



Left Ventricular Hypertrophy: Etiology-Based Therapeutic Options

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ABSTRACT

Determining the etiologies of left ventricular hypertrophy (LVH) can be challenging due to the similarities of the different manifestations in clinical presentation and morphological features. Depending on the underlying cause, not only left ventricular mass but also left ventricular cavity size, or both, may increase. Patients with LVH remain asymptomatic for a few years, but disease progression will lead to the development of systolic or diastolic dysfunction and end-stage heart failure. As hypertrophied cardiac muscle disrupts normal conduction, LVH predisposes to arrhythmias. Distinguishing individuals with treatable causes of LVH is important for prevention of cardiovascular events and mortality. Athletic's heart with physiological LVH does not require treatment. Frequent causes of hypertrophy include etiologies due to pressure/

volume overload, such as systemic hypertension, hypertrophic cardiomyopathy, or infiltrative cardiac processes such as amyloidosis, Fabry disease, and sarcoidosis. Hypertension and aortic valve stenosis are the most common causes of LVH. Management of LVH involves lifestyle changes, medications, surgery, and implantable devices. In this review we systematically summarize treatments for the different patterns of cardiac hypertrophy and their impacts on outcomes while informing clinicians on advances in the treatment of LVH due to Fabry disease, cardiac amyloidosis, and hypertrophic cardiomyopathy.

Keywords: Left ventricular hypertrophy; Amyloidosis; Fabry disease; Hypertrophic cardiomyopathy; Treatment of left ventricular hypertrophy; Treatment of amyloidosis

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Key Summary Points

Left ventricular hypertrophy (LVH) is a common finding when there is an increase in left ventricular mass, either due to an increase in wall thickness or due to left ventricular cavity enlargement, or both, in response to a wide array of pathophysiological stressors.

In this review, we summarize different etiologies of LVH and its complications, and outline the treatment and management options according to etiologies. We also describe the effect of therapy to reduce LVH and the impact on outcome.

Pertinent studies and ongoing trials of certain drug treatments have been summarized according to LVH pathologies.

Management of LVH involves lifestyle changes and medications, and may also include surgery and an implantable device for the prevention of sudden cardiac death depending upon the underlying cause.

INTRODUCTION

Left ventricular hypertrophy (LVH) is a condition in which there is an increase in LV mass (LVM) secondary to an increase in wall thickness, an increase in LV cavity enlargement, or both. The left ventricle may undergo geometric changes in response to pathophysiological stressors such as long-term pressure or volume overload that increase the size of myocardial fibers [1–4]. LVH is recognized as an independent risk factor for premature cardiovascular morbidity and mortality, including chronic heart failure, cardiac arrhythmias, and sudden cardiac death.

Table 1 Causes of left ventricular hypertrophy

LVH due to pressure/volume overload	Other risk factors for LVH	Infiltrative cardiac processes
Systemic hypertension	Athletic training	Amyloidosis
Aortic stenosis (valvular, supra- and subvalvular)	Obesity	Sarcoidosis
Aortic and mitral regurgitation	Obstructive sleep apnea	Hemochromatosis
Cardiomyopathies	Chronic kidney disease	Fabry disease
Ventricular septal defect	Diabetes mellitus Tobacco use Sodium intake	

LVH Left ventricular hypertrophy

Causes of LVH

Multiple comorbidities have been identified which can play an independent or synergistic role in the phenotype of the disease. The frequent causes of hypertrophy are listed in Table 1.

LVH is present in 15–20% of the general population, and the prevalence is similar in men and women. Hypertension and aortic valve stenosis are the most common causes of LVH, and in both of these conditions the heart is contracting against a pressure overload. Athletic's heart with physiological LVH is a relatively benign condition in which intensive training results in increased LV muscle mass, wall thickness, and chamber size, but the systolic and diastolic functions remain normal [2].

Prognosis and pathophysiology of LVH

Prognostic associations with LVH include all-cause mortality, atrial fibrillation (AF), congestive heart failure, diastolic dysfunction, myocardial infarction (MI), reduced coronary flow reserve, stroke, sudden cardiac death, and ventricular ectopic activity [1]. In the normal healthy population the posterior wall is used preferentially to the septum to avoid the impact of abnormal septal geometry. Adverse LV remodeling includes concentric remodeling (increased relative wall thickness [RWT] without an increase in LVM, $RWT = \text{posterior wall thickness} \times 2 / \text{LV internal diameter at end-diastole}$), eccentric hypertrophy (increase in LV mass without increased RWT), and concentric hypertrophy (increase in LVM and increased RWT). Transition between any two types of abnormal LV geometry is possible [5]. Hypertension, has been variably associated with either eccentric or concentric LVH in different studies [1]. Diabetes mellitus (DM) causes concentric remodeling (CR), concentric LVH, and changes LV geometry [1]. In an analysis of 1950 patients in the HyperGEN study, even after adjusting for covariates such as body mass index (BMI), systolic blood pressure (SBP), age, and sex, there was still an increased likelihood of LVH in patients with DM [6]. Milani et al. [7] have suggested that concentric LVH was associated to the highest mortality, with less difference between CR and eccentric LVH (10.4, 8.7, and 8.4%, respectively). Another study showed a 40% increase in risk of cardiovascular disease (CVD) for every 39 g/m² of increase in LVM. Despite this strong association with CVD risk, LVH is not routinely considered in risk stratification assessments [8]. A meta-analysis of 27,141 patients in ten studies showed an 11.1% risk of supraventricular tachycardia (including AF) in those with LVH versus 1.1% risk in those without ($p < 0.001$) [9]. In another study, the LVH–AF link was found to be strongest in those with eccentric and concentric LVH, less so in those with CR [10].

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

TREATMENTS

The association of LVH with increased cardiovascular morbidity and mortality demands aggressive treatment. However, the initial asymptomatic nature of LVH may lead to a delay in treatment. Treatment involves lifestyle changes (including weight reduction and exercise) and, depending upon the cause, may include medications, surgery, and implantable devices for the prevention of sudden cardiac death [1].

Treatment of LVH in Hypertension

Hypertension is a major modifiable risk factor for CVD morbidity and mortality. Lowering the blood pressure with antihypertensive agents decreases cardiac mass in patients with LVH, and weight loss or dietary sodium restriction have additional beneficial effects on the improvement in cardiac mass. Antihypertensive response and type of therapy influence the regression of LVH [11, 12]. A study with echocardiographic follow-up demonstrated that the reduction in LVH by echocardiography was also associated with a reduction in the composite endpoints of CV death, fatal or nonfatal MI, and fatal or nonfatal stroke (hazard ratio 0.78 per –25 g/m² in mass reduction, 95% confidence interval 0.65–0.94) [13]. Once the patient has received the appropriate treatment, regression of LVH continues gradually over time (≥ 3 years) and may be associated with complete reversal of LVH and other abnormalities induced by hypertension, such as left atrial enlargement and diastolic dysfunction. Numerous treatment strategies, ranging from thiazide diuretics, renin–angiotensin–aldosterone system (RAAS) inhibitors and calcium channel blockers (CCBs) to sodium–glucose cotransporter type-2 (SGLT2) inhibitors have been shown to regress LVH [14, 15]. Following the Framingham Heart Study, other trials in the early 2000s, such as the Multiple Risk-Factor Intervention Trial (MRFIT), the Heart Outcomes Prevention Evaluation (HOPE) trial, and the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) trial, confirmed the

possibility of LV regression in response to anti-hypertension therapy and related CVD prognostic benefits. The HOPE trial showed that ramipril led to the regression or prevention of LVH and reduction of the risk of CVD mortality, MI, and stroke (12.3 vs. 15.8% for regression/prevention of LVH vs. development/persistence of LVH; $p = 0.006$) [14, 16–18]. The Systolic Blood Pressure Intervention Trial (SPRINT) showed that intensive (< 120 mmHg) SBP control was associated with a 46% lower risk of developing LVH diagnosed on electrocardiography (ECG-LVH) in participants without baseline LVH and 66% higher likelihood of regression/improvement of LVH in participants with baseline LVH [19]. In the LIFE study, LVH regression (diagnosed by ECG utilizing the Sokolow-Lyon index or the Cornell product criteria) in response to losartan improved clinical cardiovascular outcomes independent of blood pressure response [20]. This study randomized 9193 people with hypertension and LVH to either losartan or atenolol and followed them for a mean time of 4.8 ± 0.9 years. There was no difference in mean blood pressure at the end of the study, but the losartan group showed significant reductions in LVH criteria by ECG, as well as a lower composite endpoint of death, stroke, or MI. Those with LVH regression by ECG in the LIFE study had a 12% lower rate of new onset AF for every standard deviation reduction in Cornell ECG product and this corresponded to a decreased rate of stroke in the losartan arm, further solidifying the relationship between changes in LVM, AF, and stroke. Changes in LVH were also associated with improved parameters of diastolic function and with decreased recurrent hospitalizations for heart failure.

Apart from LIFE study, different angiotensin II receptor blockers (ARBs) have shown comparable benefit over beta adrenergic blockers. Losartan decreased LVH and improved renal outcomes in populations with DM and chronic kidney disease (CKD). CVD risk was also decreased similarly in patients without LVH. Starting early treatment while providing the appropriate target blood pressure prevents irreversible LVH [14, 18, 21–25]. In the Prospective Randomized Enalapril Study Evaluating

Regression of Ventricular Enlargement (PRESERVE) trial, enalapril was compared to long-acting nifedipine among hypertensive participants with LVH ($n = 202$). Treatment with both medications led to a similar moderate degree of regression in LVM (26 g vs. 32 g; $p = 0.36$) (26). In a double blind randomized controlled trial (RCT), similar degrees of LVH regression were provided similarly with eplerenone and enalapril as monotherapies, and the combination of enalapril and eplerenone was found to be more effective in reducing LVM [27]. An ECG substudy of the ADVANCE trial showed a reduction in LVM index by 2.7 g/m^2 (95% CI $- 5.0$ to $- 0.1$; $p = 0.04$) and reduction in major adverse CVD events among those treated with the perindopril and thiazide combination [28]. “CHIP” diuretics (CHlorthalidone, Indapamide, and Potassium-sparing diuretic/hydrochlorothiazide) were compared with hydrochlorothiazide and found to be more effective in reducing LVM. A subsequent head-to-head systematic review involving 12 double-blind RCTs reported that “CHIP” diuretics were better than RAAS inhibitors for the reduction of LVM mass. Spironolactone was found to decrease LVM, and when studied against non-spironolactone therapy, the former improved diastolic parameters and reduced the risk of new-onset symptomatic congestive heart failure [29, 30]. In a meta-analysis of 80 trials and 3767 patients, all drug classes were assessed according to their effect on the LVM index. The results showed a significant reduction in LVM index of 13% with ARBs, 11% with CCBs, 10% with ACE inhibitors, 8% with diuretics, and 6% with β -blockers [31]. Fagard et al. [32] reported that β -blockers’ inferiority was more prominent than the superiority of ARBs. The mechanism behind the marked decrease in LVM by ARBs, angiotensin-converting enzyme (ACE) inhibitors, or CCBs might be explained by: (1) activation of RAAS that stimulates myocardial cells growth; (2) increase in plasma angiotensin II level which is independently associated with LVH; and (3) sympathetic nerve activity that is stimulated through N-type calcium channels. Hypertensive LVH is associated with almost threefold increased risk of ventricular tachycardia (VT)/ventricular fibrillation (VF). LVH increases the risk of sudden

cardiac death (SCD). Although beta blockers are not the first choice in hypertensive patients with LVH due to their insufficient capacity to reverse LVH remodeling, it is important to prevent VT/VF in patients at high risk. Therefore, certain beta blockers (such as Bisoprolol) may be reevaluated for priority in guidelines [33, 34]. SGLT2 inhibitors are relatively novel antidiabetic agents with added benefits in terms of blood pressure and weight reduction. Their potential mechanisms of action include decrease LV wall stress secondary to diuresis and natriuresis. They also suppress sodium-hydrogen exchange in cardiomyocytes, which impacts on cardiac remodeling [34]. Schmieder et al. [35] reported that sacubitril/valsartan provided a more significant reduction in LVH compared to olmesartan, which might contribute to the superiority of sacubitril in terms of its favorable outcomes in a randomized trial of 114 patients over 52 weeks. Despite a modest decrease in SBP, but not diastolic blood pressure (DBP), in the sacubitril/valsartan arm, the authors found significant reductions in LVM index (-6.83 vs. -3.55 g/m²; $p < 0.029$). A meta-analysis of 20 studies revealed a significant regression in LVM with sacubitril/valsartan treatment compared to treatments with ACE inhibitors or ARBs among subjects with heart failure with reduced ejection fraction (EF) [36]. Regression of LVH by xanthine oxidase inhibitors (allopurinol) has been shown to be effective for the treatment of hypertrophy in animal studies by reducing oxidative tissue stress. A number of RCTs have shown that allopurinol was associated with a significant regression in LVH without a change in blood pressure in adult patients with coronary artery disease (CAD), CKD or DM [37]. It has also been shown that regular aerobic exercise improves blood pressure and reduces the risk of LVH development [38]. Regular exercise has been found to prevent the development of LVH in older individuals while endurance training causes increased LVM in young individuals [1].

Treatment of Risk Factors for LVH

In a recent study, 53,666 working age Korean men were evaluated according to their smoking status and LV geometry [39]. The authors found that exposure to tobacco use and intensity of smoking were associated with LVH in the working-age population. Abnormal geometry patterns were more prevalent in smokers than in non-smokers, suggesting that the adverse impact of smoking on LV structure begins at a relatively young age. These results provide meaningful implications when establishing policy on smoking cessation [39]. Herbal medications, such as licorice or ephedrine, may cause LVH, and the use of over-the-counter medications should also be questioned. The use of oral contraceptives, cardiac stimulants such as cocaine or amphetamines, as well as excess alcohol intake should be noted in patients' history and drug cessation should be advised or treated [1, 6].

Obesity is a known risk factor for LVH. Lavie et al. [40] studied a very large population of 30,920 patients, including 11,792 patients with obesity (BMI ≥ 30). They found an increased incidence of abnormal LV geometry in obese patients indexed to body surface area, including increased CR (34 vs. 32%), eccentric LVH (7 vs. 6%), and concentric LVH (8 vs. 6%; $p < 0.0001$). Interestingly, overall mortality was lower in the obese compared with the non-obese population, but abnormal LV geometry still predicted increased mortality in both groups. A meta-analysis including 1066 patients undergoing bariatric surgery showed a standardized mean difference of -0.46 in LVM index for individuals before and after bariatric surgery ($p < 0.001$). The authors also found a significant decrease in LVM, RWT, and left atrial diameter, with a corresponding improvement in diastolic dysfunction [41].

Treatment of LVH in Aortic Stenosis

Aortic stenosis is associated with LVH and diastolic dysfunction. Unfavorable LV remodeling occurs due to adaptive microscopic changes, such as progressive cardiomyocyte

hypertrophy, extracellular matrix expansion, and interstitial fibrosis secondary to collagen deposition [42, 43].

Surgical aortic valve replacement (SAVR) has been associated with regression of LVH, improvement in LV pressure, mass-to-volume ratios, EF, and heart failure symptomatology. The LVM and LV volume indices are also improved with SAVR [44, 45]. Interest in the impact of transcatheter aortic valve replacement (TAVR) on LV reverse myocardial remodeling has also increased. Dahiya et al. [45] recently investigated the impact of TAVR among patients with preserved LV systolic function on regression of LVH, LV diastolic dysfunction and the correlation of each with heart failure-related quality of life (QoL). These authors also identified factors impacting the regression of LV hypertrophy post-TAVR. Among patients with moderate or severe LVH treated with TAVR who were alive at the 1-year follow-up, greater LVM index regression at 1 year was associated with lower death and hospitalization rates for up to 5 years. These findings may have implications for the timing of valve replacement and the role of adjunctive medical therapy after TAVR [46].

Risk factor management includes an abundance of data from previous studies, but is not within the scope of this review. Also, this subject would need a separate review article for thorough analysis. We only mention these risks and therapies because they represent some causes of LVH and therapies of underlying causes, respectively, and we wish to draw attention to the treatable causes of LVH.

HYPERTROPHIC CARDIOMYOPATHY

Hypertrophic cardiomyopathy (HCM) is a heterogeneous myocardial disease that is most often caused by autosomal dominant sarcomeric gene mutations. This disease is the most common monogenic cardiomyopathy in humans [47]. Altered levels of the sarcomere protein, calcium sensitivity, or ATPase activity result from a change in amino acid sequence in the sarcomere protein or a deficiency of a

Table 2 Alterations in cardiac function and symptoms

Changes in cardiac function	Symptoms
Impaired relaxation	Reduced exercise capacity
Reduced compliance of LV	Exertional dyspnea
LVOT obstruction	Presyncope/syncope
Mitral regurgitation	Palpitation, arrhythmias
Microvascular dysfunction	Chest pain
Subendocardial ischemia	Heart failure symptoms

LVOT Left ventricle outflow tract

sarcomere protein, causing mitochondrial dysfunction and altered transcriptomics or signaling pathways. This ultimately results in myocyte hypertrophy, myocyte disarray, and fibrosis [48]. The phenotypic expression of HCM is manifested by LVH, myocardial hypercontractility, reduced compliance, myofibrillar disarray, and fibrosis. Differential diagnosis should be made from various metabolic and multiorgan syndromes, such as RASopathies (variants in several genes involved in RASMAPK signaling), mitochondrial myopathies, and glycogen/lysosomal storage diseases in children, and Fabry disease, amyloidosis, sarcoidosis, hemochromatosis, and Danon cardiomyopathy in adults [48, 49]. Patients with HCM have an increased incidence of both supraventricular and ventricular arrhythmias and are at an increased risk for SCD. Abnormalities of the mitral valve and subvalvular apparatus contribute to systolic anterior motion and LV outflow tract (LVOT) obstruction. Alterations in cardiac function and symptoms due these changes are given in Table 2.

A resting or exercise-provoked LVOT gradient is present in 70% of patients with HCM. Therapies that directly target HCM pathophysiology are needed. Genetic testing should be offered to patients with HCM to elucidate the genetic basis and to allow for family screening. Genetic testing in an HCM proband should include testing for genes for which there is strong evidence to be disease-causing in HCM [49, 50]. Periodic re-evaluation is recommended with ECG, echocardiography (including global

Table 3 Pharmacological treatments in hypertrophic cardiomyopathy and recommendations

Medical therapy	Recommendations
Beta adrenergic receptor blockers (without intrinsic sympathetic activity)	<ul style="list-style-type: none"> • Cornerstone of pharmacological treatment • Relief of ischemic chest discomfort • Recommended in patients in nonobstructive HCM with preserved EF and symptoms of exertional angina or dyspnea * May attenuate exercise-induced LVOT obstruction and dyspnea
Disopyramide	<ul style="list-style-type: none"> • A negative inotropic agent • By adding to a beta blocker symptomatic relief can be provided in LVOT obstruction
L-type calcium channel blockers (verapamil, diltiazem)	<ul style="list-style-type: none"> • May be beneficial in patients who do not tolerate or respond to beta blockers • Harmful for patients with HOCM and severe dyspnea at rest, also in patients with very high resting gradients or hypotension
Diuretics	<ul style="list-style-type: none"> • Effective in low doses • Avoid hypovolemia, hypotension, and intensification or provocation of LVOT obstruction

Table 3 continued

Medical therapy	Recommendations
Phenylephrine (intravenous) (or other vasoconstrictors without inotropic activity)	<ul style="list-style-type: none"> • Is recommended alone or in combination with beta blockers • Can be used in obstructive HCM and in patients with acute hypotension who do not respond to fluid administration
Vasodilators (e.g. angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, dihydropyridine calcium channel blockers) or digoxin	<ul style="list-style-type: none"> • Can worsen symptoms caused by dynamic outflow tract obstruction

HCM Hypertrophic cardiomyopathy, *EF* ejection fraction

longitudinal strain), cardiac rhythm monitoring, cardiac magnetic resonance imaging (CMRI), and cardiopulmonary exercise testing (CPET), including asymptomatic patients [48, 51]. Five major approaches are available for the treatment of LVOT obstruction in patients with HCM: pharmacologic therapy, septal myectomy, alcohol septal ablation, non-alcohol septal ablation, dual chamber pacing. We have been using cyanoacrylate, and in recent years we have seen the emergence of novel pharmacotherapies, minimally-invasive procedures, and gene-directed approaches, all with the potential to fundamentally alter the therapeutic landscape. Myosin inhibitors are evolving as therapeutic targets for HCM. Surgical techniques continue to evolve and now address the mitral valve, including transcatheter mitral valve repair. Radiofrequency myocardial ablation and high-intensity focused ultrasound may offer alternatives for patients with obstructive HCM (gradient > 30 mmHg) [50, 52].

Pharmacotherapy

The pharmacological agents that are used in the the treatment HCM in different pathological conditions are given in Table 3 [47, 50, 53].

Management of atrial fibrillation in HCM

Atrial fibrillation in patients with HCM is often poorly tolerated; therefore, aggressive rhythm control strategies may be required. Rate control strategies, either with beta blockers, verapamil, or diltiazem, are recommended. Catheter ablation plays an important role in the management of AF and typical atrial flutter. However, the results of catheter ablation seem less favorable in this patient group compared with patients without HCM, with the former having a twofold higher risk of recurrence, more frequent need of repeated procedures, and higher use of concomitant antiarrhythmic drugs. In view of the lower success rate of catheter ablation in HCM compared with the general AF population, surgical AF ablation is a potential rhythm management option, especially in patients already undergoing open heart surgery for a surgical myectomy [54, 55]. New-onset and poorly tolerated AF is best treated with cardioversion. Since persistent and paroxysmal AF are risk factors for thromboembolism, long-term anticoagulation is necessary in clinical and subclinical AF (detected by an internal or external cardiac device) [50, 56]. Oral anticoagulation with direct oral anticoagulants as the first-line option and vitamin K antagonists as the second-line option should be considered the default treatment options independent of the CHA₂DS₂VASc score (Congestive Heart Failure, Hypertension, Age ≥ 75 [Doubled], Diabetes Mellitus, Prior Stroke or Transient Ischemic Attack [Doubled], Vascular Disease, Age 65–74, Female) [57].

Heart Failure Therapies and Device Therapy

In patients with HCM who develop systolic dysfunction with an LVEF $< 50\%$, guideline-directed therapy for heart failure with reduced EF

Table 4 High-risk clinical features for primary prevention

High-risk clinical features	Primary prevention
Unexplained syncope (≥ 1 recent episodes of syncope suspected by clinical history to be arrhythmic in the previous 6 months)	An ICD is reasonable (2a)
Apical aneurysm	
Left ventricular EF $< 50\%$	
Massive (≥ 30 mm) thickness of the interventricular septum	
A family history of HCM (≥ 1 first-degree relative or close relatives who are ≤ 50 years of age) with SCD	
Multiple episodes of documented NSVT (detected with continuous ambulatory ECG monitoring)	An ICD may be considered (2b)
Late gadolinium enhancement determined by CMRI ($\geq 15\%$ of the LVM)	

2a: Class of recommendation according to HCM guidelines; should be considered, 2b: Class of recommendation according to HCM guidelines; may be considered
CMRI Cardiac magnetic resonance imaging, *ECG* electrocardiography, *EF* ejection fraction, *ICD* implantable cardioverter defibrillator, *LVM* left ventricular mass, *NSVT* non-sustained ventricular tachycardia, *SCD* sudden cardiac death

is recommended. Negative inotropic agents (specifically, verapamil, diltiazem, or disopyramide) may be discontinued. Heart failure symptoms in patients with HCM, in the absence of LVOT obstruction, should be treated similarly to other patients with heart failure symptoms, including the consideration of advanced treatment options (e.g., cardiac resynchronization therapy, LV assist device, transplantation). In patients with HCM, an ejection fraction $< 50\%$ is related with significantly impaired systolic function, poor prognosis, and increased risk for SCD. The risk of SCD ranges from 0.5 to 2% per year in adults with HCM, and HCM is the most common cause of SCD in

adolescents [48, 50]. In individuals who are genotype-positive, phenotype-negative for HCM, an implantable cardioverter defibrillator (ICD) is not recommended for primary prevention. The patients who have survived a cardiac arrest (> 30 s or associated with hemodynamic compromise) due to ventricular fibrillation or sustained ventricular tachycardia are at high risk, and implantation of an ICD is strongly indicated for secondary prevention (50, 58).

The high-risk features for primary prevention are presented in Table 4. ICD implantation is typically considered in patients who have ≥ 1 of these primary risk factors (47, 50).

Either a single chamber transvenous ICD or a subcutaneous ICD is recommended after a shared decision-making discussion that takes into consideration patient preferences, lifestyle, and expected potential need for pacing for bradycardia or tachycardia termination. Single-coil ICD leads are recommended in preference to dual-coil leads. Dual-chamber ICDs are reasonable for patients with a need for atrial or atrioventricular sequential pacing for bradycardia/conduction abnormalities [50]. Antitachycardia pacing can minimize the risk of shocks. ICD placement for the sole purpose of participation in competitive athletics should not be performed [59, 60].

Apical myectomy may be considered by experienced surgeons at comprehensive centers in highly selected patients with apical HCM with severe dyspnea or despite maximal medical therapy, and with preserved EF and small LV cavity size [61–65]. Nonobstructive HCM patients with an EF < 50% should receive guideline-directed management and therapy (GDMT). After reevaluation for symptoms, if the patients have New York Heart Association (NYHA) class II to ambulatory class IV functional capacity, left bundle branch block (LBBB), and EF < 50%, cardiac resynchronization therapy (CRT) for symptom reduction is reasonable. Regardless of LVEF, if patients experience recurrent ventricular arrhythmias or severe (NYHA class III to class IV) symptoms despite optimization of medical therapy, and septal reduction therapy (SRT) is not an option, heart transplant evaluation is warranted, and cardiopulmonary exercise testing (CPET) plays a

role in risk stratification. CPET should be performed to quantify the degree of functional limitation and aid decision-making regarding the selection of patients for heart transplantation or mechanical circulatory support. For patients with NYHA class III to class IV symptoms who are candidates for heart transplantation, continuous-flow LV assist device (LVAD) therapy is reasonable as a bridge to heart transplantation [50, 64–68].

Septal Reduction Therapy and Surgical Myectomy

In patients with obstructive HCM who remain severely symptomatic or having signs of cardiac decompensation despite GDMT, SRT is indicated in eligible patients and the procedure should be performed at experienced centers [50].

General eligibility criteria for septal reduction therapy:

- 1) *Clinical*: Severe dyspnea or chest pain (usually NYHA functional class III or class IV), or occasionally other exertional symptoms (e.g., syncope, near syncope), when attributable to LVOT obstruction, that interferes with everyday activity or QoL despite optimal medical therapy.
- 2) *Hemodynamic*: Dynamic LVOT gradient at rest or with physiological provocation with approximate peak gradient of ≥ 50 mmHg, associated with septal hypertrophy and systolic anterior motion (SAM) of mitral valve.
- 3) *Anatomic*: Targeted anterior septal thickness sufficient to perform the procedure safely and effectively in the judgment of the individual operator.

Surgical myectomy at experienced centers is recommended if the patient has additional pathologies requiring surgery (e.g., associated anomalous papillary muscle, markedly elongated anterior mitral leaflet, intrinsic mitral valve disease, multivessel CAD, valvular aortic stenosis). Mitral valve replacement should not be performed for the sole purpose of relief of LVOT obstruction. Cardiac computed tomography is important in the localization of the appropriate target septal artery for alcohol

septal ablation and to limit the area of myocardial necrosis [69–72]. In a recent study, a novel strategy, targeted septal branch microcirculatory embolization with tris-acryl gelatin microspheres, was found to be an efficient and safe approach to hypertrophic obstructive cardiomyopathy (HOCM) [73].

Treatment of Ventricular Arrhythmia

Antiarrhythmic drug therapies, including amiodarone, dofetilide, mexiletine, and sotalol, are recommended in symptomatic ventricular arrhythmias or recurrent ICD shocks despite beta blocker use, with the choice of agent guided by age, underlying comorbidities, severity of disease, patient preferences, and balance between efficacy and safety. In recurrent symptomatic sustained monomorphic ventricular arrhythmia, or recurrent ICD shocks despite optimal device programming, and in whom antiarrhythmic drug therapy is either ineffective, not tolerated, or not preferred, catheter ablation can be useful for reducing arrhythmia burden. In the case of poorly tolerated life-threatening ventricular tachyarrhythmias refractory to maximal antiarrhythmic drug therapy and ablation, heart transplantation assessment is indicated [74–77].

Comorbid Conditions

Comorbid conditions may worsen the severity of HCM. Prevention of atherosclerotic CVD is recommended to reduce risk of cardiovascular events. Counseling and comprehensive lifestyle interventions are recommended for achieving and maintaining weight loss and possibly lowering the risk of developing LVOT obstruction, heart failure, and AF in patients who are obese or overweight. Hypertension treatment should include beta blockers and non-dihydropyridine CCBs. Sleep disorders need to be diagnosed and treated. Low-dose diuretics may also be used as antihypertensive agents [50].

Pregnancy

Pregnancy in most women with HCM is well tolerated and maternal mortality is very low.

Prenatal genetic counseling is helpful in explaining the risk of transmission of disease. In pregnant women with HCM, selected beta blockers may be prescribed for symptoms related to outflow tract obstruction or arrhythmias, under close monitorization of fetal growth. For pregnant women with HCM and AF or other indications for anticoagulation, low-molecular-weight heparin or vitamin K antagonists (at maximum therapeutic dose of < 5 mg daily) are recommended. Cardioversion for new or recurrent AF, particularly if symptomatic, is reasonable in pregnant patients. Vaginal delivery is recommended as the first-choice delivery option [50, 57].

Future Treatments

Recent developments in treatment include gene-based therapies. Embryonic gene editing has the potential to correct underlying genetic mutations that may result in disease. Most recent drug trials have failed; however, they have advanced our understanding of therapeutic targets, and myosin inhibitors are a promising therapeutic strategy. Novel procedures that target cardiac structural abnormalities include surgical papillary muscle realignment, chordae removal and mitral valve repair (transcatheter/surgical), apical myectomy, radiofrequency septal ablation, and high-intensity focused ultrasound septal ablation. Gene-based therapies include allele-specific gene silencing and embryonic gene repair using CRISPR/Cas 9 which target the genetic underpinnings of HCM [50, 52]. Novel pharmacotherapies and their mechanisms of action are shown in Table 5.

The open-label phase IIa trial of mavacamten (PIONEER-HCM; ClinicalTrials.gov Identifier: NCT02842242) included 21 patients with symptomatic obstructive HCM [78]. Cohort A received higher dose therapy (10, 15, or 20 mg daily); cohort B received lower dose therapy (2 or 5 mg daily). Post-exercise LVOT gradient and NT-proBNP (brain natriuretic peptide) levels were found to be reduced, and there was improvement in NYHA class. There was also a substantial (17%) improvement in exercise capacity (peak oxygen consumption

Table 5 Novel pharmacotherapies and their mechanisms of action, also clinical trials in HCM treatment

Inhibition of actin-myosin cross-bridging	Mechanism of action	Studies
Mavacamten (MyoKardia, Inc., South San Francisco, CA, USA)	<ul style="list-style-type: none"> • Allosteric modulator of cardiac β-myosin • Causes reversible inhibition of actin–myosin cross bridging 	<ul style="list-style-type: none"> • Phase IIa trial of mavacamten -oHCM (PIONEER-HCM; ClinicalTrials.gov Identifier: NCT02842242) [78] • Phase III trial-oHCM (EXPLORER-HCM) [79]
CK-274 (Cytokinetics, Inc., South San Francisco, CA, USA)	<ul style="list-style-type: none"> • Is currently under development 	<ul style="list-style-type: none"> • Ongoing phase II clinical trial in obstructive HCM
<i>Myocardial energetics</i>		
Perhexiline	<ul style="list-style-type: none"> • Used as an antianginal therapy • Oral inhibitor of carnitine palmitoyl transferase I (CPT-1) • Studied for use in noHCM 	<ul style="list-style-type: none"> • METAL-HCM study [82]
Trimetazidine	<ul style="list-style-type: none"> • Studied for use in noHCM 	
<i>Ion channels</i>		
Ranolazine	<ul style="list-style-type: none"> • Inhibitors of I_{NaL} • Studied for use in noHCM 	<ul style="list-style-type: none"> • RESTYLE-HCM [83]
Eleclazine	<ul style="list-style-type: none"> • Inhibitors of I_{NaL} • Studied in noHCM and oHCM 	<ul style="list-style-type: none"> • LIBERTY-HCM [84]

noHCM Non-obstructive hypertrophic cardiomyopathy, *oHCM* obstructive hypertrophic cardiomyopathy, I_{NaL} late sodium current activity

(VO₂): + 3.5 mL/kg/min). While improvements in LVOT obstruction (average approx. 25 mmHg decrease in post-exercise LVOT gradient) and exertional capacity were more modest, there was still significant symptomatic improvement. There was no significant effect on the end-diastolic pressure–volume relationship, which is a measure of LV stiffness, despite decreases in inotropic indices [78]. Mavacamten for the treatment of symptomatic obstructive hypertrophic cardiomyopathy (EXPLORER-HCM) is a randomized, double-blind, placebo-controlled, phase III trial. In this study treatment with

mavacamten improved exercise capacity, LVOT obstruction, NYHA functional class, and health status in patients with obstructive HCM. Findings from these phase II and III trials suggest that mavacamten is a very promising new therapy that leads to an improvement in the symptomatic and physiological metrics for symptomatic patients with HCM with minimal adverse events [79]. A phase II study of Mavacamten in Adults with Symptomatic Non-Obstructive Hypertrophic Cardiomyopathy (MAVERICK-HCM) showed that treatment was associated with a significant reduction in NT-

proBNP and cardiac troponin T (cTnI), suggesting improvement in myocardial wall stress [80]. In HCM mutation carriers, the phosphocreatine to ATP ratio is reduced, consistent with impaired high-energy phosphate metabolism. As a compensatory mechanism, there is increased carbohydrate utilization relative to fatty acids, akin to cardiomyocyte adaptation during ischemia. Perhexiline inhibits carnitine palmitoyltransferase I (CPT-1) and reduces fatty acid uptake into mitochondria, resulting in greater cellular dependence on carbohydrates for ATP production. ATP production is increased for the same O₂ consumption and consequently increases myocardial efficiency [81]. The functional capacity increased in patients. While an early phase clinical study (METAL-HCM; NCT00500552) revealed favorable changes in the cardiac metabolome and improvement in exercise capacity compared to placebo, a more recent multicenter phase IIb clinical trial (NCT02862600) was terminated early due lack of efficacy and side effects [52, 82].

Hypertrophic cardiomyopathy is associated with enhanced late sodium current (I_{NaL}) activity due to enzyme-induced sodium channel phosphorylation. Dysregulated Ca²⁺ and Na⁺ handling may contribute to altered cardiomyocyte mechanics (hyper-contractility and impaired relaxation) and predispose the myocardium to arrhythmias. Ranolazine and eleclazine (both from Gilead Sciences, Foster City, CA, USA) are inhibitors of I_{NaL}, which could in theory have several benefits in HCM related to myocardial relaxation, ischemia, and arrhythmogenesis. A reduction in premature ventricular complex burden has been noted with ranolazine; however, studies (RESTYLE-HCM) failed to demonstrate a significant effect on objective measures, such as B-type natriuretic peptide and diastolic function. Additionally, the more potent I_{NaL}-inhibitor, eleclazine, was found to be ineffective in a large (*n* = 180) placebo-controlled trial (LIBERTY-HCM) [83, 84].

Several therapies have attempted to address fibrosis and disease progression in HCM. Although improvement in fibrosis were hypothesized with ARBs, aldosterone antagonists, *N*-acetyl cysteine, and statins, these

molecules mostly failed to demonstrate beneficial effects in the studies. A phase II placebo-controlled trial of valsartan (VANISH; NCT01912534) is currently underway in HCM mutation carriers with asymptomatic or early/mild disease. Recently the introduction of sacubitril/valsartan and the sodium–glucose cotransporter 2 inhibitors (empagliflozin, dapagliflozin) found to be as effective therapies for patients with non-HCM-related systolic heart failure, and while exciting, their efficacy is yet to be established in HCM [85, 88].

Radiofrequency Ablation

Analogous to electrophysiologic procedures, radiofrequency (RF) energy is applied to the endocardial surface of the basal interventricular septum from a retrograde aortic or transseptal approach using electroanatomic or ECG guidance. More recently, percutaneous intramyocardial septal RF ablation was reported in a series of 15 patients with symptomatic obstructive HCM. This novel technique uses transthoracic ECG to guide transapical placement of an intraseptal RF electrode that delivers energy to the core of the hypertrophic segment. The authors reported an impressive septal reduction of 11 mm with resolution of obstruction (mean exercise LVOT gradient: 117–25 mmHg), improvements in NYHA class, and reduced serum NT-proBNP at 6 months [89–91].

Other Novel Therapies

High-intensity focused ultrasound (HIFU) uses ultrasound energy to create focal tissue lesions at a pre-determined depth from the ultrasound transducer. As it does not require direct contact with the target tissue, it is free from typical anatomic constraints. While there have been no human studies to date in HCM, HIFU has potential for achieving a completely non-surgical septal reduction in the future (92).

Allele-specific gene silencing and genome editing using CRISPR/Cas9 target the genetic underpinnings of hypertrophic cardiomyopathy. Current techniques including CRISPR/Cas9

cause a double-stranded DNA break at a desired genetic locus followed by intrinsic cellular repair. Germline editing is attractive for the treatment of monogenic diseases, as progeny of the treated embryo could prevent transmission of mutations to future generations [93, 94].

FABRY DISEASE AND LEFT VENTRICULAR HYPERTROPHY

Fabry disease, also called Anderson-Fabry disease, is the most prevalent lysosomal storage disorder. It is an X-linked inborn error of the glycosphingolipid metabolic pathway caused by mutations in the Galactosidase alpha (*GLA*) gene that leads to deficiency of the enzyme alpha-galactosidase A (α -Gal A). This results in accumulation of globotriaosylceramide (Gb3) within lysosomes in a wide variety of cells, causing variable manifestations of the disease [95]. Gb3 accumulation induces pathology via the release of pro-inflammatory cytokines and growth-promoting factors and by oxidative stress, resulting in myocardial extracellular matrix remodeling, LVH, vascular dysfunction, and interstitial fibrosis. Although the major accumulating molecule is Gb3, globotriaosylsphingosine (lyso-Gb3), digalactosylceramide (Gal2Cer), and blood group B and P1 antigens accumulate to a minor degree [96, 97]. Clinical presentation is variable and includes cutaneous, corneal, cardiac, renal, and neurologic manifestations. Cardiovascular manifestations of Fabry disease include LVH, aortic and mitral regurgitation, conduction defects, CAD, hypertension, and aortic root dilatation. In some cases of severe cardiac disease, the septum may appear asymmetrically hypertrophied because the basal posterior wall is thinned due to fibrosis. Many patients are asymptomatic, and a rare number of patients have advanced heart failure symptoms in the setting of unexplained LVH and generally normal LV ejection fraction. Intramural coronary arteries on endomyocardial biopsy reveal luminal narrowing due to hypertrophy and proliferation of smooth muscle and endothelial cells with glycosphingolipid deposits which may cause angina. Symptoms usually become evident in the third or fourth

decade of life. Unexplained LVH is more common and more severe in males. While males are more severely diseased, most heterozygous females are also affected, although usually at a later age. Life expectancy is reduced by approximately 20 years in untreated males. Women are more likely to present with the cardiac variant of disease [98–101].

Management

The treatment of patients with Fabry disease primarily focuses upon replacing the missing or deficient enzyme (alpha-Gal A) with enzyme replacement therapy (ERT) as well as treating the various symptoms and disease complications. Two therapeutic modalities are available clinically for the treatment of Fabry disease: ERT and chaperone therapy. Migalastat hydrochloride is an oral pharmacologic chaperone that facilitates the trafficking of alpha-Gal A to lysosomes; as such, it is a therapeutic option for eligible individuals. The impact of these therapies on mortality is unknown. Other strategies, such as substrate reduction therapy, mRNA-based therapy, and gene therapy, are in development [102, 103]. Patients with Fabry disease with cardiac manifestations should generally receive standard therapies for heart disease, including antianginal medication for angina, standard antiarrhythmic therapy, and guideline-directed therapy for heart failure [104]. Although the impact on cardiovascular outcomes is not known, ERT should be initiated in patients with cardiac manifestations. Angina is frequent caused by small vessel disease; antianginal therapies are frequently needed. Evaluation with stress testing and coronary angiography is indicated in some patients to identify concurrent epicardial CAD [98]. Possible causes of sudden death in Fabry disease include ventricular arrhythmia and bradyarrhythmia. Some patients with advanced cardiomyopathy may require implantable ICD placement to prevent sudden cardiac death. Conduction abnormalities may be caused by glycolipid deposition in the atrioventricular node, His bundle, and bundle branches. Permanent pacemaker implantation is occasionally

required to treat symptomatic bradycardia and/or advanced conduction system disease. Antiarrhythmic therapy may be needed for atrial and ventricular arrhythmias. Atrial arrhythmias, including AF, are more common and appear to be related to age. Management of hypertension is needed, and over one-half of the patients develop increases in blood pressure after the onset of CKD. Apart from patients receiving GDMT in heart failure, successful heart transplantation for advanced Fabry cardiac disease has been performed without development of Fabry disease in the graft, likely due to adequate enzyme activity in the graft. Fabry's disease is not a contraindication for organ transplantation, even in patients presenting with both renal failure and heart failure [105–108]. Given the risk of development of ascending aortic aneurysm, patients with Fabry disease should be monitored for progressive ascending aortic dilatation [109].

Enzyme Replacement Therapy

As soon as the cardiac manifestations are detected, ERT should be initiated. The effect of ERT on cardiovascular outcomes has not been established. Two formulations of recombinant human alpha-Gal A are available: agalsidase alfa (Replagal™, Shire), produced in a genetically engineered human cell line, and agalsidase beta (Fabrazyme™, Genzyme), produced in a Chinese hamster ovary cell line [110]:

- agalsidase alfa (Replagal™, Shire): 0.2 mg/kg as an intravenous infusion given over 40 min every 2 weeks;
- agalsidase beta (Fabrazyme™, Genzyme): 1 mg/kg as an intravenous infusion over a mean of 2–2.5 h every 2 weeks.

A recent 5-year study of male patients aged 5–18 years supports the efficacy of agalsidase beta when delivered as a 1 mg/kg biweekly treatment rather than at a reduced dosage [111]. Clinical trials and observational studies suggest that ERT with agalsidase alpha or agalsidase beta can reduce tissue deposition of Gb3 in endothelial cells (including deposition in the heart) and reduce neuropathic pain, although the impact of ERT on other clinical manifestations of Fabry disease is less clear [112]. Early

initiation of ERT in patients with cardiac involvement has been suggested since ERT may not improve segmental function where fibrosis (detected by CMRI) is already present. If the patient is a female carrier or an atypically affected male, ERT is recommended when clinical manifestations are present. However all classically affected males should receive migalastat regardless of clinical manifestations [113, 114]. If Fabry disease-related tissue pathology or clinical symptoms are absent, ERT may not be appropriate. These patients should be monitored regularly by a multidisciplinary care team [115].

Observational studies suggest that ERT can reduce LV wall thicknesses and/or LVM and improve myocardial function (e.g., systolic radial strain rate) but an impact on cardiovascular endpoints has not been established. A small randomized trial found that 4 months of recombinant human α -Gal A resulted in cardiac microvascular clearance of globotriaosylceramide accumulation in 72% of treated patients as compared with 3% of patients on placebo [112, 116]. Wiedemann et al. [113] suggested that treatment with recombinant α -Gal A should best be started before myocardial fibrosis has developed to achieve long-term improvement in myocardial morphology and function and exercise capacity. Data on the impact of ERT on changes in LVH are conflicting, with some studies showing a reduction in LVM and improved myocardial function as assessed by systolic radial strain rate, and others failing to show significant changes in ventricular wall thickness. ERT may cause infusion reactions and is not effective in all patients, such as those with end-stage organ disease or with antibodies to the recombinant enzyme [97, 117]. The Fabry Outcome Survey (FOS) reported that treatment with agalsidase alpha resulted in stability in the LVM index and mid-wall fractional shortening over a period of 5 years. Mehta et al. [118] also showed a sustained reduction in LVM index and a significant increase in mid-wall fractional shortening after 3 years of ERT in those patients with LVH at baseline evaluation. However, an observational study of 40 patients with Fabry disease suggested that long-term ERT may not be sufficient to alter the natural history of the

disease [119]. In late-onset Fabry disease, ERT should be considered in the presence of laboratory, histological, or imaging evidence of injury to the heart, kidney, or central nervous system, even in the absence of typical Fabry symptoms [115].

Chaperone Therapy

Migalastat can now be used instead of ERT in patients with amenable genetic variants (present in 35–50% of patients) that allow for substantial increases in enzyme activity with this medication. The concept is that a ligand (i.e., molecular chaperone) of α -Gal A may occupy its active site, thereby promoting enzyme folding and stability. Once the α -Gal A-chaperone complex enters the lysosome, the chaperone is dissociated from the enzyme due to pH-sensitive conformational changes, releasing α -Gal A to act on glycosphingolipid substrates [102]. The presence of genetic variants should be determined before starting treatment to confirm that the *GLA* gene variant is associated with deficient α -Gal A leukocyte activity. The treatment is contraindicated when the glomerular filtration rate is estimated (eGFR) to be < 30 mL/min per 1.73 m² [120]. Once it has been confirmed that the patient actually has an enzyme deficiency, the *GLA* gene variant that is likely to result in a substantial increase in enzyme level can be treated with migalastat. If these patients are already receiving treatment with ERT (α -Gal A or β -Gal), we typically switch them from ERT to migalastat. Migalastat is administered at a dose of 123 mg (equivalent to 150 mg of migalastat hydrochloride) orally once every other day [121]. In one double-blinded trial, 67 patients with Fabry disease who were not on ERT were randomly assigned to treatment with migalastat hydrochloride or placebo every other day for 6 months, followed by open-label migalastat for up to an additional 18 months. No patients progressed to end-stage kidney disease (ESKD), cardiac death, or stroke during the study, and the rate of adverse events was similar between groups. After a follow-up of 18–24 months in the open-label extension, there was a significant improvement in LVMI compared with baseline [121]. In another study, 57 adults were randomly assigned to receive

18 months of migalastat or to continue treatment with ERT. At 18 months, migalastat and ERT had comparable effects on kidney function, the LVM index had decreased from baseline in patients on migalastat but not changed significantly in those on ERT, and there was no significant difference in the rate of kidney, cardiac, or cerebrovascular events or treatment-related adverse events between the two groups [122]. Patients who are started on ERT or migalastat should have a clinical evaluation, routine laboratory tests, and complete blood count every 6 to 12 months. Estimation of the GFR and determination of the urine protein-to-creatinine ratio every 3 to 6 months are needed. Patients with cardiac involvement should have an electrocardiogram every 6 to 12 months [123]. Recent studies show that chaperone therapy coupled with ERT is more efficacious than either option as monotherapy [124]. Pegunigalsidase-a is a novel pegylated form of α -Gal A produced in a ProCellEx system (Protalix Biotherapeutics, Carmiel, Israel) with an increased heart and kidney uptake compared with current ERTs. ERT and migalastat are not recommended in persons with well-characterized benign α -Gal A variants [115].

Substrate reduction therapy (SRT) is gaining interest as an alternate approach to reducing the levels of metabolites that accumulate in Fabry disease by decreasing the synthesis of relevant precursor glycosphingolipids. In patients with residual enzyme activity, SRT might be sufficient to reduce the production of the substrate to a level compatible with the remaining enzyme activity. Glucosylceramide synthase (GCS) inhibition results in decreased Gb3 synthesis [125]. Glucosylceramide synthase inhibitors have been tested in the preclinical setting in Fabry cell and mouse models and in clinical trials for patients with Gaucher disease (glucosylceramidase deficiency). SRT that specifically targets Gb3 synthesis and avoids depletion of lactosylceramide may be a better option in these patients. Novel SRT molecules have been developed and tested for Fabry disease, such as the ceramide-based Venglustat (Sanofi Genzyme, Sanofi S.A., Paris, France) and the galactose derivative lucerastat (Idorsia Pharmaceuticals, Allschwil, Switzerland); both

molecules inhibit GCS. Combining different approaches, such as ERT with SRT, might be beneficial, but the high costs of the individual therapies currently form an important barrier to the implementation of this approach [115, 126].

Gene therapy will likely be a future therapeutic option. This therapy has the potential to systemically express α -Gal A in a manner that would be effective for the large number of genetic mutations that cause Fabry disease. Adeno-associated virus capsids are also being evaluated for gene therapy, and novel capsids are in development to improve α -Gal A expression in kidney, heart, and brain. m-RNA-based therapy is an attractive option because the translated α -Gal A would express native post-translational modification [127]. The first in-human study of gene therapy via autologous stem cell transplantation using cells transduced via a lentivirus vector containing the ‘wild-type’ allele of the *GLA* gene is currently underway [97].

CARDIAC AMYLOIDOSIS

Amyloidosis is a family of diseases in which misfolded precursor proteins aggregate to form amyloid which is then deposited in body tissues. Proteins fold inappropriately for several reasons. Some proteins have an inherent propensity to misfold and deposit in body tissues when present in high concentrations or when the patient ages (as is the case with transthyretin), while others misfold due to an alteration in the encoding genes of the protein. Abnormal proteolytic remodeling causing a conformational change to the precursor protein may make it more likely to fold inappropriately. In cardiac amyloidosis, amyloid is deposited in the extracellular space of the myocardium, resulting in thickening and stiffening of ventricular walls, with resultant heart failure and conductive dysfunction [128–130]. The most pertinent forms of the disease in the setting of cardiac amyloidosis are transthyretin amyloidosis (ATTR) and immunoglobulin-derived light-chain amyloidosis (AL). It is uncommon for secondary (AA) amyloidosis to affect the heart, and this is rarely seen in developed

countries where severe chronic inflammatory processes are generally well managed [131, 132]. A high index of suspicion is essential in the early diagnosis and for improvement of the prognosis of these patients. Cardiac complications include heart failure, AF, ventricular arrhythmias, conduction disorders, thromboembolism, aortic stenosis, and treatment should be given according to the underlying pathology.

Immunoglobulin-Derived Amyloid Light-Chain Amyloidosis

The precursor protein of amyloid light-chain amyloidosis (AL amyloidosis) is a monoclonal light chain. The disease is mostly seen in males (> 60%) aged > 50 years. The underlying disorder is plasma cell dyscrasia. AL amyloidosis almost invariably involves the cardiovascular system, with approximately 90% of cases involving the heart. Amyloid deposits in AL amyloidosis have been described to have cytotoxic effects which directly cause cell death of cardiomyocytes. Vascular involvement is common and heart failure is more severe. Other cardiac pathologies can be manifested, such as right-sided heart failure with preserved EF, valve pathologies, atrial/ventricular arrhythmias, or bradyarrhythmia; severe hypotension with ACE inhibitor use is not rare. There may be multi-organ involvement, involving nephrotic syndrome, hepatomegaly/splenomegaly, periorbital bruising (“panda eyes”), macroglossia, nail dystrophy, submandibular gland enlargement, peripheral polyneuropathy, autonomic neuropathy, and carpal tunnel syndrome, which may be seen as extracardiac manifestations [132].

Treatment

There is no disease-specific therapy and cardiac involvement in AL amyloidosis. Compared to patients with ATTR amyloidosis, those with AL amyloidosis have lower median survival rates from the onset of symptoms (1.7 vs. 6.1 years). The treatment regimens used are similar to those used for multiple myeloma. The choice of therapy is based on dedicated risk stratification

and includes criteria such as age, Karnofsky index, number of organs involved, and extent of organ involvement. The primary goal includes preventing disease progression by stopping the production of light chains and inhibiting amyloid fibril formation. The degree of cardiac involvement often limits the choice of chemotherapy [133]. Chemotherapy can include steroids (dexamethasone, prednisolone), alkylators (melphalan, cyclophosphamide), proteasome inhibitors (bortezomib, carfilzomib), immunomodulators (lenalidomide, pomalidomide), anti-CD38 antibody (daratumumab), and an anti-SLAMF7 antibody (elotuzumab) [134–136].

The drugs have potential side effects, including cardiac decompensation (steroids, carfilzomib) or thrombotic events (lenalidomide and pomalidomide). Chemotherapy using cyclophosphamide, bortezomib, and dexamethasone (CyBorD) is the current standard of care for patients with AL amyloidosis. The ANDROMEDA study effectively demonstrated that CyBorD coupled with daratumumab works effectively to produce responses in patients with AL amyloidosis. The overall organ response rate, including cardiac, kidney and liver, was 64% at 17.3 months. Several promising agents are being tested. Birtamimab (NEODOO1) is an antibody which neutralizes circulating and deposited amyloid. The phase III trial was prematurely discontinued because of a lack of efficacy; however, a post hoc analysis showed that NEODOO1 reduced all-cause mortality in those patients at the highest risk for early mortality. Another potential agent is the green tea polyphenol epigallocatechin-3-gallate (EGCG) [134, 137, 138]. Loop-diuretics and mineralocorticoid receptor antagonists can be beneficial in specific doses, avoiding doses that would decrease preload. There is no evidence for standard heart failure therapies. Sometimes beta blockers can lead to significant hemodynamic deterioration as patients with cardiac amyloidosis (CA) can increase their cardiac output only via the heart rate. Many CA patients develop AF/atrial flutter, which often makes heart rate control necessary. Digitalis derivatives bind to amyloid fibers and cause locally toxic levels. When digitalis derivatives

are needed, close monitoring of serum levels and side effects are of utmost important [134]. As a non-drug therapy option, heart transplantation may be considered in selected cases to enable patients to receive high-dose chemotherapy and autologous stem cell transplant afterwards. A complete hematological response is needed in order to avoid recurrence of AL amyloidosis/CA in the transplanted organ so cardiac transplantation as a therapeutic option should be discussed and evaluated [128, 139].

Transthyretin Amyloidosis and Treatment

Transthyretin amyloidosis is a condition in which transthyretin, a physiological protein primarily synthesized by the liver, misfolds into insoluble B-pleated sheets and deposits as amyloid in the extracellular space of the myocardium. The disease may be cardiac-predominant, neuropathy-predominant, or mixed, and usually appears in males aged > 50 years. Deposition of misfolded transthyretin either as the wild-type (ATTRwt) form or mutated/variant (ATTRv) form causes ATTR. In cardiac ATTR, amyloid deposits primarily cause myocardial stiffness and impaired function by affecting myocardial relaxation; in later stages there can be a decline in contractility [131, 140]. ATTR tends to present as heart failure with preserved EF (HFpEF) with signs of right-sided heart failure. The cardiovascular presentation of hereditary ATTR (hATTR) varies according to the causative genetic mutation. The two best well-documented mutations leading to cardiomyopathy are Val122Ile and Thr60Ala. Those persons with the Val30Met transthyretin mutation commonly have conduction issues requiring pacemaker placement, while other variants, such as Val122Ile and Thr60Ala (T60A), commonly affect the cardiovascular system, but do not primarily affect the conduction system. ATTRwt was formerly called senile systemic amyloidosis (non-hereditary ATTR). In comparison to ATTRwt, those with the Val122Ile mutation have a worse NYHA functional class with a lower QoL. Overall survival between these two forms of ATTR are similar. Rhythm

disturbances (typically AF) are more frequent in ATTRwt than in hATTR. A useful flag for suspecting ATTR is hypertension that resolves over time and an intolerance of ARBs, ACE inhibitors, or beta blockers. In ATTRwt, carpal tunnel syndrome, lumbar spinal stenosis, and isolated cardiomyopathy may occur. Subjects with ATTR usually have more severe LV thickening than those with AL amyloidosis [131, 141, 142].

The basic policies for CA management are to deal with symptomatic complaints based on HF, together with the consideration of two therapeutic possibilities: general HF pharmacotherapy and causal treatment for CA. Low cardiac output can be easily seen through the restrictive compromise in CA. Correct titration of diuretics is the primary treatment in heart failure. ACE inhibitors and ARBs promote hypotension due to autonomic dysfunction and can only be tolerated in low doses in patients with cardiac amyloidosis. There are limited data with sacubitril/valsartan therapy. Also, digitalis and calcium channel blockers should be used with caution. Intravascular volume depletion may cause hypotension in cases of restrictive hemodynamics, leading to diuretic resistance. Inotropic drugs such as catecholamines and phosphodiesterase inhibitors are used for the treatment of low perfusion. Especially in patients in sinus rhythm, one must be careful not to reduce the heart rate excessively, because an increased heart rate has a compensatory role in a restrictive heart with low stroke volume. Cardiac conduction disorders can be managed by using a pacemaker or an ICD. For AL amyloidosis a heart transplant is recommended while in ATTR, both a heart and liver transplant are needed [143, 144].

Transthyretin Amyloidosis

Transthyretin amyloidosis-modifying therapies and their mechanism of action, indications for use in treatment, and their availability in current treatment modalities are given in Table 6 [138, 145]. Tafamidis for treatment of amyloid cardiomyopathy based on the data from the recently published phase III clinical trial (ATTR-ACT) was approved by the European Medicines

Agency (EMA). The safety and efficacy of tafamidis has been evaluated (20 mg and 80 mg dosages) and compared with placebo in patients with amyloid cardiomyopathy. Compared to the placebo group, a significant reduction in mortality was observed in all subgroups. Hospitalizations due to cardiac decompensation were reduced. Also, there was an improvement in 6-min walking test and on the QoL as assessed in the Kansas City Cardiomyopathy Questionnaire (KCCQ-OS). Tafamidis was found to be effective for inhibiting disease progression in patients with ATTR whose functional capacity were NYHA I or II [128, 143, 146]. The approved dosage for treatment of amyloid cardiomyopathy is tafamidis 61 mg, the bioequivalent of 80 mg tafamidis-meglumine. Serious side effects did not occur. The effects of tafamidis are expected in patients with ATTR in the early stage, so it should be started before the patient shows obvious symptoms. Therefore, it is important to diagnose ATTR at an earlier stage using specific cardiac echocardiographic findings. Tafamidis does not seem to improve the pathology of ATTR.

In terms of echocardiographic findings as prognostic predictors in patients with ATTR, LVEF was the most reported finding. Grogan et al. [147] reported that LVEF < 50% was an independent prognostic predictor in patients with ATTRwt CA. Myocardial contraction fraction (MCF), which is the ratio of LVM to LV stroke volume, as well as LVEF should be considered as prognostic predictors for patients with amyloidosis. Moreover, some studies have reported that tricuspid annular plane systolic excursion (TAPSE) and mitral annular plane systolic excursion (MAPSE) are more useful prognostic predictors than LVEF, MCF, and LV global strain. Apical sparing is observed both in patients with ATTR and those with AL amyloidosis. The strain value at the LV apex in patients with ATTR has been shown to be lower than that in patients with AL amyloidosis [143, 148, 149]. Two transthyretin (TTR) messenger RNA (mRNA) interfering drugs, the RNA interference (RNAi) drug patisiran (Onpattro®; Alnylam Pharmaceuticals, Inc., Cambridge, MA, USA), and the antisense oligonucleotide inotersen (Tegsedi®; Ionis Pharmaceuticals,

Table 6 Pharmacological treatment strategies, mechanisms of action and indications for treatment

Disease-modifying therapies	Mechanism of action	Indication	Available or future therapies
<i>Synthesis suppression</i>	Reduce the production of mutated and overall TTR		
Genetic silencers			
Patisiran		<ul style="list-style-type: none"> • BOTH Cardiomyopathy and Polyneuropathy stage 1 • ONLY Polyneuropathy stage 1 and stage 2 	<ul style="list-style-type: none"> • Effective in ATTRv Neuro clinical trials • Ongoing ATTR trials
Inotersen		<ul style="list-style-type: none"> • ONLY Polyneuropathy stage 1 and stage 2 	<ul style="list-style-type: none"> • Effective in ATTRv Neuro clinical trials
Vutrisiran			<ul style="list-style-type: none"> • Ongoing ATTR trials
TTR-LRx			<ul style="list-style-type: none"> • Ongoing ATTR trials
- Liver transplantation			<ul style="list-style-type: none"> • Available without clinical trials
- Genetic editing			
<i>TTR stabilization</i>	Stabilize circulating TTR, prevent their dissociation or cleavage into amyloidogenic fragments		
Tafamidis		<ul style="list-style-type: none"> • ONLY Cardiomyopathy in ATTRv and ATTR wt • BOTH Cardiomyopathy and Polyneuropathy stage 1 • ONLY Polyneuropathy stage 1 	<ul style="list-style-type: none"> • Effective in ATTRv Neuro clinical trials • Effective in ATTR CARDIAC clinical trials
Diflusal			<ul style="list-style-type: none"> • Available without clinical trials • Effective in ATTRv Neuro clinical trials
Acoramidis			<ul style="list-style-type: none"> • Ongoing ATTR trials

Table 6 continued

Disease-modifying therapies	Mechanism of action	Indication	Available or future therapies
<i>Elimination of deposits</i>	Directed to remove amyloid fibrils		
Doxycycline			• Available without clinical trials
Doxycycline-TUDCA			
ECGC (green tea)			• Available without clinical trials
Antibodies			
- PRX004			
- NI006			

ECGC Polyphenol epigallocatechin gallate (dietary supplement with a dose of 800–1200 mgg), *TTR* transthyretin, *TTR-LRx* RNA-targeted gene therapy, *TUDCA* tauroursodeoxycholic acid,

Carlsbad, CA, USA) have been approved in Europe. Patisiran showed a significant reduction of LV wall thickness and NT-proBNP levels in a subgroup of ATTRv patients. Patisiran is applied intravenously every 3 weeks. There is lack of long-term evidence for its efficacy and safety [128, 138, 150–152].

AA Amyloidosis and Treatment

Cardiovascular manifestations of secondary amyloidosis include severe ventricular wall thickening with resultant motion abnormalities. Patients with secondary amyloidosis, which is caused by inflammatory disorders (rheumatoid arthritis, juvenile idiopathic arthritis), are less likely to have cardiac involvement than those with other forms of the disease. AA amyloidosis is caused by the deposition of AA fibrils, which are formed from a fragment of the serum amyloid A (SAA) protein in the context of long-lasting inflammatory states. Since AA amyloidosis primarily affects the kidneys, it usually manifests as renal insufficiency, often with proteinuria. Heart involvement is rather rare (< 10%), and there seems to

be a genetic predisposition. Important causes of AA amyloidosis are uncontrolled chronic inflammatory rheumatic diseases (e.g., rheumatoid arthritis), chronic inflammatory bowel diseases (ulcerative colitis, Crohn's disease), chronic infections (e.g., tuberculosis), and hereditary autoinflammatory diseases (e.g., familial Mediterranean fever). There is no specific drug therapy for heart involvement. The main treatment goals are improving underlying disease and preventing the synthesis of the precursor protein SAA. Depending on the underlying disease, various drugs are used, such as anti-infectives for infectious disease, anti-inflammatory drugs, immunosuppressants for autoimmune diseases, and chemotherapy for malignant diseases [153, 154].

CONCLUSION

Left ventricular hypertrophy increases cardiovascular morbidity and mortality. The asymptomatic nature of LVH may lead to delayed treatment. Creating awareness about LVH and

searching for underlying etiologies facilitates initiation of early treatment.

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