfunction, LGE in inferolateral midwall, myocardial T1 and ECV diffusely decreased	Pathogenic variants in *α-GAL A*

α-GAL A = α-galactosidase A; *AGL* = glycogen debranching enzyme gene; ECV = extracellular volume; GAA = α-glucosidase gene; HCM = hypertrophic cardiomyopathy; *LAMP2* = lysosome-associated membrane glycoprotein 2 gene; LGE = late gadolinium enhancement; LV = left ventricular; MAPK = mitogen-activated protein kinase; PRKAG2 = protein kinase AMP-activated noncatalytic subunit gamma 2; *PRKAG2* = protein kinase AMP-activated noncatalytic subunit gamma 2 gene; RV = right ventricular; TTR = transthyretin; *TTR* = transthyretin gene; T1 = time for longitudinal magnetization to reach 63% of its final value after application of radiofrequency pulse.

profound effect on patients' lives, including limitations to physical activity, emotional distress, and a detrimental impact on work. The results were similar for patients with both obstructive and nonobstructive HCM, but patients with obstructive HCM tended to have more frequent and more severe symptoms than those with nonobstructive HCM.[96]

Data from the AFFECT-HCM study reported the impact of HCM on quality of life (measured by the generic EQ-5D-5L (EuroQol 5-Dimension 5-Level) questionnaire and the Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score [KCCQ-CSS], which is used in obstructive HCM[97]) and societal costs (measured by the iMedical Consumption Questionnaire and iMTA [Institute for Medical Technology Assessment] Productivity Cost Questionnaire). Based on genotype and phenotype, data were categorized into 3 groups: genotype-positive, phenotype-negative; nonobstructive HCM; and obstructive HCM). In total, 506 participants were enrolled (genotype-positive, phenotype-negative: 84; nonobstructive HCM: 313; obstructive HCM: 109). Compared with genotype-positive, phenotype-negative participants, those with nonobstructive HCM or obstructive HCM had a significantly reduced quality of life, with patients with obstructive HCM having the worst KCCQ scores. Similarly, societal costs were also significantly higher in patients with HCM than in genotype-positive, phenotype-negative individuals (€19,035 per year vs €7,385 per year). Symptomatic patients under age 60 years in particular had a decreased quality of life.[98]

Although those with clinically mild disease (or genotype-positive, phenotype-negative individuals) may have a better quality of life, some evidence suggests there could still be some impairment in cardiopulmonary exercise capacity. A recent subanalysis of the VANISH trial[99] investigated the

health-related quality of life and cardiopulmonary exercise capacity of pediatric patients with subclinical and early-stage HCM. Although health-related quality of life was good across the 166 enrolled patients with early-stage disease and 34 patients with subclinical (genotype-positive) disease, those with subclinical disease had significantly better composite pediatric quality of life scores. Interestingly, both groups had a reduced cardiopulmonary exercise capacity, as measured by percentage achieved of predicted pVo_2 and peak oxygen pulse.[99]

However, more studies are needed to investigate the impact of nonobstructive HCM on patients' lives and the short- and long-term effects of treatment. The utility of patient-reported measures specifically validated in this patient population would be beneficial. The HCMSQ (Hypertrophic Cardiomyopathy Symptom Questionnaire), a patient-reported outcome designed to evaluate HCM symptoms specifically, has been psychometrically validated in patients with nonobstructive HCM.[100] However, to our knowledge, no clinical study evaluating changes in the HCMSQ among patients with nonobstructive HCM has been published to date. Moreover, the validation study assessing KCCQ in obstructive HCM included a qualitative cognitive debriefing to evaluate (using patient interviews) whether the questionnaire was understandable and pertinent to obstructive HCM, without external comparison with objective functional assessments.[97]

TREATMENT AND CLINICAL TRIALS

PHYSICAL ACTIVITY. Patients with HCM (obstructive or nonobstructive) are, in general, recommended to engage in exercise of mild-to-moderate intensity, given the health benefits associated with physical activity (ESC: COR 1, LOE C; AHA/ACC: COR 1, LOE B).[8,19] Vigorous exercise may also be possible after a comprehensive evaluation by a clinical expert (AHA/ACC: COR 2a, LOE B).[8] Very few studies exist in patients with nonobstructive HCM regarding exercise; however, 1 recent study investigated various outcomes in athletes with nonobstructive HCM at low risk of sudden cardiac death.[101] The results indicated that continuation of exercise or competitive sports at the same level over a mean period of 4.5 years did not negatively affect their condition (event rate for asymptomatic arrhythmias was 2.1% per year). This study indicates a potentially positive prognosis for intense exercise in low-risk patients with nonobstructive disease.[101] These data are supported by a study that showed vigorous exercise was not associated with pathologic LV hypertrophy or ventricular arrhythmias in patients with phenotype-positive HCM when compared with genotype-positive, phenotype-negative patients with HCM[102]; however, it is unclear how many of these patients had nonobstructive disease. Overall, further research is needed regarding the risk and benefit of exercise in patients with HCM, and a personalized approach may be warranted.[103]

SURGICAL TREATMENT. Current U.S. guidelines recommend consideration of surgical myectomy in patients with nonobstructive HCM and extensive apical hypertrophy with severe dyspnea or angina who are receiving maximal pharmaceutical therapy (AHA/ACC: COR 2b, LOE C).[8] An observational study of 113 patients with severely symptomatic apical HCM who underwent transapical myectomy reported clinical improvement in 76% of patients and long-term survival of 87% at 5 years and 74% at 10 years.[104]

In patients with nonobstructive HCM and advanced heart failure refractory to guideline-directed management, current guidelines recommend consideration of heart transplantation (ESC: COR 1, LOE C; AHA/ACC: COR 1, LOE B).[8,19] Although transplantation is generally performed in patients with heart failure and an LVEF <50%, patients with nonobstructive HCM who have severe heart failure symptoms refractory to pharmacologic treatments may be candidates even if they have a preserved LVEF (which accounts for about half of these cases).[105] A study of patients with nonobstructive HCM with preserved LVEF reported that all 12 patients who underwent transplantation were still alive and without symptoms at a mean follow-up of 2.3 years postsurgery.[105] It has been noted that for patients with HCM in general, survival after heart transplantation is similar to, or possibly better than, that observed in patients with other conditions, with reported 1-, 5-, and 10-year overall survival of 85%, 75%, and 61%, respectively.[106]

CARDIAC PACING. Several clinical studies have looked at the efficacy of pacing in patients with nonobstructive HCM. Atrioventricular pacing at the right ventricular apex has been shown to improve diastolic function and functional capacity in patients with nonobstructive HCM.[107] Current U.S. guidelines recommend cardiac resynchronization therapy in patients with nonobstructive HCM receiving an implantable cardioverter-defibrillator with NYHA functional class II to ambulatory class IV heart failure, left bundle branch block, and LVEF <50% (AHA/ACC: COR 2a, LOE C).[8] Cardiac resynchronization therapy has been noted to result in increased exercise capacity and improved quality of life in patients with

nonobstructive HCM who initially presented with severe exercise limitation on maximally tolerated therapies. This benefit was believed to be due to augmented diastolic filling during exercise.[108] Improvements in NYHA functional class have been noted in 40% to 70% of patients, and these have been associated with increases in LVEF.[109,110]

PHARMACOLOGIC TREATMENT. Compared with obstructive HCM, pharmacologic treatment of patients with nonobstructive HCM is more challenging. The currently recommended treatments available for patients with nonobstructive HCM are based on limited evidence and target AF, LV filling pressures, angina, and dyspnea. Beta-blockers and nondihydropyridine calcium channel blockers are recommended in patients with exertional angina or dyspnea (ESC: COR 2a, LOE C; AHA/ACC: COR 1, LOE C),[8,19] and U.S. guidelines suggest considering diuretic agents when exertional dyspnea persists (AHA/ACC: COR 2a, LOE C).[8] However, these treatments are often ineffective, especially in symptomatic patients, and side effects may not be tolerable.[50] In Europe, ranolazine may be considered for angina-like chest pain (ESC: COE 2b, LOE C).[19] The U.S. guidelines suggest that valsartan may benefit younger patients with pathogenic variants and mild symptoms for slowing cardiac remodeling (AHA/ACC: COE 2b, LOE B).[8] In Japan, beta-blockers and calcium channel blockers may be considered for patients with NYHA functional class I (JCS/JHFS: COR 2b, LOE C) and are recommended for class II to IV (JCS/JHFS: COR 1, LOE B) nonobstructive HCM, and low-dose diuretic agents are also recommended for class II to IV nonobstructive disease with congestive symptoms (JCS/JHFS: COR 1, LOE C).[91]

Over the last decade, a number of clinical trials have assessed pharmaceutical agents in symptomatic nonobstructive HCM (**Table 2**). Specific drugs that have been studied include valsartan (NCT01912534),[111] sacubitril/valsartan (NCT03832660),[112] ranolazine (EudraCT 2011-004507-20; currently recommended in Europe),[113] eleclazine (NCT02291237),[114] spironolactone (NCT00879060),[115] losartan (NCT01447654),[116,117] trimetazidine (NCT01696370),[90] and perhexiline (NCT02862600).[118,119] Of these trials, only the valsartan trial (VANISH [Valsartan for Attenuating Disease Evolution in Early Sarcomeric HCM]) reached its primary endpoint. In this phase II trial, 178 participants in the primary cohort with early-stage sarcomeric HCM were randomized 1:1 to receive valsartan (an angiotensin II receptor blocker) or placebo. All 178 patients were confirmed to have nonobstructive HCM at baseline,[120] and none developed obstructive HCM physiology during the study.[111] After 2 years of treatment, valsartan statistically significantly improved a composite *z*-score of LV wall thickness, LV mass, LV volumes, left atrial volume, tissue Doppler diastolic and systolic velocities, and serum high-sensitivity troponin T and N-terminal pro-B-type natriuretic peptide levels from baseline compared with placebo.[111] Despite this, the guidelines consider the usefulness of angiotensin receptor blockers in the treatment of symptoms (ie, angina and dyspnea) in patients with nonobstructive HCM to not be well established (ESC: no recommendation provided; AHA/ACC: COR 2b, LOE C).[8,19]

Promising results have been shown in a recent randomized controlled trial of the mineralocorticoid receptor agonist eplerenone (ACTRN12613000065796) in 61 patients with nonobstructive HCM over 12 months.[121] A reduction in myocardial T1 time on CMR was demonstrated with eplerenone treatment compared with placebo in adults with nonobstructive HCM, consistent with a reduction in diffuse myocardial fibrosis. Further trials are required to ascertain any clinical benefit.[121]

Currently, clinical trials of potential disease-modifying agents including cardiac myosin inhibitors, partial fatty acid oxidation (pFOX) inhibitors, and sodium-glucose cotransporter 2 (SGLT2) inhibitors are underway. These are discussed later.

CARDIAC MYOSIN INHIBITORS. Mavacamten is the first and only cardiac myosin inhibitor approved in 5 continents for the treatment of adults with symptomatic NYHA functional class II-III obstructive HCM. Mavacamten has been shown to result in improvements in cardiac function and structure, symptoms, and health status in clinical trials, long-term extension studies, clinical trial subanalyses, and real-world analyses in patients with obstructive HCM.[68-83]

In patients with nonobstructive HCM, a phase II, multicenter, randomized, double-blind, placebo-controlled, dose-ranging study (MAVERICK-HCM; NCT03442764) investigated the safety and tolerability of mavacamten in symptomatic adults.[122] In 59 patients (mean age: 54 years; 58% women) randomized (1:1:1) to mavacamten at a pharmacokinetic-adjusted dose (target plasma levels: 200 ng/mL or 500 ng/mL) or placebo, mavacamten was found to be well tolerated in most patients, with a low rate of serious adverse events occurring (10% in the mavacamten arm vs 21% in the placebo arm). Most treatment-emergent adverse events were mild (76%). Five patients treated with mavacamten had a reversible reduction of LVEF to 45% or lower and discontinued treatment, which was expected, given

TABLE 2 Clinical Trials in Patients With Symptomatic Nonobstructive HCM With Published Results in the Last Decade

Study Name (ID Number)	Design	Population	Therapy (Class)	Primary Endpoint(s)	Key Points
MAVERICK-HCM (NCT03442764)[122]	Multicenter, exploratory, dose-ranging, double-blind, randomized, placebo-controlled study; phase II	59 adults with NYHA functional class II-III nonobstructive HCM	Mavacamten (cardiac myosin inhibitor)	Safety and tolerability of mavacamten treatment over 16 wk	Mavacamten was well tolerated in most participants Mavacamten was associated with significant reductions in serum NT-proBNP and cardiac troponin I levels
REDWOOD-HCM (NCT04219826)[123]	Multicenter, open-label study; phase II	41 adults with NYHA functional class II-III nonobstructive HCM	Aficamten (cardiac myosin inhibitor)	Safety and tolerability of aficamten and incidence of LVEF <50% over 10 wk	Aficamten was well tolerated in most participants Aficamten was associated with significant improvement in symptom burden (NYHA functional class and KCCQ-CSS) and significant reductions in serum NT-proBNP and cardiac troponin I levels
IMPROVE-HCM (NCT04826185)[127]	Multicenter, randomized, placebo-controlled, double-blind study; phase II	67 adults with nonobstructive HCM with pVo_2 ≤80% predicted and family history of HCM	Ninerafaxstat (cardiac mitotrope partial fatty acid oxidation inhibitor)	Safety and tolerability of ninerafaxstat over 12 wk	Ninerafaxstat was well tolerated in most patients Ninerafaxstat was associated with significant improvement in ventilatory efficiency (ratio of minute ventilation-to-carbon dioxide production) slope Post hoc analysis showed a significant improvement in KCCQ-CSS in participants with a baseline score ≤80
Efficacy of SGLT2 Inhibitors in Patients With Diabetes and Nonobstructive Hypertrophic Cardiomyopathy (no clinical trial registration)[134]	Prospective, open-label, blinded endpoint trial; clinical trial phase not indicated	48 adults with NYHA functional class >II nonobstructive HCM and type 2 diabetes	Empagliflozin or dapagliflozin (SGLT2 inhibitors)	Composite endpoint of improvement of ≥1.5 in E/e′ and a reduction of ≥1 NYHA functional class after 6 mo	Significantly more patients treated with SGLT2 inhibitors met the primary composite endpoint SGLT2 inhibitors were also associated with significant improvements in diastolic function parameters, 6-min walk distance and serum NT-proBNP levels Treatment was well tolerated in most patients
SILICOFCM (NCT03832660)[112]	Prospective, multicenter, open-label, randomized, controlled trial; phase II	115 adults with NYHA functional class I-III nonobstructive HCM	Sacubitril/valsartan (angiotensin receptor-neprilysin inhibitor)	Change in pVo_2 at 16 wk	Sacubitril/valsartan treatment resulted in no significant change in pVo_2 No significant changes in blood pressure, cardiac structure and function, plasma biomarkers, or quality of life were observed
RESTYLE-HCM (EudraCT 2011-004507-20)[113]	Randomized, placebo-controlled, multicenter, double-blind study; phase II	80 adults with NYHA functional class II-III nonobstructive HCM	Ranolazine (cardiac late sodium current inhibitor)	Change in pVo_2 test after 5 mo	No significant difference in pVo_2 change vs placebo Reduction in 24-h burden of premature ventricular complexes observed with ranolazine No significant change in serum NT-proBNP levels, E/e' ratio, or quality of life vs placebo

Continued on the next page

TABLE 2 Continued

Study Name (ID Number)	Design	Population	Therapy (Class)	Primary Endpoint(s)	Key Points
Clinical and Therapeutic Implications of Fibrosis in Hypertrophic Cardiomyopathy (NCT00879060)[115]	Randomized, double-blind, placebo-controlled trial; phase IV	53 adults with obstructive or nonobstructive HCM	Spironolactone (mineralocorticoid receptor blocker)	Effect of spironolactone on serum markers of collagen synthesis and degradation at 12 mo	No significant differences vs placebo for serum markers of collagen synthesis or degradation No significant differences vs placebo for fibrosis by late gadolinium enhancement on CMR or other clinical measures (pVo_2, NYHA functional class, LV dimensions, left atrial size, or diastolic function)
INHERIT (NCT01447654)[116,117]	Single-center, randomized, double-blind, placebo-controlled trial; phase II	133 adults with obstructive or nonobstructive HCM	Losartan (angiotensin receptor blocker)	Change in LV mass on CMR or CT	No significant difference vs placebo in change in LV mass No effect on cardiac function or exercise capacity
Trimetazidine Therapy in Hypertrophic Cardiomyopathy (NCT01696370)[90]	Randomized, placebo-controlled, double-blind clinical trial; phase II	49 adults with NYHA functional class ≥II nonobstructive HCM and pVo_2 ≤80%	Trimetazidine (beta-oxidation inhibitor)	pVo_2 during upright bicycle ergometry	No significant change vs placebo in pVo_2 No significant changes vs placebo in exercise capacity, symptom status, diastolic function, LVEF, left atrial area, global LV longitudinal systolic strain, or biomarkers
VANISH (NCT01912534)[111,120]	Multicenter, randomized, placebo-controlled, double-blind clinical trial; phase II	178 participants (adults and children) with early-stage sarcomeric nonobstructive HCM	Valsartan (angiotensin II receptor blocker)	Change in composite *z*-score of LV wall thickness, LV mass, LV volume, left atrial volume, tissue Doppler diastolic and systolic velocities, and serum high-sensitivity troponin T and NT-proBNP levels from baseline to end of study (year 2)	Significant increase in composite *z*-score for valsartan vs placebo Treatment was well tolerated
Effects of aldosterone blockade in hypertrophic cardiomyopathy (https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?ACTRN=12613000065796)[121]	Single-center, prospective, placebo-controlled, double-blind trial; clinical trial phase not indicated	61 adults with nonobstructive HCM	Eplerenone (mineralocorticoid receptor antagonist)	Native T1 time on CMR	A significant reduction in myocardial T1 time with eplerenone vs placebo No significant change in functional status or markers of diastolic function between groups

CMR = cardiac magnetic resonance; E/e′ = ratio of early diastolic mitral inflow velocity-to-early diastolic mitral annulus velocity; KCCQ-CSS = Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide; pVo_2 = peak oxygen consumption; SGLT2 = sodium-glucose cotransporter 2; other abbreviations as in Table 1.

that this was a dose-ranging study with no opportunity for down-titration.[122] Mavacamten treatment was associated with a significant dose-dependent reduction in serum N-terminal pro-B-type natriuretic peptide; geometric mean decreased by 53% in the overall mavacamten arm vs 1% in the placebo arm ($P = 0.0005$). Cardiac troponin I geometric mean decreased by 34% in the mavacamten arm vs 4% in the placebo arm ($P = 0.009$).[122]

An investigational cardiac myosin inhibitor, aficamten, is in clinical trials for the treatment of patients with obstructive or nonobstructive HCM. Data from patients with nonobstructive HCM in REDWOOD-HCM (NCT04219826), a phase II, multicenter, open-label study, have recently been published. This study evaluated the safety and tolerability of aficamten in 41 patients (mean age: 56 years; 60% women) with symptomatic nonobstructive HCM over a period of 10 weeks.[123] Treatment with aficamten was well tolerated, with a low proportion of patients experiencing serious adverse events (9.8%). Three patients (8%) experienced an LVEF <50%, which resolved after a 2-week washout period. One patient died of cardiac arrest, deemed related to his or her

underlying condition. Twenty-two patients (55%) showed an improvement of at least 1 NYHA functional class and 11 (29%) became asymptomatic. KCCQ-CSS also improved by at least 5 points in 22 patients (55%). Additionally, treatment was associated with significant reductions in the cardiac biomarkers N-terminal pro-B-type natriuretic peptide and cardiac troponin I (reductions of 56% [$P < 0.0001$)] and 22% [$P < 0.005$], respectively).

The results from MAVERICK-HCM and REDWOOD-HCM suggest the potential efficacy of mavacamten and aficamten for the treatment of patients with nonobstructive HCM and support their continued investigation in larger scale studies. At the time of writing, phase III trials for mavacamten (ODYSSEY-HCM; NCT05582395) and aficamten (ACACIA-HCM; NCT06081894) are ongoing (**Table 3**). These phase III studies of the cardiac myosin inhibitors mavacamten and aficamten are both randomized, double-blind, placebo-controlled trials with similar inclusion criteria.[50] Both studies will use KCCQ-CSS and change in pVo_2 as dual primary endpoints for assessing patient-reported outcomes and functional capacity, respectively (measured at 48 weeks for ODYSSEY-HCM and 36 weeks for ACACIA-HCM). Change in pVo_2 has been shown to be a clinically relevant outcome in phase III trials of cardiac myosin inhibitors in patients with obstructive HCM.[72,124] Secondary endpoints for both studies include changes in NYHA functional class and biomarkers; ODYSSEY-HCM will also report ventilatory efficiency and the Hypertrophic Cardiomyopathy Symptom Questionnaire-Shortness of Breath subscore, whereas ACACIA-HCM will also report a composite endpoint of exercise performance measures and will evaluate structural remodeling.[50] Recruitment for ODYSSEY-HCM has been completed with 580 patients randomized to receive mavacamten or placebo, and baseline characteristics of the patient population have been published.[50] Although results have not yet been published at the time of writing, a press release from the sponsor indicated that the ODYSSEY-HCM trial did not meet its dual primary endpoints.[125] Although the study data are still being analyzed, this result underscores the potential genotypic and phenotypic complexity of nonobstructive HCM and the challenges in designing clinical trials for this disease.

pFOX INHIBITORS. Ninerafaxstat, a cardiac mitotrope pFOX inhibitor, partially inhibits fatty acid oxidation through the mitochondrial long-chain fatty acid beta-oxidation pathway, thus reducing the amount of oxygen required for ATP generation and increasing myocardial efficiency.[126,127] A phase II, multicenter, randomized, double-blind, placebo-controlled study (IMPROVE-HCM; NCT04826185) evaluated the safety and tolerability of ninerafaxstat in patients with symptomatic nonobstructive HCM.[127] In 67 patients with nonobstructive HCM randomized 1:1 to ninerafaxstat or placebo (mean age: 57 years; 55% women), ninerafaxstat was found to be well tolerated, with serious adverse events occurring in 11.8% and 6.1% of patients receiving ninerafaxstat and placebo, respectively. Patients treated with ninerafaxstat showed a significant improvement in ventilatory efficiency (ratio of minute ventilation-to-carbon dioxide production) slope from baseline to week 12 compared with those who received placebo (least-squares mean difference: −2.1 [$P = 0.006$]), suggesting greater ventilatory efficiency. No significant difference in pVo_2 was observed between arms. Post hoc analysis showed a significant improvement in KCCQ-CSS in patients with a baseline score of ≤80 in the ninerafaxstat arm compared with the placebo arm.[127] It is anticipated that ninerafaxstat will be progressing to a phase IIb study (FORTITUDE-HCM [A Trial to Evaluate the Efficacy and Safety of Ninerafaxstat in Patients With Symptomatic Non-obstructive Hypertrophic Cardiomyopathy]) later in 2025.[128]

SGLT2 INHIBITORS. SGLT2 inhibitors have been investigated in clinical trials of chronic heart failure, chronic kidney disease, and type 2 diabetes and have been shown to improve patient outcomes significantly.[129-132] Accordingly, the SGLT2 inhibitors dapagliflozin and empagliflozin are recommended for the treatment of symptomatic heart failure with preserved ejection fraction (ESC: COR 1, LOE A),[133] a condition that presents similarities to heart failure in patients with HCM. A prospective, open-label, blinded endpoint trial was conducted to evaluate the effects of SGLT2 inhibitors (empagliflozin or dapagliflozin) in patients with type 2 diabetes and symptomatic nonobstructive HCM with preserved LVEF over a period of 6 months (**Table 2**).[134] In 48 patients randomized 1:1 to SGLT2 inhibitors or placebo (mean age: 48.3 years; 70% men), significantly more patients treated with SGLT2 inhibitors achieved the primary composite endpoint of an improvement of at least 1.5 in the ratio of early diastolic mitral inflow velocity-to-early diastolic mitral annulus velocity and a reduction of at least 1 NYHA functional class after 6 months (70.8% vs 4.2% [$P < 0.001$]). Significant improvements were also observed in echocardiography-measured diastolic function parameters (including ratio of early diastolic mitral

TABLE 3 Ongoing and Upcoming Clinical Trials In Patients With Nonobstructive HCM[a]

Study Name (ID Number)	Design	Population	Therapy (Class)	Estimated Enrollment	Duration	Primary Endpoint(s)
Phase IV						
ENDEAVOR-HCM (NCT06580717)	Prospective, multicenter, randomized, double-blind, placebo-controlled study	Adults with NYHA functional class I-III nonobstructive HCM	Enavogliflozin (SGLT2 inhibitor)	200	24 wk	LV diastolic function
Use of SGLT2i in no HCM With HFpEF (NCT06401343)	Prospective, multicenter, open-label, randomized controlled trial	Adults with NYHA functional class II-IV nonobstructive HCM and HFpEF	Empagliflozin (SGLT2 inhibitor)	94	12 mo	Maximum oxygen intake on cardiopulmonary exercise testing
TEMPO II (NCT05569382)	Randomized crossover trial	Adults with NYHA functional class ≥II nonobstructive HCM	Bisoprolol (beta-blocker) and verapamil (calcium channel blocker)	100	21 d	Maximum oxygen intake on cardiopulmonary exercise testing, LV end-diastolic volume, incidence of nonsustained ventricular tachycardia
Phase III						
ODYSSEY-HCM (NCT05582395)	Randomized, double-blind, placebo-controlled clinical study	Adults with NYHA functional class II-III nonobstructive HCM	Mavacamten (cardiac myosin inhibitor)	420	48 wk	Change in KCCQ-CSS, pVo_2
MAVA-LTE (NCT03723655)	Long-term extension	Individuals who have completed MAVERICK-HCM (nonobstructive) or EXPLORER-HCM (obstructive)	Mavacamten (cardiac myosin inhibitor)	282	252 wk	Frequency and severity of treatment-emergent AEs and serious AEs
ACACIA-HCM (NCT06081894)	Multicenter, randomized, double-blind trial	Adults with NYHA functional class II-III nonobstructive HCM	Aficamten (cardiac myosin inhibitor)	420	36 wk	Change in KCCQ-CSS
FOREST-HCM (NCT04848506)	Follow-up, open-label, research evaluation	Individuals who have completed aficamten clinical trials (includes patients with obstructive or nonobstructive HCM)	Aficamten (cardiac myosin inhibitor)	900	5 y	Incidence of AEs
SONATA-HCM (NCT06481891)	Randomized, double-blind, placebo-controlled, parallel-group, multicenter study	Adults with NYHA functional class II-III, nonobstructive HCM and KCCQ-CSS < 85	Sotagliflozin (SGLT1 and SGLT2 inhibitor)	500	26 wk	Change from baseline to week 26 in KCCQ-CSS
Phase II						
CIRRUS-HCM (NCT06347159)	Open-label, nonrandomized, sequential assignment, multicenter study	Adults with NYHA functional class I-III obstructive or nonobstructive HCM	EDG-7500 (selective cardiac sarcomere modulator)	75	4 wk + 48 wk	Incidence of treatment-emergent AEs
Nonpharmaceutical trials						
EXCITE-HCM (NCT05818605)	Randomized, controlled, blinded clinical trial	Adults with nonobstructive HCM able to perform exercise training	Exercise training	70	24 wk	Effect of moderate intensity exercise training vs usual physical activity on the improvement of HCM-related symptoms and cardiac function
Transapical Beating-Heart Septal Myectomy in Patients With Symptomatic Nonobstructive Hypertrophic Cardiomyopathy (NCT05952154)	Single group assignment	Adults with NYHA functional class ≥II nonobstructive HCM	Transapical beating-heart septal myectomy	100	3 mo	All-cause mortality, procedural success

[a]Studies were ongoing at the time of writing.

AE = adverse event; HFpEF = heart failure with preserved ejection fraction; other abbreviations as in Tables 1 and 2.

inflow velocity-to-early diastolic mitral annulus velocity, ratio of the early-to-late ventricular filling velocities, and left atrial volume), 6-minute walk distance (295.1 m vs 343.0 m [$P < 0.001$]), and serum N-terminal pro-B-type natriuretic peptide levels (481.4 vs 440.9 pg/mL [$P < 0.001$]). SGLT2 inhibitors were well tolerated, with only 1 serious adverse event reported (1 patient developed a urinary tract infection 5 weeks into the study).

A global phase III study of the SGLT1 and SGLT2 inhibitor sotagliflozin is underway (SONATA-HCM; NCT06481891) that will assess the change in KCCQ-CSS over 26 weeks as the primary objective in adults with nonobstructive HCM. Two phase IV

studies of SGLT2 inhibitors are also underway. One is investigating empagliflozin in adults in China with nonobstructive HCM and heart failure with preserved LVEF, with the primary endpoint of change in Vo_{2max} on cardiopulmonary exercise testing over 12 months (NCT06401343). The other, ENDEAVOR-HCM (NCT06580717) (unrelated to the ENDEAVOR trial in patients with heart failure with preserved or mildly reduced ejection fraction; NCT04986202), is investigating enavogliflozin in adults with nonobstructive HCM in South Korea, with the primary endpoint of change in LV diastolic function.

OTHER EXPERIMENTAL THERAPIES. In addition to cardiac myosin inhibitors, pFOX inhibitors, and SGLT2 inhibitors, other experimental therapies are currently being investigated in clinical trials. One of these is a phase Ib/II dose escalation study of TN-201, an investigational adenoassociated virus serotype 9 gene therapy, in adults with obstructive or nonobstructive HCM with pathogenic variants in *MYBPC3* (MyPEAK-1; NCT05836259). Early data from the first cohort of patients in the MyPEAK-1 trial (n = 3) demonstrated robust cardiac transduction of TN-201 DNA and a corresponding increase in MYBPC3 protein. TN-201 was also associated with stabilization or improvement from baseline in clinical parameters, and the therapy was generally well tolerated.[135] Another experimental therapy is the selective cardiac sarcomere modulator EDG-7500, which is being investigated in an open-label phase II trial of adults with obstructive or nonobstructive HCM (CIRRUS-HCM; NCT06347159). Finally, a gene therapy candidate for the treatment of patients with HCM and pathogenic variants in the *TNNI3* gene (LX2022) is currently under development at the preclinical stage.[136]

SUMMARY OF UNMET NEEDS IN NONOBSTRUCTIVE HCM

The epidemiology of nonobstructive HCM is still not well reported and further up-to-date studies would be beneficial in understanding how many patients are affected by this condition worldwide. Similarly, more studies on the natural history and long-term outcomes of nonobstructive HCM would allow a better understanding of this specific patient population.

Recent studies on genetics and GWASs have shed further light on lifetime risk of HCM in patients with and without disease-causing pathogenic variants. More studies investigating the genetic differences between patients with obstructive HCM and those with nonobstructive HCM would be desirable, particularly because an identical pathogenic variant can cause obstructive or nonobstructive phenotypes in different individuals. Across the HCM spectrum, further work is also needed to understand the genotype-phenotype relationship, which would potentially enable better risk prediction and understanding of the disease course. Similarly, a greater understanding of the mechanisms of HCM is needed to allow the development of additional treatments specifically targeting the underlying pathophysiology of the disease.

It is clear that the burden of disease for patients with nonobstructive HCM is not well reported, and further research would be especially beneficial in understanding the specific needs of this population. This could form the basis for assessing short- and long-term treatment outcomes once approved therapies are available.

Compared with obstructive HCM, the treatment options in nonobstructive HCM are limited, with current treatment strategies providing only symptomatic relief. Targeted treatments for nonobstructive HCM that address the underlying pathophysiology are needed, and several clinical trials are aiming to address this. If these clinical trials are successful, further real-world studies will be needed to confirm the safety and efficacy across a broader patient population.

CONCLUSIONS

Nonobstructive HCM has become more widely investigated in recent years, but major unmet needs still exist. Developing effective treatments that target the underlying pathophysiology and improve symptom burden and outcomes in patients with nonobstructive HCM is a high priority.

ACKNOWLEDGMENTS Medical writing and editorial support under the guidance of the authors were provided by Ciaran Wright, PhD, of Oxford PharmaGenesis (Oxford, UK), funded by Bristol Myers Squibb (Princeton, New Jersey, USA).

FUNDING SUPPORT AND AUTHOR DISCLOSURES

This work was supported by Bristol Myers Squibb (Princeton, New Jersey, USA). Dr Desai has consultant and research agreements with Bristol Myers Squibb, Cytokinetics, Edgewise Therapeutics, Tenaya Therapeutics, and Viz.Ai. Dr Maurizi has received consulting fees and advisory board fees from Academic CME, Bristol Myers Squibb, and CardioLink. Dr Biagini has received consulting fees from Amicus, Bristol Myers Squibb, Chiesi, Sanofi-Genzyme, and Takeda. Dr Charron has received consulting fees from Amicus, Bristol Myers Squibb, Owkin, Pfizer, Sanofi, and Servier. Dr Fernandes has received consulting fees from Alnylam, AstraZeneca, Bristol Myers Squibb, and Pfizer. Dr González-López has received speaker fees from Alnylam, Bristol Myers Squibb, Eidos, and Pfizer; and consulting fees from Akcea, Bristol Myers Squibb, Novo Nordisk, Pfizer, and Proclara. Dr van Haelst is an employee of Bristol Myers Squibb and may own Bristol Myers Squibb stock or stock options. Dr Hermann Haugaa has received consulting fees from Bristol Myers Squibb and Solid BioSciences; and speaker fees from Boehringer Ingelheim and

Novartis. Dr Kramer has received research grants from Bristol Myers Squibb, Cytokinetics, and Eli Lilly; and consulting fees from Eli Lilly. Dr Meder has received funding regarding hypertrophic cardiomyopathy research from the Deutsches Zentrum für Herz-Kreislauf-Forschung (German Center for Cardiovascular Research), Informatics for Life (Klaus Tschira Foundation), and the Leducq Foundation; and honoraria for advising on HCM topics and/or travel support/speaker honoraria from Bristol Myers Squibb, Cytokinetics, Novo Nordisk, and Pfizer. Dr Michels has received research funding from Bristol Myers Squibb; and consulting fees from Alnylam, Bayer, Bristol Myers Squibb, Cytokinetics, Pfizer, and Sanofi. Dr Owens has received consulting and/or advisory board fees from Alexion, Avidity, Bayer, Biomarin, Bristol Myers Squibb, Corvista, Cytokinetics, Edgewise Therapeutics, Imbria, Lexeo, Pfizer, Stealth, and Tenaya Therapeutics. Dr Yuasa has received lecture fees from Amgen, Bristol Myers Squibb, Daiichi Sankyo, Kowa Company, Nippon Boehringer Ingelheim, Novartis, Pfizer Japan, and Toa Eiyo, Japan; research funding from Bayer Yakuhin; and equity ownership in Heartseed Inc. Dr Elliott has received consulting fees from Alnylam, Bristol Myers Squibb, Cardior, DiNAQOR, Freeline, Pfizer, Sanofi, and Sarepta.

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KEY WORDS heart failure, hypertrophic cardiomyopathy, nonobstructive