Full Title: Targeted Therapies in Pediatric and Adult Patients with Hypertrophic Heart Disease - From Molecular Pathophysiology to Personalized Medicine

Running Title: Target Therapies in Hypertrophic Heart Disease

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Abstract

Hypertrophic cardiomyopathy (HCM) is a myocardial disease defined by an increased left ventricular wall thickness not solely explained by abnormal loading conditions. It is often genetically determined, with sarcomeric gene mutations accounting for around 50% of cases. Several conditions, including syndromic, metabolic, infiltrative, and neuromuscular diseases, may present with left ventricular hypertrophy (LVH), mimicking the HCM phenotype but showing a different pathophysiology, clinical course, and outcome. Despite being rare, they are collectively responsible for a large proportion of patients presenting with hypertrophic heart disease, and their timely diagnosis can significantly impact patients' management.

The understating of disease pathophysiology has advanced over the last few years, and several therapeutic targets have been identified, leading to a new era of tailored treatments applying to different etiologies associated with LVH.

This review aims to provide an overview of the existing and emerging therapies for the principal causes of hypertrophic heart disease, discussing the potential impact on patients' management and clinical outcome.

Keywords: hypertrophic cardiomyopathy; RASopathy; glicogen storage disorders; Friedreich ataxia; cardiac amyloidosis; Fabry disease.

Non-standard Abbreviations and Acronyms

AAV, adeno-associated virus

AL, amyloid immunoglobulin light chain

ASO, antisense oligonucleotide

ATTR, amyloid transthyretin

CFC, cardio-facio-cutaneous syndrome

CMI, cardiac myosin inhibitor

CPET, cardiopulmonary exercise testing

CS, Costello syndrome

ERT, enzyme replacement therapy

FA, Friedreich ataxia

FXN, frataxin

Gb3, globotriaosylceramide

HCM, hypertrophic cardiomyopathy

IOPD, infantile-onset Pompe disease

LOPD, late-onset Pompe disease

LVEF, left ventricular ejection fraction

LVOT, left ventricular outflow tract

LVOTO, left ventricular outflow tract obstruction

MAPK, RAS/Mitogen-activated protein kinase

MAT, multifocal atrial tachycardia

MEK1, mitogen-activated protein kinase kinase 1

NS, Noonan syndrome

NSML, Noonan syndrome with multiple lentigines

NT-proBNP, N-terminal-pro hormone B-type natriuretic peptide

oHCM, obstructive hypertrophic cardiomyopathy

NYHA, New York Heart Association

PZR, protein-zero-related

RCT, randomized clinical trial

RVOTO, right ventricular outflow tract obstruction

SHP2, Src homology-2 domain-containing protein tyrosine phosphatase-2

siRNA, small interfering RNA molecule

SRX, super-relaxed state

TTR, transthyretin

Background

Hypertrophic cardiomyopathy (HCM) is a myocardial disease characterized by increased left ventricular (LV) wall thickness not solely explained by abnormal loading conditions[1,2]. The etiology of HCM is heterogeneous, with sarcomeric gene mutations identified in up to 40-60% of cases[2]. However, several other conditions may be associated with LV hypertrophy (LVH) mimicking an HCM phenotype, including malformative syndromes, metabolic, infiltrative, and neuromuscular disorders[3].

International expert panels have suggested several work-up strategies to improve the recognition of underlying etiology in patients presenting with hypertrophic heart disease[2–4]. Since the causes can be significantly different between adults and children, the diagnostic assessment should be tailored according to the age of presentation and clinical characteristics[3] **(Figure 1)**.

Identifying the underlying etiology of hypertrophic heart disease is crucial, as certain causes could benefit from specific treatment[5]. Additionally, early diagnosis plays a key role in preventing disease progression and related complications by appropriately starting a tailored therapy[3]. In recent years, our understanding of the pathophysiology of several inherited cardiac conditions has improved and led to the development of novel therapies that target the underlying substrate.

This review aims to provide an overview of the existing and emerging therapies for the principal causes of hypertrophic heart disease, discussing the potential impact on patients' management and clinical outcome.

Hypertrophic heart disease in children

Hypertrophic heart disease in children may underlie several disorders with different clinical courses and management[6]. According to current registries, non-sarcomeric causes (including inborn error of metabolism, neuromuscular disorders, and malformative syndromes) are responsible for up to 40% of cases of hypertrophic heart disease, with differences according to the age of presentation[7]. Infants are more likely to have a non-sarcomeric etiology than children or adolescents. In contrast, the prevalence of sarcomeric mutations increases with age, with sarcomeric HCM responsible for most cases of hypertrophic heart disease in adolescence.

Sarcomeric HCM

Mutations in genes encoding for sarcomeric proteins are the most common cause of HCM[8], with about half of the cases associated with a pathogenic variant in *MYH7* or *MYBCP3*[8]. The presentation and progression of sarcomeric HCM in children are variable, ranging from a mild phenotype with a benign clinical course to severe disease combined with complications, evolving to

end-stage[9]. In the future, disease-modifying therapies (such as mavacamten or gene therapy, discussed below) will offer a unique opportunity to modify the natural history and improve patients' outcome **(Figure 2)**.

RASopathies

RASopathies are multisystemic disorders caused by germline mutations in the RAS/Mitogen-activated protein kinase (MAPK) pathway[10]. These disorders include Noonan syndrome (NS), Noonan syndrome with multiple lentigines (NSML), Costello syndrome (CS), and cardio-facio-cutaneous syndrome (CFC). From a cardiac perspective, RASopathies present with hypertrophic heart disease in childhood, commonly characterized by biventricular involvement, end-stage remodeling, frequent heart failure-related hospitalizations, and increased mortality[11,12].

MEK1 inhibitors

The RAS/MAPK cascade has been considered a promising therapeutic target in animal and human studies. Several studies have recently suggested that mitogen-activated protein kinase kinase 1 (MEK1) inhibitors may effectively treat cardiovascular and lymphatic abnormalities associated with RASopathies **(Figure 2)**. For example, regression of LVH has been documented in mouse models carrying the *RAF1* p.L613V gain-of-function variant after treatment with MEK1 inhibitors[13]. Trametinib, a highly selective allosteric MEK1 inhibitor, was associated with regression of LVH and significant improvement in clinical status combined with decongestion in two cases of *RIT1*-associated NS[14]. After 17 months of follow-up, both patients showed sustained clinical improvement, with regression of LVH, reduction of right ventricular outflow tract (RVOT) gradients, and normalization of N-terminal-pro hormone B-type natriuretic peptide (NT-proBNP) levels. Of interest, treatment cessation was associated with LVH recurrence.

The administration timing appears crucial for successful treatment. Indeed, murine models of NS-associated LVH showed that prenatal administration of MEK1 inhibitors caused LVH regression, but postnatal use failed to demonstrate evidence of effectiveness[15]. Recently, trametinib was administered in an infant with NS carrying a *RAF1* pathogenic variant associated with severe LVH and pulmonary hypertension[16]. After trametinib was introduced, a significant improvement in the Ross functional class and a reduction of LV wall thicknesses was observed, allowing the patients to be weaned off inotropes. Unfortunately, the patient developed severe pulmonary hypertension and died due to respiratory failure.

In addition, trametinib improves multifocal atrial tachycardia (MAT) on top of anti-arrhythmic treatment[17]. Although the mechanism of action is not entirely understood, trametinib modulates

intracellular calcium handling by reducing ryanodine receptor phosphorylation. Consequently, it reduces the delayed after-depolarizations responsible for the MAT occurrence[18]. Trametinib was also shown to alleviate lymphatic abnormalities and reduce the need for mechanical support in a patient with NS. This effect may contribute to the reduction of atrial arrhythmias[18].
Despite the beneficial effects on the cardiovascular system, safety reviews and data from the experience of trametinib use in melanoma report increased cardiovascular events, including systemic hypertension, LV systolic dysfunction, arrhythmias, and venous thromboembolism. Further studies with pre-specified endpoints are needed to investigate the long-term outcomes of MEK inhibition in NS and evaluate the timing of therapy weaning to minimize possible adverse reactions.

mTOR inhibitors

Increased Akt/mTOR pathway activity is associated with specific *PTPN11* variants and contributes to LVH in patients with NSML **(Figure 2)**. Pharmacological studies on *PTPN11* p.Y279C murine models showed that postnatal administration of rapamycin attenuated the development of LVH[19]. Based on these findings, everolimus was administered for compassionate use in an infant with severe LVH. Unfortunately, despite the decrease in NT-proBNP concentration, there was no evidence of LVH regression or clinical improvement, and the patient underwent cardiac transplantation[20].

Src family kinase inhibitors

In recent years, the identification of protein-zero-related led to the hypothesis of a common pathway both in NS and NSML, as this protein was found to be hyperphosphorylated and bound to Src homology-2 domain-containing protein tyrosine phosphatase-2 (SHP2) both in *PTPN11* p.Y279C NSML and *PTPN11* p.D61G NS mice. Subsequently, it was shown that dasatinib, an inhibitor of Src homology proteins, improved cardiac function and reversed LVH in NSML mice. Similar results were obtained in *PTPN11* p.D61G knock-in mice models of NS-associated LVH[21,22]. Given that LVH regression was obtained with low doses of dasatinib, its use in clinical trials appears promising.

Glycogenosis

Glycogenosis is a rare inborn disorder of glycogen metabolism caused by defects along the synthesis or degradation pathway of glycogen, leading to its abnormal tissue and organ accumulation[6]. The classification of the disease is based on the degree of enzyme deficiency[23]. The

organs primarily affected are the liver and muscles, where glycogen is stored, and processes like glycolysis, gluconeogenesis, and glycogen synthesis are regulated[23]. Disease manifestations are caused by the toxic effect of glycogen deposits on lysosomal function, cellular architecture, and tissue biophysical properties[23]. Only Pompe disease, Cori disease, Danon disease, and PRKAG2 disease within the glycogenosis spectrum have been associated with the occurrence of LVH[5]. However, no targeted therapies are currently available for any of these disorders except for Pompe disease.

Pompe disease

Pompe disease is a rare autosomal recessive neuromuscular disorder caused by *GAA* mutation leading to alpha-glucosidase deficiency and abnormal lysosomal glycogen storage[24]. According to the degree of residual enzyme activity, two main phenotypes have been described. The severe infantile-onset form (IOPD [infantile-onset Pompe disease]) includes patients with less than 1% enzyme activity who present with early clinical involvement characterized by LVH and pulmonary disease[25]. On the other hand, the late-onset form (LOPD [late-onset Pompe disease]) is characterized by higher residual enzyme activity and is not associated with cardiac involvement in most cases[26]. Patients with IOPD have limited life expectancy due to severe cardio-respiratory complications unless specific therapy is delivered.

Enzyme replacement therapy

Enzyme replacement therapy (ERT) based on recombinant human alpha-glucosidase received FDA approval in 2006 to treat patients with infantile and late-onset Pompe disease **(Figure 2)**. In phase I-II clinical trials, the administration of ERT to infants with Pompe disease was associated with significant improvement in overall survival and cardio-respiratory and motor function[27]. These data were confirmed in phase III trials and long-term studies, showing that, when administered in the first years of life, alglucosidase alfa reduced the risk of death and invasive ventilation and improved LVH and functional capacity[28,29]. Several factors can influence the treatment response, including age, disease severity degree, cross-reactive immunologic material status and development of IgG antibodies[30].

Limitations of ERT include its insufficient uptake into some affected tissues[31], responsible for variable treatment response in some patients, the rare occurrence of severe anaphylactic and immunological reactions, and the inability to cross the blood-brain barrier[31]. These limitations and the requirement for lifelong intravenous infusions have prompted the active search for alternative targeted strategies, such as pharmacological chaperone therapy, substrate reduction therapy, and

gene therapy[32–34]. Although studies are still limited, these treatments may become an active part of the pharmacological armamentarium for patients with Pompe disease in the future.

Danon disease

Danon disease is a rare X-linked disorder caused by *LAMP2* mutation, leading to the accumulation of autophagosomes and glycogen, with prominent effects on the skeletal and cardiac muscle, which ultimately leads to heart failure and, for male patients, premature death during adolescence or early adulthood[5,6]. Unfortunately, no etiological therapy is currently available to treat Danon disease.

Gene therapy

Due to its monogenic etiology, gene therapy represents a promising therapy for treating Danon disease **(Figure 2)**. In mouse models, the administration of adeno-associated virus 9 (AAV9) carrying the wild-type human *LAMP2B* complementary DNA (AAV9:LAMB2B) resulted in a dose-dependent restoration of human LAMP2B protein in the heart, liver, and skeletal muscle, improved heart and liver function, and increased survival[35]. Subsequently, an open-label, single-dose, phase I trial enrolling seven Danon disease male patients with *LAMP2* mutation and cardiomyopathy was designed to evaluate the safety of RP-A501, an AAV9:LAMP2B gene therapy. The first results of this trial demonstrated that RP-A501 administration was safe and responsible for increased LAMP2B expression, improved autophagy, and improved or stabilized serologic, echocardiographic, and clinical parameters. In detail, improvement or stabilization of BNP, troponin, left ventricular ejection fraction (LVEF), LV wall thickness, and New York Heart Association (NYHA) class were observed in 6-12 months of treatment (NCT03882437). Based on these enthusiastic results, the FDA has granted Regenerative Medicine Advanced Therapy (RMAT) designation to RP-A501, thus expediting the drug development and review process.

Friedreich Ataxia

Friedreich ataxia (FA) is an autosomal recessive neuromuscular disorder that principally affects the heart and the nervous system[36]. It is caused by a triplet repeat expansion mutation in the gene encoding frataxin (*FXN*). Approximately 96% of affected individuals are homozygous for an expanded GAA trinucleotide repeat in intron 1 of *FXN*, while the remaining 4% are compound heterozygous[36]. The expanded GAA repeat in FA results in the formation of repressive chromatin, an essential mediator of *FXN* transcriptional deficiency[37]. Repressive chromatin spreads upstream from the expanded GAA repeat in intron 1 towards the *FXN* promoter, silencing the gene[37]. In

addition, abnormal DNA methylation also occurs upstream of the expanded GAA repeat in FA and contributes to reduced gene expression[37].

Frataxin is a highly conserved protein that acts as an iron chaperone protein. It is essential to energy metabolism and positively correlates to tissue with high requirements of energy metabolism[38]. It plays a critical role in synthesizing Fe-S (iron-sulfur) cluster proteins that regulate mitochondrial iron content[38]. Because of complete frataxin deficiency in cardiac and skeletal muscle, the activities and levels of mitochondrial Fe-S proteins are reduced, and mitochondrial iron levels are increased, with associated mitochondrial dysfunction and severe oxidative stress despite normal iron levels in the blood[39].

FA is a common cause of LVH in children and adolescents[3,5]. Cardiac involvement can range from asymptomatic cases to severe cardiomyopathy with progressive LV systolic dysfunction and chronic heart failure[39]. The hypertrophic phase is caused by the striking proliferation of mitochondria within the cardiomyocytes, while the hypokinetic phase is due to the increased sensitivity to oxidative stress and the respiratory chain defects caused by the deficiency of the inner mitochondrial membrane protein frataxin in addition to progressive iron accumulation, fibrosis, and loss of contractile fibers[40]. Other systemic manifestations of FA include ataxia, progressive cerebellar dysfunction, diabetes mellitus, impaired speech, loss of vision and hearing, and scoliosis. There are several past and emerging therapies for FA with potential clinical benefits for affected individuals. These therapies include, among others, antioxidants and mitochondrial-related agents, transcription factor NF-E2 p45-related factor 2 (NRF2) agonists (e.g., omaveloxolone, which improves mitochondrial function, restores the balance of reduction and oxidation, and reduces inflammation), vatiquinone (which reduces neuroinflammation and oxidative stress), deuterated polyunsaturated fatty acids, iron chelators, histone deacetylase inhibitors, transactivator of transcription-frataxin, transcription elongation factor, interferon-gamma, erythropoietin, resveratrol, PPARγ agonist, gene therapy, and antisense oligonucleotides. Some of these therapies (e.g., antioxidants) continue to be used off-label in selected patients.

Coenzyme Q10 analogues

Idebenone, a coenzyme Q10 analogue, has antioxidant activity and facilitates mitochondrial phosphorylation as an electron carrier. It has shown the potential to reduce LV mass in open-label studies. However, randomized controlled trials (RCTs) have not demonstrated any clear benefit[41]. Specifically, although the first preliminary study showed promising improvement of the cardiac outcomes in FA patients[42], four randomized placebo-controlled phase III RCTs failed to

demonstrate any significant effects on the neurologic or cardiac function in FA patients[43–46] **(Table 1)**.

Transcription factor NF-E2 p45-related factor 2 agonists

The NRF2 pathway is essential in protecting against several diseases with oxidative stress and inflammation as underlying substrate[47]. Proteins encoded by NRF2-target genes have different roles in antioxidation, detoxification and anti-inflammation[47]. Patients with FA show an impairment of the NRF2 signaling, responsible for increased sensitivity to oxidative insults[48].

Omaveloxolone is an NRF2 agonist that has been shown to improve mitochondrial function and reduce oxidative stress and inflammation in models of FA. Furthermore, it was evaluated in an international, double-blind, randomized, placebo-controlled, parallel-group, phase II trial enrolling 103 patients with FA who were randomly assigned to receive omaveloxolone or placebo[49] **(Figure 2)**. Omaveloxolone significantly improved the neurological function of FA patients, as assessed by the baseline modified Friedreich's Ataxia Rating Scale (mFARS), compared with placebo[49]. The results of this trial led to the FDA approval of omaveloxolone for the treatment of FA.

Gene therapy

Gene therapy and stem cell-based therapy might be future therapeutic strategies for patients with FA[50]. Gene therapy is based on the use of attenuated viral vectors expressing *FXN*[51]. Early experiments have shown that gene therapies in FA are promising but may have toxicities[50,52].

Hypertrophic heart disease in adults

The underlying etiology of adults with hypertrophic heart disease is significantly different from that observed in pediatric patients. While sarcomeric HCM is the most common disease observed, several conditions associated with LVH are also prevalent in the adult and aging population.

Sarcomeric HCM

In the sarcomere, myosin is the molecular engine that catalyzes ATP-hydrolysis to power cyclical coupling with actin filaments. However, only 10% of the myosin molecules are thought to be involved in generating force[53], suggesting the presence of energy-saving systems[54]. Sarcomeric mutations disrupt sarcomere equilibrium and increase cardiac contractility by making more myosin heads accessible to build cross-bridges with actin while leaving fewer myosin molecules in their energy-saving super-relaxed state (SRX)[55]. Current guidelines-recommended treatments[1,2] operate

on downstream targets trying to mitigate hypercontractility, rely on observational studies[56,57], and are often insufficient to manage symptoms. Thus, an unmet medical need weigh on HCM patients.

Cardiac myosin inhibitors

Several preclinical studies have elucidated the main steps of the mechanochemical myosin cycle laying the groundwork for a potential paradigm shift in HCM therapy with the discovery of cardiac myosin inhibitors (CMIs) **(Figure 3)**.

Mavacamten (previously MYK-461) is a first-in-class cardio-selective, allosteric, reversible myosin inhibitor that works at different levels in the myosin cycle[58]. Indeed, it decreases ATPase activity, reduces phosphate and ADP release, and stabilizes the SRX form of myosin shifting myosin heads to an "OFF-state", thus limiting myocardial force generation. In addition, mavacamten accelerates cross-bridge detachment and reduces calcium sensitivity, suggesting a beneficial effect on diastolic function[59].

In parallel with this ground-breaking preclinical research, many RCTs were conducted. At first, an open-label, dose-finding phase II study[60] was performed to assess pharmacodynamic and pharmacokinetic features in two small cohorts of obstructive HCM (oHCM) patients. After 12 weeks of therapy, patients in PIONEER-HCM (A Phase 2 Open-label Pilot Study Evaluating MYK-461 in Subjects With Symptomatic Hypertrophic Cardiomyopathy and Left Ventricular Outflow Tract Obstruction) who received tailored daily doses exhibited a significant decrease in the post-exercise LV outflow tract (LVOT) gradient and an improvement in exercise capacity and symptoms when a plasma concentration of 350-700 ng/mL was achieved. Individuals with and without history of medical treatment for oHCM had similar dose-response associations[60].

These results led to the EXPLORER-HCM (Clinical Study to Evaluate Mavacamten [MYK-461] in Adults With Symptomatic Obstructive Hypertrophic Cardiomyopathy), the first phase III RCT on mavacamten[61]. In this study, enrolled participants had symptomatic (NYHA ≥2) oHCM on beta-blockers or non-dihydropyridine calcium-channel blockers, resulting in a population similar to those observed in clinical practice. It was observed that a significant proportion of patients treated with mavacamten fulfilled the primary endpoint, which consisted of an increase in peak O2 consumption (pVO2) at cardiopulmonary exercise testing (CPET) and a reduced or at least stable NYHA class[62]. Moreover, 27% of patients treated with mavacamten experimented a full response, defined as a stable decrease in LVOT gradients <30 mmHg and a NYHA class I, suggesting that mavacamten may be able to achieve remarkable alleviation of symptoms and LVOT obstruction (LVOTO). Beneficial effects and tolerance to the study drug were uniform across all subgroups. Seven patients in the treatment group had a decrease in LVEF <50%. However, this complication was rapidly

reversible with medication suspension in all patients[62]. Nevertheless, patients on disopyramide and those with severe symptoms (NYHA class IV) were not included in the EXPLORER-HCM.
Thus, the VALOR-HCM (A Study to Evaluate Mavacamten in Adults With Symptomatic Obstructive HCM Who Are Eligible for Septal Reduction Therapy)[63] aimed to evaluate if mavacamten was able to delay needing for septal reduction therapy (SRT). Several studies have established that SRT, such as surgical myectomy or alcohol septal ablation, significantly improves long-term survival and quality of life in individuals with severe symptomatic oHCM despite medical therapy. However, these interventions, especially in low-volume institutions, are associated with a significant risk of morbidity and death. In addition, repeated interventions, increased need for pacemakers, limited access to high-volume facilities, and prolonged hospital stays are all possible outcomes of an unsuccessful operation[64]. Despite facing a challenging goal, after 16 weeks of therapy, mavacamten significantly reduced the proportion of patients fulfilling the guidelines criteria for SRT compared with placebo[63]**.**
Translational efforts led to the development of a second-generation CMI, aficamten (at first CK-274)[65]. Compared with mavacamten, this novel agent has attractive pharmacokinetic properties, such as a shorter half-life (about three days) allowing rapid washout or dose adjustments when adverse effects occur, combined with less interaction with cytochromes[65].
A phase II dose-finding RCT, REDWOOD-HCM (Randomized Evaluation of Dosing With CK-3773274 in HCM) (https://clinicaltrials.gov/ct2/show/NCT04219826), was started analyzing four different cohorts of patients. The first two cohorts[66] included patients receiving first-line background therapy assigned to lower and higher aficamten regimens. The third cohort included patients on background therapy with a first-line treatment associated with disopyramide, and the last cohort included non-obstructive HCM (noHCM) patients. Valsalva and resting LVOT gradients were significantly lower in the first three experimental groups. These positive results were mirrored by improvements in clinical status and biomarkers levels. Finally, a phase III RCT, SEQUOIA-HCM (CY 6031 Study Will Evaluate the Effects of Treatment With Aficamten [CK-3773274] Over a 24-week Period on Cardiopulmonary Exercise Capacity and Health Status in Patients With Symptomatic oHCM) (https://clinicaltrials.gov/ct2/show/NCT05186818), randomly assigning participants to receive either aficamten or placebo on top of standard of treatment, including disopyramide, is still ongoing **(Table 2)**.
However, current studies have not reported the impact of disease-modifying therapies (e.g., mavacament, aficamten) on the risk of SCD. Further data, including Holter sub-studies, are required to address this unsolved question.

Angiotensin receptor blockers

Studies in mouse models of sarcomeric HCM showed that the activation of the transforming growth factor-beta (TGF-β) pathway has a dominant role in triggering the development of myocardial hypertrophy and fibrosis. Angiotensin receptor blockers (ARBs) can inhibit TGF-β and theoretically prevent fibrosis progression. Although clinical trials using ARBs failed to demonstrate significant benefit in patients with clinically manifested HCM, a phase 2 trial (The Valsartan for Attenuating Disease Evolution in Early Sarcomeric Hypertrophic Cardiomyopathy [VANISH] trial) showed that, if administered in early stages, ARBs could improve both cardiac structure and function[67]. However, further studies are needed to characterize the long-term treatment effects and define the optimal timing of ARBs administration.

Gene therapy

The improved knowledge of the molecular basis of HCM enables early gene-based diagnosis, with the potential to identify pathogenic variants carriers who have not already developed the disease phenotype. Since dominant missense pathogenic variants in sarcomeric genes are the leading cause of HCM, base editing has emerged as an attractive method to cure this condition **(Figure 3)**. Gene editing strategies have recently been shown to efficaciously convert pathogenic variants of *MYH7* and *MYH6* to non-pathogenic alleles in mouse models of HCM[68,69]. Chai et al. reported the use of different base editing strategies and showed their efficacy in correcting pathological phenotypes of HCM in patient-derived cells[68]. Moreover, they applied the base editing to humanized mouse models containing the *MYH7* p.R403Q pathogenic missense variant and showed that its postnatal correction might prevent the onset of the HCM phenotype. In addition, Reichart et al. assessed the role of different genetic therapies in preventing disease in mice carrying the same *MYH7* variant[69]. They observed that one dose of AAV9 vector delivering an adenine base editor and Cas9 nuclease corrected the pathogenic variant in more than 70% of cardiomyocytes, thus stabling and providing a durable and normal cardiac structure and function. Despite their promising results, the potential benefit of gene therapies should be evaluated in the context of potential safety issues, such as the introduction of bystander and off-target mutations, which could lead to severe genotoxic effects.

TTR amyloidosis

Cardiac amyloidosis is a progressive infiltrative disease characterized by the extracellular deposition of misfolded proteins in the heart, responsible for a hypertrophic phenotype with restrictive physiology[70]. Most cases of cardiac amyloidosis result from two protein precursors,

namely amyloid immunoglobulin light chain (AL), in which the misfolded protein is a monoclonal immunoglobulin light chain typically produced by bone marrow plasma cells, and amyloid transthyretin (ATTR) amyloidosis, in which the misfolded protein is transthyretin (TTR), a serum transport protein for thyroid hormone and retinol that is synthesized primarily by the liver[71]. ATTR amyloidosis is subtyped into wild-type (ATTRwt) and hereditary (ATTRv), the latter resulting from genetic variants in the *TTR* gene[72].

The management of cardiac amyloidosis includes preventing and treating complications through halting or delaying organ damage due to amyloid deposition [73]. While treatment of AL amyloidosis is limited to treating the underlying hematological condition, there is an increasing availability of novel, effective, targeted therapeutic options for ATTRwt and ATTRv[73]. Disease-modifying therapies target the pathophysiological cascade that ranges from the synthesis of TTR to fibrillogenesis. Effective treatments reduce the production of mutated and overall *TTR* (liver transplantation, genetic silencers), stabilize circulating TTR molecules (stabilizers), avoid misfolded monomer aggregation, or promote amyloid reabsorption[72] **(Figure 3)**.

Silencing TTR production

Silencing of the TTR protein is currently achievable by promoting TTR mRNA degradation [antisense oligonucleotides (ASOs) and small interfering RNA molecules (siRNA)] or editing the *TTR* gene (CRISPR Cas9)[74]. Avoiding TTR protein production has been achieved in the past in ATTRv patients by liver transplant (Ltx). Long-term survival after Ltx is excellent, especially for early-onset *TTR* p.V30M patients. In contrast, non-*TTR* p.V30M patients show a worse outcome, most commonly characterized by a mixed neurological and cardiological phenotype[75].

ASOs are single-stranded amphipathic molecules which bind to proteins in the serum, on the cell surface, and within cells. Within the target cell's nucleus, the ASO binds to the target mRNA and, via the endonuclease RNase H2, initiates mRNA degradation[73].

Inotersen is a 2′-O-methoxyethyl–modified ASO. In a recent RCT (the NEURO-TTR study, NCT01737398), the administration of inotersen three times during the first week, followed by a once-weekly subcutaneous injection for the next 64 weeks, demonstrated an improvement in neurological disease and quality of life in patients with ATTRv amyloidosis[76]. The clinical response to inotersen treatment depends on the individual rate of disease progression, baseline amyloid burden, and the rate of amyloid clearance from tissue[76]. These benefits are independent of *TTR* variant, disease stage, and cardiomyopathy status at baseline.

Eplotersen is a new generation ASO conjugated to the triantennary N-acetyl galactosamine, which facilitates hepatocyte uptake to reduce immunogenic reactions and promotes *TTR* gene expression

reduction. A phase III RCT (CARDIO-TTRansform, NCT04136171) is currently investigating its efficacy and safety in patients with ATTR cardiomyopathy.

siRNAs are double-stranded oligonucleotides containing sense and antisense strands, the former acting as a drug delivery device and the latter being the active moiety. Once within the cytoplasm, the antisense strand is loaded onto Ago2, creating a complex that binds to the target mRNA to form the RNA-induced silencing complex with subsequent mRNA degradation[73].

Patisiran is a siRNA encapsulated into lipid nanoparticles, which protect the RNA molecule from degradation by circulatory endonucleases and exonucleases and facilitate delivery to the liver[77]. The APOLLO study assessed the efficacy and tolerability of patisiran in patients with ATTRv amyloidosis[78]. In this trial, patisiran decreased mean LV wall thickness, global longitudinal strain, NT-proBNP, and adverse cardiac outcomes at 18 months, compared with placebo[78]. These data suggest that patisiran may halt or reverse the progression of the cardiac manifestations of ATTRv amyloidosis. The APOLLO-B phase III RCT (NCT03997383), specifically aimed to evaluate its efficacy and safety in patients with ATTR cardiomyopathy, is ongoing.

Vutrisiran (ALN-TTRsc02) is a second-generation siRNA approved for treating amyloid polyneuropathy[79] and is currently under investigation for its use in ATTR cardiomyopathy (NCT04153149).

Genomic editing using CRISPR Cas9 is a promising therapeutic strategy in ATTR amyloidosis, achievable using a nuclease (Cas9) linked to a single-stranded RNA, leading to irreversible silencing of the *TTR* gene[80]. Recently, Gillmore et al. showed a significant reduction of TTR serum levels in ATTRv patients with polyneuropathy after a single administration[80]. A Phase I clinical trial (NCT04601051) is evaluating its safety, tolerability, pharmacokinetics, and pharmacodynamics in participants with ATTRv polyneuropathy, or ATTRv and ATTRwt cardiomyopathy.

Transthyretin stabilization

Tetramer stabilizers are small molecules that influence the rate-limiting step in forming amyloid fibrils (i.e., the dissociation of TTR tetramers into amyloidogenic monomers)[73]. Previous treatments with small non-specific molecules, such as diflunisal and tolcapone, have been tested in small studies. However, their use is limited primarily by their dose-dependent side adverse effects. Indeed, TTR tetrameter stabilization requires a high concentration of TTR stabilizer to prevent its dissociation and misfolding[81].

Tafamidis is an orally bioavailable benzoxazole derivative that stabilizes the TTR tetramer by binding to the T4-binding sites, preventing their dissociation or cleavage into amyloidogenic fragments. The ATTR-ACT trial showed that tafamidis was superior to placebo in reducing the

occurrence of the combined endpoint of all-cause mortality and cardiovascular-related hospitalizations[82]. Tafamidis was also associated with a significant reduction in the decline in functional capacity and quality of life at 30 months, with the first differences observed at six months[82] **(Table 3)**. While ATTR-ACT was not designed for a dose-specific assessment, further analysis from ATTR-ACT and its long-term extension study can guide the determination of the optimal dose. The long-term extension of the ATTR-ACT showed a 30% relative reduction in the risk of death with tafamidis 80 mg compared with 20 mg. These data support the use of tafamidis 80 mg (bioequivalent to tafamidis free acid 61 mg) as the optimal dose in patients with ATTR cardiomyopathy[83]. Two phase III RCTs (NCT03860935 and NCT04622046) are ongoing to evaluate the efficacy and safety of acoramidis, a new TTR stabilizer, in patients with ATTR cardiomyopathy.

Immune-mediated amyloidolysis.

Immuno-mediated amyloidolysis is based on monoclonal antibodies (mAbs), which bind to specific epitopes of amyloid, opsonize the deposits and promote their degradation by the activity of native immunity[84]. NI006 is a recombinant human anti-ATTR monoclonal IgG1 antibody that selectively binds amyloid conformations of both wild-type and variant TTR but does not bind physiological folded TTR[85]. It showed to deplete ATTR by inducing ATTR fibrils phagocytosis and removal of ATTR deposits from tissue[85]. Recently, a phase I, double-blind trial showed that its use was associated with no-apparent drug-related serious adverse events in patients with ATTR cardiomyopathy[86]. In addition, it reduced the cardiac tracer uptake on scintigraphy and extracellular volume on cardiac magnetic resonance, which are surrogate markers of cardiac amyloid burden, over a 12-month period[86].

Fabry disease

Fabry disease is an X-linked lysosomal storage disorder caused by a pathogenic mutation in *GLA*, which encodes for alpha-galactosidase[87]. The *GLA* mutation is thereby responsible for a reduced or absent enzyme activity resulting in the accumulation of lysosomal globotriaosylceramide (Gb3) and related globotriaosylsphingosine (lyso-Gb3) in several organs and tissues[87].

The cardiac involvement in Fabry disease is variable and, when present, is the main determinant of adverse outcome of affected patients[88]. LVH represents the most common manifestation of cardiac involvement[89]. Other cardiac manifestations include conduction abnormalities, chronotropic incompetence, ventricular and supraventricular arrhythmias, valve disease, and microvascular dysfunction[89].

In the last two decades, several treatment options emerged for Fabry disease. Available treatments include ERT and oral chaperone therapy migalastat. However, several other emerging therapies are under investigation and may become available soon **(Figure 3)**.

Enzyme replacement therapy

ERT is available for treating Fabry disease in two different forms, agalsidase alfa and agalsidase beta, at a dosage of 0.2 mg/kg and 1.0 mg/kg every two weeks, respectively. Several studies and clinical trials documented the sustained benefit of treatment with ERT, leading to the FDA and EMA approval of agalsidase alfa and beta for patients with Fabry disease.

The efficacy and safety of agalsidase alfa were investigated for the first time in a multicenter, randomized, double-blind, placebo-controlled trial, which demonstrated that recombined agalsidase alfa was able to reduce microvascular endothelial deposits of Gb3 from the kidneys, heart, and skin of affected patients, thus reversing the pathogenesis of the disease[90]. Subsequent long-term studies confirmed that the beneficial effects were sustained and that treatment with agalsidase alfa was associated with a slower decline of renal function and slower progression of LVH, reducing the morbidity and mortality of Fabry disease patients[91,92]. Similar results were observed in patients treated with agalsidase beta[93].

However, it was observed that the response to ERT was not homogeneous among different patients. In particular, it was reduced in patients with advanced disease (e.g., proteinuria, presence of myocardial fibrosis), suggesting the need for an early initiation, especially in male patients[94,95]. In addition, ERT presents several limitations, such as high costs, infusion-related reactions, and the life-long burden of biweekly intravenous infusions.

A novel second-generation ERT, pegunigalsidase-alpha is a pegylated form of alfa galactosidase, which was developed to increase the half-life and reduce immunogenicity, thus enhancing its efficacy compared with available ERT[96]. A phase III trial (NCT03018730) investigating its efficacy and safety is ongoing.

Chaperone therapy

Chaperone therapy consists of small molecules that restores the endogenous activity of the alfa-galactosidase enzyme and its ability to degrade Gb3, preventing tissue accumulation[97]. Migalastat is the only agent approved for treating patients with Fabry disease and amenable mutation (i.e., those mutations that retain enzyme catalytic activity despite abnormal protein folding). In particular, it acts by selectively binding the active sites of the alfa-galactosidase enzyme, preventing its degradation and facilitating trafficking to lysosomes, where the enzyme can properly solve its

function[98]. The efficacy of migalastat was assessed in two RCTs, the FACETS and the ATTRACT[99,100]. In both studies, migalastat treatment was associated with a slower decline in glomerular filtration rate and improved LV mass[99,100].

Substrate reduction therapy

Substrate reduction therapy consists of molecules acting as glucosylceramide synthase inhibitors to reduce the rate of synthesis of Gb3 to a level compatible with its residual clearance. This therapy can potentially delay disease progression and improve outcomes of Fabry disease patients, irrespective of *GLA* mutation. Currently, lucerastat and venglustat are two substrate reduction therapies under investigation in phase III and II trials.

Future directions

The development of disease-modifying therapies, with their ability to improve clinical features and long-term outcomes of rare diseases manifesting with hypertrophic heart disease, advocate the promotion of educational programs and multicenter networks to enhance public and physician awareness.

Any efforts should be made to identify these rare conditions, especially when a disease-modifying therapy is available. The systematic investigation for specific diagnostic clues associated with these conditions (e.g., X-linked inheritance in Fabry disease, RVOTO in RASopathies) is likely to represent the most effective strategy for suspecting a rare disease and triggering specific diagnostic and management procedures. This “red flags” approach, often called the cardiomyopathy mindset, aims to look for rare diseases in common conditions (e.g., LVH, heart failure, arrhythmias).

Current disease-modifying therapies are mainly developed for patients presenting overt phenotypes or disease-related complications. However, it has been observed that patients are more likely to benefit from treatment when it is started during the early stages of the disease. Nevertheless, whether specific treatments effectively prevent disease phenotype in genotype-positive phenotype-negative individuals remains unsolved.

Conclusions

Hypertrophic heart disease is a condition characterized by a highly heterogenous etiology. Target therapies are now available for different underlying conditions and provide the opportunity to alter the natural history of these progressive disorders.

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Table 1. Summary of the studies investigating the effects of Idebenone in patients with Friedreich Ataxia.

Reference	Patients n (age in years)*	Treatment duration	Idebenone dose†	Type	Clinical endpoints	Effects
Rustin et al. [42]	3 (11-21)	4–9 months	5 mg/kg daily	OL	Cardiac: SWT, PWT, LVMI	↓ SWT 31-36 %, ↓ PWT 8–20 %, ↓ LVMI 21-32 %
Di Prospero et a.[44]	48 (9–17)	6 months	Randomization to receive placebo or one of three doses of idebenone. The total dose of idebenone was stratified by body weight (≤45 kg/ >45 kg): L (180/360 mg/d), M (450/900 mg/d), H (1350/2250 mg/d)‡	RCT	Neurological: ICARS, FARS, ADL Biomarker: urinary 8OH2'dG[c]	No significant difference in ICARS, FARS, or ADL total scores, but dose-related response. No difference in 8OH2′dG concentrations.
Lynch et al[45]	70 (8-18)	24 weeks	Randomization into 1 of 3 treatment arms: 450 or 900 mg of idebenone per day (in those with a body weight ≤ or > 45 Kg, respectively; n=22); 1350 or 2250 mg of idebenone per day (n=24); or placebo (n=24).	RCT	Neurological: ICARS (primary endpoint) FARS, and ADL (secondary efficacy variables)	For both endpoints, the difference between the idebenone and placebo groups was not statistically different.
Lagedrost et al[46]	70 (<18)	6 months	Randomization: idebenone (450/900 mg/d or 1,350/2,250 mg/d) or placebo	RCT	ECGs were assessed at each visit, and echocardiograms, at baseline and week 24	LVMI, PWT, LVEF, and ECG parameters were not significantly improved by treatment with idebenone
Cook et al[43]	29 patients (16 idebenone group, 13 placebo group)	2 months	Randomization to placebo or idebenone continuation (patients who had already received continuous high-dose	RCT	Patient assessment of treatment assignment	No significant differences between the idebenone and placebo groups on assessment of treatment assignment or early study withdrawal. A small but significant difference in ataxia rating scale scores

			idebenone (1350mg/day if ≤45kg or 2250mg/day if >45kg) for at least 12 months in the open-label MICONOS Extension Study (MES) for two-month treatment cycles			detected between treatment groups when considering ambulatory patients only.

Abbreviations: ADL, activities of daily living scale (Note: a decrease in ADL score indicates improvement); ECG, electrocardiograms; FARS, Friedreich Ataxia Rating Scale (Note: a decrease in FARS score indicates improvement); ICARS, International Cooperative Ataxia Rating Scale (Note: a decrease in ICARS score indicates improvement); LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; OL, open-label trial; pt(s), patient(s); PWT, (left ventricular) posterior wall thickness; RCT, randomized, placebo-controlled trial; SWT, (interventricular) septal wall thickness; 8OH2'dG, 8-hydroxy-2-deoxyguanosine normalized for creatinine; ↑, Increase; ↓, Decrease.

*Age at baseline of study (rounded numbers).

†Where available, max. daily dose provided in brackets.

‡Daily dose adapted to body weight. Low-dose group (L):180 mg/d for pts ≤ 45 kg; 360 mg/d for patients > 45 kg; mid-dose group (M): 450 mg/d for pts ≤ 45 kg, 900 mg/d for pts > 45 kg; high-dose group (H): 1350 mg/d for pts ≤ 45 kg; 2250 mg/d for pts > 45 kg.

Table 2. Main clinical trials of cardiac myosin inhibitors in hypertrophic cardiomyopathy.

Trials (Reference or NCT Number)	Drug	Country	Phase	Population	Background Therapy	Design	Dose	Duration	Outcomes
PIONEER-HCM[60]	Mavacamten	International	II	oHCM, NYHA II-III	BB	Open label, Non randomized	2 mg - 20 mg	12 weeks treatment	↓ mean postexercise LVOT gradient ↑ pVO2 ↓ Dyspnea score
EXPLORER-HCM[62]	Mavacamten	United States	III	oHCM, NYHA II-III	BB or CCB	Randomized, double-blind, placebo-controlled	2.5 mg - 15 mg	30 weeks treatment	↓ mean postexercise LVOT gradient ↑ KCCQ-CSS, ↑ pVO2 ↓NYHA class
VALOR-HCM[63]	Mavacamten	United States	III	oHCM, NYHA III-IV or NYHA II with syncope or near syncope.	BB, CCB and disopyramide taken together or as monotherapy	Randomized, double-blind, placebo-controlled	2.5 mg - 15 mg	16 weeks treatment	↓ guideline eligible patients for SRT ↓ mean postexercise LVOT gradient ↑ KCCQ-CSS ↓ NT-proBNP

REDWOOD-HCM[66]	Aficamten	International	II	oHCM, NYHA II-III	BB, CCB	Randomized, double-blind, placebo-controlled	5 mg - 30 mg	10 weeks treatment	↓ mean postexercise LVOT gradient ↓ NT-proBNP
SEQUOIA-HCM (NCT05186818)	Aficamten	International	III	oHCM, NYHA II-III	BB, CCB and disopyramide	Randomized, double-blind, placebo-controlled	5 mg - 20 mg	24 weeks treatment	pVO2 KCCQ-CSS NYHA class mean postexercise LVOT gradient (Ongoing)

Abbreviations: CMIs, Cardiac Myosin Inhibitors; oHCM, obstructive Hypertrophic Cardiomyopathy; NCT, National Clinical Trial Identifier Number; NYHA, New York Heart Association; BB, Beta Blockers; CCB, Calcium Channel Blockers; LVOT, Left Ventricular Outflow Tract; pVO2, Peak oxygen uptake; KCCQ-CSS, Clinical Summary Score of the Kansas City Cardiomyopathy Questionnaire; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

Table 3. Main clinical trials of disease-modifying therapies for ATTR amyloidosis.

Trials (Reference or NCT Number)	Drug	Mechanism	Study design	Population	Results
ATTR-ACT[82]	Tafamidis	Benzoxazole derivative of NSAIDs, binds to T4-binding site on TTR.	Phase III, multicentre, randomized, double blind, placebo controlled.	Patients with transthyretin amyloid cardiomyopathy (ATTRwt or ATTRv).	Reduction of all-cause mortality and cardiovascular-related hospitalizations. Reduction of the decline in functional capacity (6-minute walking test) and the decline in quality of life (KCCQ-CSS).
NEURO-TTR[76]	Inotersen	2'-O-methoxyethyl-modified phosphonothioate antisense ASO, binds to target mRNA in liver and initiates mRNA degradation.	Phase III, multicentre, randomized, double-blind, placebo controlled.	Patients with stage 1-2 AATRv-polyneuropathy.	Improvement in the course of neuropathy and QOL.
APOLLO[78]	Patisiran	siRNA, target the 3' untranslated region of TTR mRNA in the liver to form the RNA-induced silencing complex, initiating mRNA degradation.	Phase III, multicentre, randomized, double-blind, placebo controlled.	Patients with ATTRv amyloidosis with a baseline left ventricular wall thickness ≥13 mm and no history of hypertension or aortic valve disease.	Reduction of mean left ventricular wall thickness, global longitudinal strain, *N*-terminal prohormone of brain natriuretic peptide, and adverse cardiac outcomes.
APOLLO-B (NCT03997383)	Patisiran	siRNA, target the 3' untranslated region of TTR mRNA in the liver to form the RNA-induced silencing complex, initiating mRNA degradation.	Phase III, multicentre, randomized, double-blind, placebo-controlled.	Patients with transthyretin amyloid cardiomyopathy.	Improvement in 6 -minute walking test and in KCCQ-CSS.

Abbreviations: ASO, antisense oligonucleotide; KCCQ-CSS, Clinical Summary Score of the Kansas City Cardiomyopathy Questionnaire; NCT, National Clinical Trial Identifier Number; NSAIDs, non-steroidal anti-inflammatory drugs; TTR, transthyretin.

Figure legends

Figure 1. ***Diagnostic work-up and etiology of pediatric and adult patients with hypertrophic heart disease.*** Patients with hypertrophic heart disease should undergo first-line evaluation. Subsequently, the second-line investigations should be tailored to the clinical suspicion to identify the underlying etiology. *Abbreviations:* CMR, cardiac magnetic resonance; ECG, electrocardiogram; Echo, echocardiography.

Figure 2. ***Etiology, pathophysiology, and novel therapies for children with hypertrophic heart disease.*** The figure reports the pathophysiology and the disease-modifying therapies for treating children with hypertrophic heart disease according to the underlying etiology. *Abbreviations:* HCM, hypertrophic cardiomyopathy; LVH, left ventricular hypertrophy; MEK1, mitogen-activated protein kinase kinase; NRF2, NF-E2 p45-related factor 2; NS, Noonan syndrome; NSML, Noonan syndrome with multiple lentigines; PI3K-AKT-mTor, phosphatidylinositol 3-kinase-protein kinase B-mammalian target of rapamycin; RAS-MAPK, Ras-mitogen activated protein kinase.

Figure 3. ***Etiology, pathophysiology, and novel therapies for adults with hypertrophic heart disease.*** The figure reports the pathophysiology and the disease-modifying therapies for treating adults with hypertrophic heart disease according to the underlying etiology. Abbreviations: Gb3, Globotriaosylceramide; HCM, hypertrophic cardiomyopathy; LysoGb3, Globotriaosylsphingosine LVH, left ventricular hypertrophy.