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Review article

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Tailored therapeutics for cardiomyopathies

Athanasios Bakalakos[1], Emanuele Monda[1,2] & Perry Mark Elliott[1]

Abstract

The term cardiomyopathy is used to describe a large family of complex heart muscle disorders of diverse aetiology and pathophysiology. For decades, the management of individual cardiomyopathy subtypes has focused primarily on the management of symptoms and the prevention of disease-related complications, such as heart failure and sudden cardiac death. Treatment of progressive myocardial dysfunction has relied on conventional evidence-based heart failure therapies, with variable success. In contrast to other areas of medicine, cardiology is characterized by few aetiology-targeted therapies, but cardiomyopathies offer an ideal model for innovation because, in many individuals, the disorder has a monogenic cause, the expression of which is modified by complex genetic mechanisms, comorbidities and lifestyle. Elucidation of the complex cellular and molecular pathways that result in downstream tissue phenotypes has led to the investigation of new or repurposed pharmacological agents and, in parallel, therapies that modify or mitigate the effects of causative genetic variants, offering the prospect of targeting the disease at its source. In this Review, we describe some of the most promising therapeutic approaches in cardiomyopathy and discuss their potential effect on the lives of patients and relatives.

Sections

[1]Institute of Cardiovascular Science, University College London, London, UK. [2]Department of Translational Medical Sciences, University of Campania "Luigi Vanvitelli", Naples, Italy. e-mail: perry.elliott@ucl.ac.uk

Key points

- The term cardiomyopathy encompasses a large family of heart muscle disorders of diverse aetiology and pathophysiology that are defined by structural and functional characteristics of the ventricles.
- Cardiomyopathies have a complex genetic architecture that spans disease caused by single rare variants to myocardial dysfunction that results from the cumulative effect of multiple common variants of low individual pathogenicity, often acting in concert with comorbidities and environmental triggers.
- Irrespective of aetiology, most cardiomyopathies share downstream disease pathways that lead to myocardial hypertrophy, fibrosis and inflammation and progressive cardiac remodelling.
- Advances in molecular biology and platform technologies have driven the development of new and repurposed pharmacological agents and gene-targeted therapies for cardiomyopathies, offering the potential to modify and prevent disease.
- Precision therapies for cardiomyopathies have transformative potential but require parallel innovation in clinical trial design and policies that ensure equity and affordability.

Introduction

Cardiomyopathies are disorders characterized by structural and functional abnormalities of the heart muscle, which are not explained entirely by coronary artery disease, hypertension, valvular disease or congenital heart disease[1]. This clinical definition of cardiomyopathies is useful in clinical practice to orient diagnostic and management pathways (Table 1), but the emergence of aetiology-specific treatments is propelling the diagnosis and management of cardiomyopathies towards a multidimensional approach that also captures the diversity and complexity of mechanisms that result in heart muscle dysfunction (Table 2). In this Review, we explore groundbreaking therapeutic strategies for cardiomyopathies within this framework.

Cardiomyopathy phenotypes

By longstanding convention, cardiomyopathies have been classified into subtypes based on a small number of clinical traits, such as ventricular wall thickness and function[1]. This approach applies to both children and adults and makes few assumptions about aetiology or myocardial pathology. The five main cardiomyopathy types are described below (Table 1).

Hypertrophic cardiomyopathy (HCM) is defined by increased left ventricular (LV) wall thickness in the absence of abnormal loading conditions[1], often accompanied by architectural abnormalities such as anterior or apical displacement and hypertrophy of the papillary muscles, as well as elongation of the anterior mitral valve leaflet. The condition often features systolic anterior motion of the mitral valve, which can obstruct the LV outflow tract (LVOT). The HCM phenotype is typically characterized by asymmetrical LV hypertrophy, most commonly affecting the basal septum and anterior wall, and hyperdynamic radial systolic function.

Dilated cardiomyopathy (DCM) is characterized by LV dilatation and global or regional systolic dysfunction unexplained solely by abnormal loading conditions, such as hypertension, valvular heart disease or coronary artery disease. LV dilatation can occur with a normal LV ejection fraction (LVEF) as a consequence of physiological adaptation (for example, in response to athletic training) but can sometimes represent an early manifestation of DCM.

Non-dilated left ventricular cardiomyopathy (NDLVC) is a newly proposed entity defined as non-ischaemic LV scarring or fatty replacement of the myocardium and normal LV dimensions, with or without global or regional wall motion abnormalities. NDLVC also includes the presence of global LV hypokinesia without scarring.

Restrictive cardiomyopathy (RCM) is characterized by diastolic dysfunction with preserved systolic function and increased ventricular stiffness. The hallmark is restrictive physiology, with normal ventricular volumes, elevated intraventricular pressure and, commonly, biatrial enlargement. RCM is associated with rare genetic variants and can be the result of infiltrative, storage or fibrotic endocardial disorders. However, given that restrictive physiology can also occur in other cardiomyopathy phenotypes (in particular hypertrophic and dilated forms), diagnosis can be challenging[2].

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is defined as the presence of predominantly right ventricular dilatation and/or dysfunction in the presence of classical histological changes (fibrofatty replacement of cardiomyocytes) and/or electrocardiographic abnormalities in accordance with published consensus criteria[3,4].

Pathogenesis of cardiomyopathies

The pathogenesis of cardiomyopathies involves various molecular disturbances that result in myocardial hypertrophy, fibrosis, inflammation and progressive myocardial remodelling. A comprehensive description of all possible causes of cardiomyopathy is beyond the scope of this Review, so we focus instead on disorders primarily driven by pathogenic genetic variants that affect proteins of the sarcomere, cytoskeleton and ion channels, as well as selected metabolic and infiltrative disorders for which there are established and emerging therapies.

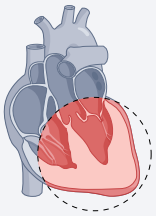
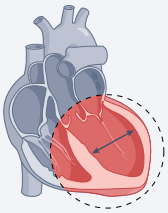
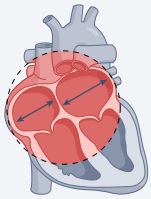
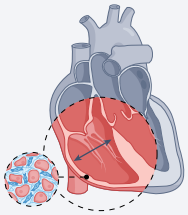
Genetic architecture of cardiomyopathies

Cardiomyopathies have a complex genetic architecture that spans dominant disease caused by single rare variants to myocardial dysfunction caused by the cumulative effect of multiple common variants of low individual pathogenicity[5–7].

Hypertrophic cardiomyopathy. HCM has been viewed primarily as a disease of the cardiac sarcomere caused by dominantly inherited pathogenic variants in eight key genes encoding cardiac sarcomeric proteins: myosin-binding protein C, cardiac-type (*MYBPC3*); β-myosin heavy chain, also known as myosin 7 (*MYH7*); troponin T, cardiac muscle (*TNNT2*); troponin I, cardiac muscle (*TNNI3*); troponin C, slow skeletal and cardiac muscles (*TNNC1*); tropomyosin-α1 chain (*TPM1*); myosin regulatory light chain 2, ventricular/cardiac muscle isoform (*MYL2*); myosin light chain 3 (*MYL3*); and actin, α-cardiac muscle 1 (*ACTC1*).

Variants in *MYBPC3* and *MYH7* account for approximately 70% of pathogenic HCM-causing variants[8]. However, variants in sarcomere-related genes are identified in fewer than 50% of patients with a clinical diagnosis of HCM[9]. Evidence from population cohort studies suggests that HCM has an oligogenic or polygenic basis in a substantial proportion of patients[10]. Variants in other genes encoding sarcomeric proteins, including those coding for Z-disc-associated

Table 1 | Diagnostic features, aetiology, risk factors and treatment of cardiomyopathies

Parameter	HCM	DCM and NDLVC	RCM	ARVC
Image				
Diagnostic features	Increased LV wall thickness	DCM: LV dilatation with reduced ejection fraction NDLVC: non-dilated left ventricle with impaired regional or global LV function and/or fibrosis	LV diastolic dysfunction with preserved systolic function and increased ventricular stiffness; biatrial enlargement	Right ventricular dilatation and/or dysfunction; fibrofatty replacement
Aetiology	Monogenic disease: 29 genes with definite/strong or moderate link; sarcomeric (most common: *MYH7*, *MYBPC3* and thin filament genes); other genes Phenocopies: genetic (AFD, TTR amyloidosis) or non-genetic Common variants and polygenic risk	Monogenic disease: 19 genes with definite/strong or moderate link to DCM. Shared genetic background with NDLVC: sarcomeric (*TTN*); cytoskeletal (*DES*, *FLNC*); calcium homeostasis (*PLN*); nuclear envelope (*LMNA*); other (*DSP*, *RBM20*) Non-genetic disease Autoimmunity Common variants and polygenic risk	Monogenic disease: shared background with HCM; aetiology not fully understood	Monogenic disease: desmosomal (*PKP2*, *DSP*, *JUP*, *DSG2*); other genes (*CDH2*, *TMEM43*, *DES*, *PLN*) Phenocopies: sarcoidosis, Chagas disease, congenital heart disease with volume overload
Environmental and other risk factors	Hypertension, high BMI, diabetes mellitus	Cardiotropic viral infections and myocarditis, alcohol, cancer drug toxicity, pregnancy and peripartum DCM, arrhythmia-induced, hypertension, high BMI, OSA	Hypertension, high BMI, OSA	Intensive exercise
Treatment	Manage LVOT obstruction with non-vasodilating β-blockers, disopyramide, verapamil or diltiazem, SRT, right ventricular pacing; avoid digoxin, arterial and venous dilators such as nitrates and PDE5 inhibitors If no LVOT obstruction, reduce LV diastolic pressures and improve LV filling (β-blockers, verapamil or diltiazem) Heart transplantation	First-line therapy for HFrEF: SGLT2 inhibitor, ARNI, ACE inhibitor or ARB, β-blocker, MRA Second-line therapy for HFrEF: hydralazine, nitrates, CRT, ivabradine, digoxin Heart transplantation Treat comorbidities: diabetes mellitus, hypertension, iron deficiency, OSA, atrial fibrillation	Treatment for HFpEF: diuretics, SGLT2 inhibitor, ARNI, MRA, ARB Treat comorbidities: diabetes mellitus, hypertension, OSA, AF Heart transplantation	Manage arrhythmia: β-blocker (sotalol), flecainide, ICD Heart transplantation

ACE, angiotensin-converting enzyme; AF, atrial fibrillation; AFD, Anderson–Fabry disease; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; ARVC, arrhythmogenic right ventricular cardiomyopathy; CRT, cardiac resynchronization therapy; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardioverter–defibrillator; LV, left ventricular; LVOT, left ventricular outflow tract; MRA, mineralocorticoid receptor antagonist; NDLVC, non-dilated left ventricular cardiomyopathy; OSA, obstructive sleep apnoea; PDE5, phosphodiesterase type 5; RCM, restrictive cardiomyopathy; SGLT2, sodium–glucose cotransporter 2; SRT, septal reduction therapy; TTR, transthyretin.

proteins, genes encoding proteins involved in calcium homeostasis such as phospholamban (*PLN*) and junctophilin 2 (*JPH2*), or in actin filament polymerization such as FH1/FH2 domain-containing protein 3 (*FHOD3*), as well as mitochondrial DNA variants causing isolated non-syndromic LV hypertrophy, contribute to fewer than 10% of cases of HCM[8]. Depending on the age of onset, a proportion of cases might be caused by variants in genes encoding proteins of the RAS–mitogen-activated protein kinase (MAPK) pathway (such as Noonan syndrome)[11], disorders of metabolism (such as Pompe disease in infants or Anderson–Fabry disease in adults), neuromuscular disorders (such as Friedreich ataxia and mitochondrial disorders) and familial amyloidosis[12,13].

Dilated cardiomyopathy. More than 25% of cases of DCM are associated with rare variants in genes encoding sarcomeric proteins (such as titin (*TTN*)), cytoskeletal proteins (such as filamin C (*FLNC*) and desmin (*DES*)), calcium homeostasis proteins (such as *PLN*), nuclear envelope proteins (such as lamin A/C (*LMNA*) and emerin (*EMD*)) and desmosomal proteins (such as desmoplakin (*DSP*)), as well as protein splicing modifiers (such as RNA-binding protein 20 (*RBM20*))[14]. *TTN*-truncating variants (*TTN*tv) are the most common, occurring in 15–25% of patients with DCM but also in 0.5–3.0% of the general population[15,16]. Additionally, genome-wide association studies have broadened our understanding of the genetic background by identifying common variants of modest individual effect associated with susceptibility to DCM, indicating a complex inheritance pattern[5,6].

Non-dilated left ventricular cardiomyopathy. As with DCM, NDLVC is caused by pathogenic variants in genes that encode cytoskeletal proteins (such as *DES*, *FLNC* and *LMNA*) and desmosomal proteins

Table 2 | Emerging and investigational therapies in cardiomyopathies

Therapeutic approach	Mechanistic concept	Emerging or investigational approaches
Myosin modulators	State shift in β-myosin heavy chain	HCM (mavacamten, aficamten); DCM (omecamtiv mecarbil, danicamtiv)
Modulators of myocardial energetics	Shift in metabolic substrate	HCM (perhexiline, trimetazidine, ninerafaxstat, SGLT2 inhibitors)
Modulators of cardiac inflammation, apoptosis or fibrosis	Modification of downstream pathogenic pathways	DCM (MAPK inhibitors in laminopathies); HCM (ARBs as TGFβ inhibitors); ARVC (NF-κB inhibitors, modulators of WNT–β-catenin signalling and Hippo pathways)
RNA interference	Silencing of gene expression by degrading or blocking the target mRNA	TTR amyloidosis (ASOs such as eplontersen and inotersen; siRNAs such as patisiran and vutrisiran); DCM (*PLN*-targeting ASOs)
Gene replacement	Inserting a functional gene copy to correct haploinsufficiency	HCM (TN-201: AAV9.*MYBPC3*); DCM (REN-001: AAV9.*BAG3*; AVB-401: AAVrh74.*BAG3*); ARVC (TN-401: AAV9.*PKP2*; RP-A601: AAVrh74.*PKP2*; LX2020: AAVrh10.*PKP2*); Anderson–Fabry disease (ST-920: AAV2 or AAV6 vector+functional *GLA*); Danon disease (RP-A501: AAV9.*LAMP2B*)
Gene editing	Precise gene editing	HCM (investigational in animal models of *MYH7*-associated HCM); ARVC (investigational in in animal models of *PKP2*-associated ARVC)

AAV, adeno-associated virus; ARB, angiotensin receptor blocker; ARVC, arrhythmogenic right ventricular cardiomyopathy; ASO, antisense oligonucleotide; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor-κB; SGLT2, sodium–glucose cotransporter 2; siRNA, small interfering RNA; TGFβ, transforming growth factor-β; TTR, transthyretin.

(such as *DSP*)[17]. Although *DSP* variants have historically been linked to ARVC[18], many primarily cause LV disease with fibrosis and recurrent myocardial injury and are probably responsible for most cases of NDLVC[19–21]. Genes linked to increased risk of arrhythmia include those encoding nuclear envelope, desmosomal and some cytoskeletal proteins.

Arrhythmogenic right ventricular cardiomyopathy. ARVC primarily results from pathogenic variants in genes encoding desmosomal proteins, such as plakophilin 2 (*PKP2*), *DSP*, junction plakoglobin (*JUP*) and desmoglein 2 (*DSG2*)[22]. Desmosomes, alongside fascia adherens junctions and gap junctions, are crucial elements of the intercalated disc, which maintains mechanical integrity and facilitates cellular communication between cardiomyocytes. Pathogenic variants in these genes compromise cellular adhesion, leading to cardiomyocyte detachment and injury, often accompanied by inflammation and replacement by fibrofatty tissue. Approximately 50% of patients with ARVC carry a pathogenic variant in one of the main desmosomal genes[23,24]. Rarer cases of ARVC involve pathogenic variants in non-desmosomal components of the intercalated disc, such as cadherin 2 (*CDH2*), transmembrane protein 43 (*TMEM43*), *DES* and *PLN*[23].

Restrictive cardiomyopathy. Pathogenic variants in genes encoding sarcomeric proteins are key contributors to genetic forms of RCM. Variants in genes encoding cytoskeletal, Z-disc and intermediate filament proteins (such as *FLNC*, *DES* and *ACTN2* (encodes α-actinin 2)) are less commonly implicated[2].

Role of the cardiac sarcomere in disease pathogenesis

The cardiac sarcomere is the basic contractile unit of cardiac muscle and consists of an array of filaments and associated proteins (Fig. 1). There are two main components: the thin filaments (composed of actin) and the thick filament (composed of β-myosin, which is the key motor molecule responsible for sarcomere shortening through an ATP-dependent process). The thin filament is associated with tropomyosin and the troponin complex, which together regulate the interaction between actin and the thick myosin filament in response to calcium binding.

β-Myosin exists in various conformational states, including an inactive form known as the interacting-heads motif, in which the myosin heads are sequestered and unable to generate force[25] (Fig. 1). In the active state, ATP binding and hydrolysis induce conformational changes that enable the myosin heads to engage with actin, resulting in sarcomere contraction[26]. The balance between the active and inactive states of β-myosin, and in particular the transition between the super-relaxed (SRX) and disordered relaxed (DRX) states, is crucial for regulation of ATPase activity and optimization of energy efficiency[27,28]. The SRX state is thought to represent an autoinhibitory arrangement of the myosin heads, whereby interactions between the myosin heads and the myosin tail S2 region prevent crossbridge cycling[29]. This state contributes to energy efficiency by limiting the number of myosin heads available for contraction at rest.

Pathogenic variants in sarcomere proteins disrupt normal sarcomeric function, triggering a cascade of molecular events that contribute to distinct clinical phenotypes and cardiac remodelling. Specifically, in HCM and RCM, hypercontractility and increased myocardial stiffness predominate, whereas DCM and NDLVC are characterized by hypocontractility. These mechanical abnormalities are further exacerbated by abnormal energy metabolism, which is a unifying feature across all cardiomyopathies[30–32].

Pathogenic variants in genes encoding sarcomere proteins can destabilize the SRX state or disrupt its regulatory control, leading to excessive ATPase activity at rest, increasing metabolic demand and contributing to disease progression[33,34]. In HCM, destabilization of the SRX state has been identified as a key pathological mechanism associated with some variants in *MYH7* that shift the equilibrium away from the SRX towards a DRX state or an actively engaged 'on' state[35,36]. In the DRX conformation, myosin heads are available for actin binding but are not yet actively cycling, leading to a substantial increase in ATPase activity compared with the SRX state[35,36]. This shift towards higher-energy β-myosin heavy chain states increases sarcomere force generation and contributes to the hypercontractility seen in HCM[33,37].

Role of the nuclear envelope and cytoskeleton

The cytoskeleton is essential for maintenance of normal cardiac structure and function. Various protein families contribute to the scaffolding and signalling functions of the cytoskeleton through protein–protein interaction, and defects in cytoskeletal protein function compromise

structural integrity and impair mechanotransduction, the process by which cells convert mechanical stimuli into biochemical signals[38].

Lamin A/C anchors the nuclear envelope to the cytoskeleton, providing structural support to the nucleus and regulating chromatin organization and DNA replication. Lamin A/C connects the nuclear lamina to the inner nuclear membrane through interactions with emerin and SUN domain proteins, which, in turn, link to the outer nuclear envelope via nesprins[38]. In lamin-related cardiomyopathy, pathogenic variants in *LMNA* compromise nuclear integrity, leading to an irregular nuclear shape and weakened nuclear–cytoskeletal connections in cardiomyocytes, impairing force transmission and causing changes in gene expression[39,40].

Similarly, emerin interacts with lamin A/C and components of the linker of nucleoskeleton and cytoskeleton complex (LINC) to tether the nucleus to the cytoskeleton[41,42]. Pathogenic variants in *EMD* disrupt these interactions, leading to impaired mechanotransduction and destabilized nuclear organization[43]. These defects are characteristic of Emery–Dreifuss muscular dystrophy (EDMD type 1), a syndrome that presents with skeletal muscle weakness, joint contractures and cardiomyopathy[44]. Other genes implicated in EDMD, such as *FHL1*, encode multiple isoforms of the four-and-a-half LIM domain protein 1. Although FHL1 is not a direct component of the LINC complex, its isoforms, particularly FHL1B, interact with lamin A/C and emerin, contributing to nuclear stability and mechanotransduction through structural and signalling pathways[45]. Pathogenic variants in *FHL1* are implicated in X-linked EDMD and HCM[44,46].

Desmin intermediate filaments, encoded by *DES*, normally connect the nucleus to the cytoskeleton and Z-discs, and their detachment in cells with pathogenic variants in *DES* also weakens structural integrity. Pathogenic missense variants in *DES* have been associated with DCM, HCM, RCM and, more rarely, ARVC[47,48].

In addition to abnormalities in the mechanical framework linking the nuclear envelope and cytoskeleton, pathogenic variants in these genes are also associated with dysregulated intracellular signalling and key molecular downstream pathways. Hyperactivation of the p38–MAPK pathway promotes cardiomyocyte apoptosis, cardiac fibrosis and impaired contractility[49,50]. Lamin A/C haploinsufficiency disrupts chromatin organization, favouring a peripheral distribution in the nucleus instead of uniform chromatin arrangement, leading to nuclear dysfunction[51]. Upregulation of the RACα

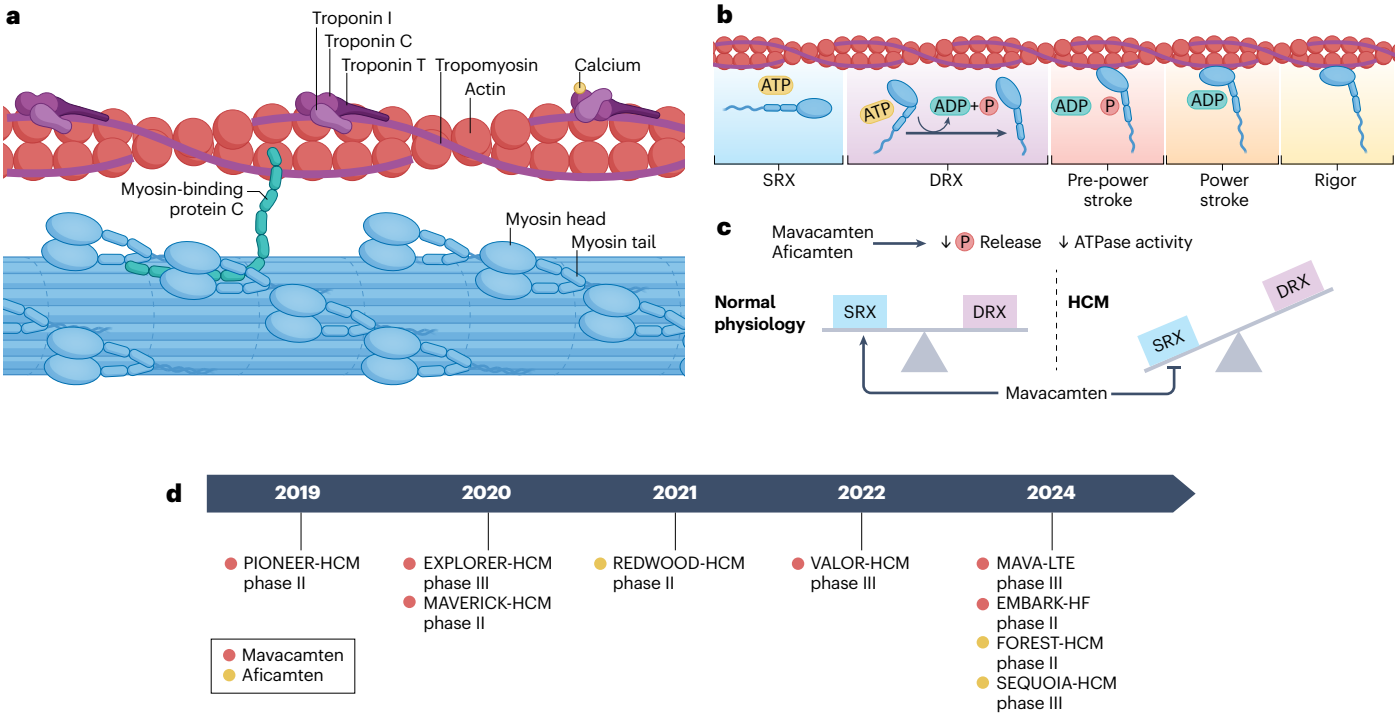


Fig. 1 | The cardiac sarcomere and the role of myosin inhibitors in HCM. **a**, The cardiac sarcomere, the fundamental contractile unit of cardiac muscle, contains an intricate arrangement of thin filaments (actin) and thick filaments (β-myosin), as well as regulatory proteins. Actin is associated with tropomyosin and the troponin complex (troponin C, troponin I and troponin T), which modulate actin–myosin interactions in response to calcium binding. **b**, β-Myosin, the motor molecule that drives sarcomere shortening, operates via an ATP-dependent mechanism and transitions between conformational states that are crucial for energy efficiency and force generation. The super-relaxed (SRX) state represents an autoinhibitory conformation of β-myosin in which interactions between the myosin heads and the myosin tail S2 region limit crossbridge cycling, thereby conserving ATP at rest. By contrast, the disordered relaxed (DRX) state involves myosin heads primed for actin binding but not yet actively cycling, resulting in higher ATPase activity. Dysregulation of the SRX–DRX balance, driven by pathogenic variants in genes encoding sarcomere proteins, destabilizes the SRX state, contributing to the hypercontractility and increased metabolic demand that are characteristic of hypertrophic cardiomyopathy (HCM). **c**, The mechanism of action of myosin inhibitors, such as mavacamten and aficamten. These agents restore the SRX state by modulating ATPase activity, reducing power stroke generation and preventing excessive energy expenditure. **d**, The timeline shows randomized controlled trials of the myosin inhibitors mavacamten (PIONEER-HCM[210], EXPLORER-HCM[126], MAVERICK-HCM[134], VALOR-HCM[128], MAVA-LTE[129] and EMBARK-HFpEF[137]) and aficamten (REDWOOD-HCM[211], FOREST-HCM[212] and SEQUOIA-HCM[131]) in patients with HCM or heart failure with preserved ejection fraction. P, phosphate.

serine/threonine-protein kinase (AKT)–mechanistic target of rapamycin (mTOR) pathway, with increased mTOR complex 1 activity and elevated expression of platelet-derived growth factor receptor (PDGFR), further drives apoptosis, fibrosis and maladaptive remodelling[52]. Although preclinical research has targeted these pathways, the phase III REALM-DCM trial of a p38α MAPK inhibitor (ARRY-371797) did not show benefit in patients with *LMNA*-related DCM[53,54].

Filamins are large actin-binding and crosslinking proteins that have a crucial role in connecting the cytoskeleton to the plasma membrane, contributing to structural stability and membrane-associated signal transduction[55]. Filamin C stabilizes polymerized actin and anchors the sarcolemma to the cytoskeleton in cardiac and skeletal muscle[55]. Several studies have linked pathogenic variants in *FLNC* to DCM and myofibrillar myopathies, as well as NDLVC with or without skeletal muscle involvement[56,57].

RAS–MAPK signalling pathway in RASopathies

Although not directly related to nuclear and cytoskeletal architecture, the RASopathies share downstream signalling pathways with the mechanisms described above. RASopathies are developmental syndromes caused by gain-of-function variants in genes encoding proteins in the RAS–MAPK signalling pathway. HCM is commonly observed in individuals with RASopathies[58,59]. In addition to its role during development, the RAS–MAPK signalling cascade also has an oncogenic function, contributing to the pathogenesis of more than 25% of all cancers[60]. This overlap has led to the exploration of repurposing RAS–MAPK inhibitors (such as trametinib) to restore signalling to physiological levels, focusing on regulating the cascade to support normal cellular function instead of using these medications as cytotoxic agents[61,62]. Studies have demonstrated that inhibition of the RAS–MAPK pathway provides clinical benefits in patients with severe Noonan syndrome-associated HCM[63]. Specifically, retrospective cohort analyses showed that trametinib reduces the need for LVOT surgery, lowers the likelihood of heart transplantation and mortality compared with historical control individuals, and leads to clinical improvement within weeks, followed by reductions in plasma amino-terminal pro-B-type natriuretic peptide (NT-proBNP) levels and regression of cardiac hypertrophy assessed by echocardiography. Although longer-term follow-up is needed, these findings suggest that RAS–MAPK inhibitors can modify the disease course, particularly in early-onset, life-threatening cases[63,64].

Myocardial energetics in cardiomyopathies

Cardiomyocytes are dependent on high levels of ATP to sustain contraction and relaxation cycles, with most of this energy generated through mitochondrial oxidative phosphorylation[65]. The healthy myocardium primarily uses fatty acids as its main energy substrate, but remains metabolically flexible and can switch to glucose oxidation or ketone metabolism[66]. In heart failure (HF), mitochondrial dysfunction impairs ATP production, creating an energy-deficient state that accelerates disease progression[67]. Mitochondrial dysfunction also leads to increased generation of reactive oxygen species (ROS), which damage cellular structures and further impair ATP synthesis. In HF, the myocardium compensates by increasing glucose use, but as the condition progresses, both glucose and fatty acid oxidation decline, exacerbating the ATP deficit and worsening LV dysfunction[68]. Similar to the HF paradigm, a metabolic shift also occurs in HCM, whereby abnormal sarcomere energetics lead to increased ATP consumption and oxygen demand, the latter exacerbated by microvascular ischaemia and impaired substrate oxidation[30,31].

Calcium homeostasis

Maintenance of calcium homeostasis is essential for excitation–contraction coupling and electrical stability in cardiomyocytes. Central to this process is the sarcoplasmic/endoplasmic reticulum calcium ATPase 2a (SERCA2a), which facilitates the rapid re-uptake of calcium into the sarcoplasmic reticulum, ensuring efficient relaxation of myofilaments and preventing intracellular calcium overload.

Reduced activity of SERCA2a is common in HF[69,70] and results in impaired calcium re-uptake into the sarcoplasmic reticulum and intracellular calcium overload, which contributes to arrhythmias. Phospholamban is a key regulator of calcium handling by modulation of SERCA2a activity, thereby controlling cardiac lusitropy[71]. The *PLN* p.Arg14del variant, a founder variant in the Netherlands, is one of the most prevalent single-variant alterations globally, is associated with DCM and NDLVC phenotypes, and carriers often experience a malignant clinical course characterized by increased risk of progressive HF and sudden cardiac death[72,73]. The variant disrupts calcium homeostasis, leading to calcium mishandling, compromised cardiomyocyte function and arrhythmogenesis[74,75].

In HCM, impaired SERCA2a activity contributes to increased intracellular calcium levels and impaired calcium kinetics, which are also influenced by mechanisms such as abnormal L-type calcium current kinetics mediated by increased calcium/calmodulin-dependent protein kinase type II autophosphorylation, transverse tubule disorganization, attenuated calcium release from the sarcoplasmic reticulum and sodium–calcium exchanger abnormalities[76–80]. Variants in genes encoding sarcomere proteins exacerbate calcium dysregulation by slowing calcium release from the troponin complex, increasing energy consumption and reducing ATP availability for SERCA2a function[81]. Calcium dysregulation contributes not only to arrhythmogenesis but also to diastolic dysfunction and LV remodelling[76].

In ARVC, pathogenic variants in *PKP2* and *DSG2* also affect calcium signalling pathways[22]. Variants in these genes alter the expression of calcium-handling proteins, such as the ryanodine receptor 2 and L-type calcium channel ($Ca_V1.2$), resulting in calcium mishandling and triggering cell death[22].

Therapeutic approaches targeting calcium handling in cardiomyopathies to mitigate delayed after-depolarizations linked to arrhythmogenesis have been investigated in animal models. Ranolazine is a piperazine-derivative small molecule that principally inhibits the late inward sodium current (I_{NaL}). In healthy cardiomyocytes, I_{NaL} contributes minimally to the action potential, but I_{NaL} is substantially upregulated in HCM, leading to intracellular sodium and calcium overload, which is arrhythmogenic and can also affect diastolic function[77]. Ranolazine also inhibits the delayed rectifier potassium current (I_{Kr}), which prolongs the ventricular action potential duration and is an inhibitor of fatty acid oxidation[82]. However, despite these mechanistic benefits, the phase II RESTYLE-HCM trial[83] showed no significant improvements in exercise capacity, diastolic function or quality of life with ranolazine treatment compared with placebo in patients with HCM.

Desmosomes

Desmosomes are cell-to-cell junctions found predominantly in the heart and the skin. Desmosomes maintain intercellular adhesion by anchoring the intermediate filaments to desmosomal plaques[84] and also mediate intracellular and intercellular signal transduction pathways.

Pathogenic variants in genes encoding desmosomal proteins result in the redistribution of junction plakoglobin (also known as

γ-catenin), which competes with β-catenin, leading to disruption of the canonical WNT–β-catenin signalling and related transcription factor pathways, a process that is thought to contribute to apoptosis and fibrofatty infiltration in the myocardium[85]. Furthermore, increased activity of the Hippo pathway modulated by activation of intercalated disc-related proteins such as neurofibromin 2 (also known as merlin) and inactivation of transcriptional coactivator YAP1 by phosphorylation further inhibits WNT–β-catenin signalling and increases fat accumulation[86]. An inhibitor of glycogen synthase kinase 3β (GSK3β), a key regulator of WNT–β-catenin signalling, has been investigated in a range of animal models and has been shown to improve myocardial function and reduce arrhythmias in mouse models of ARVC[87]. The randomized TARGET trial[88] to investigate the use of tideglusib (a small-molecule inhibitor of GSK3β) in patients with genotype-positive ARVC is ongoing.

Myocardial fibrosis and inflammation

Cardiomyopathies are associated with alterations in the collagen-rich cardiac extracellular matrix, which, together with cardiomyocyte changes such as hypertrophy, necrosis and apoptosis, contribute to HF and provide a structural substrate for electrical instability and arrhythmias.

Myocardial fibrosis has a crucial role in cardiomyopathy disease progression and is a potential target for early-stage, disease-modifying treatments. Fibrosis is primarily driven by transforming growth factor-β (TGFβ) signalling, which activates fibroblasts and promotes extracellular matrix deposition[89]. Modulation of the TGFβ pathway, particularly through the use of angiotensin receptor blockers, can reduce fibrotic remodelling, but direct targeting of TGFβ is challenging owing to its crucial role in tissue repair[89,90]. The INHERIT and VANISH trials[91,92] were based on studies in preclinical mouse models of sarcomeric HCM demonstrating that angiotensin receptor blockers inhibit TGFβ signalling and prevent early LV hypertrophy and fibrosis[93,94]. However, compared with placebo, neither losartan nor valsartan significantly slowed the progression of subclinical HCM in these trials[91,92].

Inflammation and activation of both the innate and adaptive immune systems are important pathogenic drivers in cardiomyopathies, contributing to cardiomyocyte damage and myocardial collagen deposition and fibrosis[95]. Inflammation is particularly important in ARVC and certain subtypes of NDLVC associated with desmosomal variants, in which so-called hot phases accelerate disease progression and increase the risk of arrhythmia[17]. In genetically susceptible individuals, exercise or exposure to viruses can initiate inflammation, driving cardiac structural remodelling and life-threatening arrhythmias[96]. Inflammatory signalling, particularly through nuclear factor-κB (NF-κB), contributes to pathological cardiac remodelling in cardiomyopathies[97], and NF-κB inhibitors have shown promise in reducing cytokine production and inflammation-induced apoptosis of the hearts of animal models of ARVC[97], suggesting a potential benefit of anti-inflammatory treatment in patients with ARVC.

Expanding on the role of inflammation, autoimmunity is increasingly recognized as a contributing factor in DCM, particularly in systemic autoimmune and autoinflammatory conditions and especially in individuals who carry pathogenic variants in cardiomyopathy-associated genes[98]. In addition, autoantibodies that target cardiac-specific antigens such as myosin heavy chain isoforms and cardiac troponins are detected in up to 60% of patients with DCM and are associated with disease progression and the risk of arrhythmia[99,100]. Although these findings highlight a potential role for autoimmunity in the pathogenesis of DCM, further research is needed to clarify their causal relevance.

Storage and infiltration

Several genocopies and phenocopies, such as lysosomal, glycogen storage and infiltrative diseases, result in diverse cardiomyopathy phenotypes driven by distinct pathological mechanisms involving intracellular or extracellular deposition of byproducts[1]. These conditions often mimic classical HCM and RCM, and their differential diagnosis is crucial, because targeted therapies are increasingly available and have shown the potential to stabilize or even reverse clinical phenotypes[101]. Some examples include Anderson–Fabry disease and cardiac amyloidosis.

Anderson–Fabry disease is an X-linked lysosomal storage disorder caused by pathogenic variants in *GLA*, which result in reduced or absent α-galactosidase A enzyme activity and the accumulation of globotriaosylceramide (Gb_3) and globotriaosylsphingosine (lyso-Gb_3) in various organs and tissues. Anderson–Fabry disease is responsible for 1% of cases of HCM[102]. Cardiac involvement arises from multiple mechanisms, including intracellular Gb_3 storage, oxidative stress and inflammation[103].

Cardiac amyloidosis is a progressive infiltrative disease characterized by the extracellular deposition of misfolded proteins in various tissues. In the heart, amyloid deposition typically results in a hypertrophic phenotype, often with restrictive physiology[104]. Most cases of cardiac amyloidosis arise from one of two protein precursors: monoclonal immunoglobulin light chains (typically produced by bone marrow plasma cells)[105] or transthyretin (TTR; a serum transport protein synthesized primarily in the liver that transports thyroid hormone and retinol). TTR amyloidosis (ATTR) is classified as being wild type (ATTRwt) or hereditary (ATTRv), with the latter caused by pathogenic variants in the *TTR* gene. The pathophysiology of cardiac amyloidosis is multifactorial, resulting from a combination of extracellular amyloid infiltration and the proteotoxicity of amyloid fibrils, which leads to cardiac oxidative stress, inflammation and apoptosis[106].

Influence of sex on disease expression

In addition to genetic and environmental influences, sex-specific factors further complicate the pathogenesis of cardiomyopathies[107]. Sex-based differences influence clinical presentation, disease progression and outcomes in heart muscle diseases. For example, men diagnosed with DCM typically present with more severe characteristics and have a less favourable prognosis than women[108]. By contrast, women with HCM tend to be diagnosed later than men and, when diagnosed, present with a higher symptom burden, lower exercise capacity and increased rates of HF progression and all-cause death[109]. These differences are influenced by distinct molecular and remodelling patterns, supported by proteomic and RNA-sequencing profiles, with sex hormones potentially having a role[107]. Women tend to have increased pro-inflammatory gene expression, reduced mitochondrial enzyme activity and increased detyrosinated microtubules, contributing to worse diastolic function, cardiac fibrosis and inflammation-driven remodelling[7,107]. Oestrogens also influence electrophysiological remodelling by modulating ion channel activity and calcium handling[107]. These mechanisms have mostly been described outside the context of cardiomyopathy but are generally associated with prolonged repolarization and increased susceptibility to arrhythmia and are likely to be relevant to the arrhythmogenic substrate in cardiomyopathies[107].

Management of comorbidities and conventional therapies

Effect of environmental and lifestyle factors and comorbidities

In patients with HCM, the presence of hypertension and obesity is associated with greater LV hypertrophy and a higher likelihood of disease development among carriers of variants in genes encoding sarcomeric proteins[7]. Moreover, hypertension, diabetes mellitus and obesity in patients with HCM are associated with older age at presentation, increased symptoms, worse LV diastolic function and microvascular ischaemia[110]. In DCM, several factors can contribute to phenotype development in carriers of DCM-associated genetic variants, including hypertension, pregnancy, toxic factors (such as exposure to chemotherapeutic agents), autoimmune disorders and myocarditis[111].

Lifestyle choices have an important role in modulating disease expression in carriers of cardiomyopathy-associated genetic variants, with the strongest evidence available for variants in *PKP2*, whereby participation in endurance sports is linked to earlier disease onset, more severe cardiac structural abnormalities, an increased risk of ventricular arrhythmia and a higher likelihood of HF[112]. By contrast, no compelling evidence is available to suggest that intense exercise has a similar effect on carriers of pathogenic variants associated with HCM. Small studies in carriers of *LMNA* variants suggest that greater cumulative lifetime exercise exposure is associated with reduced LV systolic function, increased risk of atrial fibrillation and adverse outcomes[113].

Identification and management of risk factors are key to improving outcomes, with a personalized approach guided by genotype and phenotype. Across all cardiomyopathies, maintaining a healthy BMI, avoiding dehydration and excessive alcohol intake, and addressing comorbidities such as hypertension and obstructive sleep apnoea — particularly in individuals with atrial fibrillation — are crucial.

Regular low-intensity to moderate-intensity exercise is recommended for all able individuals. High-intensity exercise and competitive sports are contraindicated in patients with HCM and LVOT obstruction, high-risk features or exercise-induced complex arrhythmias; patients with ARVC; and symptomatic patients with DCM and reduced LVEF, arrhythmias, or pathogenic *LMNA* or *TMEM43* variants[1]. In genotype-positive, phenotype-negative individuals, high-intensity exercise can be considered in those with HCM-related variants, and moderate-intensity to high-intensity exercise can be considered in those with DCM-related variants (excluding individuals with variants in *LMNA* or *TMEM43*)[1]. By contrast, individuals who carry an ARVC-associated genetic variant but have no clinical signs of disease are advised to refrain from high-intensity activities, including competitive sports[1].

Guideline-directed medical therapy

Conventional pharmacological therapies have a crucial role in reducing disease burden and improving outcomes in patients with some cardiomyopathy subtypes. Guideline-directed drug and device therapies[114] based on randomized controlled clinical trials are primarily applicable to cardiomyopathies characterized by symptomatic LV dysfunction, such as DCM and NDLVC (Table 1). Although no clinical trials have been conducted, observational studies suggest that sodium–glucose cotransporter 2 (SGLT2) inhibitors are well tolerated and might be effective in patients with non-obstructive HCM[115] and in patients with cardiac amyloidosis[116]. Similarly, sacubitril–valsartan has been studied in the phase II, randomized SILICOFCM trial[117] in patients with non-obstructive HCM, demonstrating good tolerability but no significant effect on exercise capacity or cardiac structure or function. Currently, β-blocker therapy remains the first-line treatment for management of LVOT obstruction in patients with HCM[1], owing to its efficacy in relieving obstruction and improving symptoms and quality of life. If β-blockers are contraindicated or ineffective, verapamil or disopyramide can be considered, with disopyramide often used in combination therapy or as an adjunct to β-blockers[1]. Atrial and ventricular arrhythmias are managed according to standard guidelines[118,119].

Targeted therapies in cardiomyopathies

Advances in genomics, sequencing technologies and disease registries are revolutionizing cardiomyopathy care and, combined with an improved mechanistic understanding of disease pathways, are enabling targeted therapies for specific disease subgroups. This approach moves beyond symptom management to interventions that are aimed to modify or reverse disease progression (Table 2).

Myosin modulation

Advances in our understanding of the molecular mechanisms of cardiomyopathy have led to the development of a new class of agents that modulate cardiac myosin. The main characteristics and results of phase III trials of cardiac myosin modulators in patients with DCM or HCM are reported in Table 3.

Omecamtiv mecarbil is a cardiac myosin activator that directly activates cardiac myosin in a calcium-independent manner, promoting the transition of myosin into the actin-bound, force-generating state[120]. By increasing the duration of systolic ejection without altering the rate of contraction, omecamtiv mecarbil improves systolic function without increasing oxygen consumption, as is the case with conventional positive inotropes[121]. The phase III, double-blind, placebo-controlled GALACTIC-HF trial[122] evaluated the effect of omecamtiv mecarbil in patients with HF with reduced ejection fraction. In comparison with placebo, patients treated with omecamtiv mecarbil were less likely to reach the primary end point of cardiovascular death and HF events, but the difference was modest (37.0% versus 39.1%; HR 0.92, $P = 0.03$), and mortality was not significantly different between the two groups (Table 3). The METEORIC-HF trial[123] showed that, compared with placebo, omecamtiv mecarbil did not significantly improve exercise capacity over 20 weeks in patients with HF with reduced ejection fraction. Another myosin activator, danicamtiv, was well tolerated in a phase II clinical trial and was associated with improvements in LV and left atrial echocardiographic parameters compared with placebo[124]. However, an open-label study to assess the safety and preliminary efficacy of danicamtiv in patients with DCM due to *MYH7* or *TTN* variants has been prematurely terminated[125], and no studies on danicamtiv are ongoing.

Myosin inhibitors reduce myosin ATPase activity, stabilize the SRX state of myosin and decrease the increased contractile force and calcium sensitivity induced by sarcomeric variants[33] (Table 3 and Fig. 1). Mavacamten, a selective, allosteric, reversible, small-molecule cardiac myosin inhibitor, is a first-in-class therapy for obstructive HCM, which, in the randomized, double-blind, placebo-controlled, phase III EXPLORER-HCM trial[126] involving patients with symptomatic obstructive HCM, improved exercise capacity, reduced LVOT obstruction, and improved symptoms and patient-reported health status compared with placebo. These findings were confirmed in a Chinese population with symptomatic obstructive HCM in the EXPLORER-CN trial[127] trial and further explored in the VALOR-HCM trial[128], in which treatment with mavacamten significantly reduced the proportion of patients with severe obstructive HCM who met the criteria for septal

Table 3 | Clinical trials of cardiac myosin modulators in HCM and HFrEF

Cardiac myosin modulator	Clinical trial	Region	Key inclusion criteria	Duration	Primary end point	Results
Myosin inhibitors in patients with HCM						
Mavacamten	EXPLORER-HCM[126]	International	Age ≥18 years; peak LVOT gradient ≥50 mmHg at rest, after Valsalva manoeuvre or exercise; LVEF 55%; NYHA class II–III symptoms	30 weeks	Clinical response defined as: ≥1.5 ml increase in pVO_2 and ≥1 NYHA class reduction, or ≥3.0 ml increase in pVO_2 and no NYHA class worsening	Improvements in pVO_2, NYHA class and KCCQ-CSS; decreases in LVOT gradient and HCMSQ-SoB
	VALOR-HCM[128]	USA	Age ≥18 years; criteria for invasive SRT: peak LVOT gradient ≥50 mmHg at rest or provocation and NYHA class III–IV or NYHA class II with exertion-induced syncope or near syncope, despite maximally tolerated drug therapy; LVEF ≥60%	16 weeks	Composite of eligibility for SRT or a patient decision to proceed with SRT	Improvements in NYHA class and KCCQ-CSS; decreases in SRT eligibility, LVOT gradient, plasma NT-proBNP and cTnI levels
	EXPLORER-CN[127]	China	Age ≥18 years; peak LVOT gradient ≥50 mmHg at rest or after Valsalva manoeuvre; LVEF ≥55%; NYHA class II–III symptoms	30 weeks	Change in LVOT gradient	Improvements in NYHA class and KCCQ-CSS; decreases in LVOT gradient and plasma NT-proBNP and hs-cTnI levels
Aficamten	SEQUOIA-HCM[131]	International	Age ≥18 years; peak LVOT gradient ≥30 mmHg at rest or ≥50 mmHg after Valsalva manoeuvre; LVEF ≥60%; NYHA class II–III symptoms	24 weeks	Change in pVO_2	Improvements in pVO_2, KCCQ-CSS, NYHA class and total workload during CPET; decreases in LVOT gradient and SRT eligibility
Myosin activators in patients with HFrEF						
Omecamtiv mecarbil	GALACTIC-HF[122]	International	Age ≥18 years; LVEF ≤35%; NYHA class II–IV symptoms	22 months	A composite of heart failure events or cardiovascular death	Decrease in the risk of the primary end point
	METEORIC-HF[123]	International	Age ≥18 years; LVEF ≤35%; NYHA class II–III symptoms; plasma NT-proBNP level ≥200 pg/ml; pVO_2 ≤75%	20 weeks	Change in pVO_2	No significant differences

The studies included in the table are all randomized, double-blind, placebo-controlled, phase III clinical trials. CPET, cardiopulmonary exercise testing; cTnI, cardiac troponin I; HCM, hypertrophic cardiomyopathy; HCMSQ-SoB, Hypertrophic Cardiomyopathy Symptom Questionnaire – Shortness of Breath; HFrEF, heart failure with reduced ejection fraction; hs-cTnI, high-sensitivity cardiac troponin I; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire – Clinical Summary Score; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; NT-proBNP, N-terminal pro-B-type natriuretic peptide; pVO_2, peak oxygen consumption; SRT, septal reduction therapy.

reduction therapy. Results from the MAVA-LTE study[129] (a long-term safety extension study of participants from the MAVERICK-HCM and EXPLORER-HCM trials) showed that mavacamten treatment resulted in sustained improvements in LVOT gradients, plasma NT-proBNP level and NYHA class over a median follow-up period of 166 weeks. The safety of mavacamten treatment was further evaluated in a real-world study involving 6,299 patients in the USA who received at least one dose of mavacamten. The analysis showed that the need for temporary interruption because of a LVEF of <50% occurred in only 4.6% of patients and was rarely associated with HF that required hospitalization[130].

A second-in-class myosin inhibitor, aficamten, produced similar results in the SEQUOIA-HCM trial[131] in patients with symptomatic obstructive HCM. By comparison with placebo, aficamten was associated with significant improvements in exercise capacity, NYHA functional class, patient-reported health status and LVOT obstruction[131]. Based on these data, the use of cardiac myosin inhibitors is recommended in practice guidelines as a second-line therapy for patients with obstructive HCM and drug-refractory symptoms[1].

Cardiac magnetic resonance substudies of the EXPLORER-HCM[132] and SEQUOIA-HCM[133] trials suggest macrostructural improvements with myosin inhibitor therapy, including reductions in LV mass index and left atrial volume index, as well as microstructural remodelling, such as decreases in myocardial native T1 time, extracellular volume fraction and cardiomyocyte mass. This apparent reverse remodelling suggests that the effects of myosin inhibitors might extend beyond a reduction in LVOT obstruction, but this hypothesis requires further study.

Although most symptomatic patients with HCM have LVOT obstruction, an important minority have non-obstructive disease. The multicentre, double-blind, placebo-controlled, phase II MAVERICK-HCM trial[134] showed that treatment of non-obstructive HCM with mavacamten was associated with a reduction in plasma NT-proBNP and cardiac troponin I levels at 16 weeks compared with placebo. On the basis of these results, the phase III ODYSSEY[135] and ACACIA-HCM[136] trials of mavacamten and aficamten, respectively, in patients with non-obstructive HCM are ongoing. Positive results have

also emerged from the primary results of the EMBARK-HFpEF trial[137], which showed that mavacamten treatment in symptomatic patients with HF with preserved ejection fraction and a LVEF of ≥60% was associated with an improvement in NYHA class and reductions in plasma NT-proBNP and cardiac troponin levels at 26 weeks.

Finally, EDG-7500, a novel selective sarcomere regulator, has shown promise in a preclinical minipig model of non-obstructive HCM by reducing LVOT gradients, improving diastolic function, and reducing left atrial and ventricular remodelling, with minimal effects on LVEF, potentially addressing the limitations of existing myosin inhibitors in patients with a reduced LVEF[138]. EDG-7500 is being tested in the phase II CIRRUS-HCM trial[139] in adults with HCM.

Targeting myocardial energetics and mitochondrial dysfunction

Abnormalities in myocardial energy metabolism are thought to have an important role in the pathogenesis of cardiomyopathies. Oxidative phosphorylation, fuelled by oxygen, is central to ATP production in cardiomyocytes. However, free fatty acids are an inefficient substrate, requiring more oxygen than is required by carbohydrates to generate the same amount of ATP. Therefore, pharmacologically shifting myocardial substrate utilization from fatty acid oxidation to glucose oxidation might improve cardiac energetics, diastolic function and overall myocardial efficiency.

Perhexiline, a metabolic modulator, inhibits carnitine *O*-palmitoyltransferase 1 (CPT1), preventing fatty acid entry into the mitochondria and promoting glucose utilization[140,141]. The ongoing RESOLVE-HCM trial[142] is evaluating the potential of perhexiline to regress LV hypertrophy in patients with symptomatic HCM. Preliminary findings suggest that perhexiline might improve diastolic function and alleviate symptoms by improving myocardial energetics[142].

Trimetazidine, a direct inhibitor of fatty acid β-oxidation, acts by reversibly competing with 3-ketoacyl-CoA thiolase. In a clinical trial, trimetazidine did not significantly improve exercise capacity in 49 patients with non-obstructive HCM compared with placebo[143], but the sample size might have been underpowered. Similar outcomes have been reported with ranolazine, which also acts as an inhibitor of fatty acid oxidation[83].

The novel agent ninerafaxstat also shifts cardiac metabolism from fatty acid oxidation to glucose oxidation through partial inhibition of 3-ketoacyl-CoA thiolase[144]. In the phase II IMPROVE-HCM trial[144] involving patients with non-obstructive HCM, ninerafaxstat was well tolerated, improved ventilatory efficiency and was associated with a trend towards better quality of life, particularly in patients with higher baseline symptoms, compared with placebo. Further studies are ongoing.

Genetic therapies

Genetic therapies encompass various techniques from RNA-targeted approaches that silence the expression of specific genes in vivo without modifying the human genome to gene therapies such as gene-replacement or gene-editing approaches using in vivo, in vitro or ex vivo strategies[145,146] (Fig. 2 and Box 1). Although a definitive monogenic cause of a cardiomyopathy cannot always be identified, gene therapies offer unique opportunities for targeted intervention in individuals with a known pathogenic variant.

Among individuals with a genetically confirmed diagnosis of HCM, pathogenic variants in *MYBPC3* are the most frequently identified cause[147,148]. The prevailing evidence supports haploinsufficiency as the predominant disease mechanism in *MYBPC3*-related HCM[147]. More than 60% of disease-causing variants in *MYBPC3* result in reduced levels of functional cardiac myosin-binding protein C, because mutant transcripts are typically degraded via nonsense-mediated mRNA decay, and truncated proteins, when produced, are rapidly cleared by the ubiquitin–proteasome system[149].

Although haploinsufficiency is widely accepted as the key pathological mechanism, the potential role of toxic peptides remains under investigation. Some studies suggest that specific mutant *MYBPC3* transcripts might escape degradation and produce unstable or misfolded proteins, which could impair proteasomal function, contribute to cellular stress and exacerbate disease progression[149,150]. Preclinical studies in mice demonstrated that adeno-associated virus 9 (AAV9)-mediated delivery of *Mybpc3* cDNA restored the expression of cardiac myosin-binding protein C, directly addressing the haploinsufficiency[151]. In addition, this approach reduced the levels of mutant *Mybpc3* mRNA, suggesting a potential secondary benefit of mitigating any residual toxic peptide effects[151]. The ongoing MyPEAK-1 trial[152,153] and the associated MyCLIMB study[154] are investigating the use of TN-201 (an AAV9 vector containing a functional *MYBPC3* gene copy) to restore protein expression and halt LV hypertrophy in patients with *MYBPC3*-associated HCM.

MYH7-associated HCM is predominantly caused by missense pathogenic variants, making this condition a candidate for allele-specific gene editing or gene silencing strategies. High efficiency of editing has been achieved using CRISPR-based adenine base editing in human induced pluripotent stem cell-derived cardiomyocytes carrying the common *MYH7* c.1208G>A (p.R403Q) pathogenic missense variant, as well as in a humanized mouse model of HCM containing the human *MYH7* c.1208G>A (p.R403Q) missense variant within the mouse *Myh6* gene (*Myh6*$^{h403/+}$)[155,156]. In these models, gene correction significantly improved contractile function and reduced LV hypertrophy[155,156]. Beyond gene editing, RNA-targeted therapies, such as antisense oligonucleotides (ASOs) and RNA interference, offer alternative therapeutic options for *MYH7*-associated HCM, although these strategies are also at preclinical stages of investigation. These approaches selectively silence mutant transcripts, allowing the wild-type allele to maintain essential levels of β-myosin heavy chain protein. Owing to the low prevalence of individual *MYH7* pathogenic variants, a variant-specific approach might be impractical. Instead, studies have explored allele-specific silencing using ASOs that target highly heterozygous SNPs in the general population, such as rs7157716, to selectively suppress mutant transcripts without affecting wild-type expression[157].

In addition, preclinical models of HCM, such as the previously described heterozygous *Myh6*$^{h403/+}$ mice, have demonstrated that allele-specific RNA interference delivered via AAV vectors can achieve an almost 30% reduction in mutant transcript levels, which was sufficient to prevent LV hypertrophy, fibrosis and cardiomyocyte disarray[158].

Phospholamban is a key regulator of SERCA2a, and pathogenic variants in *PLN* lead to DCM or NDLVC[75]. Gene therapy targeting *PLN* aims to restore normal calcium homeostasis. A CRISPR–Cas9 gene editing system delivered via AAV9 was used to correct the pathogenic effects in a humanized mouse model expressing the human *PLN*-R14del pathogenic variant, selectively targeting the mutant allele and sparing the wild-type allele[159]. Preclinical studies in mice and rats have shown that *Pln* ASOs can hybridize specifically with *Pln* mRNA, leading to RNase H-mediated degradation and reduced phospholamban transcript and protein levels[160].

Many cases of ARVC are caused by loss-of-function variants in *PKP2* (ref. 22). In a preclinical study involving a neonatal mouse model

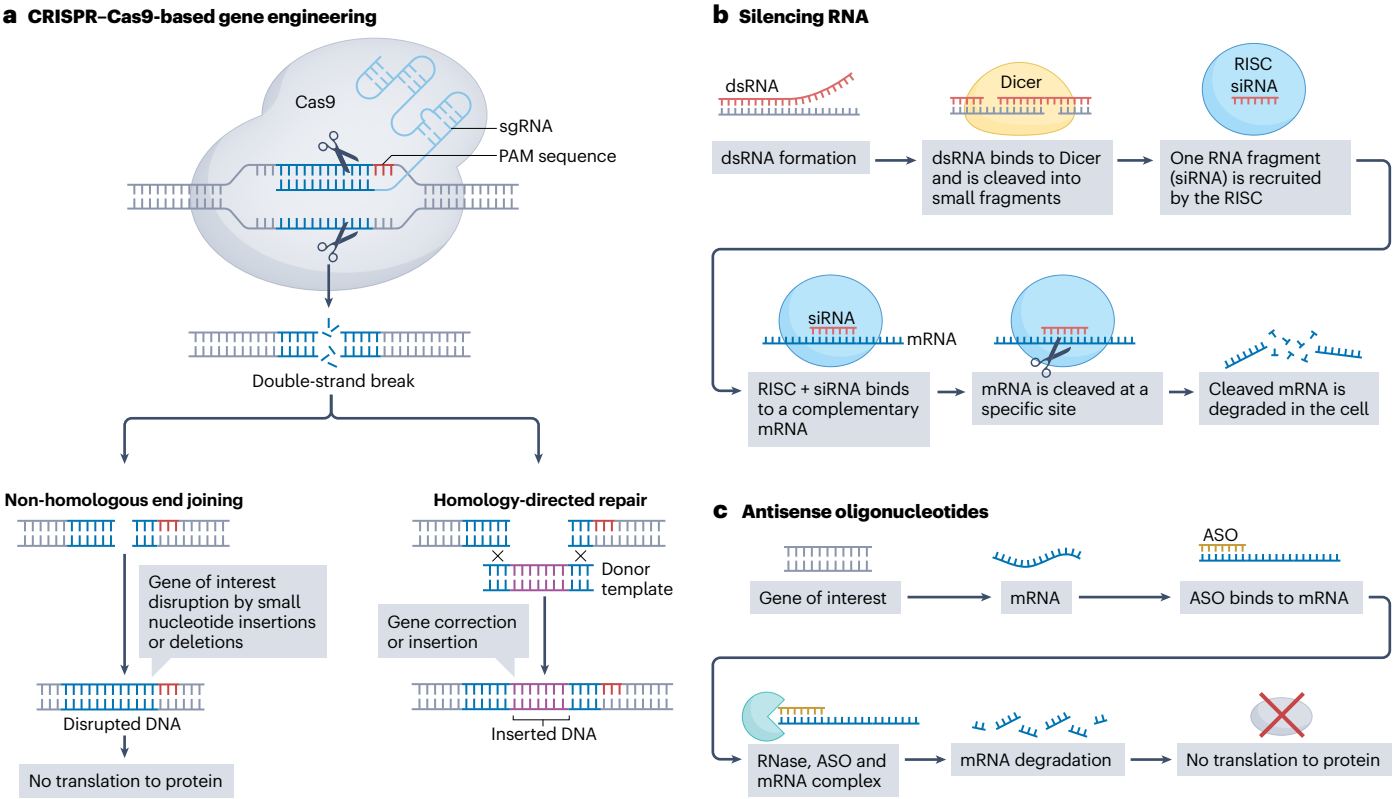


Fig. 2 | Mechanisms of RNA-based and DNA-based gene therapies. **a**, CRISPR–Cas9 technology enables targeted DNA editing through the generation of double-strand breaks guided by a single guide RNA (sgRNA). After binding to the target sequence via the protospacer adjacent motif (PAM) sequence, Cas9 induces double-strand breaks. Repairs occur through non-homologous end joining, leading to small nucleotide insertions or deletions for gene disruption, or through homology-directed repair, enabling precise gene corrections, insertions or gene knockout. **b**, Small interfering RNA (siRNA) mechanisms involve the formation of double-stranded RNA (dsRNA), which is cleaved by Dicer into small fragments. One siRNA fragment is incorporated into the RNA-induced silencing complex (RISC), which binds to complementary mRNA. The target mRNA is cleaved and degraded, resulting in reduced protein expression. **c**, Antisense oligonucleotides (ASOs) bind to complementary mRNA sequences, forming a complex that recruits ribonuclease (RNase) for specific mRNA cleavage. This degradation prevents mRNA translation, effectively silencing the target gene.

of ARVC caused by a *Pkp2* variant affecting RNA splicing, *Pkp2* gene therapy administered via an AAV vector restored wild-type PKP2 levels and prevented key features of the disease[161]. Furthermore, in both human induced pluripotent stem cell-derived cardiomyocytes derived from patients with ARCV and a mouse model of ARVC, AAV-mediated *PKP2* gene therapy improved desmosomal stability, sodium current conduction and contractility, mitigating the arrhythmogenic substrate[162]. Several clinical trials are investigating the use of AAV9 or simian AAVrh.74 vector for *PKP2* gene replacement therapy in adults with *PKP2*-associated ARVC. A phase I trial is evaluating the safety and early efficacy of RP-A601, an AAVrh.74 vector carrying the human *PKP2* gene[163]. The RIDGE-1 trial[164] is investigating the use of TN-401 gene therapy, a recombinant AAV9 vector containing a *PKP2* transgene[165]. Finally, a phase I/II trial is studying the use of LX2020 gene therapy, an AAVrh.10 vector carrying *PKP2* (ref. 166).

Rare metabolic phenocopies are also the subject of investigation into the use of gene therapy. Danon disease is an X-linked disorder caused by pathogenic variants in LAMP2 (ref. 167). These variants disrupt autophagy, leading to autophagic vacuole accumulation and severe cardiomyopathy, particularly in male patients, with limited treatment options and a median survival of approximately 19 years[168]. The first-in-human trial of RP-A501, an AAV9-mediated gene-replacement strategy targeting LAMP2B deficiency in patients with Danon disease, established its safety and initial efficacy[169]. Results from the phase I trial[169] in seven male patients indicated that a single infusion of RP-A501 seemed to be safe and was associated with cardiac *LAMP2* expression and evidence of clinical improvement over a period of 24–54 months[169]. A phase II trial is ongoing[170].

Storage and infiltrative cardiomyopathies

Anderson–Fabry disease. Available therapeutic approaches for Anderson–Fabry disease, such as enzyme replacement therapy (ERT) and molecular chaperones, slow disease progression and reduce the burden of cardiovascular manifestations, particularly when initiated early[171].

ERT for Anderson–Fabry disease is available in the form of agalsidase alfa and agalsidase beta, administered intravenously every other week at dosages of 0.2 mg/kg and 1.0 mg/kg. Multiple observational studies and clinical trials have demonstrated the long-term efficacy of ERT[172–174]. The efficacy of agalsidase alfa was first evaluated in a multicentre, randomized, double-blind, placebo-controlled trial more than 20 years ago, which showed that agalsidase alfa treatment in patients

Box 1 | Gene therapies

Gene replacement therapy

Gene replacement therapy targets the pathogenic gene variant by delivering a non-pathogenic copy of the gene before the stages of transcription and translation. In cases of loss-of-function variants, gene replacement therapy can correct haploinsufficiency and reduce the dominant-negative effect of the mutant protein. For in vivo applications, the non-pathogenic gene copy is delivered using either a viral or non-viral vector.

- Advantages: potentially effective in early-stage disease, especially for sarcomeric cardiomyopathies and phenocopies, by restoring gene function, which can modify and delay the onset and progression of the disease. Gene replacement therapy can also modify secondary pathophysiological pathways associated with disease progression, such as cardiac calcium handling, fibrosis or metabolic remodelling.
- Limitations: potentially reduced efficacy in advanced stages of disease owing to irreversible cardiac remodelling. The durability of gene expression remains uncertain, with potential for the development of neutralizing antibodies that could limit repeat dosing. The high viral titres that are required to achieve sufficient cardiomyocyte transduction can activate the immune system, leading to adverse effects such as thrombotic microangiopathy or systemic inflammation, necessitating immunosuppression.

Gene editing therapy

Gene editing uses CRISPR–Cas9 to target DNA through double-strand breaks guided by a single guide RNA, allowing for precise or knockout edits. After binding to the target site, the Cas9 protein creates double-strand breaks in the DNA, which are then repaired via either non-homologous end joining or the homology-directed repair pathway, facilitating gene knockout or patient-specific gene edits. Base editors enable single-nucleotide changes without the generation of double-strand breaks: cytosine base editors convert C–G into T–A, and adenine base editors convert A–T into G–C. Prime editors use a Cas9 nickase combined with a reverse transcriptase to perform precise insertions, deletions or substitutions guided by prime editing RNA.

- Advantages: suited for diverse genetic edits, including corrections of point mutations, small indels and more complex gene repairs. Single-nucleotide precision reduces off-target and bystander mutations, which is ideal for postmitotic cells such as cardiomyocytes.
- Limitations: risks of off-target effects from double-strand breaks, especially when homology-directed repair is low in non-dividing cells. Limitations inherent to delivery vectors and immunogenicity also apply.

Vectors

Types include viral (such as adeno-associated virus (AAV) and lentivirus) and non-viral (such as lipid nanoparticles and extracellular vesicles). The cardiotropic serotypes AAV8 and AAV9, as well as newer, capsid-engineered variants, provide heart-specific targeting, thereby minimizing off-target effects. Non-viral options such as lipid nanoparticles encapsulate RNA and other nucleic acids with components such as ionizable lipids and cholesterol, supporting stable delivery. Although primarily liver targeted to date, engineered lipid nanoparticles for heart-specific applications are emerging.

- Advantages: viral vectors offer high efficiency, whereas non-viral vectors are more versatile and less immunogenic.
- Limitations: viral vectors are size limited and can trigger immune responses, whereas non-viral vectors are more difficult to target to the heart.

Non-coding nucleic acids

Non-coding nucleic acids, such as small interfering RNAs and antisense oligonucleotides, regulate gene expression by degrading or blocking the translation of target mRNA. These non-coding sequences offer an effective way to silence gene expression, although heart-specific delivery remains challenging. Chemical modifications increase stability and target specificity, and AAV vectors are used in some cases to achieve cardiotropic delivery.

- Advantages: offer precise silencing of dominant-negative mutations without affecting wild-type alleles. These approaches can also target pathological pathways that contribute to disease progression.
- Limitations: challenges in achieving heart-specific delivery remain substantial. Sustained use can unintentionally affect endogenous RNA pathways. Effectiveness in reversing advanced stages of disease is limited, emphasizing the importance of early treatment.

with Anderson–Fabry disease reduced Gb_3 deposits in the kidneys, heart and skin[172]. Long-term studies confirmed these beneficial effects, showing that agalsidase alfa treatment slowed the decline in renal function and the progression of LV hypertrophy[174]. Similar outcomes were observed with agalsidase beta treatment[175]. However, some patients show little improvement with ERT and show disease progression[176]. The effectiveness of ERT might be limited by the rapid clearance of the enzyme from the circulation and by the development of antidrug antibodies. Pegunigalsidase alfa, a novel second-generation ERT, is a pegylated form of α-galactosidase designed to increase the efficacy of the agent by increasing its half-life and reducing immunogenicity. The randomized, double-blind, head-to-head, non-inferiority, phase III BALANCE trial[177] compared pegunigalsidase alfa with agalsidase beta in patients with Anderson–Fabry disease and worsening renal function who had previously been treated with agalsidase beta. The results demonstrated a similar decline in glomerular filtration rate in both groups, supporting the non-inferiority of pegunigalsidase alfa. The effect of treatment on LV mass progression has not yet been evaluated, and the long-term efficacy and safety of this therapy remain to be determined.

Molecular chaperones are small molecules that improve enzyme stability and facilitate intracellular transport to lysosomes. The efficacy of the chaperone therapy migalastat was evaluated in patients with Anderson–Fabry disease in two randomized, controlled trials — FACETS[178] and ATTRACT[179] — both of which demonstrated that migalastat slowed the decline in glomerular filtration rate and reduced LV mass. The stability of renal function and the reduction in LV mass in patients with Anderson–Fabry disease receiving migalastat were further supported by the 30-month results from the open-label extension of the ATTRACT study[180] and real-world experiences[181,182].

Approximately 60% of *GLA* variants that cause Anderson–Fabry disease might be amenable to treatment with chaperone therapy, based on data from a standardized in vitro assay[183]. However, in vitro responses do not always correlate with in vivo outcomes[184], suggesting that the efficacy of migalastat in patients with particular *GLA* variants might be lower than expected.

Substrate-reduction therapy for Anderson–Fabry disease is a novel approach aimed at inhibiting the activity of glucosylceramide synthase, thereby reducing the synthesis of Gb_3 and increasing its clearance. However, the efficacy of the two substrate-reduction therapies that are in development — lucerastat[185] and venglustat[186] — has not been demonstrated, and studies are ongoing.

Cardiac amyloidosis. The primary management objective in cardiac amyloidosis is to alleviate symptoms caused by HF and arrhythmia, but new options are now available that delay organ damage caused by amyloid deposits (Fig. 3). Treatment for light-chain amyloidosis focuses on addressing the underlying haematological condition and includes proteasome inhibitors (such as bortezomib), immunomodulatory drugs, monoclonal antibodies (such as daratumumab or isatuximab), alkylating agents and risk-adjusted autologous stem cell transplantation[187].

TTR stabilizers are small molecules that target the rate-limiting step in TTR amyloid fibril formation, specifically the dissociation of TTR tetramers into amyloidogenic monomers. Although earlier treatments using nonspecific molecules, such as diflunisal and tolcapone, showed promise in small studies, their application has been limited owing to dose-dependent adverse effects[188]. Tafamidis, an orally bioavailable derivative of benzoxazole, stabilizes the TTR tetramer by binding to T4-binding sites, preventing dissociation and cleavage into amyloidogenic fragments. In the ATTR-ACT trial[189], tafamidis treatment in patients with ATTR cardiomyopathy reduced the combined end point of cardiovascular-related hospitalizations and all-cause mortality compared with placebo. Tafamidis treatment also slowed the decline in functional capacity and quality of life over 30 months, with measurable benefits emerging as early as 6 months[189]. Data from the long-term extension of the ATTR-ACT trial[190] confirmed the reduction in cardiovascular mortality at 58 months of follow-up and suggested that even patients with advanced disease might benefit from prompt initiation of tafamidis treatment. Furthermore, a post hoc analysis of the ATTR-ACT trial and its long-term extension study demonstrated the efficacy of tafamidis treatment for patients age 80 years or older[191]. Acoramidis, a novel TTR stabilizer, was designed to mimic the action of the *TTR* p.T119M variant, a rare mutation that increases tetramer stability compared with that of wild-type TTR[192]. Acoramidis achieves near-complete stabilization of both wild-type and variant TTR[193]. The efficacy and safety of acoramidis treatment in patients with ATTR cardiomyopathy were demonstrated in the double-blind, placebo-controlled, phase III ATTRibute-CM trial[194], showing treatment-related benefits in the primary outcome, which included cardiovascular-related hospitalization, plasma NT-proBNP level, 6-min walking distance and all-cause death.

TTR gene silencing can be achieved through strategies such as promoting *TTR* mRNA degradation (using ASOs or small interfering RNA (siRNA)) or editing the *TTR* gene via CRISPR–Cas9 technology. Inotersen and eplontersen, two modified ASOs, were evaluated in patients with ATTRv amyloidosis in the NEURO-TTR[195] and NEURO-TTRansform[196] studies, respectively, demonstrating improvements in neurological disease and quality of life. Eplontersen has the same nucleotide sequence as inotersen but incorporates ligand-conjugated technology to deliver ASOs to target cells, as well as a triantennary *N*-acetylgalactosamine moiety (GalNAc3), which increases the drug potency, allowing patients to receive lower and less frequent doses. The randomized, phase III CARDIO-TTRansform trial[197] is assessing the efficacy and safety of eplontersen in patients with ATTR cardiomyopathy.

Patisiran is an siRNA encapsulated in a lipid nanoparticle that protects the RNA from degradation and facilitates delivery to the liver. In the APOLLO trial[198] involving patients with ATTRv, patisiran treatment reduced mean LV wall thickness, global longitudinal strain, plasma NT-proBNP levels and adverse cardiac outcomes at 18 months compared with placebo. Subsequently, the double-blind, randomized, phase III APOLLO-B trial[199] involving patients with ATTR cardiomyopathy showed that patisiran treatment was associated with a smaller decline in the 6-min walking distance at 12 months compared with placebo. However, no significant differences were observed in the occurrence of the secondary end point, a composite of cardiovascular events, change from baseline in the 6-min walking test distance and all-cause death over 12 months. Vutrisiran is a second-generation siRNA

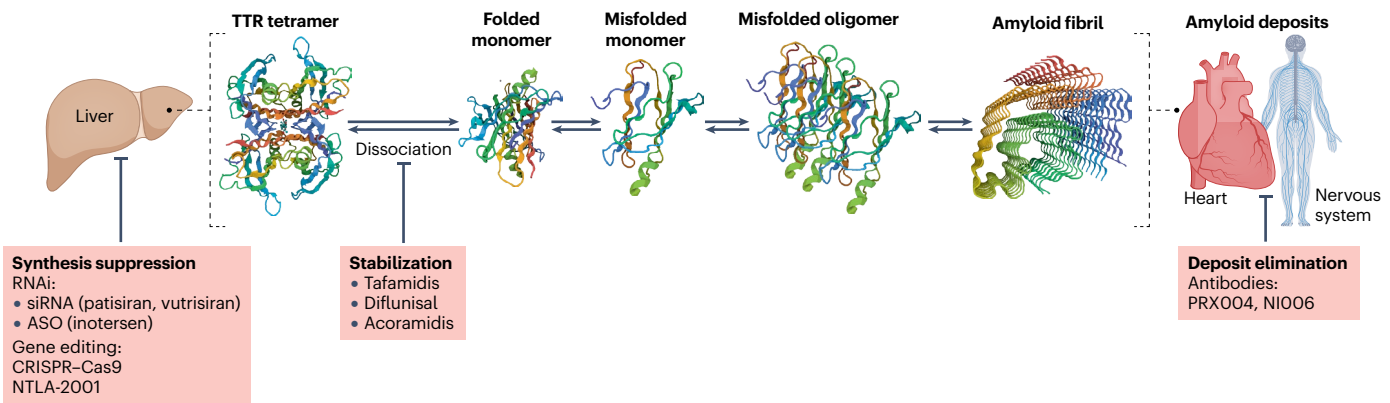


Fig. 3 | Targeted therapies for cardiac amyloidosis. Transthyretin (TTR) physiology and pathophysiological mechanisms in TTR amyloidosis, from normal physiology to pathological amyloid deposition in amyloidosis. TTR is produced in the liver and forms tetramers, which can dissociate into monomers. Misfolded monomers can aggregate into oligomers and ultimately form amyloid fibrils. These fibrils deposit in the heart and peripheral nervous system, contributing to disease manifestations. Therapeutic interventions include drugs that suppress TTR synthesis (such as RNA interference (RNAi) via a small interfering RNA (siRNA) or antisense oligonucleotide (ASO) or gene editing via CRISPR–Cas9) or stabilize TTR tetramers, or antibodies that eliminate amyloid deposits.

approved for the treatment of ATTRv amyloidosis with polyneuropathy, based on the results of the phase III HELIOS-A trial[200]. This trial demonstrated significant improvements in multiple disease-relevant outcomes in patients with ATTRv amyloidosis with polyneuropathy who were treated with vutrisiran compared with those in an external placebo group. The results of the phase III HELIOS-B trial[201] demonstrated that treatment with vutrisiran in patients with ATTR cardiomyopathy was associated with lower risk of cardiovascular events and all-cause death compared with placebo.

Nexiguran ziclumeran, a CRISPR–Cas9-based gene therapy, has been evaluated in a phase I trial involving patients with ATTRv-related polyneuropathy, demonstrating a sustained reduction in plasma TTR levels, with a favourable safety profile[202]. The phase III MAGNITUDE trial[203] is assessing the efficacy and safety of nexiguran ziclumeran in patients with ATTR cardiomyopathy.

A potential future approach in the treatment of cardiac amyloidosis is immuno-mediated amyloidolysis, which relies on monoclonal antibodies that selectively target TTR amyloid, without binding to physiologically folded TTR[204]. These antibodies opsonize the deposits and promote their degradation through activation of the innate immune system. A double-blind, phase I trial demonstrated that treatment with NI006, a recombinant human anti-TTR monoclonal IgG1 antibody, reduced cardiac tracer uptake on scintigraphy and decreased extracellular volume on cardiac MRI (both surrogate markers of cardiac amyloid burden) in patients with ATTR cardiomyopathy over a 12-month period[205]. Moreover, NI006 treatment was not associated with any serious drug-related adverse events.

Challenges to implementing precision medicine

Precision medicine holds the promise of therapies that target the molecular causes of cardiomyopathies instead of just their symptoms, but several barriers hamper the translation of these targeted therapies from experimental models to clinical settings.

Interpretation of genetic variants

A prerequisite for actionable gene therapies is a robust framework for validation and standardization of genomic data in patients. This objective requires the development of complex workflows that include genetic testing, an understanding of genotype–phenotype relationships and stratification of patient cohorts based on genetic risk. Consequently, developing clinical-grade, reproducible methodologies for variant interpretation is crucial[206] but requires substantial investment in infrastructure, bioinformatics support and clinician training. Leveraging shared data platforms, multi-institutional collaborations and open-access genomic databases can provide standardized resources to support variant interpretation and enable clinical applications.

Clinical trial design and outcome measures

Designing clinical trials for precision therapies in cardiomyopathy presents unique methodological challenges. Traditional trial designs with hard end points, such as hospitalization or mortality, might be difficult owing to the rarity of cardiomyopathy subtypes and the limited number of eligible patients. Small sample sizes and phenotypic variability necessitate alternative adaptive trial designs that maximize data utility. Examples include basket trials, which test therapies across multiple genetic variants or cardiomyopathy subtypes, and umbrella trials, which target specific molecular mechanisms; both provide frameworks that optimize statistical power in small patient populations. Platform trials, which allow treatments to be added or removed as data accumulate, offer flexible options that can expedite therapeutic assessment while reducing patient burden.

Given the progressive nature of cardiomyopathies and the slow accumulation of clinical events, surrogate end points such as biomarkers, imaging-based metrics and functional measurements are increasingly used to measure therapeutic efficacy[207,208]. Examples include plasma NT-proBNP level, LVEF and myocardial fibrosis, which can serve as proxies for long-term outcomes, allowing for shorter follow-up periods and greater feasibility in rare disease contexts. However, gene therapy trials might also require invasive assessments, such as endomyocardial biopsies, to confirm genome delivery and expression, which raises safety concerns and further complicates trial design. Importantly, all surrogate end points require rigorous validation to ensure that they accurately reflect disease modification and align with regulatory standards.

Barriers to clinical adoption and cost considerations

A potential obstacle to the clinical adoption of precision therapies is their high cost. Some (especially gene therapies) have expensive specialized manufacturing processes and require rigorous safety monitoring. For rare genetic subtypes of cardiomyopathy, these high costs present a substantial challenge for health-care systems, raising concerns about the adoption of these therapies into routine clinical care. Moreover, although some patients have identifiable disease-causing variants, the diversity of genes and variant-specific effects complicate the development and application of targeted gene therapies and reduce their generalizability. Optimal deployment of gene therapies also requires robust models to predict disease trajectories. Potential solutions include integration of affordability and accessibility into trial design. For example, the use of adaptive and point-of-care manufacturing models can lower costs by reducing logistical challenges and decentralizing production. Collaborative funding models involving academic institutions, government agencies and pharmaceutical companies might also be required to offset development costs. Furthermore, patient-centric licensing agreements can ensure that trial findings are accessible across diverse socioeconomic groups, addressing disparities in access and maximizing the societal benefit of precision therapies[209].

To further increase affordability, the adoption of value-based pricing models, which tie therapy costs to clinical benefits, can support sustainable pricing frameworks. These models balance industry incentives with patient access, aligning therapeutic advances with equitable care objectives. Additionally, regulatory innovations that streamline the comparability assessment process can reduce the high costs associated with manufacturing transitions, making these therapies more attainable for health-care systems.

Ethical and societal considerations

Ethical and societal considerations arise as precision medicine becomes a reality. For example, the handling of genomic data requires stringent privacy safeguards to protect patient identity and prevent misuse, particularly as sequencing becomes mainstream in clinical diagnostics. Moreover, the deployment of precision therapies often necessitates selective patient eligibility, which might exclude individuals based on genetic criteria. Ethical frameworks must address these disparities, ensuring that precision treatments are accessible without compromising inclusivity or creating tiered health-care models.

Logistical and regulatory hurdles

Logistical hurdles persist to the integration of novel therapies into standard cardiology practice. Multimodally informed treatments require coordinated care from geneticists, cardiologists and molecular pathologists, but few health-care systems support interdisciplinary infrastructures. The limited availability of specialists, particularly in community or rural settings, further restricts precision care to major centres. Additionally, the rapid pace of advances in genomics and gene-editing technology often outpaces the capacity of regulatory bodies to evaluate novel therapeutics, creating bottlenecks in clinical trial approvals and delaying broader adoption.

Conclusions

Despite the many challenges, precision medicine in cardiomyopathy is a reality. Maximization of its potential requires a combination of policy reform, investment in genomic infrastructure and commitment to equitable access. As genotype-driven therapies advance, aligning these developments with clinical realities and optimizing trial designs will be essential. Collaborative frameworks that combine clinical trial flexibility, regulatory adaptability and innovative business models will be crucial to bridge the gap between experimental therapies and real-world clinical implementation.

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