JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 77, NO. 7, 2021

PUBLISHED BY ELSEVIER

JACC REVIEW TOPIC OF THE WEEK

Cardiac Involvement in Fabry Disease

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ABSTRACT

Fabry disease (FD) is a rare X-linked inherited lysosomal storage disorder caused by deficient α-galactosidase A activity that leads to an accumulation of globotriasylceramide (Gb3) in affected tissues, including the heart. Cardiovascular involvement usually manifests as left ventricular hypertrophy, myocardial fibrosis, heart failure, and arrhythmias, which limit quality of life and represent the most common causes of death. Following the introduction of enzyme replacement therapy, early diagnosis and treatment have become essential to slow disease progression and prevent major cardiac complications. Recent advances in the understanding of FD pathophysiology suggest that in addition to Gb3 accumulation, other mechanisms contribute to the development of Fabry cardiomyopathy. Progress in imaging techniques have improved diagnosis and staging of FD-related cardiac disease, suggesting a central role for myocardial inflammation and setting the stage for further research. In addition, with the recent approval of oral chaperone therapy and new treatment developments, the FD-specific treatment landscape is rapidly evolving. (J Am Coll Cardiol 2021;77:922–36) © 2021 by the American College of Cardiology Foundation.

Cardiac involvement represents the main cause of impaired quality of life and death in patients with Fabry disease (FD) (1,2) and an under-recognized cause of heart failure with preserved ejection fraction and ventricular arrhythmias in men age older than 30 years and women age older than 40 years (3). Cardiac damage starts early in life, progresses sub-clinically before significant symptoms occur, and usually manifests as left ventricular hypertrophy (LVH) mimicking hypertrophic cardiomyopathy (HCM) (4,5). A recent reanalysis of 5,491 patients with a clinical diagnosis of LVH and/or HCM screened for FD reported a prevalence of *GLA* pathogenic genetic variants of 0.93% in males and 0.90% in females (5).

Following the introduction of enzyme replacement therapy (ERT), early recognition of FD and differential diagnosis from other causes of LVH have become

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

Manuscript received November 12, 2020; accepted December 11, 2020.

ISSN 0735-1097/$36.00 https://doi.org/10.1016/j.jacc.2020.12.024

HIGHLIGHTS

- The cardiomyopathy associated with FD manifests mainly as LVH.
- In addition to glycosphingolipid accumulation, secondary mechanisms of cardiac damage in FD include inflammation and immune activation.
- Cardiac imaging, particularly CMR imaging, is essential for diagnosis and staging of FD.
- Early treatment can improve clinical outcomes in patients with FD and cardiomyopathy.

crucial to limit disease progression (1,6). Recent advances in understanding FD pathophysiology and cardiac imaging have improved diagnostic and therapeutic approaches to FD cardiac manifestations. In addition, the FD-specific treatment landscape is evolving, with the recent approval of an oral chaperone and development of new treatments, including modified enzymes, substrate reduction therapy, and genetic treatments (7).

This paper aims to provide a comprehensive review of current knowledge and ongoing research into the pathophysiology, diagnosis, and treatment of cardiac involvement in FD.

GENERAL FEATURES OF FD

FD is a pan-ethnic, X-linked lysosomal storage disorder caused by pathogenic variants in the *GLA* gene that result in reduced α-galactosidase A (α-Gal A) enzyme activity (1). This leads to an accumulation of lysosomal globotriaosylceramide (Gb3) and related globotriaosylsphingosine (lyso-Gb3) in affected tissues, including the heart, kidneys, vasculature, and peripheral nervous system (2). The reported incidence, between 1 in 40,000 and 1 in 117,000, may be underestimated because screening in newborns suggests a prevalence of up to 1 in 8,800 newborns (8).

More than 1,000 *GLA* variants have been identified (1,9) and are categorized as pathogenic, benign without clinical relevance, or of unclear significance (10). Nonsense, missense variants, and premature stop codons that lead to absent or low α-Gal A enzyme activity are usually associated with classic early-onset FD, characterized in males by childhood onset of symptoms, multiorgan involvement, and rapid disease progression, with clinical manifestations often affecting the heart, kidney, and central nervous system (1–3). Extracardiac clinical manifestations of FD are summarized according to decade of presentation in **Figure 1**. Missense genetic variants that are associated with residual α-Gal A activity cause late-onset FD, which predominantly affects the heart (cardiac variant). Genetic variants associated with the cardiac variant include p.N215S (prevalent in North America and Europe), p.F113L (prevalent in Portugal), and IVS4+919G>A (prevalent in Taiwan) (10–12).

In female patients, X-chromosome random inactivation (lyonization) results in mosaicism, with some cells expressing the normal allele and others the mutated allele (13). This causes heterogeneous manifestations, from an asymptomatic or mild phenotype manifesting later in life and affecting >1 organ, to a severe phenotype resembling classic FD.

In males with classic FD, confirmation of severely reduced or absent α-Gal A activity is often sufficient for a diagnosis. Male patients with late-onset FD have higher residual α-Gal A activity compared with classic FD, although far below normal values. In heterozygous females, α-Gal A activity may be normal or slightly deficient, and diagnosis requires genotype confirmation. Consequently, all FD diagnoses should be confirmed by genetic testing. Both enzymatic and genetic testing are easily performed on dried blood-spot cards with some European and U.S.-based laboratories providing the service free of charge often in the context of research projects supported by drug-producing companies. Following diagnostic confirmation, cascade family genetic screening according to X-linked inheritance is highly recommended (1).

PATHOPHYSIOLOGY OF CARDIAC INVOLVEMENT IN FD

Accumulation of Gb3 affects all cardiac cell types and tissues, including myocytes, endothelial and smooth muscle cells of intramyocardial vessels, endocardium, valvular fibroblasts, and conduction tissue (14). Myocardial accumulation leads to progressive LVH and diastolic dysfunction. Involvement of intramural vessels induces structural and functional changes, causing myocardial ischemia (15). Fibrosis and involvement of conduction tissue underlie the development of ventricular arrhythmias and conduction disturbances (**Figure 2A**).

However, Gb3 accumulation does not explain the whole spectrum of FD pathophysiology (16). Together with mechanical effects, Gb3 accumulation triggers secondary processes, which lead to biochemical and

ABBREVIATIONS AND ACRONYMS

ADAs = anti-drug antibodies
α-Gal A = α-galactosidase A
CMR = cardiac magnetic resonance
ERT = enzyme replacement therapy
FD = Fabry disease
Gb3 = globotriaosylceramide
HCM = hypertrophic cardiomyopathy
LGE = late gadolinium enhancement
LVH = left ventricular hypertrophy
lyso-Gb3 = globotriaosylsphingosine

FIGURE 1 Fabry Disease Red Flags for Differential Diagnosis

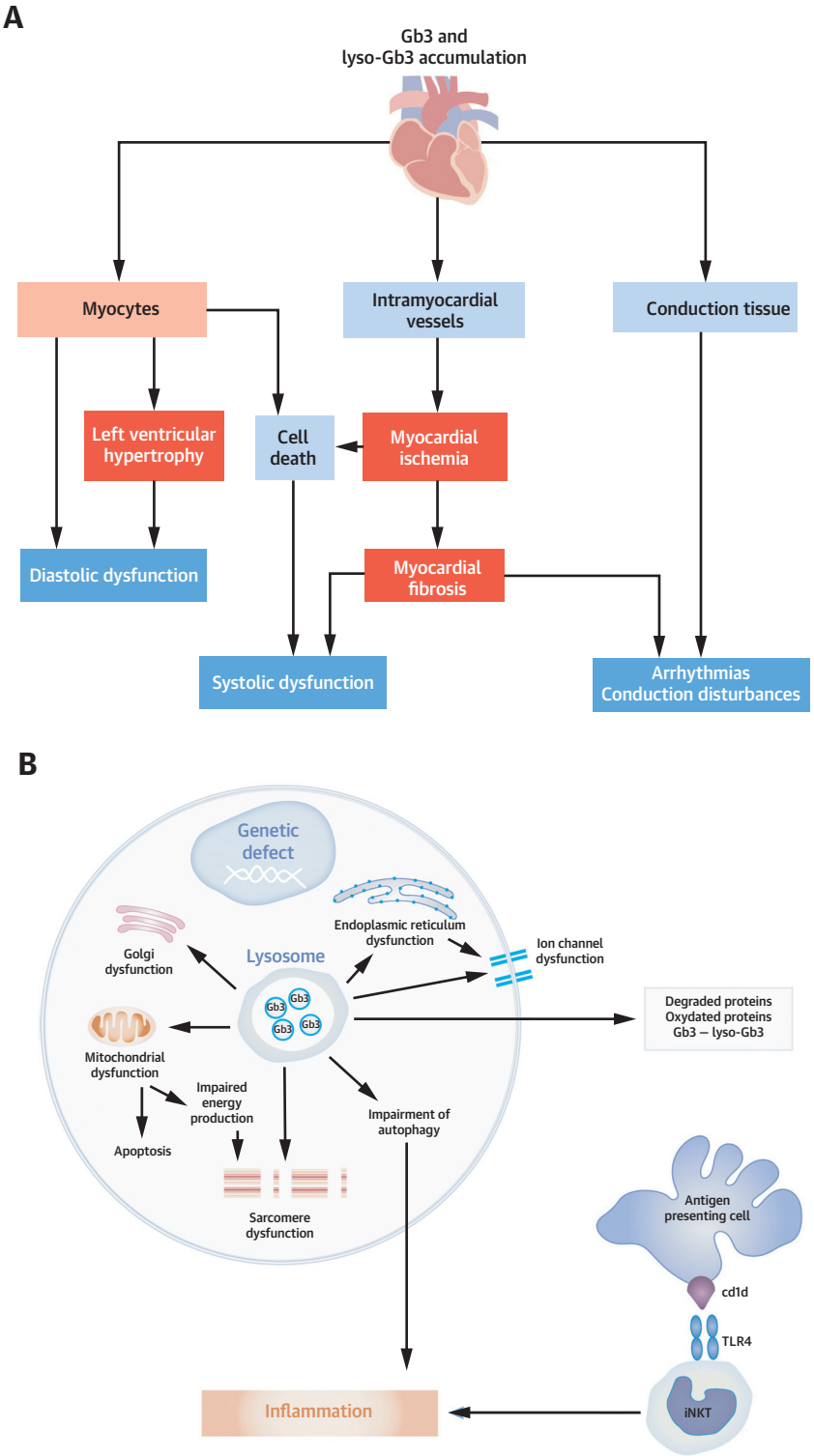
Extra-Cardiac Red Flags			Cardiac Red Flags		
Presenting Decades of Age	Any time	Family history of renal failure and/or stroke	Family history of LVH, particularly if no evidence of male-to-male transmission	History	Diagnostic Tool
	1–2	Neuropathic pain			
	1–2	Gastrointestinal symptoms	Short PQ interval†	Electrocardiography	
	1–2	Angiokeratomas	Bradycardia		
	1–2	Cornea verticillata*	Chronotropic incompetence		
	1–2	Hypohidrosis, heat/cold, and exercise intolerance	Atrioventricular blocks†		
	1–2	Albuminuria	LVH with normal systolic function	2D-echocardiography	
	3–4	Juvenile and/or cryptogenic TIA/stroke	Reduced global longitudinal strain		
	3–4	Hearing loss (either progressive or sudden)	Mild-to-moderate aortic root dilation		
	3–4	Dolichoectrasia of the basilar artery, chronic white matter hyperintensities at brain MRI	Mitral and aortic valve thickening with mild-to-moderate regurgitation		
	3–4	Proteinuria	Hypertrophy of papillary muscles	Cardiac Magnetic Resonance	
	3–4	Renal failure	Mid-layer posterolateral late gadolinium enhancement		
	3–4	Lymphedema	Low native T1		

Fabry disease red flags for differential diagnosis of patients with idiopathic left ventricular hypertrophy (LVH) and/or hypertrophic cardiomyopathy. *In the absence of iatrogenic causes (chloroquine/amiodarone). †Short PQ interval in early stages; atrioventricular and bundle branch blocks are more common in advanced disease. 2D-echo = 2-dimensional echocardiography; MRI = magnetic resonance imaging; TIA = transient ischemic attack.

functional impairment in myocytes (**Figure 2B**). In vitro studies show that intra-lysosomal Gb3 impairs endocytosis and autophagy, induces apoptosis, and interferes with mitochondrial energy production (17). Energy depletion and trophic factors, like sphingosine, may activate cellular hypertrophy pathways common to other HCMs. Studies on cardiomyocytes isolated from endomyocardial biopsies demonstrated that intracellular glycosphingolipids elicited sarcomeric myofilament dysfunction and myofibrillolysis (18). Birket et al. (19) demonstrated enhanced sodium and calcium channel function that resulted in higher and shorter spontaneous action potentials in FD cardiomyocytes derived from induced pluripotent stem cells. These findings suggested that stored glycosphingolipids might alter ion channel expression and/or cell membrane trafficking, altering the electrical properties of cardiomyocytes. Namdar et al. (20) proposed increased conduction velocity in atrial and ventricular myocardium as possible causes of electrocardiographic abnormalities in FD, including a short PR interval without evidence of an accessory pathway.

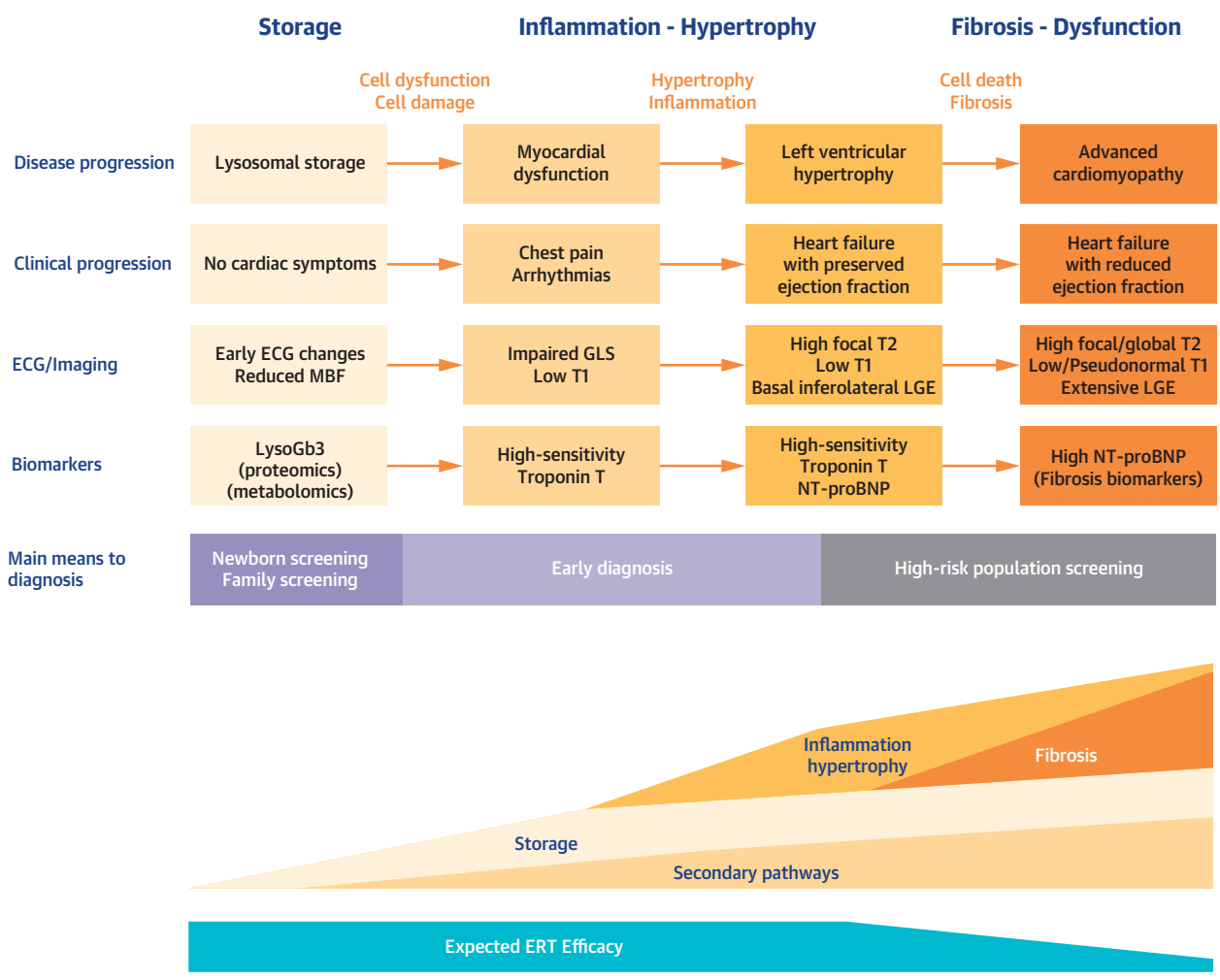
The model of FD as a simple storage cardiomyopathy has been challenged further by cardiac magnetic resonance (CMR) imaging studies with T1 and T2 mapping assessing myocardial lipid content and inflammation at different disease stages and suggesting a central role for inflammation in early FD progression (21,22) (**Central Illustration**). Clinical and experimental evidence also support the role of inflammation in FD and other lysosomal storage disorders (16,23-26). Deficiency of α-Gal A limits degradation, thus favoring accumulation of lipidic antigens, whereas Gb3 and lyso-Gb3 may act as antigens themselves that activate invariant natural killer T-cells and lead to chronic inflammation and autoimmunity (23-25) (**Figure 2B**). Glycosphingolipid-mediated effects are abolished by anti-toll–like receptor-4 antibodies, suggesting a pivotal role of this inflammatory pathway (23,24), promoting tumor growth factor-β–mediated extracellular matrix

FIGURE 2 **Pathophysiology of FD**



(A) Classic pathophysiology of Fabry disease (FD) as a myocardial storage disease and **(B)** recently reported secondary pathways operating in FD. Gb3 = globotriaosylceramide; iNKT = invariant natural killer T; lyso-Gb3 = globotriaosylsphingosine; TLR4 = toll-like receptor-4.

CENTRAL ILLUSTRATION **Proposed Evolution of Cardiac Involvement in Fabry Disease**



Pieroni, M. et al. J Am Coll Cardiol. 2021;77(7):922-36.

Proposed stages of Fabry disease (FD) cardiac involvement evolution along with clinical progression, imaging, biomarkers, main means to diagnosis, and in relation to expected treatment efficacy. ECG = electrocardiography; ERT = enzyme replacement therapy; GLS = global longitudinal strain; LGE = late gadolinium enhancement; lyso-Gb3 = globotriaosylsphingosine; MBF = myocardial blood flow; NT-proBNP = NT-pro–brain natriuretic peptide.

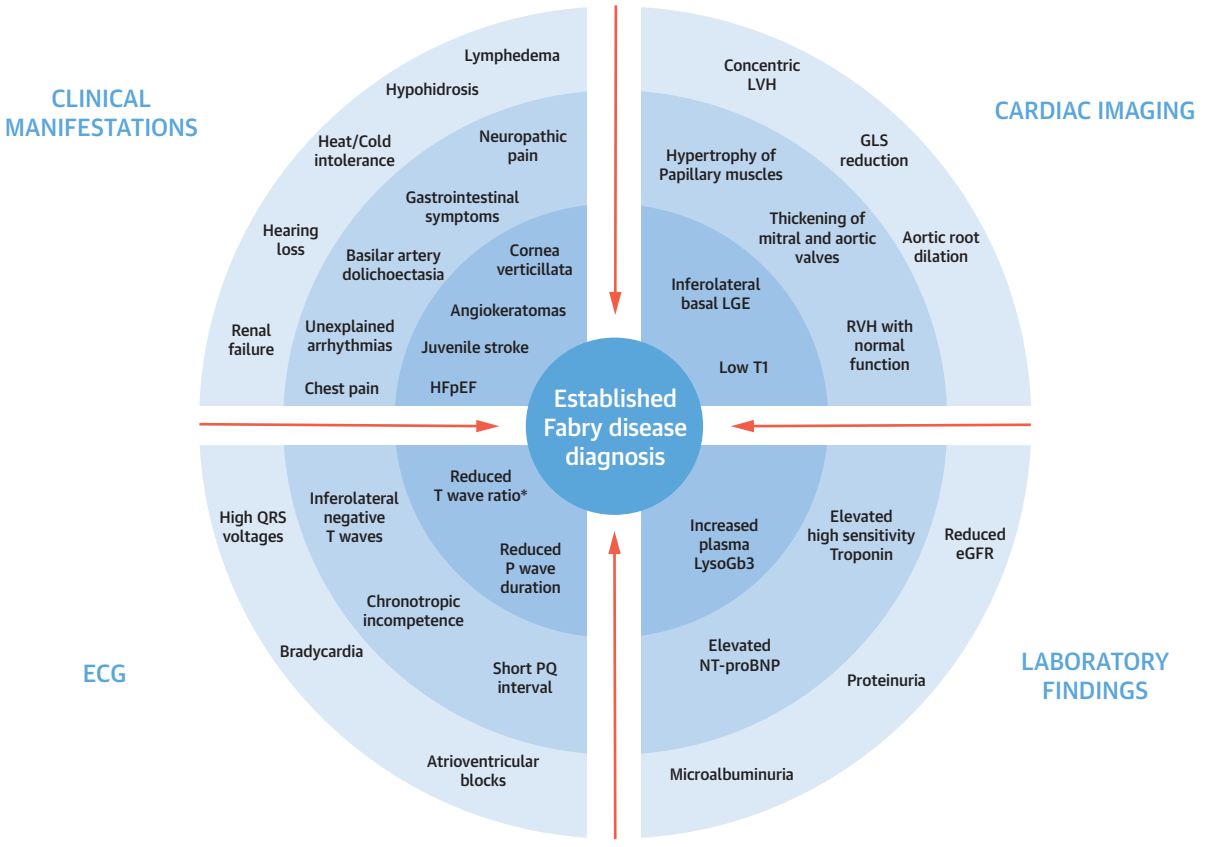
remodeling and fibrosis (25). Defective autophagy also promotes inflammation through inflammasome activators and release of reactive oxidative species (23). Yogasundaram et al. (26) recently reported elevated inflammatory and cardiac remodeling biomarkers that were correlated with disease progression in patients with FD, while chronic inflammatory activation was observed in endomyocardial biopsies from patients with FD (27). Knott et al. (15) recently linked myocardial inflammation with microvascular dysfunction and perfusion abnormalities in early cardiac involvement.

DIAGNOSIS AND STAGING OF CARDIAC INVOLVEMENT

New insights into disease pathophysiology and accrual of long-term ERT data have informed management of FD-related cardiac disease. Although early diagnosis remains essential to maximize benefit from disease-specific therapies (1–3), it is clear that accurate staging of cardiac involvement with imaging and biomarkers has important clinical implications.

In FD registries, LVH is reported in 53% of men and ≥33% of women after the third decade of life,

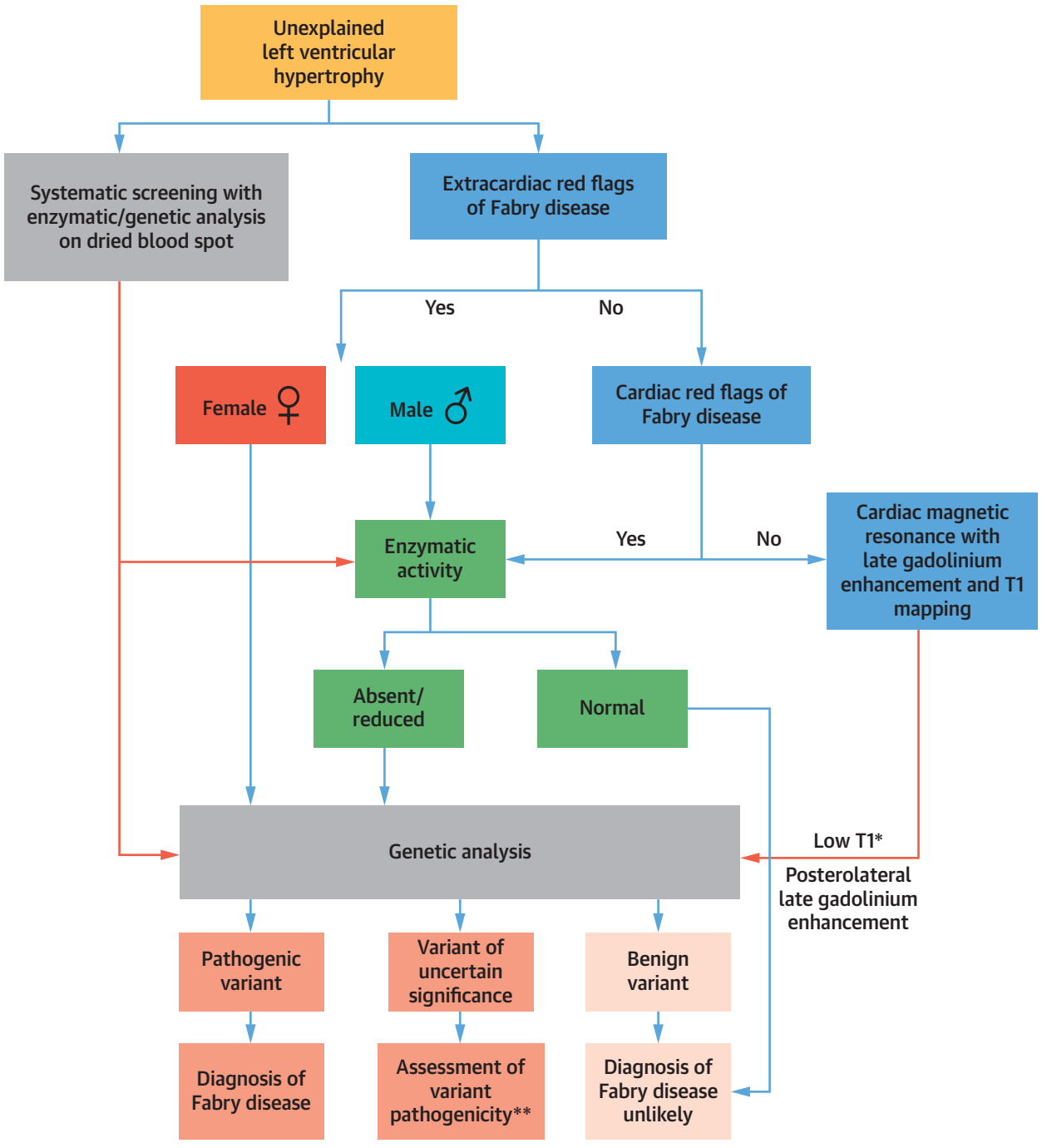
FIGURE 3 **Red Flags in FD**



Cardiac and systemic red flags with increasing likelihood of FD diagnosis from outer and/or brighter to inner and/or darker circles. *T-wave ratio = (Tonset-Tpeak)/(Tpeak-Tend) ratio. eGFR = estimated glomerular filtration rate; GLS = global longitudinal strain; HFpEF= heart failure with preserved ejection fraction; LVH = left ventricular hypertrophy; NT-proBNP = NT-pro-brain natriuretic peptide; RVH = right ventricular hypertrophy; other abbreviations as in **Figure 2**.

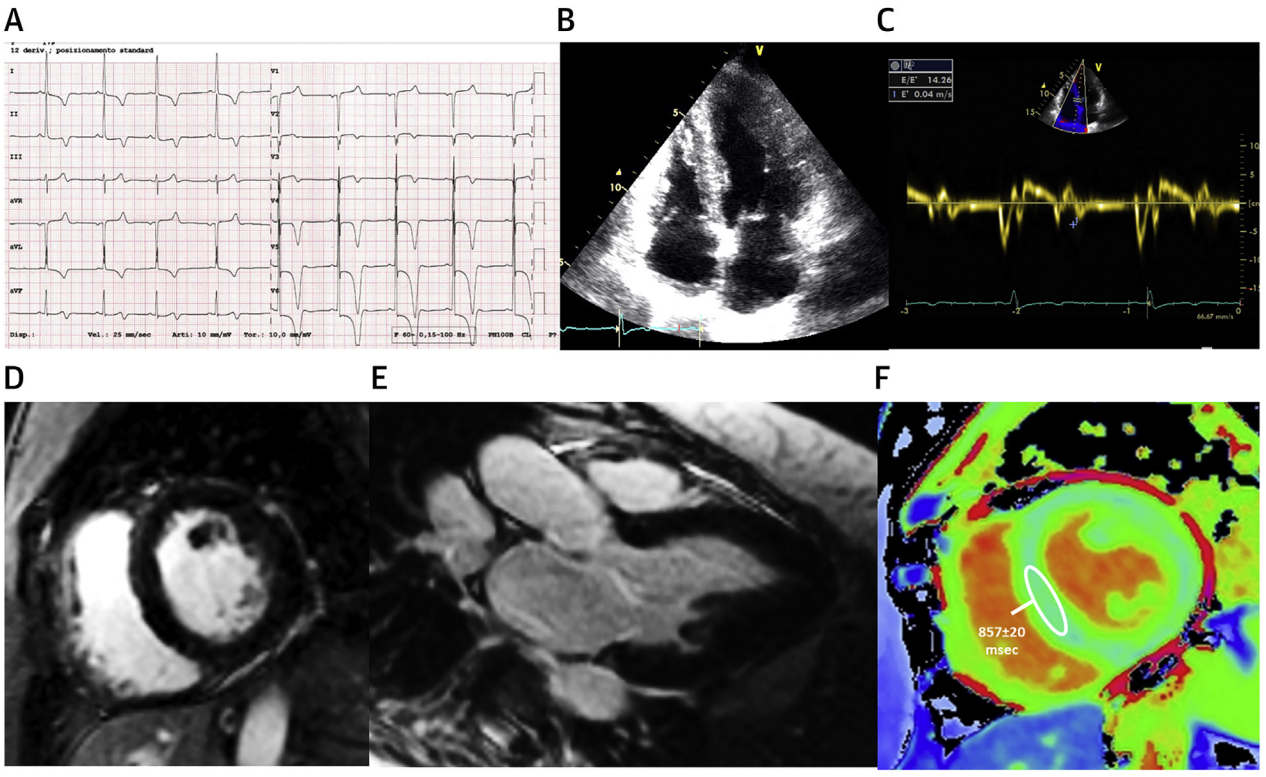
with 60% of patients presenting with symptoms that include heart failure with preserved ejection fraction, chest pain, and arrhythmias (1-3). Therefore, FD should be suspected in adult patients with such symptoms of unclear origin. According to a stepwise approach previously proposed for the diagnostic workup of cardiomyopathies (28), recognition of extracardiac red flags should raise the index of suspicion of classic FD (**Figures 1, 3, and 4**). In patients with cardiac variant FD, differential diagnosis from other HCMs is more challenging in the absence of systemic manifestations, considering that all patterns of LVH have been reported in FD (**Figure 5**). Cardiology red flags, with variable sensitivity and specificity (29), may rule out FD in the diagnosis of patients with idiopathic LVH or HCM (**Figures 1, 3, and 4**). Subtle electrocardiographic changes, including a short PQ interval and repolarization abnormalities, precede LVH and may be observed from childhood (20,30). Progressive cardiomyopathy is associated with high voltages, left ventricular strain pattern, and T-wave inversion in the precordial leads. ST-T segment depression and T-wave inversion in the inferolateral leads may develop, reflecting posterolateral fibrosis (**Figures 5 and 6**). Echocardiography is important for initial diagnosis and monitoring of FD-related cardiomyopathy; typical findings include concentric LVH, disproportionate hypertrophy of papillary muscles, loss of base-to-apex circumferential strain gradient, and right ventricular hypertrophy with normal systolic function, but none of them are pathognomonic (4). In carriers of pathogenic variants,

FIGURE 4 Proposed Flowchart for Diagnosis of FD in Patients With Idiopathic LVH



Suggested red flag diagnostic approach in patients with idiopathic LVH. Systematic screening of patients with LVH represents an alternative approach. *Low native T1 values reinforce or generate suspicion of FD. Normal native T1 values do not exclude FD, being rarely observed in untreated patients with mild LVH (mostly females), or in advanced disease due to "pseudo-normalization." With normal native T1 values, genetic analysis remains indicated if other findings suggest FD. **By lyso-Gb3 levels assessment and endomyocardial biopsy. Abbreviations as Figures 2 and 3.

FIGURE 5 **A Representative Case of p.N215S Cardiac Variant With Apical LVH**



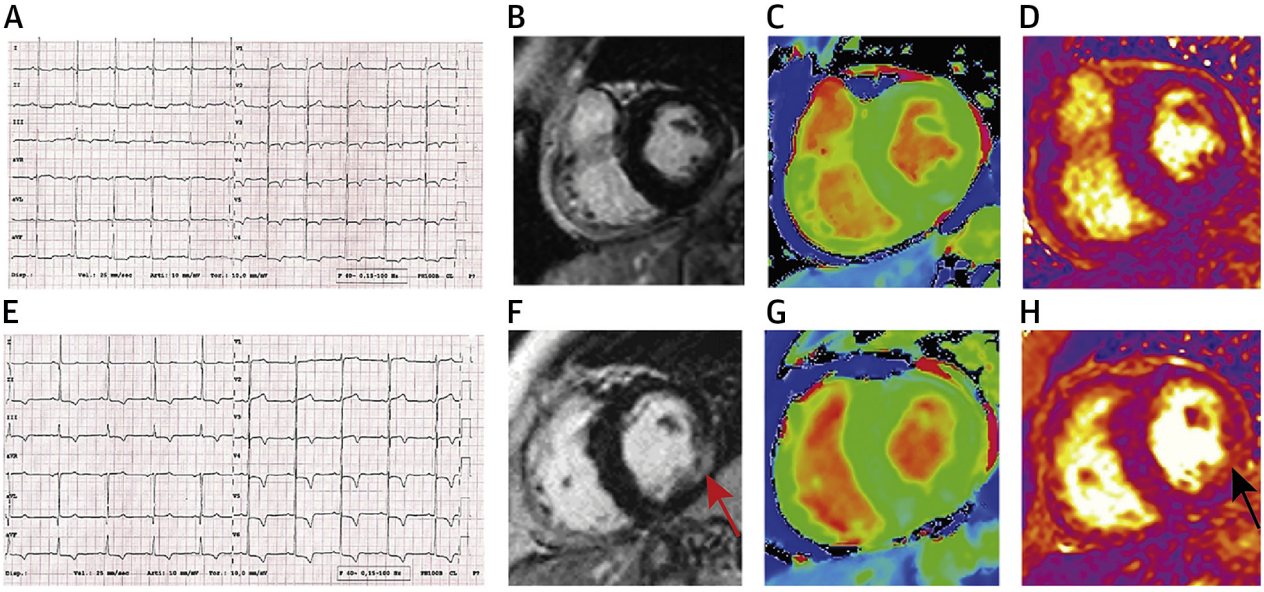
A 54-year-old woman referred for chest pain with no systemic red flags suggesting FD. **(A)** Electrocardiography showed giant negative T-waves. **(B)** Two-dimensional echocardiography showed apical hypertrophic cardiomyopathy (HCM) with reduced systolic and **(C)** diastolic velocities at tissue Doppler. **(D and E)** Cardiac magnetic resonance confirmed apical HCM with **(F)** low myocardial T1 values (857 ± 20 ms; normal reference value 984 ± 18 ms) suggesting FD. Genetic analysis detected N215S mutation causing the FD cardiac variant.

global longitudinal strain and speckle tracking allow early detection of cardiac involvement independently of LVH (4).

CMR has become central to the early differential diagnosis and staging of cardiac FD (**Figure 4**). Typical features include late gadolinium enhancement (LGE), initially in the basal inferolateral wall, and low native T1, likely reflecting glycosphingolipid myocardial storage and occurring before the development of significant LVH. FD is predominantly an intracellular storage disease at variance with cardiac amyloidosis; extracellular volume is typically normal except for LGE-positive areas (15,30–32).

Application of multiparametric CMR has provided valuable insights into myocardial biology of FD at different stages and on patients' responses to specific therapies. In a prospective observational study that included 182 patients with FD, Nordin et al. (21) proposed a 3-phase model of cardiac FD progression: 1) accumulation, starting in childhood and characterized by progressive lowering of T1 with no LVH or LGE; 2) inflammation and/or hypertrophy, with low T1, initial LVH (mostly in males), and T2 mapping evidence of inflammation in the basal inferolateral segment associated with LGE (sometimes preceding LVH, particularly in females and Taiwanese patients with the IVS4 variant); and 3) fibrosis and/or impairment, with increasing T1 values (pseudo-normalization) and LGE with wall thinning in the basal inferolateral segment (21). Increase of myocardial hypertrophy versus the storage component, increased interstitial and replacement fibrosis, and myocardial inflammation are all possible mechanisms of progressive T1 pseudo-normalization in advanced phases. Other groups reported low native T1 was detectable in up to 59% LVH-negative patients and was associated with clinical worsening at 12-month follow-up, whereas reduction of myocardial blood flow seemed to precede T1 lowering in an initial stage (30,31).

FIGURE 6 A Representative Case of a 59-Year-Old Woman With Classic FD (c.124-125delAT) Showing Progression of Myocardial Damage and Inflammation



(Top) Baseline. **(Bottom)** changes at 2-year follow-up. **(A and E)** Electrocardiographic progression (deeper, more extensive T-wave inversion). **(B and F)** New basal inferolateral late gadolinium enhancement (LGE) with progression of fibrosis **(red arrow)**. **(C and G)** Low T1 (875 ± 22 ms; normal reference value 984 ± 18 ms). **(D and H)** T2 mapping with new increase in T2 signal (edema) in area of LGE **(black arrow)**. Abbreviations as in Figures 2 and 3.

Concerning T2 mapping, Augusto et al. (32) showed that when LGE was present, there were significant associations between increased T2 values in the LGE segments, an increase of troponin and N-terminal pro-B-type natriuretic peptide, electrocardiographic changes, and global longitudinal strain impairment. In these patients, both LGE-related and global T2 elevation were higher than those in other myocardial disorders (e.g., sarcomeric HCM). Persistent T2 and troponin elevation over 1 year suggested chronic myocardial edema and injury, with associated clinical deterioration (32). If validated by histology or other methods, these findings could demonstrate a pivotal role for inflammation in FD pathogenesis, with potential therapeutic implications.

In association with clinical assessment and imaging, biomarkers like troponin and N-terminal pro-B-type natriuretic peptide are important for cardiac disease staging (**Central Illustration**). Preliminary findings also suggest a correlation between inflammation and cardiac remodeling biomarkers and disease progression (26). Lyso-Gb3 levels increase since childhood, and their assessment may help in evaluating the pathogenicity of *GLA* variants of uncertain significance (33), whereas the role of lyso-Gb3 in disease monitoring is still debated. Endomyocardial biopsy with electron microscopy may be considered for diagnosis of FD in patients with variants of unknown significance and low lyso-Gb3 levels (**Figure 4**).

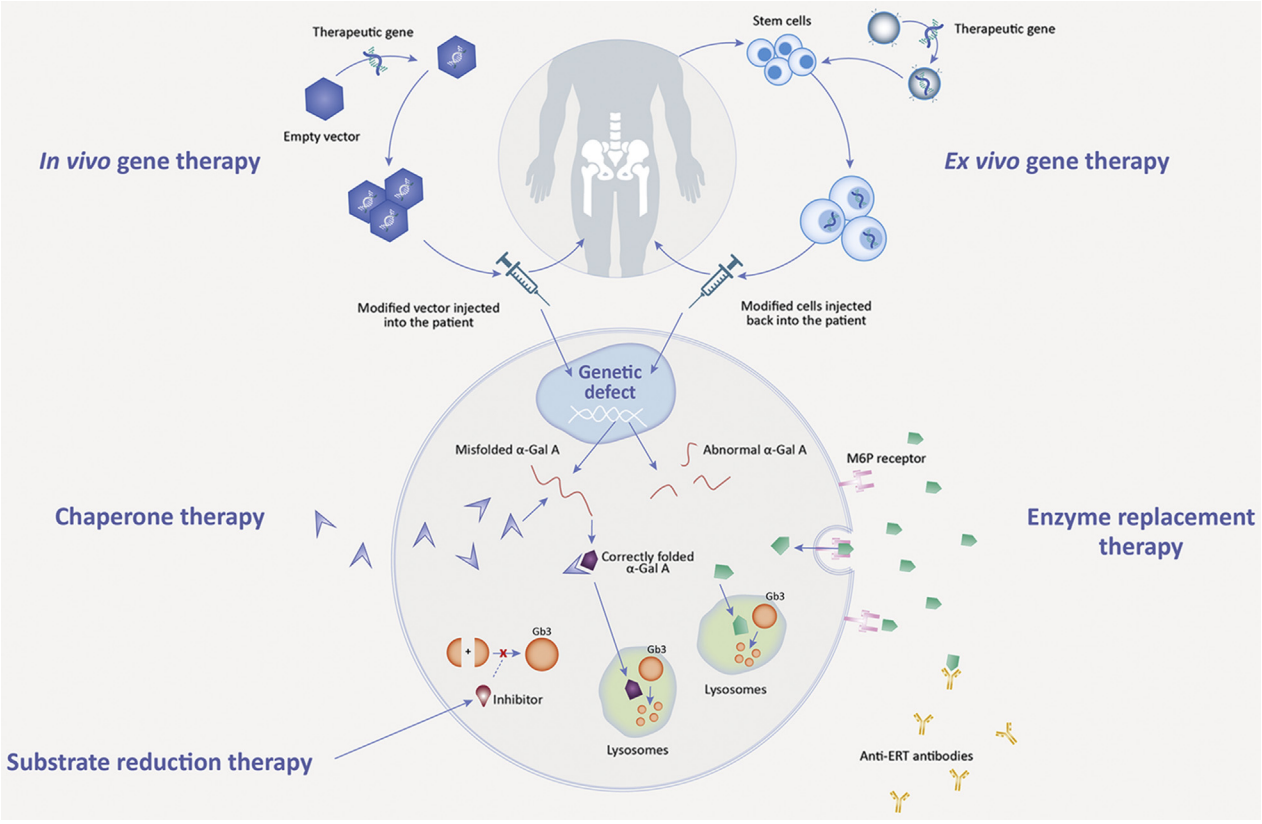
CLINICAL MANAGEMENT OF CARDIAC FD

The main goal of FD treatment is to prevent disease progression and irreversible organ damage. Optimal management of patients with FD requires a multidisciplinary approach involving physicians from different specialties, specialized nurses, and psychological support (3). The pharmacological treatment of FD includes disease-specific therapies, as well as therapies to manage cardiovascular symptoms and prevent major cardiovascular events.

FD-SPECIFIC THERAPIES. Approved FD-specific treatments include ERTs and the pharmacological chaperone migalastat while new therapeutic approaches are in development (7) (**Table 1 and Figure 7**).

ERT. ERT is administered intravenously bi-weekly and is indicated in symptomatic patients with an established FD diagnosis. ERT has profoundly changed the natural history of FD and improved patients' quality of life through effective treatment of

FIGURE 7 **Currently Approved and Investigational Drugs for FD**



Schematic representation of mode-of-action for approved and investigational therapies for FD. α-Gal A = α-galactosidase A; ERT = enzyme replacement therapy; other abbreviations as in Figure 2.

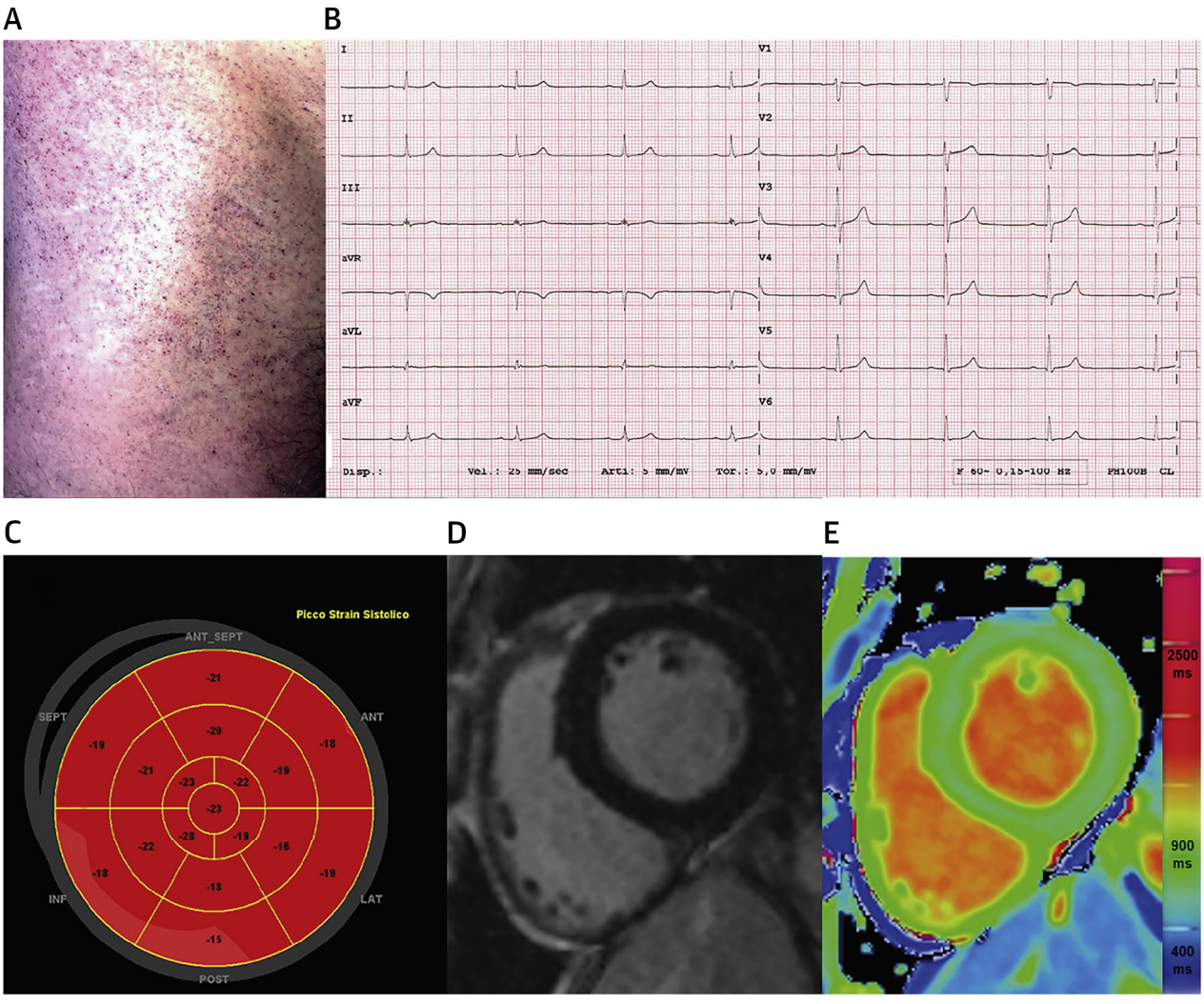
neuropathic pain, gastrointestinal manifestations, as well as heat and exercise intolerance (1–3,6). Long-term follow-up studies and registry data show that ERT delays cardiac disease progression and reduces the cardiovascular event rate (1–3,6). Evidence suggests that LVH may be prevented by early treatment (**Figure 8**), and regression of mild LVH has been reported in patients with both classic and cardiac phenotypes, although evidence for late-onset cardiac FD variants is limited. In advanced cardiac FD, response to ERT is poor (**Central Illustration**) (1–3,6), with no data suggesting any effect on myocardial fibrosis and LVH progression.

Several factors influence cardiac response to ERT, including phenotype, sex, timing and dosage of ERT, and antidrug antibody (ADA) development against exogenous α-Gal A (1–3,34).

Chaperone therapy. Chaperone molecules are orally administered iminosugars that bind to the catalytic domain of α-Gal A and promote its proper folding and transportation to the lysosome. The same molecules at higher doses may act as inhibitors of α-Gal A. The chaperone molecule migalastat is approved for administration every other day in adult patients with amenable *GLA* variants, defined by the presence of residual α-Gal A activity of at least 3% of normal, and an increase in activity by at least 20% in the presence of 20 μM migalastat in patients' cultured lymphocytes.

Clinical trials and open-label extension studies showed that treatment with migalastat was associated with a significant decrease in the left ventricular mass index (35). However, recent real-world data showed a significant discrepancy between predicted in vitro amenability and the effective in vivo increase in α-Gal A activity and clinical response in some genetic variants (36). This may be related to intrinsic limitations of the in vitro amenability test and

FIGURE 8 Long-Term Effect of Early ERT



A 42-year-old man with classic FD (c.946delG) after 19 years of ERT. **(A)** Angiokeratomas in bathing-trunk region. **(B)** Normal electrocardiogram with sinus bradycardia. **(C)** Echocardiography showing mild reduction of longitudinal strain in postero-inferior basal segment. **(D and E)** CMR with no evidence of LVH nor LGE **(D)** but with low myocardial T1 values (820 ms; normal reference value 959 ± 20 ms) **(E)**. Abbreviations as in Figures 2, 3, 5, and 7.

possible dosage-dependent inhibitory effects of migalastat. These data suggest that biochemical and clinical response to chaperone therapy must be carefully monitored to confirm clinical efficacy.

MANAGEMENT OF CARDIAC COMPLICATIONS AND MONITORING. In addition to FD-specific therapies, conventional therapies are necessary to manage cardiovascular manifestations of FD. Updated expert recommendations have been provided in a recent consensus document (3). Clinical monitoring is essential to assess disease progression and requires a multidisciplinary approach. Disease progression may be variable between organs, particularly in patients receiving ERT, due to specific secondary pathways of damage and variable response to therapy of different tissues. Accordingly, a multiparametric clinical scoring system has been recently validated (37). The role of lyso-Gb3 in monitoring disease evolution and treatment efficacy is still debated, although new biomarkers, including microRNAs and lyso-Gb3 isoforms, are under investigation. The use of new CMR techniques in FD monitoring is promising. A recent

TABLE 1 Currently Approved and Under Development Therapies for Fabry Disease

Drug Name	Mechanism of Action	Route of Administration	Dose	Notes
Approved				
Agalsidase alfa	ERT	Intravenous	0.2 mg/kg/every other week	Agalsidase alfa is the human protein α-galactosidase A produced in a human cell line by genetic engineering technology.*
Agalsidase beta	ERT	Intravenous	1.0 mg/kg/every other week	Agalsidase beta is a recombinant form of human α-galactosidase A and is produced by recombinant DNA technology using a mammalian Chinese hamster ovary cell culture. The amino acid sequence of the recombinant form, as well as the nucleotide sequence that encoded it, are identical to the natural form of α-galactosidase A.†
				In patients with late-onset Fabry disease, ERT should be considered in the presence of laboratory, histological, or imaging evidence of injury to the heart, kidney, or central nervous system, even in the absence of typical Fabry symptoms.‡
				In the absence of demonstrable Fabry disease–related tissue pathology or clinical symptoms, ERT may not be appropriate, particularly in heterozygous female patients; however, these patients should be monitored regularly by a multidisciplinary care team.
				ERT is not recommended in those patients with well-characterized benign α-galactosidase variants.‡
Migalastat	Pharmacological chaperone	Oral	123 mg/every other day	Indicated only for adult patients with migalastat-amenable α-galactosidase variants (i.e., a GLA variant translating into a-Gal A proteins that may be stabilized by migalastat, thereby restoring their trafficking to lysosomes and their intralysosomal activity).
				No food 2 h before and after intake.§
				Not recommended in those patients with well-characterized benign α-galactosidase benign variants.‡
Under development (phase III trials)‖*				
Pegunigalsidase-alfa	ERT	Intravenous	1 mg/kg/every other week	Produced in tobacco cells and chemically modified with polyethylene glycol Three ongoing phase III clinical trials.
Moss-aGal	ERT	Intravenous	Being tested as 0.2 mg/kg to measure pharmacokinetics and safety	Produced in moss. Phase I trial completed. Plans for phase II and III studies in progress.
Venglustat	SRT	Oral	15 mg/once daily	Ongoing long-term, phase II trial. Plans for phase III trials in progress.
Lucerastat	SRT	Oral	1.0 g/ twice daily (dose adjusted for renal function)	Ongoing phase III trial for patients with Fabry disease with neuropathic pain.

*Shire Pharmaceuticals Limited. Agalsidase alfa. Summary of product characteristics. †Sanofi Genzyme. Agalsidase beta. Summary of product characteristics. ‡Ortiz A, Germain DP, Desnick RJ, et al. Fabry disease revisited: management and treatment recommendations for adult patients. Mol Genet Metab 2018;123:416–27. §Amicus Therapeutics UK Limited. Migalastat hydrochloride. Summary of product characteristics. ‖Information therapies under development taken from ClinicalTrials.gov.

ERT = enzyme replacement therapy; SRT = substrate reduction therapy.

study showed that in ERT-naïve patients, 1 year of ERT attenuated T1 lowering, with small reductions in maximum wall thickness and stabilization of the left ventricular mass index. However, in patients with advanced disease and established ERT, CMR showed a 1-year increase of T2 in the LGE area and worsening global longitudinal strain (22).

NEW THERAPIES IN DEVELOPMENT. Therapeutic strategies currently in development include second-generation ERTs, substrate reduction therapies, and gene and mRNA therapies (8) (**Table 1 and Figure 7**). Plant-derived ERTs have been developed to reduce ADA development and improve enzyme biodistribution. Pegunigalsidase-α is a novel pegylated form of α-Gal A produced in a ProCellEx system (Protalix Biotherapeutics, Carmiel, Israel) with a longer circulatory half-life and increased heart and kidney uptake compared with current ERTs (38).

Substrate reduction therapy is based on oral administration of iminosugars that inhibit glycosphingolipid synthesis directly, thereby lowering the cellular load of Gb3. These drugs, previously validated in Gaucher disease, may be administered, regardless of FD genotype. Two substrate reduction therapies, venglustat and lucerastat, are currently in phase II and III clinical trials, respectively (39,40).

In a recent phase II trial that adopted an ex vivo approach, hematopoietic stem cells from a patient with FD, transfected with lentiviruses (AVR-RD-01, Avrobio) and re-administered, provided persistent elevation in α-Gal A activity (7). Preclinical in vivo approaches using liver-targeted, adenoviral-mediated gene transfer in an α-Gal A knockout mouse model demonstrated a dramatic increase of α-Gal A activity and marked lyso-Gb3 reduction (41). However, it remains unclear whether enzyme release by transfected cells will result in adequate uptake by affected tissues. In heterozygous females, cross correction does not seem sufficient to prevent Gb3 accumulation and disease development. It is also unclear whether males

with classic FD and null α-Gal A activity could develop ADAs against the expressed enzyme, although continuous exposure and endogenous synthesis and glycosylation could result in tolerance in most treated patients. Novel cardiotropic vectors that specifically target myocardial tissue with increased delivery and reduced immunogenicity (compared with conventional adenoviral vectors) are currently undergoing testing in nonhuman primates. Finally, gene delivery systems continue to be developed. Encapsulation of human α-Gal mRNA within lipid nanoparticles increased α-Gal levels in the liver, heart, and kidney in mice and nonhuman primates (42).

CURRENT CHALLENGES AND AVENUES FOR FUTURE RESEARCH

Although ERT has significantly changed the natural history of FD, cardiac involvement remains a key prognostic determinant. Cardiac manifestations benefit from early ERT, but clinical effects are limited in more advanced cases. Several mechanisms that potentially reduce ERT efficacy in myocardial tissue have been proposed. Histological studies demonstrated that clearance of Gb3 deposits, although significant in endothelial cells, appear limited in cardiomyocytes (43). Clearance of endothelial cells is facilitated by their higher turnover compared with terminally differentiated cells such as myocytes and renal podocytes. In addition, myocardial concentrations of the exogenous enzyme can be significantly lower than those that reach endothelial cells. The relevance of ERT dosage has also been debated, with evidence suggesting that higher doses provide more effective clearance of podocytes in serial kidney biopsies in children with FD (44). Development of ADAs may also reduce enzyme uptake in target tissues. Lenders et al. (36) showed that neutralizing ADAs impaired ERT efficacy, particularly in males with classic FD, suggested a need for routine ADA titer assessment and dose adjustments to achieve supersaturation and to overcome neutralizing activity. Other strategies to minimize the detrimental impact of ADAs are being investigated, including immunosuppressive therapy and tolerance induction (7,36).

Exogenous enzyme instability at tissue level has also been hypothesized, highlighting potential benefits of ERT and chaperone co-administration. A phase II study demonstrated a 1.2- to 5.1-fold increase of enzyme activity in target tissues following ERT/migalastat co-administration compared with ERT alone (45). With the advent of new treatments, different therapeutic combinations may provide opportunities to target different stages of the lysosomal lipid storage pathway, although the increased cost of treatment per patient using 2 disease-specific therapies would represent a potential limitation of clinical applicability.

Considering the limited accessibility to myocardial tissue from living patients, the use of cardiomyocytes derived from isolated pluripotent stem cells offers an opportunity to assess early changes in FD cardiomyocytes at a genome- and proteome-wide level. Additional studies should also clarify whether pathogenic pathways may become storage independent, thus representing alternative therapeutic strategies. Recent studies showed that pentosan polysulfate, a mixture of semi-synthetic sulfated polyanions, demonstrated anti-inflammatory activity in patients with type 2 mucopolysaccharidosis and reduced proinflammatory cytokine secretion in cultured peripheral blood mononuclear cells from patients with FD or Gaucher disease (46).

A deeper understanding of mechanisms of cardiac damage in FD may also provide insights for other cardiomyopathies and other noncardiac conditions. Understanding the central role of defective lysosomal and/or endosomal transport recently revealed links between Gaucher and Parkinson's disease (18). In addition, the lysosomal protein NPC1, in which defects result in Niemann Pick disease, is also involved in the Ebola virus infection replication cycle.

CONCLUSIONS

Recent advances in our understanding of the complexity of cardiac FD have significantly improved diagnostic and therapeutic approaches, particularly with respect to identifying storage-triggered mechanisms of damage and detecting early cardiac involvement. A deeper understanding of secondary pathogenic pathways, particularly myocardial inflammation, may influence future therapeutic strategies.

Although new disease-specific therapies appear promising, diagnostic delay and timely initiation of current treatments remain critical concerns for many patients with FD, particularly those with late-onset cardiac variant disease, in whom the effects of disease-specific treatment can be more limited. Therefore, collaboration between FD specialists and cardiologists remains essential to identify patients before the onset of cardiac involvement, to enable them to gain maximum benefit from current and future therapeutic approaches.

ACKNOWLEDGMENTS The authors thank Ugo Battaglia, PhD and Alex Goonesinghe, PhD from HealthCare21, Lucid, a Lucid Group agency, Macclesfield, Cheshire, United Kingdom, for providing medical

writing support, which was funded by Sanofi Genzyme.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr. Pieroni has received advisory board honoraria from Amicus Therapeutics and Sanofi Genzyme; and has received speaker honoraria from Amicus Therapeutics, Sanofi Genzyme, and Shire. Dr. Moon has received advisory board honoraria and speaker honoraria from Sanofi Genzyme and Shire; and has received an investigator-led research grant from Sanofi Genzyme. Dr. Arbustini has received travel support from Sanofi Genzyme, Shire, and Amicus Therapeutics. Dr. Barriales-Villa has received an unrestricted educational grant from Sanofi Genzyme; and has received advisory board/speaker's fees from Amicus Therapeutics, Sanofi Genzyme, and Pfizer. Dr. Camporeale has received honoraria for presentations and board meetings from Amicus Therapeutics, Sanofi Genzyme, and Shire; and has received a research grant from Amicus Therapeutics. Dr. Vujkovac has received speaker honoraria and travel support from Sanofi Genzyme and Takeda. Dr. Elliott has received an unrestricted educational grant from Pfizer; and has received advisory board and/or speaker's fees from Myokardia, Cytokinetics, Sanofi Genzyme, Shire, Alnylam, and Pfizer. Dr. Hagege has received support from Amicus, Gilead, Myokardia, Novartis, and Sanofi Genzyme. Dr. Kuusisto has received advisory board attendance fees from Sanofi Genzyme; and has received speaker honoraria and travel support from Sanofi Genzyme, Shire, and Amicus. Dr. Linhart has been a consultant for Amicus Therapeutics, Sanofi Genzyme, and Takeda; and has received speaker honoraria and travel support from Sanofi Genzyme and Takeda. Dr. Nordbeck has received honoraria for lecturing and advisory board participation from Amicus Therapeutics, Genzyme/Sanofi, Greenovation, Idorsia, and Shire/Takeda. Dr. Olivotto has received grants from Myokardia, Sanofi Genzyme, Shire, Bayer, Amicus, and Menarini International; and has received board and/or speaker's fees from Myokardia, Cytokinetics, Sanofi Genzyme, and Shire. Dr. Pietila-Effati has received advisory board attendance and speaker honoraria, and travel support from Sanofi Genzyme; and has been a consultant for Shire. Dr. Namdar has received research support, advisory board attendance, and speaker honoraria, and travel support from Sanofi Genzyme; and has received research support from Shire HGT.

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KEY WORDS Fabry disease, hypertrophic cardiomyopathy, lysosome function, T1 mapping