Review Article

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Fabry cardiomyopathy: pathophysiology, multimodality imaging, and evolving therapeutic strategies

Abstract

Fabry disease is an X-linked lysosomal storage disorder caused by deficient α-galactosidase A activity, leading to progressive accumulation of glycosphingolipids in multiple organs. Cardiac involvement, commonly referred to as Fabry cardiomyopathy, represents a major determinant of morbidity and mortality and may occur as an isolated late-onset phenotype. The pathophysiology is characterized by intracellular lipid accumulation, microvascular dysfunction, inflammation, and progressive myocardial fibrosis, ultimately resulting in left ventricular hypertrophy, diastolic dysfunction, conduction abnormalities, and arrhythmias. Early diagnosis remains challenging due to phenotypic heterogeneity and overlap with more common causes of left ventricular hypertrophy. Multimodality imaging, particularly cardiac magnetic resonance with T1 mapping and late gadolinium enhancement, plays a pivotal role in early detection, tissue characterization, and risk stratification. Diagnostic strategies integrate enzymatic assays, genetic testing, and biomarkers such as plasma lyso-globotriaosylsphingosine. Disease-modifying therapies, including enzyme replacement therapy and pharmacological chaperone therapy (migalastat), have significantly improved patient outcomes, particularly when initiated before the development of advanced myocardial fibrosis. However, therapeutic efficacy is limited in later stages, and novel approaches such as gene therapy and substrate reduction therapy are under investigation. Arrhythmias and heart failure remain major clinical challenges, requiring individualized management strategies and, in selected cases, device therapy. Despite substantial progress, important knowledge gaps persist, particularly regarding optimal timing of therapy, management of variants of uncertain significance, and risk stratification for sudden cardiac death. Future directions include precision medicine approaches, advanced imaging techniques, and the development of disease-specific risk models. Early recognition and timely intervention remain critical to improving long-term outcomes in Fabry cardiomyopathy.

Keywords: fabry disease, fabry cardiomyopathy, lysosomal storage disorder, cardiac magnetic resonance imaging, enzyme replacement therapy

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Introduction

Fabry disease is an X-linked lysosomal storage disorder caused by deficient or absent activity of the enzyme α-galactosidase A, resulting in progressive intracellular accumulation of glycosphingolipids, predominantly globotriaosylceramide (Gb3) and its deacylated derivative lyso-globotriaosylsphingosine (lyso-Gb3).[1,2] This pathological substrate accumulation occurs within lysosomes of vascular endothelial cells, cardiomyocytes, renal epithelial cells, and neurons, leading to widespread cellular dysfunction and progressive organ involvement over time. As a consequence, multiple organ systems, including the kidneys, nervous system, and cardiovascular system, are affected, contributing to substantial morbidity and reduced life expectancy if the disease remains untreated.[3-5] The clinical presentation is heterogeneous and may range from early-onset multisystem disease to later-onset variants with predominantly cardiac manifestations, which can delay recognition and diagnosis in affected individuals.

Cardiac involvement is a major determinant of morbidity and mortality in Fabry disease and may represent the predominant or even isolated clinical manifestation, particularly in patients with late-onset variants.[2,4] Fabry cardiomyopathy is typically characterized by progressive left ventricular hypertrophy (LVH), myocardial fibrosis, microvascular dysfunction, and conduction system abnormalities, which may resemble hypertrophic cardiomyopathy and frequently contribute to delayed or missed diagnosis.[4,6] In addition to structural remodeling, patients may develop diastolic dysfunction, atrial enlargement, and an increased susceptibility to atrial and ventricular arrhythmias, all of which further influence clinical course and prognosis. Early recognition of cardiac involvement is therefore essential for timely initiation of disease-specific therapies and prevention of irreversible myocardial damage.

Importantly, Fabry disease is increasingly recognized as a treatable cause of otherwise unexplained LVH, highlighting the importance of maintaining clinical suspicion, particularly in patients without typical risk factors for hypertrophy.[4,6] Early identification of Fabry cardiomyopathy allows timely initiation of disease-specific therapies before the development of advanced myocardial fibrosis and irreversible structural damage. In recent years, advances in multimodality imaging, circulating biomarkers, and targeted treatment strategies have substantially improved both the understanding of disease mechanisms and the ability to detect cardiac involvement at earlier stages, thereby expanding therapeutic opportunities in patients with Fabry cardiomyopathy.[2,5,7]

This review was prepared using a structured, non-systematic literature search focusing on the cardiac involvement of Fabry disease, diagnostic approaches, and contemporary treatment strategies. Relevant publications were identified primarily through searches of the PubMed database using the keywords "Fabry disease," "cardiac involvement," "left ventricular hypertrophy," "cardiac magnetic resonance imaging," "enzyme replacement therapy," "migalastat," "gene therapy," and "arrhythmia." Studies published after 2000 were preferentially considered, including clinical trials, observational studies, systematic reviews, guidelines, and expert consensus documents. Priority was given to publications with higher levels of evidence addressing cardiac phenotype, early diagnostic tools, and therapeutic strategies. Reference lists of selected articles were also reviewed to identify additional relevant sources and ensure comprehensive coverage of the topic.

This review aims to provide an updated overview of the pathophysiological mechanisms, clinical manifestations, diagnostic strategies, and current treatment approaches in Fabry cardiomyopathy. Particular emphasis is placed on the progression from early subclinical myocardial involvement to advanced structural changes such as LVH, myocardial fibrosis, and arrhythmias. The role of multimodality cardiac imaging, especially echocardiography and cardiovascular magnetic resonance, is highlighted for early detection and disease monitoring. In addition, contemporary therapeutic options, including enzyme replacement therapy, pharmacological chaperone therapy, and emerging gene-based treatments, are discussed with respect to their clinical relevance and impact on patient outcomes.

Epidemiology

Fabry disease has historically been considered a rare disorder; however, contemporary data suggest that its true prevalence is higher than previously estimated, largely due to increased recognition of late-onset variants and the implementation of systematic screening strategies.[4,8] While the classic phenotype has been traditionally reported in approximately 1 in 40,000-117,000 males, newborn screening programs have revealed substantially higher incidences, particularly for later-onset cardiac variants.[8,9]

Population-based newborn screening studies have demonstrated incidences ranging from approximately 1 in 1,250 to 1 in 3,000 live births in certain regions, largely driven by variants associated with predominantly cardiac phenotypes (9,10). These findings underscore the significant contribution of previously unrecognized late-onset disease to overall Fabry disease prevalence.[8,10]

Fabry disease remains markedly underdiagnosed in adult cardiology practice, particularly among patients presenting with unexplained LVH. Targeted screening studies in such populations have identified Fabry disease in approximately 0.5-1% of individuals, supporting routine consideration of Fabry disease in the differential diagnosis of hypertrophic cardiomyopathy-like phenotypes.[4,11] The diagnostic yield may be higher in selected subgroups, including older males with isolated cardiac involvement.[8,11]

As an X-linked disorder, Fabry disease demonstrates sex-specific differences in prevalence and clinical expression. Hemizygous males typically develop earlier and more severe manifestations, whereas heterozygous females exhibit a wide phenotypic spectrum due to random X-chromosome inactivation, leading to variable degrees of organ involvement, including significant cardiomyopathy.[12,13]

Geographic variability in Fabry disease prevalence has also been reported, reflecting differences in genetic background, founder mutations, and screening practices. Notably, specific late-onset variants associated with predominant cardiac involvement have been identified with higher frequency in certain populations, particularly in East Asia, contributing to regional differences in epidemiological patterns.[10,14]

Genetics and molecular basis

GLA gene mutations

Fabry disease is caused by pathogenic variants in the GLA gene encoding the lysosomal enzyme α-galactosidase A, leading to impaired degradation of glycosphingolipids and progressive intracellular accumulation.[4,8] A wide range of mutations has been identified, including missense, nonsense, splice-site variants, and small insertions or deletions, contributing to marked heterogeneity in enzymatic activity and clinical presentation.[8,15]

Missense mutations are the most frequently observed and are often associated with residual enzyme activity, particularly in late-onset phenotypes with predominant cardiac involvement.[8,15] In contrast, variants resulting in absent or severely reduced enzyme activity are typically associated with the classical phenotype, characterized by early-onset multisystem disease.[4,15]

Despite these general trends, genotype-phenotype correlations remain incomplete. Significant variability has been observed even among individuals sharing identical mutations, suggesting that additional genetic and non-genetic modifiers influence disease expression.[15,16]

X-linked inheritance

Fabry disease follows an X-linked inheritance pattern, resulting in marked differences in clinical expression between males and females. Hemizygous males typically exhibit little or no α-galactosidase A activity and develop the classical phenotype with early and progressive organ involvement.[4,8]

In contrast, heterozygous females display a broad spectrum of clinical manifestations due to random X-chromosome inactivation (lyonization), which leads to variable levels of enzyme activity and organ involvement.[12] Importantly, female patients are increasingly recognized as being at risk for clinically significant cardiac disease, including LVH and myocardial fibrosis.[4,12] This phenotypic variability limits the diagnostic utility of enzyme activity measurements in females and underscores the importance of genetic testing for accurate diagnosis and risk stratification.[4,8]

Biomarkers

Biomarkers play a critical role in the diagnosis and monitoring of Fabry disease. Measurement of α-galactosidase A activity remains the cornerstone of diagnosis in males but has limited sensitivity in females due to variable enzyme expression.[4,8] Plasma lyso-Gb3 has emerged as a key biomarker reflecting disease burden and pathogenicity. Elevated lyso-Gb3 levels have been shown to correlate with disease severity and genotype, particularly in classical Fabry disease.[17] In addition, lyso-Gb3 may assist in distinguishing pathogenic variants from benign polymorphisms and has potential utility in monitoring disease progression and therapeutic response.[18] Beyond lyso-Gb3, additional biomarkers related to myocardial involvement, including fibrosis and structural remodeling, are being investigated, particularly in the context of Fabry cardiomyopathy, where early detection of cardiac disease remains a major clinical challenge.[4,17,19]

Pathophysiology of fabry cardiomyopathy

Fabry cardiomyopathy develops as a consequence of progressive intracellular glycosphingolipid accumulation within cardiomyocytes, vascular endothelial cells, and cells of the cardiac conduction system, leading to a cascade of structural and functional myocardial alterations over time. In the early stages of the disease, lysosomal substrate

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storage disrupts cellular metabolism and myocardial relaxation, while persistent accumulation promotes hypertrophic remodeling, microvascular dysfunction, and inflammatory activation. With ongoing disease progression, interstitial expansion and replacement fibrosis emerge as central features that contribute to impaired ventricular compliance, arrhythmogenesis, and eventual systolic dysfunction.

These interconnected mechanisms collectively explain the transition from subclinical myocardial involvement to overt hypertrophic cardiomyopathy and advanced heart failure phenotypes observed in Fabry disease. The key pathophysiological mechanisms together with the role of multimodality imaging and emerging therapeutic strategies in Fabry cardiomyopathy are summarized in Figure 1.

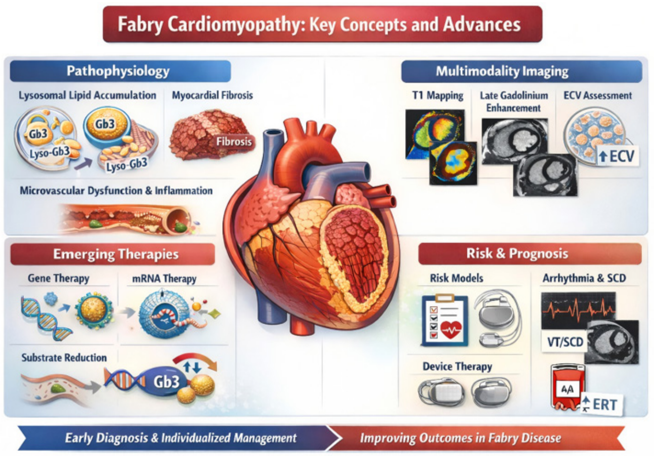

Figure 1 This schematic illustration summarizes the key mechanisms underlying Fabry cardiomyopathy, including lysosomal glycosphingolipid accumulation, microvascular dysfunction, inflammatory activation, and progressive myocardial fibrosis. The figure also highlights the role of multimodality imaging, particularly cardiac magnetic resonance techniques such as native T1 mapping, late gadolinium enhancement, and extracellular volume assessment, in early detection and disease staging. In addition, emerging disease-modifying therapies, including gene therapy, mRNA-based approaches, and substrate reduction therapy, are presented alongside established treatment strategies. Integration of imaging findings, genetic information, and clinical risk markers supports individualized management and improved risk stratification in patients with Fabry disease (ECV, extracellular volume; ERT, Enzyme Replacement Therapy; Gb3, globotriaosylceramide; ICD, implantable cardioverter-defibrillator; lyso-Gb3, lyso-globotriaosylsphingosine; mRNA, messenger ribonucleic acid; SCD, sudden cardiac death; VT, ventricular tachycardia).

Glycosphingolipid accumulation

The fundamental mechanism underlying Fabry cardiomyopathy is the progressive accumulation of glycosphingolipids, primarily Gb3 and its deacylated form lyso-Gb3, within lysosomes of cardiomyocytes.[4,8] This intracellular storage leads to cellular enlargement, disruption of normal sarcomeric architecture, and progressive myocardial hypertrophy.[4,20]

Beyond passive accumulation, lyso-Gb3 has been shown to exert direct biological effects, acting as a signaling molecule that promotes cellular dysfunction and contributes to disease progression.[18,21] These processes play a central role in the development of LVH, which represents the dominant structural manifestation of Fabry cardiomyopathy.[4,17]

Microvascular dysfunction

Microvascular dysfunction is an early and critical component of cardiac involvement in Fabry disease. Glycosphingolipid deposition within endothelial and vascular smooth muscle cells leads to structural and functional abnormalities of the coronary microcirculation.[4,20] These alterations result in impaired myocardial perfusion and reduced coronary flow reserve, even in the absence of obstructive epicardial coronary artery disease.[20,22] Chronic microvascular dysfunction contributes to repeated ischemic injury, which plays a key role in the progression from myocardial hypertrophy to fibrosis.[4,23]

Inflammation and fibrosis

In addition to substrate accumulation, Fabry cardiomyopathy is characterized by activation of inflammatory and profibrotic pathways. Lyso-Gb3-mediated signaling has been implicated in promoting inflammation, oxidative stress, and cellular injury.[18,23]

Myocardial fibrosis represents a hallmark of advanced disease and is typically localized to the basal inferolateral wall, as demonstrated by cardiac imaging studies.[17,23] The extent of fibrosis has been strongly associated with adverse clinical outcomes, including ventricular arrhythmias, heart failure progression, and increased mortality.[19,23]

Conduction system involvement

Glycosphingolipid accumulation and progressive interstitial fibrosis also affect the cardiac conduction system in Fabry disease. Involvement of the sinus node, atrioventricular node, and His-Purkinje network contributes to electrical disturbances such as atrioventricular conduction delay, bundle branch block, and other intraventricular conduction abnormalities.[4,6] These structural and electrophysiological alterations increase susceptibility to both bradyarrhythmias and tachyarrhythmias, including atrial fibrillation and ventricular arrhythmias, which represent important contributors to morbidity and may adversely influence long-term clinical outcomes in patients with Fabry disease.[6,19]

Energetic and metabolic disturbance

Emerging evidence suggests that metabolic and energetic alterations contribute to the pathophysiology of Fabry cardiomyopathy. Cellular dysfunction related to substrate accumulation, mitochondrial impairment, and altered energy utilization has been described, even in early disease stages.[17,23] These metabolic disturbances likely precede overt structural remodeling and may contribute to disease progression, supporting the concept of Fabry cardiomyopathy as a dynamic process involving both storage and secondary cellular dysfunction.[4,23]

Cardiac phenotype

Left ventricular hypertrophy

LVH is the predominant structural hallmark of Fabry cardiomyopathy and typically presents as concentric thickening of the ventricular walls.[4,6] This phenotype results from progressive intracellular glycosphingolipid accumulation within cardiomyocytes, leading to cellular enlargement and myocardial remodeling.[4,20] Although concentric LVH is the classical pattern, asymmetric hypertrophy may also occur, occasionally mimicking sarcomeric hypertrophic cardiomyopathy and contributing to diagnostic uncertainty.[4,6] Importantly, structural hypertrophy is often preceded by a prehypertrophic phase characterized by subtle functional and metabolic abnormalities detectable by advanced imaging techniques.[2,17]

Diastolic dysfunction

Diastolic dysfunction is an early and consistent feature of Fabry cardiomyopathy and may be present before the development of overt LVH.[2,4] Impaired myocardial relaxation is primarily driven by intracellular lipid accumulation and early alterations in myocardial compliance.[2,20] With disease progression, increasing myocardial stiffness and fibrosis lead to worsening diastolic function, which may evolve into a restrictive filling pattern.[4,23]. These changes contribute significantly to the development of heart failure with preserved ejection fraction, (HFpEF), a common clinical manifestation in Fabry disease.[6,23]

Systolic dysfunction

Left ventricular systolic function is generally preserved in the early stages of Fabry cardiomyopathy; however, progressive disease is associated with gradual impairment of systolic performance.[4,6] This decline is largely attributable to the accumulation of myocardial fibrosis and chronic cardiomyocyte injury.[17,23]

Even in patients with preserved ejection fraction, subclinical systolic dysfunction may be detected using advanced imaging modalities such as strain analysis, reflecting early myocardial involvement.[2,17] In advanced stages, extensive fibrosis may lead to overt systolic dysfunction and symptomatic heart failure.[4,19]

Right ventricular involvement

Although left ventricular involvement predominates in Fabry disease, the right ventricle may also be affected as part of the diffuse myocardial storage process. Right ventricular hypertrophy and varying degrees of functional impairment have been reported, particularly in more advanced stages of the disease and in patients with established myocardial fibrosis.[4,6] Right ventricular involvement reflects the systemic nature of glycosphingolipid accumulation and may contribute to global cardiac dysfunction, worsening hemodynamic status, and overall disease severity, highlighting the importance of comprehensive biventricular assessment during cardiac evaluation.[4,23]

Valvular abnormalities

Valvular involvement in Fabry disease is typically mild and characterized by thickening of valve leaflets due to glycosphingolipid deposition. The mitral and aortic valves are most commonly affected. These structural changes may result in mild-to-moderate regurgitation but rarely lead to clinically significant stenosis or require surgical intervention.[4,6] Valvular abnormalities are generally considered secondary manifestations of systemic storage rather than primary drivers of clinical outcomes.

Electrocardiographic and rhythm manifestations

Fabry cardiomyopathy is frequently associated with a wide spectrum of electrocardiographic abnormalities and arrhythmias, reflecting both glycosphingolipid accumulation within cardiomyocytes and progressive replacement fibrosis involving the cardiac conduction system.[4,6] Electrocardiographic changes may include PR interval abnormalities, repolarization disturbances, signs of LVH, and various intraventricular conduction delays, which may appear even in early disease stages. As myocardial involvement progresses, these electrical abnormalities become more prominent and are often accompanied by clinically significant arrhythmias, contributing to symptom burden and increased cardiovascular risk in patients with Fabry disease.

Early electrocardiographic changes

Electrocardiographic abnormalities may appear early in the disease course, sometimes preceding overt structural cardiac involvement. One of the characteristic early findings is a shortened PR interval, which is thought to result from accelerated atrioventricular conduction rather than the presence of an accessory pathway.[24,25] Additional early electrocardiographic findings may include increased QRS voltages reflecting incipient LVH and repolarization abnormalities, even in the absence of overt morphological changes on imaging.[2,24]

Conduction abnormalities

As Fabry disease progresses, involvement of the conduction system leads to a range of conduction disturbances. These include first-degree atrioventricular block, bundle branch block, and, in advanced stages, high-grade atrioventricular block requiring pacemaker implantation.[4,6] Conduction abnormalities are primarily driven by progressive glycosphingolipid deposition and replacement fibrosis within the atrioventricular node and His-Purkinje system.[4,23] The burden of fibrosis has been shown to correlate with the severity of conduction disease.[19,23]

Atrial arrhythmias

Atrial arrhythmias, particularly atrial fibrillation, are common in Fabry disease and are associated with atrial remodeling, increased left ventricular filling pressures, and myocardial fibrosis. The prevalence of atrial fibrillation increases with age and disease severity. Atrial fibrillation contributes significantly to morbidity, increasing the risk of thromboembolic events and heart failure decompensation.[6,23] Early detection and appropriate anticoagulation are therefore critical components of management.

Ventricular arrhythmias and sudden cardiac death

Ventricular arrhythmias represent a major cause of morbidity and mortality in Fabry disease. Non-sustained and sustained ventricular tachycardia may occur, particularly in patients with advanced myocardial fibrosis. Myocardial fibrosis, as detected by cardiac magnetic resonance (CMR) imaging, is a key substrate for ventricular arrhythmogenesis and has been strongly associated with adverse outcomes, including sudden cardiac death.[19,23] Importantly, arrhythmic risk may persist even in patients with preserved left ventricular ejection fraction.

Risk stratification and device therapy

Risk stratification for sudden cardiac death in Fabry disease remains challenging due to the heterogeneity of the disease. However, the extent of myocardial fibrosis, history of ventricular arrhythmias, and degree of LVH are considered important risk markers.[4,23] Implantable cardioverter-defibrillator (ICD) therapy may be indicated in selected high-risk patients, particularly those with documented ventricular arrhythmias or extensive fibrosis.[4,6] Pacemaker implantation is frequently required in patients with advanced conduction disease.[6]

Diagnostic approach

Clinical suspicion

Early diagnosis of Fabry disease remains challenging due to its heterogeneous clinical presentation and frequent overlap with more common cardiovascular conditions. Clinical suspicion should be raised in patients presenting with unexplained LVH, particularly in the absence of hypertension or significant valvular disease.[4,6]

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Extracardiac manifestations, including neuropathic pain, renal dysfunction, angiokeratomas, and a positive family history, provide important diagnostic clues and should prompt further evaluation.[3,8] Importantly, late-onset variants may present with isolated cardiac involvement, increasing the likelihood of underdiagnosis in cardiology practice.[4,10]

Enzymatic testing

Measurement of α-galactosidase A activity in plasma, leukocytes, or dried blood spots represents the first-line diagnostic approach in males.[8,9] Markedly reduced or absent enzyme activity is highly indicative of Fabry disease in hemizygous males.[8] However, enzymatic testing has limited sensitivity in heterozygous females due to random X-chromosome inactivation, and normal enzyme activity does not exclude the diagnosis in this population.[12,8] Therefore, additional diagnostic strategies are required in female patients.

Genetic testing

Genetic testing through sequencing of the GLA gene is essential for definitive diagnosis, particularly in females and in patients with inconclusive enzymatic results.[8,16] Identification of pathogenic variants allows confirmation of the diagnosis, enables family screening, and contributes to genotype-phenotype correlation analyses.[15,16] However, interpretation of genetic variants remains challenging, especially in cases involving variants of uncertain significance (VUS). Accurate classification requires integration of clinical phenotype, biomarker data, family segregation analysis, and, in selected cases, functional or histopathological evidence.[16,18,26]

Biomarkers

Biomarkers play a complementary role in both diagnosis and disease assessment. Plasma lyso-Gb3 has emerged as a clinically relevant biomarker, particularly in classical Fabry disease, where it correlates with disease severity and pathogenic mutations. Although lyso-Gb3 levels may be less consistently elevated in late-onset variants and female patients, the biomarker remains valuable for distinguishing pathogenic variants from benign polymorphisms and may support disease monitoring and therapeutic evaluation.[18]

Tissue biopsy

Endomyocardial biopsy is not routinely required but may be considered in cases with diagnostic uncertainty. Histological examination demonstrates characteristic lysosomal inclusions within cardiomyocytes, often described as lamellar "zebra bodies" on electron microscopy.[4,6] Although biopsy provides definitive evidence of glycosphingolipid storage, its invasive nature limits its routine use, particularly given the availability of non-invasive diagnostic modalities.[4] A structured stepwise diagnostic strategy integrating clinical suspicion, enzymatic testing, genetic analysis, biomarkers, and multimodality imaging is summarized in Table 1.

Table 1 Diagnostic approach to suspected Fabry cardiomyopathy in patients with unexplained left ventricular hypertrophy

Step	Clinical scenario	Recommended test	Interpretation	Next step
1	Unexplained LVH (≥12 mm) without clear secondary cause	Clinical evaluation (family history, extracardiac signs)	Suspicion increases if neuropathy, angiokeratomas, renal dysfunction present	Proceed to enzyme testing
2	Male patient	α-galactosidase A activity	Reduced activity strongly suggests Fabry disease	Confirm with genetic testing
3	Female patient	GLA gene sequencing	Normal enzyme activity does not exclude disease	Genetic confirmation required
4	Borderline biochemical findings	Plasma lyso-Gb3	Elevated levels support pathogenic variant	Integrate with genotype
5	Cardiac involvement suspected	Echocardiography with strain imaging	Basal inferolateral strain reduction suggests early involvement	Perform CMR
6	Tissue characterization required	CMR with T1 mapping and LGE	Low native T1 supports lipid storage; LGE suggests fibrosis	Risk stratification
7	Variant of uncertain significance	Multidisciplinary evaluation	Combine imaging, biomarkers, family screening	Longitudinal follow-up ± biopsy

Abbreviations: CMR, cardiac magnetic resonance; GLA, galactosidase alpha gene; LGE, late gadolinium enhancement; LVH, left ventricular hypertrophy; lyso-Gb3, lyso-globotriaosylsphingosine

Imaging modalities

Multimodality imaging plays a central role in the diagnosis, phenotypic characterization, and longitudinal monitoring of Fabry cardiomyopathy. The combined use of echocardiography and CMR imaging allows comprehensive evaluation of cardiac structure, function, and myocardial tissue composition, thereby improving diagnostic accuracy in patients with suspected cardiac involvement.[4,6] Advanced imaging techniques also enable detection of early myocardial changes before the development of overt hypertrophy, facilitate assessment of disease progression over time, and contribute to risk stratification by identifying markers such as myocardial fibrosis and regional functional impairment that are associated with adverse clinical outcomes.[4,6]

Echocardiography

Echocardiography remains the first-line imaging modality in the evaluation of patients with suspected Fabry cardiomyopathy because of its wide availability, noninvasive nature, and ability to provide comprehensive structural and functional cardiac assessment. It enables detailed evaluation of left ventricular wall thickness, geometry, and distribution of hypertrophy, which is typically concentric but may occasionally present with asymmetric patterns that can resemble other hypertrophic phenotypes.[4,6] In addition to quantifying left ventricular mass and systolic function, echocardiography also allows assessment of atrial size, right ventricular involvement, and associated valvular abnormalities, all of which contribute to the overall characterization of cardiac disease burden.

Beyond conventional echocardiographic parameters, speckle-tracking echocardiography has emerged as a particularly sensitive technique for the detection of early myocardial dysfunction before the development of overt structural changes. Reduced global longitudinal strain, especially involving the basal inferolateral segments, has been consistently reported as a characteristic early feature of Fabry cardiomyopathy and may reflect regional myocardial involvement related to glycosphingolipid accumulation and early fibrosis.[2,27] This regional strain pattern may assist in differentiating Fabry cardiomyopathy from other causes of LVH and therefore has important diagnostic implications.

Diastolic dysfunction is another common echocardiographic finding and may be present even in early disease stages, reflecting impaired myocardial relaxation and increased ventricular stiffness. Additional findings such as increased left ventricular mass index, mild thickening of the mitral and aortic valves, and left atrial enlargement may also be observed and contribute to a more comprehensive assessment of cardiac involvement and disease progression in patients with Fabry disease.[4,6]

Cardiac magnetic resonance

CMR imaging represents the reference standard for myocardial tissue characterization in Fabry cardiomyopathy and provides detailed information on myocardial structure, composition, and disease distribution that cannot be obtained with conventional imaging modalities alone.[4,23] A hallmark feature of Fabry disease on CMR is reduced native T1 relaxation time, which reflects intracellular glycosphingolipid accumulation within cardiomyocytes. Importantly, low native T1 values may be detected in early disease stages, even before the development of overt LVH, making T1 mapping a valuable tool for early diagnosis and screening in patients with suspected cardiac involvement.[27,28]

With disease progression, replacement fibrosis becomes increasingly prominent and can be identified by late gadolinium enhancement (LGE) most commonly localized to the basal inferolateral wall. This characteristic distribution pattern represents one of the typical imaging signatures of Fabry cardiomyopathy and helps distinguish it from other hypertrophic phenotypes.[17,23] The extent of LGE has been shown to correlate with disease severity and is associated with adverse clinical outcomes, including ventricular arrhythmias, progressive systolic dysfunction, and heart failure progression.[19,23]

In addition to native T1 mapping, extracellular volume (ECV) quantification further improves the detection of myocardial involvement by allowing assessment of interstitial expansion and fibrosis. These advanced CMR techniques enhance diagnostic accuracy, support earlier recognition of cardiac disease, and facilitate differentiation of Fabry cardiomyopathy from other causes of LVH, particularly cardiac amyloidosis and hypertrophic cardiomyopathy, which demonstrate distinct tissue characterization patterns on CMR.[23,28]

Nuclear imaging

Nuclear imaging techniques, including myocardial perfusion imaging, may demonstrate microvascular dysfunction and perfusion abnormalities in Fabry disease. Reduced myocardial blood flow and impaired coronary flow reserve can be detected even in the absence of epicardial coronary artery disease, supporting the concept of early microvascular involvement.[22,29] However, nuclear imaging is generally considered complementary and is less frequently used compared to echocardiography and CMR. The evolution of multimodality imaging findings across different stages of Fabry cardiomyopathy is summarized in Table 2.

Table 2 Multimodality imaging findings across stages of Fabry cardiomyopathy

Disease stage	Echocardiography	CMR findings	Nuclear imaging	Clinical implication
Preclinical stage	Normal wall thickness	Low native T1	Reduced perfusion reserve	Early storage phase
Early cardiomyopathy	Mild LVH	Low native T1 without LGE	Microvascular dysfunction	Optimal treatment window
Intermediate stage	Concentric LVH + diastolic dysfunction	Low native T1 + focal LGE	Reduced myocardial blood flow	Fibrosis initiation
Advanced stage	LVH + systolic dysfunction	Extensive LGE	Severely impaired perfusion	High arrhythmic risk
End-stage disease	Dilated phenotype possible	Extensive fibrosis	Limited utility	HF and arrhythmia risk high

Abbreviations: CMR, cardiac magnetic resonance; HF, heart failure; LGE, late gadolinium enhancement; LVH, left ventricular hypertrophy.

Differential diagnosis

Fabry cardiomyopathy should be considered in the differential diagnosis of patients presenting with LVH, particularly when the clinical presentation is atypical or unexplained by common etiologies. Accurate differentiation is essential, as Fabry disease represents a potentially treatable condition.[4,6]

Hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is the most important differential diagnosis, as both conditions may present with increased left ventricular wall thickness and similar clinical features.[4,6] However, Fabry cardiomyopathy typically demonstrates concentric hypertrophy, whereas HCM more commonly exhibits asymmetric septal hypertrophy. Advanced imaging plays a key role in differentiation. In Fabry disease, low native T1 values reflect intracellular lipid accumulation, whereas HCM is typically associated with normal or elevated T1 values.[23,27] Additionally, the pattern of LGE differs, with Fabry disease showing characteristic involvement of the basal inferolateral wall.[17,23]

Cardiac amyloidosis

Cardiac amyloidosis represents another critical differential diagnosis, particularly in patients with increased ventricular wall thickness and diastolic dysfunction.[4,6] Unlike Fabry disease, amyloidosis is characterized by extracellular protein deposition, leading to increased myocardial T1 values and markedly elevated ECV.[23] Echocardiographic findings such as apical sparing on strain imaging are more typical of amyloidosis, whereas Fabry disease often demonstrates segmental strain abnormalities, particularly in the basal inferolateral region.[2,23]

Hypertensive heart disease

Hypertensive heart disease is a common cause of LVH and may mimic Fabry cardiomyopathy, especially in older patients.[4,6]

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Advanced cardiac imaging plays an important role in distinguishing Fabry disease from hypertensive remodeling. In particular, CMR-based tissue characterization techniques such as native T1 mapping demonstrate reduced T1 values in Fabry cardiomyopathy due to lipid storage, whereas hypertensive heart disease is typically associated with normal or increased T1 values reflecting interstitial fibrosis rather than intracellular storage. In addition, the absence of the characteristic basal inferolateral LGE pattern further supports differentiation from Fabry disease and contributes to a more accurate etiological assessment of unexplained LVH.[23]

Aortic stenosis

Aortic stenosis may also present with concentric LVH and should be carefully excluded through detailed clinical evaluation and comprehensive echocardiographic assessment.[4,6]. In patients with aortic stenosis, LVH develops as a compensatory response to chronic pressure overload caused by valvular obstruction and is typically accompanied by characteristic findings such as increased transvalvular gradients, reduced aortic valve area, and progressive valvular calcification. In contrast, Fabry cardiomyopathy results from intracellular glycosphingolipid accumulation rather than hemodynamic overload and therefore lacks primary valvular obstruction as the underlying mechanism of hypertrophy. Recognition of associated systemic manifestations, including renal involvement, neuropathic symptoms, or cerebrovascular disease, together with disease-specific imaging findings such as reduced native T1 values and characteristic patterns of myocardial fibrosis on CMR, may further support the diagnosis of Fabry disease over pressure overload-related hypertrophy due to valvular pathology.[4,6]

Athlete's heart

Physiological cardiac remodeling in athletes may lead to increased left ventricular wall thickness and can occasionally mimic pathological hypertrophy on routine imaging, particularly in individuals engaged in long-term endurance or high-intensity training.[4,6] However, athlete's heart is typically characterized by balanced chamber enlargement, preserved or enhanced diastolic function, normal myocardial tissue characteristics, and absence of replacement fibrosis. In contrast, Fabry cardiomyopathy is associated with progressive and non-physiological hypertrophy, impaired diastolic function, and characteristic myocardial tissue abnormalities such as reduced native T1 values and LGE on CMR, which can be detected by advanced imaging modalities and support differentiation from physiological remodeling.[2,23] Key distinguishing clinical and imaging features between Fabry cardiomyopathy and other major causes of LVH are summarized in Table 3.

Table 3 Differential diagnosis of Fabry cardiomyopathy compared with other causes of left ventricular hypertrophy

Feature	Fabry cardiomyopathy	Hypertrophic cardiomyopathy	Cardiac amyloidosis	Hypertensive heart disease
Pattern of LVH	Typically concentric	Often asymmetric septal	Concentric with wall thickening	Concentric
Native T1 (CMR)	Reduced	Normal or increased	Markedly increased	Normal or mildly increased
LGE distribution	Basal inferolateral wall	Patchy mid-wall	Diffuse subendocardial	Variable
Extracellular volume	Normal or mildly increased	Mildly increased	Markedly increased	Normal
GLS pattern	Basal inferolateral reduction	Regional variability	Apical sparing	Mild global reduction
Systemic involvement	Renal, neurologic, dermatologic	Rare	Multiorgan infiltration	Usually absent
Biomarkers	Lyso-Gb3 elevated	None specific	Elevated light chains or transthyretin	None specific
Genetic inheritance	X-linked	Autosomal dominant	Variable	Not inherited
Disease-specific therapy	Available	Limited	Available	No

Abbreviations: CMR, cardiac magnetic resonance; GLS, global longitudinal strain; LGE, late gadolinium enhancement; LVH, left ventricular hypertrophy

Disease-modifying therapies

Disease-modifying therapies have fundamentally changed the natural history of Fabry disease by targeting the underlying enzymatic defect and substrate accumulation. Early initiation of therapy is critical, particularly before the development of irreversible myocardial fibrosis.[4,8]

Enzyme replacement therapy (ERT)

ERT with recombinant α-galactosidase A, available as agalsidase alfa and agalsidase beta, represents the cornerstone of disease-specific treatment in Fabry disease.[1,5] ERT aims to restore enzymatic activity, reduce glycosphingolipid accumulation, and slow disease progression.[1,8]

Clinical studies have demonstrated that ERT can reduce left ventricular mass and improve or stabilize cardiac function, particularly when initiated in early disease stages before the development of significant fibrosis.[4,5] However, its efficacy is limited in advanced cardiomyopathy, where established fibrosis is largely irreversible.[4,19] The development of anti-drug antibodies may reduce treatment efficacy in some patients, particularly in males with classical disease, representing an important limitation of ERT.[5,11]

Chaperone therapy

Pharmacological chaperone therapy with migalastat represents an oral treatment option for patients with amenable GLA mutations. Migalastat stabilizes specific mutant forms of α-galactosidase A, facilitating proper folding and lysosomal trafficking.[11] Clinical data suggest that migalastat can reduce left ventricular mass, stabilize renal function, and improve cardiac parameters in selected patients.[11,30] Importantly, its efficacy is restricted to patients with amenable mutations, highlighting the importance of genetic characterization prior to therapy initiation.[11,16]

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Emerging therapies

Novel therapeutic strategies are under active investigation, aiming to overcome the limitations of current treatments. These include substrate reduction therapy, gene therapy, and mRNA-based approaches.[1,11] Gene therapy, in particular, has shown promising early results, with sustained increases in α-galactosidase A activity and reductions in substrate accumulation reported in preliminary studies.[31] These approaches have the potential to provide long-term or even curative treatment but require further validation regarding safety and durability.

Substrate reduction therapies aim to decrease glycosphingolipid synthesis, thereby reducing substrate burden, while mRNA-based therapies seek to enable endogenous production of functional enzyme.[1,31] Current disease-modifying and supportive treatment strategies in Fabry cardiomyopathy according to clinical presentation are summarized in Table 4.

Table 4 Disease-modifying and supportive treatment strategies in Fabry cardiomyopathy

Clinical scenario	Recommended therapy	Expected benefit	Limitations
Early cardiac involvement	Enzyme replacement therapy	Reduction in LV mass progression	Limited effect after fibrosis develops
Amenable GLA mutation	Migalastat	Stabilization of cardiac parameters	Mutation-dependent eligibility
Progressive fibrosis	Rhythm surveillance ± ICD consideration	Sudden cardiac death prevention	No fibrosis reversal
HFpEF phenotype	Diuretics, RAAS inhibitors	Symptom improvement	Limited disease-specific evidence
HFrEF phenotype	Guideline-directed therapy	Improved outcomes	Evidence extrapolated
Advanced disease	CRT, transplantation	Survival improvement	Patient selection critical
Family screening	Cascade genetic testing	Early diagnosis	Requires counseling infrastructure

Abbreviations: CRT, cardiac resynchronization therapy; GLA, galactosidase alpha gene; HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; ICD, implantable cardioverter-defibrillator; LV, left ventricle; RAAS, renin–angiotensin–aldosterone system.

Heart failure management

Heart failure is a major determinant of morbidity and mortality in Fabry disease, particularly in patients with advanced cardiomyopathy and myocardial fibrosis.[4,19] Management of heart failure in Fabry disease includes both disease-specific therapy and standard heart failure treatment, although specific considerations are required due to the unique pathophysiology of the disease.[4,6].

General principles

Optimal management requires a combination of enzyme replacement or chaperone therapy and conventional heart failure pharmacotherapy. Early initiation of disease-specific treatment is essential to prevent irreversible myocardial damage and to slow disease progression.[4,8] Standard heart failure therapies, including renin-angiotensin-aldosterone system (RAAS) inhibitors, beta-blockers, and diuretics, are commonly used to manage symptoms and improve hemodynamics.[6,32]

Heart failure with preserved ejection fraction

Fabry cardiomyopathy most frequently presents as HFpEF, primarily driven by progressive diastolic dysfunction, increased myocardial stiffness, and concentric left ventricular remodeling related to glycosphingolipid accumulation and interstitial fibrosis.[2,4] Impaired ventricular relaxation and reduced compliance contribute to elevated filling pressures and exercise intolerance, often representing early clinical manifestations of cardiac involvement. Management in this setting focuses mainly on symptom control, optimization of blood pressure, and careful volume regulation to reduce congestion and improve functional capacity.[6,32] Diuretics are commonly used for relief of volume overload, while RAAS inhibitors may help reduce afterload and support diastolic function, particularly in patients with coexisting hypertension.[6]. However, evidence supporting a disease-specific benefit of conventional heart failure therapies in Fabry cardiomyopathy remains limited, and treatment is generally combined with disease-targeted therapies to slow progression of myocardial involvement.[4,32]

Heart failure with reduced ejection fraction (HFrEF)

In advanced stages, Fabry disease may progress to HFrEF, particularly in patients with extensive myocardial fibrosis and long-standing myocardial involvement.[19,23] Progressive replacement fibrosis contributes to impaired systolic function, ventricular remodeling, and worsening clinical status, representing a late manifestation of Fabry cardiomyopathy. In such cases, guideline-directed medical therapy should be implemented, including angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, beta-blockers, and mineralocorticoid receptor antagonists to improve symptoms and reduce the risk of adverse cardiovascular events.[32] Although these treatment strategies are largely extrapolated from evidence obtained in general heart failure populations rather than Fabry-specific randomized trials, they are considered appropriate and recommended in patients with Fabry disease who develop systolic dysfunction. Careful clinical follow-up is required, as these therapies are typically used alongside disease-specific treatments and supportive management strategies in order to optimize overall cardiac outcomes.[6,32]

Advanced heart failure therapies

In patients with advanced Fabry cardiomyopathy and persistent symptoms despite optimal medical therapy, advanced heart failure treatment strategies may be considered. These include device-based therapies such as cardiac resynchronization therapy (CRT) in appropriately selected patients with ventricular dyssynchrony, as well as mechanical circulatory support in cases of severe refractory heart failure.[4,6] Such interventions may help improve functional status and stabilize hemodynamics in selected individuals with progressive systolic dysfunction.

In carefully selected patients with end-stage cardiac involvement and limited extracardiac disease burden, heart transplantation represents a potential therapeutic option. Favorable outcomes after transplantation have been reported in patients with Fabry disease, particularly when systemic manifestations such as severe renal or cerebrovascular involvement are absent or well controlled. In this context, heart transplantation may provide meaningful symptomatic improvement and survival benefit in advanced stages of the disease.[4,6,33]

Special considerations

Certain therapeutic considerations are specific to patients with Fabry disease and should be taken into account during clinical management. Excessive use of negative chronotropic agents, particularly beta-blockers and some calcium channel blockers, may exacerbate underlying conduction system abnormalities, which are relatively common in this population due to progressive involvement of the atrioventricular node and His-Purkinje system.[6] Therefore, careful dose adjustment and close rhythm monitoring are often required, especially in patients with pre-existing conduction delay or bradyarrhythmias.

In addition, the presence of established myocardial fibrosis represents an important determinant of treatment response and clinical prognosis. Replacement fibrosis is generally associated with irreversible myocardial injury and may limit the potential for functional recovery despite optimal medical and disease-specific therapy. This observation highlights the importance of early recognition of cardiac involvement and timely initiation of targeted treatment strategies before the development of advanced structural myocardial damage.[19,23]

Arrhythmia and device therapy

Arrhythmias represent a major source of morbidity in Fabry disease and include a broad spectrum of electrical disturbances such as conduction abnormalities, atrial fibrillation, and ventricular tachyarrhythmias.[4,6] Conduction system involvement may manifest as sinus node dysfunction, atrioventricular conduction delay, or bundle branch block, whereas atrial fibrillation is frequently associated with left atrial enlargement and diastolic dysfunction. Ventricular arrhythmias, particularly in advanced stages of the disease, are often related to the presence of myocardial fibrosis and structural remodeling.

The pathogenesis of these rhythm disturbances is multifactorial and involves intracellular glycosphingolipid accumulation, progressive myocardial hypertrophy, microvascular dysfunction, and replacement fibrosis affecting both the working myocardium and the specialized conduction system.[19,23,25] Together, these structural and electrophysiological changes create a substrate for arrhythmogenesis and contribute to an increased risk of adverse cardiovascular outcomes, including symptomatic bradyarrhythmias and malignant ventricular arrhythmias.

Bradyarrhythmias and pacemaker therapy

Involvement of the atrioventricular node and the His-Purkinje system in Fabry disease frequently leads to progressive conduction abnormalities, including PR interval prolongation, bundle branch block, and, in more advanced stages, high-grade atrioventricular block.[6,25] These conduction disturbances reflect progressive glycosphingolipid accumulation and replacement fibrosis within the specialized conduction tissue and may evolve over time, sometimes requiring repeated reassessment during follow-up.

Pacemaker implantation should follow established guideline-based indications in patients with symptomatic bradycardia or advanced conduction disease. However, close rhythm surveillance is particularly important in Fabry patients because conduction abnormalities may progress even after initial device implantation, and additional pacing dependency may develop over time. Regular clinical and electrocardiographic monitoring therefore plays an important role in the timely identification and management of evolving conduction system involvement in this population.[4,6,19]

Atrial arrhythmias

Atrial fibrillation is the most common sustained arrhythmia in Fabry disease and is closely associated with atrial remodeling, increased ventricular stiffness, and progressive myocardial fibrosis.[6,23,25] Structural changes such as left atrial enlargement and impaired diastolic function contribute to the development and maintenance of atrial fibrillation, particularly as cardiac involvement advances over time. The prevalence of atrial fibrillation increases with disease progression and is associated with worsening heart failure symptoms, reduced exercise capacity, and an elevated risk of thromboembolic complications, including stroke.[6,34] Early recognition through regular rhythm monitoring and timely initiation of appropriate anticoagulation therapy are therefore essential components of management, even in patients with relatively mild symptoms, given the progressive nature of cardiac involvement in Fabry disease.

Ventricular arrhythmias and ICD therapy

Ventricular arrhythmias are strongly associated with advanced Fabry cardiomyopathy and represent an important cause of sudden cardiac death, particularly in patients with significant LVH and myocardial fibrosis.[19,23,34] These arrhythmias are typically observed in later disease stages and reflect the progression of structural myocardial remodeling and electrical instability. The presence and extent of myocardial fibrosis, especially when identified by CMR with late gadolinium enhancement, constitute a major substrate for ventricular arrhythmogenesis and have been consistently associated with adverse clinical outcomes, including sustained ventricular tachyarrhythmias and progressive heart failure.[19,23]

In addition, increasing fibrosis burden may serve as a marker of disease severity and help guide risk stratification in clinical practice. ICD therapy is clearly indicated for secondary prevention in patients with prior sustained ventricular arrhythmias or resuscitated cardiac arrest. However, decisions regarding primary prevention remain challenging due to the absence of validated Fabry disease-specific risk prediction models, and therefore require individualized assessment based on clinical features, imaging findings, and overall disease severity.[4,34].

Risk stratification

Risk stratification in Fabry disease requires a comprehensive multiparametric approach that integrates structural, functional, and clinical variables. Important predictors of adverse cardiovascular outcomes include the extent of myocardial fibrosis, particularly when detected by LGE on CMR imaging, the severity of LVH, a history of ventricular arrhythmias, and episodes of unexplained syncope.[19,23,34] Additional factors such as progressive conduction abnormalities, reduced left ventricular systolic function, and increasing arrhythmic burden on ambulatory monitoring may further support identification of patients at higher risk.

Conventional risk stratification algorithms developed for other cardiomyopathies, such as hypertrophic cardiomyopathy, may not be fully applicable to Fabry disease because of differences in underlying pathophysiology and patterns of myocardial involvement. This limitation highlights the importance of individualized clinical assessment and disease-specific judgment when evaluating arrhythmic risk and determining the need for preventive strategies, including device therapy.[4,34]

Practical considerations

Management decisions regarding device therapy in Fabry cardiomyopathy should be individualized and are preferably made in

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specialized centers with experience in the evaluation and treatment of inherited cardiomyopathies and lysosomal storage disorders.[4,6] Such centers can integrate clinical findings, multimodality imaging results, and arrhythmic risk markers to support more accurate patient selection for device-based interventions.

Pacemaker implantation is frequently required in patients with progressive conduction system involvement, particularly those with symptomatic bradycardia or advanced atrioventricular block. In contrast, ICD therapy is generally reserved for patients with documented ventricular arrhythmias or those considered to have a high-risk arrhythmogenic substrate based on imaging and clinical features.[4,6,35] Ongoing rhythm surveillance with periodic electrocardiographic monitoring and ambulatory rhythm assessment remains essential, as arrhythmic risk may evolve over time even in patients with preserved systolic function or initially limited structural cardiac involvement.[23,35]

Prognosis and disease progression

Fabry disease is a progressive multisystem disorder in which cardiac involvement represents a major determinant of long-term prognosis and overall disease burden.[4,6] The natural history of Fabry cardiomyopathy is characterized by a gradual transition from early intracellular glycosphingolipid accumulation within cardiomyocytes to the development of LVH, progressive interstitial and replacement fibrosis, and ultimately clinically overt heart failure and arrhythmias.[17,23] These structural and functional myocardial changes typically evolve over time and are closely associated with worsening symptoms, increasing arrhythmic risk, and adverse cardiovascular outcomes, underscoring the importance of early recognition and longitudinal cardiac monitoring in affected patients.

Natural history

The progression of Fabry cardiomyopathy follows a well-recognized continuum that reflects the gradual transition from metabolic storage disease to structural myocardial remodeling. Early disease stages are characterized by intracellular glycosphingolipid accumulation and subtle functional abnormalities that may occur in the absence of overt structural changes on conventional imaging, often detectable only with advanced techniques such as strain imaging or native T1 mapping.[17,23] With ongoing disease progression, LVH becomes evident, followed by the development of replacement fibrosis, which represents a key marker of advanced myocardial involvement.

Clinical deterioration is largely driven by the extent of myocardial fibrosis, which marks a transition toward irreversible myocardial injury and is associated with declining cardiac function, worsening diastolic and eventually systolic performance, and an increased risk of clinically significant arrhythmias. The presence and progression of fibrosis therefore play a central role in determining long-term prognosis and guiding therapeutic decision-making in patients with Fabry cardiomyopathy.[19,23]

Impact of early therapy

Early initiation of disease-specific therapy has a significant impact on the progression of Fabry cardiomyopathy and overall cardiovascular outcomes. ERT and pharmacological chaperone therapy are most effective when introduced before the development of advanced myocardial fibrosis, a stage at which structural myocardial damage becomes largely irreversible.[4,5] Early treatment targets intracellular glycosphingolipid accumulation and may help preserve myocardial structure and function over time.

Patients treated during earlier disease stages may demonstrate stabilization or even partial regression of left ventricular mass, improvement in myocardial function, and delayed progression of cardiac involvement. In contrast, therapy initiated after the establishment of extensive replacement fibrosis generally has limited impact on reversing structural myocardial injury, although it may still contribute to slowing further disease progression and reducing extracardiac complications.[4,19]

Predictors of adverse outcomes

Several clinical and imaging parameters have been identified as predictors of adverse outcomes in Fabry cardiomyopathy and play an important role in risk stratification during follow-up. Among these, the presence and extent of myocardial fibrosis, particularly when detected by CMR imaging, increased left ventricular wall thickness, and the occurrence of ventricular arrhythmias represent the most important prognostic markers and are consistently associated with a higher risk of heart failure progression and sudden cardiac death.[19,34] These structural and electrical abnormalities reflect advanced myocardial involvement and often indicate a transition toward a more severe disease phenotype.

Additional clinical factors such as older age, male sex, and delayed diagnosis have also been associated with worse cardiovascular outcomes, likely reflecting longer disease exposure and more advanced myocardial remodeling at the time of treatment initiation.[6,34] Circulating biomarkers, including lyso-Gb3, may further contribute to risk stratification by reflecting disease activity and storage burden; however, their independent prognostic value in predicting cardiac outcomes remains less clearly defined and continues to be investigated.[18,23]

Sex-specific prognosis

Although Fabry disease has historically been considered more severe in males because of its X-linked inheritance pattern, female patients are increasingly recognized as being at risk for clinically significant cardiac involvement and adverse cardiovascular outcomes.[12,4] Heterozygous females may develop LVH, myocardial fibrosis, and arrhythmias, sometimes even in the absence of prominent extracardiac manifestations, which can contribute to underrecognition and delayed diagnosis.

Due to random X-chromosome inactivation, disease expression in females is more heterogeneous and may range from asymptomatic carriers to individuals with advanced cardiomyopathy. Nevertheless, clinically relevant myocardial involvement and replacement fibrosis may develop over time, particularly with advancing age, underscoring the importance of regular cardiac surveillance and timely initiation of appropriate disease-specific therapy when cardiac manifestations become evident.[12,23]

Role of myocardial fibrosis

Myocardial fibrosis represents one of the most important determinants of prognosis in Fabry cardiomyopathy and serves as a key marker of advanced myocardial involvement. The presence of LGE on CMR imaging has been strongly associated with an increased risk of ventricular arrhythmias, progressive heart failure, and higher mortality, reflecting the transition from reversible metabolic storage to irreversible structural myocardial injury.[19,23] The extent and distribution of fibrosis may also provide incremental value in risk stratification and clinical decision-making during follow-up.

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In addition to its prognostic significance, myocardial fibrosis is associated with reduced responsiveness to disease-specific therapies such as ERT and chaperone therapy. Once replacement fibrosis has developed, the potential for reversal of myocardial dysfunction becomes limited, reinforcing the importance of early diagnosis and timely therapeutic intervention before irreversible myocardial damage occurs.[4,19]

Screening strategies

Early identification of Fabry disease is essential, as timely initiation of disease-specific therapy can significantly influence the course of cardiac involvement, particularly when treatment is started before the development of irreversible myocardial fibrosis.[4,8] Recognition of early cardiac manifestations and targeted evaluation of patients with unexplained LVH are therefore critical steps in improving diagnostic yield and preventing delays in therapy.

Screening strategies play an important role not only in individual patient management but also in broader public health approaches aimed at detecting affected individuals earlier in the disease course. Targeted screening of high-risk populations, including patients with unexplained LVH, cryptogenic stroke, chronic kidney disease of unknown origin, or conduction system abnormalities, may facilitate earlier diagnosis and allow timely initiation of disease-specific treatment before the onset of advanced organ involvement.

Family screening

Family screening (cascade screening) represents a cornerstone of Fabry disease diagnosis because of its X-linked inheritance pattern and the high likelihood of identifying additional affected relatives once an index case is detected. Systematic genetic testing of at-risk family members enables early recognition of affected individuals, including those who are asymptomatic or have only subtle clinical manifestations at the time of evaluation.[8,16] This strategy facilitates earlier confirmation of diagnosis and supports timely initiation of structured clinical surveillance.

Cascade screening is particularly valuable for identifying female heterozygotes and individuals with late-onset variants, in whom disease expression may be variable and diagnosis is often delayed until significant organ involvement develops. Early detection through family-based screening allows implementation of regular cardiac, renal, and neurological monitoring and supports appropriate timing of disease-specific therapy when clinical or imaging evidence of organ involvement becomes apparent.[12,16]

Screening in LVH cohorts

Screening for Fabry disease in patients with unexplained LVH has emerged as an effective strategy in cardiology practice. Several studies have demonstrated that Fabry disease is present in approximately 0.5-1% of patients with hypertrophic cardiomyopathy-like phenotypes.[4,6] Targeted screening in this population is particularly important because Fabry disease represents a treatable cause of LVH, and diagnosis may significantly alter management and prognosis.[4,6,8] Screening approaches typically include measurement of α-galactosidase A activity, followed by confirmatory genetic testing.[8,9]

Newborn screening programs

Newborn screening programs have substantially improved the detection of Fabry disease, particularly late-onset variants that may not be clinically apparent in early life. These programs utilize enzyme assays in dried blood spots, often combined with genetic testing. Newborn screening has revealed a higher-than-expected prevalence of Fabry disease, especially for cardiac variants, highlighting the extent of underdiagnosis in the general population.[9,10] However, the identification of VUS and late-onset phenotypes raises challenges in clinical interpretation and long-term management.[10,16]

Cost-effectiveness and challenges

Despite the benefits of screening, several challenges remain. These include the cost-effectiveness of widespread screening programs, ethical considerations related to the identification of asymptomatic individuals, and uncertainty regarding the optimal timing of treatment initiation.[8,10] Additionally, variability in disease expression, particularly among females and late-onset cases, complicates decision-making and requires individualized clinical assessment.[12,16] Therefore, screening strategies should be integrated into a multidisciplinary framework that includes genetic counseling and long-term follow-up.[4,8]

Special clinical scenarios

Fabry cardiomyopathy may present in several special clinical contexts that complicate diagnosis, therapeutic decision-making, and prognostic assessment. These scenarios include female heterozygotes, late-onset cardiac variants, patients after renal transplantation, individuals with advanced myocardial fibrosis, and those presenting with HFpEF.[4,6] In such settings, clinical expression may be heterogeneous and sometimes dominated by cardiac manifestations, which can delay recognition of the underlying storage disorder.

These complex presentations require careful integration of clinical findings, multimodality imaging, genetic testing, and longitudinal follow-up to establish an accurate diagnosis and guide management. Awareness of these special clinical situations is important because they may influence the timing of disease-specific therapy, interpretation of imaging findings, and overall risk stratification in patients with Fabry cardiomyopathy.[4,6]

Female heterozygotes

Female patients with Fabry disease exhibit marked phenotypic variability due to random X-chromosome inactivation, and they should not be regarded as merely asymptomatic carriers.[12,4] Although disease onset is often later and progression may be more heterogeneous than in males, clinically significant cardiac involvement, including LVH and myocardial fibrosis, is well documented in women.[12,23] This variability has important diagnostic implications because enzyme activity may be normal in heterozygous females, making genetic testing essential in suspected cases.[8,12] Careful longitudinal follow-up is also required, as cardiac manifestations may emerge progressively with age.[4,6]

Late-onset cardiac variant

Late-onset Fabry disease may present predominantly as isolated cardiomyopathy, often without the classical extracardiac manifestations seen in early-onset disease.[10,15] In such patients, unexplained LVH, conduction abnormalities, or myocardial fibrosis may be the first and only major clinical clues.[4,6] This phenotype is particularly important in cardiology practice because it may closely mimic hypertrophic cardiomyopathy, hypertensive heart disease, or cardiac amyloidosis, contributing to delayed diagnosis.[4,23] Recognition of this scenario is critical, as targeted therapy may still modify disease course when initiated before advanced fibrosis develops.[4,11]

Renal transplantation recipients

Cardiac disease may continue to progress in Fabry patients after renal transplantation because transplantation corrects renal failure but does not eliminate the underlying enzymatic defect in extra-renal tissues.[3,8] As a result, Fabry cardiomyopathy remains a major determinant of long-term outcomes in this subgroup.

These patients require continued cardiovascular surveillance and ongoing consideration of disease-specific therapy, since cardiac hypertrophy, fibrosis, and arrhythmias may still evolve despite successful renal replacement.[4,6] Management should therefore remain multidisciplinary and not be limited to renal follow-up alone.[8]

Advanced fibrosis stage

Patients with extensive myocardial fibrosis represent a particularly challenging subgroup. Once replacement fibrosis is established, the likelihood of reversing cardiac damage with enzyme replacement or chaperone therapy becomes limited.[4,19] In this setting, treatment goals often shift from prevention of structural progression to mitigation of symptoms, arrhythmia surveillance, and heart failure management.[19,23] The burden of fibrosis also carries important prognostic implications, as it is closely linked to ventricular arrhythmias and adverse cardiovascular outcomes.[19,34]

Fabry disease with preserved ejection fraction

A substantial proportion of Fabry patients develop heart failure symptoms despite preserved left ventricular ejection fraction, reflecting the dominant role of diastolic dysfunction and myocardial stiffening in the disease.[2,4] This phenotype may be particularly challenging because conventional systolic indices can remain normal despite significant symptomatic burden. In such cases, advanced imaging and careful clinical assessment are essential to identify underlying myocardial involvement, fibrosis, and evolving disease progression.[17,23] Management should combine disease-specific therapy with symptom-directed heart failure treatment and rhythm surveillance when appropriate.[4,6]

International guidelines and consensus

The management of Fabry disease has become increasingly standardized through international guidelines and expert consensus documents that provide structured recommendations regarding diagnosis, initiation of disease-specific therapy, and long-term clinical monitoring.[4,6] These documents highlight the importance of early recognition of organ involvement, particularly cardiac manifestations, and support the use of multimodality imaging and genetic testing as key components of the diagnostic process.

In addition, current recommendations emphasize the role of multidisciplinary care involving cardiology, nephrology, neurology, and medical genetics specialists to ensure comprehensive evaluation and follow-up. Individualized treatment strategies based on disease stage, organ involvement, sex-specific differences, and genotype-phenotype relationships are strongly encouraged in order to optimize long-term clinical outcomes and improve quality of life in patients with Fabry disease.

Diagnostic recommendations

Current consensus recommendations highlight the importance of a structured diagnostic approach that integrates clinical suspicion with targeted laboratory and imaging evaluation. This approach typically combines assessment of characteristic clinical features with enzymatic testing, genetic analysis, and biomarker evaluation to ensure accurate and timely diagnosis of Fabry disease.[4,8] Such a strategy is particularly important in patients presenting with unexplained LVH or multisystem involvement suggestive of a storage disorder.

In male patients, reduced α-galactosidase A activity is usually sufficient to establish the diagnosis because of the X-linked inheritance pattern and the typically marked reduction in enzyme activity. In contrast, enzyme activity levels in females may be normal or only mildly reduced due to random X-chromosome inactivation, making genetic testing essential for diagnostic confirmation in this group.[12,8]

Imaging plays an important complementary role in evaluating cardiac involvement and supporting risk stratification. In particular, CMR imaging with native T1 mapping and LGE provides detailed myocardial tissue characterization, enabling detection of early glycosphingolipid accumulation and replacement fibrosis, which are key markers of disease stage and prognosis in Fabry cardiomyopathy.[23,27]

Treatment initiation criteria

Guidelines recommend initiating disease-specific therapy in patients with confirmed Fabry disease who demonstrate evidence of organ involvement, including cardiac, renal, or neurological manifestations, as these findings indicate clinically relevant disease activity and risk of progression.[4,8] Early identification of such involvement allows timely initiation of therapy aimed at slowing glycosphingolipid accumulation and limiting irreversible tissue injury.

In the context of Fabry cardiomyopathy, treatment is generally indicated in patients with LVH, myocardial fibrosis detected by CMR imaging, or progressive functional impairment identified through imaging or clinical evaluation.[4,6] Additional findings such as worsening diastolic dysfunction or emerging arrhythmias may further support the decision to initiate therapy in selected patients. Importantly, initiation of treatment before the development of advanced replacement fibrosis is associated with more favorable structural and functional cardiac outcomes and represents a central principle of contemporary management strategies in Fabry disease.[4,19]

Monitoring and follow-up

Regular follow-up is essential for evaluating disease progression and monitoring response to therapy in patients with Fabry disease, particularly those with cardiac involvement. Consensus documents recommend periodic reassessment using a combination of clinical evaluation, laboratory biomarkers, and multimodality imaging to detect early changes in organ involvement and guide treatment decisions over time.[4,6]

Cardiac monitoring should include serial echocardiographic examinations to assess ventricular structure and function, CMR imaging for detailed myocardial tissue characterization and fibrosis assessment, and rhythm surveillance with electrocardiography or ambulatory monitoring, especially in patients with established myocardial fibrosis or documented arrhythmias.[23,25] These assessments allow timely identification of disease progression and emerging complications that may require modification of therapeutic strategies. The frequency and extent of follow-up should be individualized according to disease severity, sex-specific disease expression, genotype, and treatment status, with closer surveillance recommended in patients with advanced cardiac involvement or progressive clinical findings.[4,8]

Multidisciplinary management

Fabry disease requires a multidisciplinary approach involving cardiologists, nephrologists, geneticists, and neurologists, reflecting the complex multisystem nature of the disorder and the variability of organ involvement among affected individuals.[4,6] Coordinated collaboration between these specialties is essential for comprehensive evaluation, appropriate timing of disease-specific therapy, and long-term monitoring of cardiac, renal, and neurological manifestations.

This integrated strategy facilitates early recognition of progressive organ involvement and supports individualized management decisions across different stages of the disease. In addition, genetic counseling represents a key component of care, particularly in the context of cascade screening, risk assessment among family members, and reproductive planning, helping to identify affected relatives at earlier stages and guide appropriate clinical follow-up.[8,16]

Controversies and knowledge gaps

Despite significant advances in the understanding and management of Fabry disease, several important controversies and knowledge gaps remain. These unresolved issues have direct implications for diagnosis, treatment decisions, and long-term patient outcomes, particularly in patients with heterogeneous clinical presentations or late-onset variants. Uncertainty persists regarding the optimal timing of disease-specific therapy in asymptomatic individuals, the selection of patients most likely to benefit from early intervention, and the interpretation of imaging and biomarker findings in borderline or early-stage disease.

In addition, challenges remain in arrhythmic risk stratification and in identifying patients who may benefit from primary prevention device therapy, as disease-specific predictive models are still lacking. Questions also continue regarding the long-term comparative effectiveness of available therapeutic options, especially in patients with established myocardial fibrosis or advanced cardiac involvement. Addressing these gaps through prospective studies and disease-specific registries remains essential to further refine management strategies and improve outcomes in Fabry cardiomyopathy.

Optimal timing of therapy

One of the major controversies in Fabry disease is the optimal timing of disease-specific therapy initiation. While early treatment is generally recommended to prevent irreversible organ damage, the precise threshold for initiating therapy, particularly in asymptomatic patients or those with minimal organ involvement, remains unclear.[4,8] This issue is especially relevant in individuals identified through family or newborn screening, where clinical manifestations may be absent or subtle. Balancing early intervention against the risk of overtreatment continues to be a challenge in clinical practice.[10,16]

Management of VUS

The increasing use of genetic testing in Fabry disease has led to the identification of numerous VUS, which may complicate both diagnostic interpretation and clinical decision-making.[16,18] In some cases, these variants are detected in patients undergoing screening for unexplained LVH or other suggestive clinical features, creating uncertainty regarding their true pathogenic relevance and the need for disease-specific therapy.

Distinguishing pathogenic mutations from benign polymorphisms requires careful integration of clinical presentation, α-galactosidase A activity, biomarker levels such as lyso-Gb3, family segregation analysis, and, when available, functional or in vitro studies assessing variant effects on enzyme activity.[16,26] Evaluation within specialized centers and reference laboratories may further improve the accuracy of variant classification in complex cases.

However, standardized approaches for interpreting VUS are still evolving, and uncertainty in classification may lead to delays in diagnosis, difficulties in treatment initiation decisions, and challenges in family screening strategies. These limitations highlight the importance of continued refinement of variant interpretation frameworks and the integration of genetic findings with clinical and imaging data in the management of Fabry disease.

Limited reversibility of advanced disease

Although disease-specific therapies such as ERT and pharmacological chaperone therapy can slow disease progression and reduce glycosphingolipid accumulation, their ability to reverse established organ damage, particularly replacement myocardial fibrosis, remains limited.[4,19] This limitation reflects the transition from potentially reversible intracellular storage to irreversible structural remodeling, which significantly influences long-term cardiac outcomes in patients with Fabry cardiomyopathy.

These observations raise important questions regarding the effectiveness of currently available therapies in advanced disease stages and underscore the importance of initiating treatment before the development of extensive fibrosis. They also highlight the need for improved therapeutic strategies specifically targeting myocardial fibrosis and irreversible tissue injury, including emerging gene-based therapies and novel antifibrotic approaches that may further modify disease progression in the future.[19,23]

Heterogeneity of clinical expression

Fabry disease demonstrates substantial phenotypic variability, even among individuals carrying the same GLA mutation, reflecting the complex interaction between genetic and non-genetic determinants of disease expression.[15,16] Clinical presentation may range from early-onset multisystem involvement to predominantly cardiac phenotypes appearing later in life, which can complicate recognition of the disease and delay diagnosis in selected patient groups.

This heterogeneity creates important challenges in prognostic assessment and therapeutic decision-making, particularly in female patients and individuals with late-onset variants, in whom disease severity and rate of progression are often less predictable.[12,15] Variability in cardiac involvement, including the timing and extent of LVH and myocardial fibrosis, further contributes to uncertainty in clinical management. The role of modifier genes, environmental influences, and epigenetic mechanisms in shaping disease expression remains incompletely understood, and further research is needed to clarify their contribution to individual disease trajectories and treatment response.

Arrhythmic risk stratification

Risk stratification for sudden cardiac death remains insufficiently defined in Fabry disease despite increasing recognition of arrhythmic complications in advanced stages of cardiomyopathy. Although myocardial fibrosis detected by CMR imaging, the degree of LVH, and a history of ventricular arrhythmias are established risk markers, no validated Fabry disease-specific risk prediction models are currently available to guide clinical decision-making with confidence.[19,34] Additional factors such as declining left ventricular systolic function, conduction abnormalities, and unexplained syncope may further contribute to risk assessment but remain insufficiently standardized across clinical practice.

As a result, decisions regarding ICD therapy for primary prevention are frequently based on extrapolation from other cardiomyopathies together with individualized clinical judgment rather than disease-specific evidence. This limitation underscores the need for prospective studies and registry-based data to improve arrhythmic risk prediction and support more consistent selection of patients who may benefit from preventive device therapy.[4,34].

Biomarker limitations

While lyso-Gb3 is a valuable biomarker reflecting glycosphingolipid storage burden and overall disease activity in Fabry disease, its prognostic utility, particularly in female patients and those with late-onset variants, remains limited.[18] In these subgroups, lyso-Gb3 levels may be normal or only mildly elevated despite clinically relevant cardiac involvement, which restricts its usefulness as a standalone marker for risk stratification and therapeutic decision-making.

At present, there is no universally accepted biomarker that reliably reflects cardiac disease activity, predicts long-term cardiovascular outcomes, and guides treatment strategies across all Fabry disease subgroups. As a result, biomarker interpretation must be integrated with clinical findings and multimodality imaging parameters, especially cardiac magnetic resonance-based markers of myocardial involvement. Further research is needed to identify more sensitive and disease-specific biomarkers capable of improving early detection and prognostic assessment in Fabry cardiomyopathy.

Future perspectives

The evolving landscape of Fabry disease research continues to reshape diagnostic and therapeutic strategies, with ongoing advances improving both early recognition and long-term disease management. Developments in molecular genetics and biomarker research are enhancing understanding of genotype-phenotype relationships and may support more accurate risk stratification and individualized treatment planning in the future. At the same time, progress in multimodality cardiac imaging, particularly techniques enabling early detection of myocardial involvement and fibrosis, is contributing to earlier diagnosis and more precise monitoring of disease progression.

In parallel, emerging therapeutic approaches, including gene-based treatments and novel targeted strategies, are expected to expand the available treatment options beyond current enzyme replacement and chaperone therapies. These advances have the potential to address important unmet needs, particularly in patients with advanced disease or limited response to existing therapies, and may further improve long-term cardiovascular outcomes in Fabry cardiomyopathy.

Precision medicine and genotype-based therapy

Future management of Fabry disease is likely to become increasingly individualized, with therapeutic decisions guided by genotype, biomarker profiles, and the extent of organ involvement at the time of diagnosis.[16,18] Integration of genetic findings with clinical presentation and multimodality imaging results is expected to support more precise identification of patients who are most likely to benefit from early disease-specific therapy and closer longitudinal monitoring.

Improved classification of GLA variants and a better understanding of genotype-phenotype correlations may further enhance risk stratification and treatment selection, particularly in patients with VUS. Refinement of variant interpretation frameworks, together with expanding data from registries and functional studies, is expected to reduce diagnostic uncertainty and facilitate more consistent clinical decision-making in complex cases.[16,26].

Advances in imaging

Innovations in cardiac imaging, particularly quantitative CMR techniques such as native T1 mapping and ECV assessment, are expected to further enhance the early detection of myocardial involvement in Fabry disease and enable more accurate monitoring of disease progression over time.[23,27] These techniques allow identification of intracellular glycosphingolipid accumulation and interstitial expansion before the development of overt structural remodeling, thereby supporting earlier recognition of cardiac involvement and more timely initiation of disease-specific therapy.

In addition to their diagnostic value, advanced tissue characterization methods may improve differentiation of Fabry cardiomyopathy from other causes of LVH, including hypertrophic cardiomyopathy and cardiac amyloidosis, which demonstrate distinct myocardial signal patterns on CMR imaging. Quantitative imaging parameters may also provide incremental prognostic information by helping to identify patients at higher risk for fibrosis progression, arrhythmias, and functional deterioration during longitudinal follow-up.

Novel therapeutic strategies

Emerging therapies, including gene therapy, substrate reduction therapy, and mRNA-based approaches, have the potential to substantially modify the treatment paradigm of Fabry disease by addressing key limitations of currently available disease-specific therapies.[1,11,31] Unlike enzyme replacement and chaperone therapies, which require lifelong administration and may have variable effects on established organ involvement, these novel strategies aim to provide more sustained correction of the underlying enzymatic defect.

Gene therapy approaches are designed to restore endogenous α-galactosidase A production through long-term expression of functional GLA sequences, whereas substrate reduction therapies target upstream pathways to decrease glycosphingolipid accumulation. Similarly, mRNA-based therapies aim to enable transient but repeated endogenous enzyme synthesis without permanent genomic modification. If demonstrated to be safe and effective in long-term clinical studies, these strategies may offer more durable disease control and, potentially, disease-modifying or curative treatment options for selected patients with Fabry disease.

Targeting fibrosis and inflammation

Given the central role of myocardial fibrosis in disease progression and prognosis, future research is increasingly focused on antifibrotic and anti-inflammatory therapeutic strategies aimed at modifying downstream pathways involved in myocardial remodeling.[19,23] These approaches are particularly relevant in patients with established cardiac involvement, in whom replacement fibrosis represents a key determinant of functional decline and arrhythmic risk. Targeting mechanisms such as chronic inflammation, microvascular dysfunction, and extracellular matrix expansion may complement existing disease-specific therapies that primarily address glycosphingolipid accumulation. Integration of antifibrotic strategies with enzyme replacement, chaperone therapy, or emerging gene-based treatments may help improve clinical outcomes in patients with advanced Fabry cardiomyopathy, especially in stages where structural myocardial injury has already developed.[19,23].

Improved risk stratification

Development of Fabry disease-specific risk models that integrate clinical findings, multimodality imaging parameters, genetic information, and circulating biomarkers represents an important future direction in the management of Fabry cardiomyopathy.[19,34] Such integrated approaches may allow more accurate identification of patients at increased risk for disease progression and cardiovascular complications across different stages of cardiac involvement.

In particular, the incorporation of markers such as myocardial fibrosis detected by CMR imaging, severity of LVH, arrhythmic burden, genotype characteristics, and biomarker profiles may improve prediction of adverse outcomes, including sudden cardiac death. The availability of validated disease-specific risk models could support more consistent decision-making regarding ICD therapy, follow-up intensity, and timing of therapeutic interventions, thereby contributing to more individualized long-term management strategies in patients with Fabry disease.[19,34]

Emerging biomarkers: potential role of sirtuin 1

Sirtuin 1 (SIRT1), a NAD^+-dependent deacetylase involved in the regulation of cellular metabolism, oxidative stress responses, mitochondrial function, and lysosomal activity, has emerged as a potential biomarker and therapeutic target in cardiovascular disease.[36] Experimental studies suggest that reduced SIRT1 activity may contribute to myocardial remodeling through activation of profibrotic signaling pathways, impaired autophagy, and increased oxidative stress, mechanisms that are also relevant to the pathophysiology of lysosomal storage disorders such as Fabry disease.[37] In addition, SIRT1 has been implicated in the regulation of inflammatory responses and endothelial dysfunction, both of which play important roles in the progression of Fabry cardiomyopathy. Although circulating SIRT1 levels have been proposed as a candidate biomarker reflecting cellular stress and disease activity, their clinical utility in Fabry disease remains uncertain, and routine measurement is not currently recommended. Nevertheless, modulation of SIRT1-related pathways may represent a promising area for future research, particularly with respect to myocardial fibrosis progression, risk stratification, and the development of novel disease-modifying therapeutic strategies.[38]

Conclusions

Fabry cardiomyopathy represents a central determinant of morbidity and mortality in Fabry disease and reflects the progressive transition from intracellular glycosphingolipid accumulation to myocardial hypertrophy, fibrosis, heart failure, and arrhythmias. Increasing recognition of cardiac involvement as an early and sometimes predominant manifestation has improved diagnostic awareness, particularly in patients presenting with otherwise unexplained LVH. The integration of clinical evaluation with multimodality imaging and genetic testing has substantially enhanced the ability to detect cardiac disease at earlier stages and to characterize its phenotypic spectrum more accurately.

Early initiation of disease-specific therapy remains a key principle in the management of Fabry cardiomyopathy, as treatment is most effective before the development of advanced myocardial fibrosis. Contemporary management requires a multidisciplinary approach supported by structured follow-up strategies and individualized therapeutic decision-making based on disease stage, sex-related variability, genotype, and imaging findings. Despite important progress in enzyme replacement therapy, chaperone therapy, and supportive cardiac care, challenges remain in arrhythmic risk stratification, interpretation of genetic variants, and optimization of treatment strategies in advanced disease stages.

Future advances in cardiac imaging, biomarker research, and emerging therapies, including gene-based and targeted molecular approaches, are expected to further improve early diagnosis and long-term outcomes. Development of disease-specific risk models and refinement of genotype-phenotype correlations may support more precise prognostic assessment and personalized management strategies. Continued progress in these areas will be essential for improving clinical care and reducing the cardiovascular burden associated with Fabry disease.

Contributorship

All of the authors contributed planning, conduct, and reporting of the work. All authors had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Competing interests

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