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POSITION PAPER

An expert consensus document on the management of cardiovascular manifestations of Fabry disease

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Fabry disease (FD) is an X-linked lysosomal storage disorder caused by pathogenic variants in the α-galactosidase A (*GLA*) gene that leads to reduced or undetectable α-galactosidase A enzyme activity and progressive accumulation of globotriaosylceramide and its deacylated form globotriaosylsphingosine in cells throughout the body. FD can be multisystemic with neurological, renal, cutaneous and cardiac involvement or be limited to the heart. Cardiac involvement is characterized by progressive cardiac hypertrophy, fibrosis, arrhythmias, heart failure and sudden cardiac death. The cardiac management of FD requires specific measures including enzyme replacement therapy or small pharmacological chaperones in patients carrying amenable pathogenic *GLA* gene variants and more general management of cardiac symptoms and complications. In this paper, we summarize current knowledge of FD-related heart disease and expert consensus recommendations for its management.

Keywords Fabry disease • *GLA* gene • Enzyme replacement therapy • Cardiomyopathy

Introduction

Fabry disease (FD) is an X-linked lysosomal storage disorder caused by pathogenic variants in the α-galactosidase A (*GLA*) gene that lead to reduced or undetectable α-galactosidase A (AGAL-A) enzyme activity and progressive accumulation of glycosphingolipids, primarily globotriaosylceramide (Gb_3), and its deacylated form globotriaosylsphingosine (lyso-Gb_3) in cells throughout the body, including vascular endothelial and smooth muscle cells and cardiomyocytes.[1,2] Specific enzyme replacement therapy (ERT) for FD administered by intravenous infusion became available in 2001, and has been shown to clear Gb_3 from the vascular endothelium; its effects on cardiovascular manifestations have been reviewed elsewhere.[3–5] Novel therapy based on pharmacological chaperone is approved for FD patients carrying amenable pathogenic variants[6] and several treatments including modified enzymes, substrate reduction therapy and gene therapy are in development.[7–10] Many studies have demonstrated a benefit in FD when ERT is initiated early.[11–13] In spite of ERT, several studies have shown that some patients develop progressive structural heart

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disease, with complications refractory to treatment, particularly when ERT is commenced in those with already advanced stages of the disease with considerable left ventricular hypertrophy (LVH) or fibrosis.[13–17] In these patient, the benefit of ERT may be attenuated. Consequently, cardiovascular complications now represent the predominant cause of FD-related mortality.[18]

The aim of this project was to undertake a critical evaluation of diagnostic and therapeutic procedures likely to be beneficial in Fabry-related cardiac disease, based on a review of published evidence. This document presents a summary of the review and provides consensus recommendations for the management of cardiovascular disease in FD.[19–21]

Methods

For the purposes of this document, a group of cardiologists and physicians with expertise in the diagnosis and management of FD undertook a comprehensive review of published studies on the prevalence, clinical profile and management of cardiovascular complications in FD up to 2019. Applicability of recommendations from general cardiovascular guidelines, including those for hypertrophic cardiomyopathy (HCM), atrial fibrillation (AF), ventricular arrhythmias, cardiac resynchronization and pacing, valvular heart disease, hypertension, and heart failure, was also assessed.[22] The level of evidence and the strength of each recommendation were graded according to the methods used by the European Society of Cardiology (ESC).[23–25]

Genetics of Fabry disease

Fabry disease is caused by pathogenic variants in the *GLA* gene located on the X chromosome (Xq22.1). So far, over 1000 variants distributed across the *GLA* gene have been identified, the majority of which are missense. Many are unique or 'private' (i.e. confined to one or a few families) and the frequency of *de novo* variants is under 10%.[26,27]

Bi-directional sequencing (Sanger) of the seven coding exons and the exon-intron boundaries of *GLA* is the gold standard for molecular diagnosis. In females, multiplex ligation-dependent probe amplification or quantitative polymerase chain reaction should be performed if no mutation has been identified by Sanger sequencing, to exclude large deletions or a copy number variation.[26–28]

High-throughput next-generation sequencing is increasingly used with a number of gene panels incorporating *GLA* for the screening of high-risk patient cohorts, including individuals with HCM. As a result, many *GLA* variants of unknown significance (VUS) are being identified.[29–31] As a cautionary example, the p.Asp313Tyr change results in a serum pseudodeficiency of AGAL-A activity and is not disease-causing. Similarly, a number of *GLA* variants previously thought to be disease-causing (e.g. p.Arg118Cys) have been shown to be of uncertain significance or likely benign[26,31,32] and therefore reclassified.[27] Individualized assessment of *GLA* variants is advised, particularly in patients with evidence of FD pathology associated with non-disease-causing variants, in whom additional mutations should be sought.[29–31] Detailed assessment of individual genetic VUS is important and correlation with clinical phenotype and familial history is essential to prevent delays in diagnosis and delayed or inappropriate treatment.[30,31]

Female carriers of *GLA* pathogenic variants may also develop disease, albeit in a delayed and generally milder form.[33–36] Variable clinical penetrance in women is partly explained by the process of Lyonisation in which one of the two X chromosomes in each cell is inactivated during embryonic development and remains inactivated for all subsequent mitotic divisions. This results in a mosaic pattern of expression with some cells expressing the normal X chromosome and others the mutated *GLA* allele located on the other X chromosome. Females with skewed X inactivation expressing the mutated allele have similar disease severity as hemizygous males.[37,38]

Epidemiology

Fabry disease affects all ethnicities, with some geographical clusters based on founder mutations.[39–41] The reported prevalence of FD varies according to the screening method employed. Historical data based on clinically diagnosed cases of predominant classic FD suggested prevalence figures of 1 in 117 000.[42] In contrast, neonatal screening programmes have reported an unexpectedly high incidence of disease-causing variants, ranging from 1:1250 to 1:7800.[39,43–45]

Most prevalence data are based on systematic screening of high-risk populations with manifestations typical for advanced FD such as HCM, cryptogenic stroke, or end-stage renal disease.[46,47] The prevalence of FD in patients with unexplained LVH ranges from 0% to 12% in highly selected cohorts, but most studies suggest a value around 0.5% to 1% in adult patients.[27,48–62]

Diagnosis of Fabry disease

The multisystem nature of FD means that patients can present with a variety of symptoms and signs that, in context, provide diagnostic clues. However, the absence of multiple organ manifestations does not exclude the diagnosis.

Classic FD in males is characterized by onset of symptoms in childhood, absent or severely reduced (<1% of normal) AGAL-A enzyme activity and microvascular endothelial Gb_3 accumulation.[2,27,63] Typical manifestations include cutaneous lesions (angiokeratoma), hypohidrosis, peripheral neuropathy (with acral pain and painful febrile crises), premature stroke, microalbuminuria and proteinuria, renal insufficiency, and cardiomyopathy (*Figure 1*).

A large number of patients have a late-onset phenotype manifesting mostly as LVH or HCM. This so-called 'cardiac variant' has slower progression due to residual AGAL-A enzyme activity and less vascular endothelial Gb_3 accumulation.[41,64] However, the cardiac variant may occasionally present with some degree of extra-cardiac involvement including stroke and renal dysfunction, but the attribution of such complications to FD should be made with caution, and a kidney biopsy should be considered for differential diagnosis in all cases exhibiting albuminuria/proteinuria with

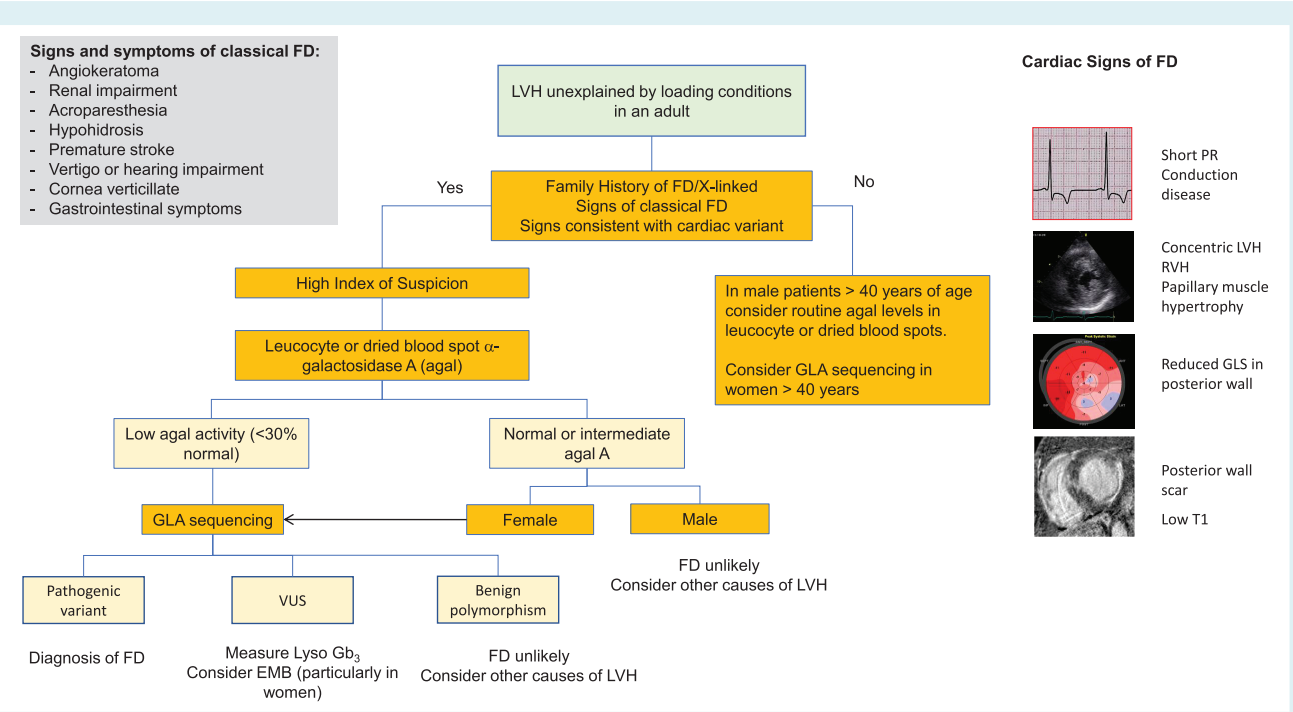

Figure 1 Diagnosis. Flow chart showing a suggested approach to the diagnosis of Fabry disease (FD) in a patient with unexplained left ventricular hypertrophy (LVH). Agal, α-galactosidase A; Gb_3, globotriaosylceramide; GLA, α-galactosidase A gene; GLS, global longitudinal strain; EMB, endomyocardial biopsy; RVH, right ventricular hypertrophy; VUS, variant of unknown significance.

deteriorating renal function, particularly in patients with concurrent risk factors for chronic kidney disease.[40,65]

As most cardiovascular signs of FD develop from the third decade of life onwards, LVH in children and young adults is very unlikely to be caused by FD.[66] The probability of FD is also low in the presence of an autosomal dominant inheritance pattern (but not excluded in patients carrying simultaneously a sarcomeric cardiomyopathy variant).[67]

Male patients with the classic form of disease have very low (<1%) or absent AGAL-A activity and can be diagnosed reliably by an enzymatic test in blood leukocytes or dried blood spot.[46] Some male patients with late-onset, predominantly cardiac forms of the disease have residual AGAL-A activity, although still far below normal values, i.e. below 30% of normal.[68]

Heterozygous female patients from families with classical and late-onset disease can have a wide range of clinical phenotypes that vary with the type of *GLA* pathogenic variant and as a result of skewed X-chromosome inactivation.[37,38] In women with FD, the activity of AGAL-A may be normal, meaning that a diagnosis usually requires genotyping and accurate interpretation of detected *GLA* variants. In both genders, suspicion of FD should be carefully verified by confirmation of a disease-causing variant before ERT or chaperone therapy is initiated.[26,31,65,69]

Currently, gene sequencing is the first-choice method for screening all female patients and for confirmation of the diagnosis in males with low AGAL-A activity. Biopsy of an affected organ may be necessary in women with signs and symptoms suggestive of FD in whom a genetic VUS has been identified and no informative male relative is available for investigation. Biopsy of an affected organ provides definitive evidence of FD by demonstrating vacuolization and typical lysosomal inclusions or 'zebra' bodies on electron microscopy. However, evidence of lysosomal deposits does not necessarily correlate with disease severity and organ damage.[30,70,71]

In many patients, Gb_3 is elevated in plasma or urine[72,73] but may be normal in patients with isolated cardiac involvement.[52,74] Recently, assessment of lyso-Gb_3 was proposed as a useful tool for prediction of pathogenicity of detected VUS.[75–77] It has been demonstrated that pathogenic variants leading to classical FD are associated with higher lyso-Gb_3 levels as compared to later-onset variants, which may even be associated with normal lyso-Gb_3 levels.[78] Benign *GLA* variants are associated with normal lyso-Gb_3 levels (*Table 1*).[2,26,27,31,33,43,47–51,63,69,75–80,82–99]

Diagnosis of cardiovascular involvement in Fabry disease

Electrocardiography

Children and adolescents may have subtle electrocardiographic (ECG) changes[100] and a left ventricular (LV) mass at the upper limits of normal range reported for the general population, but cardiovascular symptoms at this age are very rare.[103–103] In adults, the earliest clinical manifestations of Fabry-related cardiac disease are ECG abnormalities associated with slowly progressive LVH that

Table 1 Recommendations for the diagnosis of Fabry disease

Recommendations	Class	Level	Ref.
Fabry disease should be considered in adults with unexplained LVH.	IIa	C	47–51
Assessment of AGAL-A activity is recommended as the first-line diagnostic approach in men with clinically suspected FD.	I	C	2,27,63,82,83
Sequencing of the *GLA* gene is recommended as the first-line diagnostic approach in women with clinically suspected FD.	I	C	2,33,83–88
Sequencing of the *GLA* gene is recommended in all patients to: (i) identify and confirm the presence of a pathogenic or likely pathogenic variant; (ii) to test for amenability to the pharmacological chaperone migalastat; and (iii) to assist family cascade gene screening and prognostic assessment.	I	C	2,89–92
Assessment of plasma lyso-Gb_3 should be considered for assessment of disease severity in FD patients or in the diagnostic algorithm for patients with *GLA* genetic variants of unknown significance.	IIa	C	26,75–80,93–96
Genetic counselling is recommended in all patients with FD, including those with late-onset cardiac variants.	I	B	2,43,69,97
Cascade genetic screening is recommended for all affected families.	I	C	2,31,89,97,98
In all cases of FD-related cardiomyopathy, clinicians should consider evaluation of patients in centres with multidisciplinary teams that have expertise in the diagnosis and management of FD.	IIa	C	97–99

AGAL-A, α-galactosidase A; FD, Fabry disease; GLA, α-galactosidase A gene; LVH, left ventricular hypertrohy.

is clinically manifest after the third decade in males and fourth decade in females.

A short PR interval without evidence of an accessory pathway (most probably due to accelerated intra-atrial conduction), repolarization abnormalities and signs of LVH (voltage criteria and repolarization abnormalities – 'strain' pattern) are early ECG features which precede the development of overt structural abnormalities in the heart.[104] Voltage signs of LVH, strain pattern and T-wave inversion in precordial leads are virtually always present when FD cardiomyopathy has developed. In older patients, sinus bradycardia and progressive conduction disease in the atrio-ventricular (AV) node/His bundle and distal conduction system are common and are an adverse prognostic marker.[105] ST-segment depression and T-wave inversion may be associated with the presence of fibrosis.[105,106]

Patients with FD are at high risk for developing symptomatic bradycardia, chronotropic incompetence, AV block of any degree, and supraventricular or ventricular arrhythmia. For this reason, regular 24 h ambulatory ECG monitoring is recommended in patients with cardiac involvement.[105,107,108] Recent studies using implantable loop recorders (ILR) have demonstrated a high prevalence of arrhythmia and conduction disturbances in patients with FD despite normal initial 24 h Holter monitoring.[109]

The incidence of cardiac device implantation (pacemakers, defibrillators and loop recorders) in adult FD patients is between 1.07% and 1.9% per year.[14,105,108] The likelihood of pacemaker or defibrillator implantation increases in those with a severe phenotype, particularly in the presence of myocardial fibrosis, in patients with a late diagnosis and in those with late initiation of ERT.[109]

Echocardiography

Echocardiography is the most useful method for diagnosing and monitoring FD-related cardiomyopathy (*Figure 2*). Typical findings include concentric LV remodelling or hypertrophy without resting LV outflow tract obstruction.[110] However, asymmetric thickening of the interventricular septum or apical hypertrophy is not exceptional[111] and dynamic LV outflow tract obstruction caused by systolic anterior motion of the mitral valve can be provoked by exercise[112] or be present at rest, mimicking classical HCM.[113] As myocardial fibrosis develops, the posterior and inferior LV wall can thin and become hypokinetic or akinetic. Other typical features include papillary muscle hypertrophy and right ventricular wall thickening.[114–118] The 'binary sign',[115,116] characterized by a bright endocardial layer and adjacent hypoechogenicity of the intraventricular septum, may be seen in FD[119] but similar findings occur in other types of LVH and the sensitivity and specificity of this feature are low.[120–122]

Left ventricular ejection fraction is usually normal in FD, but can be reduced in patients with extensive fibrosis, coexisting coronary artery disease and ventricular dyssynchrony induced by conduction disease.[123] Systolic and diastolic tissue Doppler velocities at the mitral annulus are decreased in cases with LVH but may overlap with normal ranges in early stages of the disease.[124–127]

Myocardial strain and strain rate are usually abnormal in patients with LVH,[125] particularly in the posterolateral basal LV segment, sometimes with post-systolic thickening.[16,125,128–133] These findings may, in some cases, precede development of significant LVH and may correlate with functional limitation.[134] Myocardial performance (Tei) index is abnormal in patients with overt cardiomyopathy.[135]

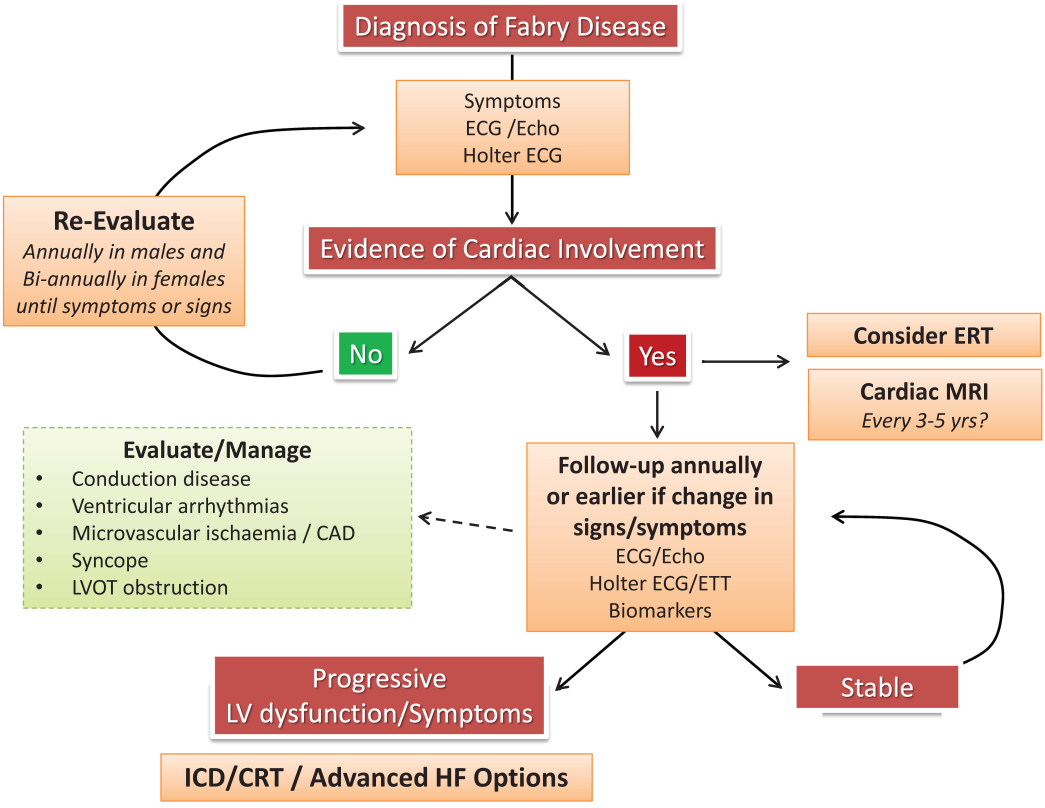

Figure 2 Fabry flow chart. CAD, coronary artery disease; CRT, cardiac resynchronisation therapy; ECG, electrocardiogram; ERT, enzyme replacement therapy; ETT, exercise treadmill test; ICD, implantable cardioverter-defibrillator; LV, left ventricular; LVOT, left ventricular outflow tract; MRI, magnetic resonance imaging.

Diastolic function can be normal in the early phase of cardiac involvement, but as the disease progresses, transmitral flow and mitral annular tissue Doppler velocities become abnormal. A restrictive filling pattern is rarely present and is usually associated with advanced cardiomyopathy.[123,124,130,136,137] Left atrial dilatation is common.[137] The assessment of diastolic function should be based on a comprehensive integration of Doppler diastolic indices and left atrial volume and interpreted in the context of clinical and laboratory findings.[138] Elevated LV filling pressures as assessed by E/e′ ratio are associated with unfavourable prognosis.[139]

The mitral and aortic valves are often thickened, with mild-to-moderate regurgitation. A small proportion of patients have mitral valve prolapse or severe mitral regurgitation due to leaflet degeneration that in some cases requires surgical repair.[140] Stenotic valvular lesions are exceptional.[140,141]

Mild-to-moderate aortic dilatation involving the bulb and ascending aorta is frequently seen in advanced cases.[142] The risk of aortic dissection is not known but is almost certainly very low. Vascular changes in FD are extensive, including ectasia of basilar or vertebral arteries, increased carotid or radial artery intima–media thickness and increased aortic stiffness.[142–147]

Cardiac magnetic resonance imaging

Cardiac magnetic resonance imaging (CMRI) provides an accurate assessment of LV size, mass and geometry and can – with the use of gadolinium contrast agents – visualize myocardial fibrosis typically distributed in the mid-myocardial layer of the posterolateral wall.[148,149] The presence of extensive fibrosis is associated with reduced response to ERT and with an increased risk of arrhythmia.[13,111,150] In some patients, particularly females, areas of replacement fibrosis are detectable before development of significant LVH.[128,151] Thus, systematic use of CMRI may help to reclassify patients in whom standard echocardiography fails to detect relevant cardiac involvement.[152]

Cardiac magnetic resonance imaging can be useful in the detection of LV apical hypertrophy and to assess papillary muscle hypertrophy, an early marker of cardiac involvement.[153,154] CMRI can also be used to detect changes in the myocardium with native (non-contrast) T1 mapping that reflects myocardial disease involving the myocyte and interstitium. Quantitative measures of myocardial T1 in FD patients demonstrate low values particularly within the interventricular septum, possibly due to the increase in myocardial lipid content.[155–159] Reduced T1 values are also reported within the right ventricular wall.[160] Of note, T1 reduction is

detectable in more than 90% of FD patients with LVH but also in 40% patients without LVH.[155,157,161] In pre-hypertrophic FD, the presence of low T1 values correlates with early ECG, morphological cardiac changes, and predicts worsening of global disease severity.[162] In contrast, T1 values may become 'pseudo-normal' or even increased within the posterolateral wall affected by fibrosis. Unlike native T1, the extracellular volume in FD is typically normal as FD is an intracellular storage disease.[163] Imaging studies using positron emission tomography/CMRI suggest an inflammatory process linked to fibrosis as well as disturbances of energy metabolism (^{31}P spectroscopy).[164–166]

Endomyocardial biopsy

Endomyocardial biopsy (EMB) may be considered in patients with VUS, high residual enzyme activity (>10%) and/or low lyso-Gb_3 levels, to confirm or exclude FD as the cause of LVH.[30,167–169] EMB may be useful whenever another cause of myocardial damage is suspected or in unusual phenotypic presentations or clinical evolution.[170,171] EMB is not recommended to determine treatment efficacy or to follow-up cardiac involvement. EMB should be evaluated by expert pathologists and always include electron microscopy studies to detect lamellar bodies and intracellular inclusions and to exclude phenocopies of FD.

Electrophysiological studies

Invasive electrophysiological study (EPS) is recommended in patients with documented persistent or recurrent supraventricular tachycardia (atrial flutter, focal atrial tachycardia, AV nodal re-entry tachycardia, accessory AV pathway-mediated tachycardia) to guide therapy and may be considered in those who have evidence from other non-invasive tests suggesting either sino-atrial disease or AV block. EPS should also be considered in patients with manifest pre-excitation (presence of delta-wave) in whom ablation should be performed in the presence of symptoms such as syncope or palpitations and/or when the refractory period of the accessory pathway is ≤240 ms. In view of an increased risk of developing AF, investigation of the anterograde and retrograde conduction properties with determination of the effective refractory period of the accessory pathway is recommended. EPS should include measurement of the shortest pre-excited RR interval during induced AF (or the shortest pre-excited RR interval during rapid atrial pacing).[172–175] The presence of a short PR interval as an isolated finding is not an indication for an EPS[176] and there is no evidence that the routine use of EPS to determine risk of ventricular arrhythmia in patients with FD provides clinical benefit.[20]

Laboratory tests

Routine laboratory testing aids detection of non-cardiac conditions that cause or exacerbate ventricular dysfunction (e.g. thyroid disease and diabetes mellitus) and secondary organ dysfunction. Regular monitoring of renal function and detection of microalbuminuria or proteinuria should be part of routine assessment even in patients with known cardiac variant mutations, as renal dysfunction can occur both due to FD-related renal involvement and other causes.[65,177] Severe renal dysfunction is associated with an increased risk of cardiac complications.[139]

Plasma inflammatory markers, including C-reactive protein and interleukin-6, are elevated in FD patients and are associated with increased symptom and disease burden (LVH and fibrosis) as well as progressive disease.[178,179]

Plasma lyso-Gb_3 values decrease with ERT and chaperone therapy. An increase can be seen in patients treated with ERT that have developed antibodies and treatment resistance. Therefore, lyso-Gb_3 may be used for treatment monitoring.[180] Recently, an association between the presence of neutralizing anti-drug antibodies and clinical progression has been demonstrated.[181,182]

Plasma N-terminal pro B-type natriuretic peptide (NT-proBNP) is elevated in patients with cardiac manifestations and correlates with symptom class, echocardiographic surrogates of elevated LV filling pressure (left atrial size and E/e′) and LV mass. Although NT-proBNP concentrations may be raised in patients without echocardiographic evidence of LVH, the highest values are encountered in patients with LVH, diastolic dysfunction, reduced T1 relaxation times on CMRI mapping and myocardial fibrosis.[183–185] Elevated high sensitivity troponin indicates advanced disease and a worse prognosis[186] (*Table 2*)[1,13,76,81,90,104,111,112,156,157,161,167,169,170,178,184,186–215].

Assessment of cardiac symptoms

Heart failure

Heart failure symptoms are reported in up to a quarter of patients in FD registries[66] and large cohort studies.[14] In the majority of patients, LV ejection fraction is normal and symptoms are caused by increased LV diastolic pressures. In a minority of patients with advanced disease, there may be systolic dysfunction or significant valvular disease. In all symptomatic patients, Doppler echocardiography during exercise in the standing, sitting or semi-supine position is recommended to detect provocable LV outflow tract obstruction and exercise-induced mitral regurgitation in line with the ESC guidelines for HCM.[90] In patients presenting with significant conduction impairment and progressive decline of systolic function, signs of asynchrony should be evaluated. As pulmonary involvement is also common in FD and muscular fatigue/myopathy may be present,[216] breathless patients should undergo spirometry.[217–220]

In some patients, chronotropic incompetence probably caused by autonomic nervous dysfunction can be a contributing factor to exertional dyspnoea.[105,191,221,222] For this reason, symptom-limited exercise stress testing or cardiopulmonary exercise stress testing if available is useful in the differential diagnosis of dyspnoea.[223,224]

Chest pain

Although large disease registries do not report an increased incidence of acute coronary syndromes in FD (a history of acute myocardial infarction is reported in only around 2%), patients

Table 2 Recommendations for diagnosis and monitoring of cardiac disease in patients with Fabry disease

Recommendations	Class	Level	Ref.
ECG and heart rhythm monitoring			
A standard 12-lead ECG is recommended at first clinical evaluation, with the development of new symptoms, and every 6–12 months in adult patients.	I	B	90,104,187
24 h ambulatory ECG monitoring (or longer if available) should be considered at initial assessment and every 6–12 months in adult patients to document atrial and ventricular arrhythmias.	IIa	C	90,188–191
Cardiac imaging			
2D and Doppler echocardiography is recommended in all patients at first clinical visit, with the development of new symptoms, and every 12 to 24 months.	I	B	90,192
In symptomatic patients with LVH, Doppler echocardiography during exercise in the standing, sitting or semi-supine position is recommended to detect provocable LV outflow obstruction and exercise-induced mitral regurgitation.	I	C	90,112,193–199
In the absence of contraindications, contrast enhanced CMRI should be considered in all adult patients in order to assess cardiac anatomy, ventricular function and the presence of myocardial fibrosis at initial evaluation.	IIa	C	90,111,157,161,200–205
In the absence of contraindications, contrast enhanced CMRI may be considered every 5 years in adult patients in order to assess the progression of fibrosis and LV function depending on disease severity and CMRI availability.	IIb	C	13,90
Non-contrast T1 mapping may be considered in adult FD patients to detect early cardiac involvement or in the differential diagnosis from other causes of LVH.	IIb	C	156,157,206
Endomyocardial biopsy			
Endomyocardial biopsy with sample evaluation including electron microscopy should be considered in patients with LVH, genetic variants of unknown significance in the *GLA* gene, and significant residual AGAL-A activity (>10%) in order to confirm a diagnosis of FD.	IIa	C	167,169,170
Biomarkers			
Regular assessment of renal function and urine analysis for microalbuminuria/proteinuria is recommended in all patients.	I	C	207–209
Measurement of plasma BNP/NT-proBNP is recommended in symptomatic patients with suspected heart failure.	I	B	178,184,210,211
High-sensitivity cardiac troponin (hs-cTnT or hs-cTnI) may be considered for the assessment of disease severity.	IIb	C	186,212,213
Measurement of lyso-Gb_3 may be considered as a prognostic marker, particularly in patients with genetic variants of unknown significance and/or late-onset genetic variants.	IIb	C	1,76,81,214,215

2D, two-dimensional; AGAL-A, α-galactosidase A; BNP, B-type natriuretic peptide; CMRI, cardiac magnetic resonance imaging; ECG, electrocardiogram; FD, Fabry disease; Gb_3, globotriaosylceramide; GLA, α-galactosidase A gene; hs-cTnI, high-sensitivity cardiac troponin I; hs-cTnT, high-sensitivity cardiac troponin T; LV, left ventricular; LVH, left ventricular hypertrohy; NT-proBNP, N-terminal pro B-type natriuretic peptide.

have abnormal vessels due to endothelial and medial Gb_3 storage and may develop epicardial coronary stenotic lesions.[225,226] In many patients, symptoms probably result from microvascular dysfunction.[168,227] Stress testing is of limited value in patients with baseline ECG changes[228] and coronary artery imaging should be considered in all patients with angina in accordance with the ESC guidelines on chronic coronary syndromes.[229,230] Perfusion imaging with positron emission tomography shows a decrease in coronary flow reserve in FD patients with normal epicardial coronary arteries, including females without significant LVH, but contributes little to routine clinical evaluation and decision-making.[227,231,232]

Palpitations

Palpitations are reported by 15% to 43% of adult patients depending on sex and stage of the disease.[66] The most frequent cause is probably atrial arrhythmia and all patients with frequent or prolonged episodes should undergo ambulatory ECG monitoring

for AF. When episodes are prolonged or highly symptomatic, an ILR should be considered.[109]

Syncope

A history of syncope in adult patients ranges between 3.6% and 5.6% in men and 1.7% and 2.6% in women.[66] Patients with FD experience syncope for many reasons, including autonomic dysfunction, sinus node dysfunction, complete heart block and sustained ventricular tachyarrhythmia. Patients with syncope should undergo 12-lead ECG, standard upright exercise test and 48 h ambulatory ECG monitoring.[191,223] Exercise stress echocardiography should be considered, particularly in patients with exertional or postural syncope, to detect provocable LV outflow tract obstruction.[112,113] In patients with unexplained syncope, an EPS and an ILR may be considered[111,237] (*Table 3*).[90,109,172–175,223,224,233–241]

Management of cardiac complications

General aspects of Fabry disease management

The management of FD requires a broad understanding of the disease and in some important aspects differs from the usual standard of care in other cardiovascular diseases. General measures for cardiovascular prevention, including lifestyle advice and smoking cessation in line with current guidelines for cardiovascular disease prevention and blood pressure control.[242,243] Special attention should be paid to the management of dyslipidaemia.[244] Patients with FD and preserved functional capacity should not be discouraged from participating in recreational sports but should be advised against intense competition. In young patients with classic FD, special attention should be paid to maintain adequate hydration and avoid overheating, which may provoke febrile painful crises.[245]

Enzyme replacement therapy

Enzyme replacement therapy targets the underlying process causing organ damage in FD. Studies have shown that ERT can reduce endothelial Gb_3 inclusions in the heart, but evidence for clearance of Gb_3 from cardiomyocytes is less convincing.[4,168,246] Most evidence suggests that the heart responds less well to therapy when disease is advanced, particularly in patients with extensive fibrosis.[4,13,168,246,247]

Enzyme replacement therapy is indicated in all symptomatic patients with classical disease, including children, at the earliest signs of organ involvement. Three preparations of recombinant ERT are currently available: agalsidase alfa (Replagal®, Shire), agalsidase beta (Fabrazyme®, Sanofi Genzyme) and agalsidase beta (Fabagal®, ISU Abxis). The major difference between them is the prescribed dose, which is fivefold higher for agalsidase beta (1.0 mg/kg every 2 weeks) than for agalsidase alfa (0.2 mg/kg every 2 weeks).

There is evidence from long-term follow-up studies[248,249] and registry data[250] that ERT halts or slows disease progression and reduces the burden of clinical events when started early in the course of the disease.[34] There are also data showing that the heart responds less well to therapy when disease is advanced[13,247] or when antibodies to the exogenous enzyme have developed.[251,252] There is limited evidence for a beneficial effect of ERT in late-onset cardiac variants.[167,253]

Mild LVH may partially regress in classical[254,255] and cardiac variant patients[167] and one study has suggested that LVH may be prevented by early therapy.[13] However, there are no data showing that ERT prevents myocardial fibrosis[150] and patients with extensive myocardial fibrosis probably respond less well in terms of functional improvement.[13,247]

Chaperone therapy

Orally administered migalastat is an alternative treatment option[6,256–259] reserved for patients with specific 'amenable' *GLA* pathogenic variants. Binding of the pharmacological chaperone, migalastat, to the active site of α-galactosidase stabilizes some mutant enzymes, thus facilitating proper trafficking to lysosomes, where dissociation of migalastat allows α-galactosidase to catabolize accumulated substrates.[258] Although data are limited, migalastat has been shown to slow organ damage. Furthermore, a promising, albeit modest decrease in LV mass index has been observed.[6,256,257,260,261] The ability of migalastat to mitigate the glomerular filtration rate decline associated with some amenable *GLA* variants has recently been questioned.[261]

Heart failure

Heart failure symptoms should be treated according to current ESC recommendations but with several caveats. As patients with FD are prone to sinus and AV node dysfunction, beta-blockers and ivabradine should be used with caution and be monitored using repeated Holter recordings.[23] Angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and mineralocorticoid receptor antagonists are indicated in patients with systolic impairment, paying special attention to hyperkalaemia and renal function in patients with nephropathy. In symptomatic patients with preserved ejection fraction, the use of spironolactone may be considered.[262,263] There is no published experience with sacubitril/valsartan in FD.

In patients receiving pacemakers, there is a concern about the long-term effects of non-physiological right ventricular pacing. Although significant ventricular dysfunction in unselected patients develops rarely,[264] the main predictors of this unfavourable outcome include LVH and heart failure.[265] Two-year data from the PACE trial suggest that biventricular pacing for bradycardia in patients with preserved ejection fraction may lead to more favourable outcomes as compared to right ventricular pacing alone.[266] For this reason, cardiac resynchronisation therapy should be considered in patients with FD that require pacing, particularly when the LV ejection fraction is impaired.

Classic FD may be associated with some degree of peripheral oedema, often due to lymphoedema or renal disease rather than

Table 3 Recommendations for assessment of symptoms

Recommendations	Class	Level	Ref.
Exercise testing			
Cardiopulmonary exercise stress testing (or standard treadmill or bicycle ergometry when unavailable) should be considered to assess the severity and mechanism of exercise intolerance and change in systolic blood pressure and heart rate.	IIa	C	90,223,224,234
Chest pain			
Coronary angiography (or CT coronary angiography) is recommended in all patients with angina CCS class ≥II.	I	C	235–238
Invasive coronary angiography is recommended in adult survivors of cardiac arrest, in patients with sustained ventricular tachyarrhythmia and in patients with severe stable angina (CCS class III) and unstable angina.	I	C	90,236,239
Syncope and palpitation			
12-lead ECG, upright exercise test, resting and exercise 2D and Doppler echocardiography, and at 48 h ambulatory ECG monitoring are recommended in patients with unexplained syncope, to identify the cause of their symptoms.	I	C	90,233,240,241
A prolonged ECG monitoring or preferably an ILR should be considered in patients with recurrent episodes of unexplained syncope.	IIa	C	90,109,233,241
An ILR may be considered in patients with palpitations or recent stroke in the presence of negative ambulatory ECG monitoring.	IIb	C	90,109,233,241
Invasive EPS may be considered in patients with unexplained syncope to exclude conduction abnormalities.	IIb	C	172–175

2D, two-dimensional; CCS, Canadian Cardiovascular Society; CT, computed tomography; ECG, electrocardiogram; EPS, electrophysiological study; ILR, implantable loop recorder.

ventricular failure. In these instances, it is often unresponsive to diuretic therapy.[267,268]

Angina

Coronary artery disease in FD patients should be managed conventionally, but caution is required when using negative chronotropic drugs such as beta-blockers, verapamil, diltiazem, and ivabradine due to the increased risk of bradycardia. CMRI using late gadolinium enhancement visualization of fibrosis should be considered for the assessment of myocardial viability taking into account the non-ischaemic character of replacement fibrosis within the posterolaterlal LV wall. FD patients with significant LVH represent high-risk operative candidates for coronary artery bypass grafting and percutaneous coronary intervention and should be managed in experienced centres.

Management of left ventricular outflow tract obstruction

Patients with exertional symptoms caused by LV outflow tract obstruction should be managed in accordance with the ESC guidelines on HCM.[90] However, as FD patients may be prone to develop symptomatic bradycardia, drugs affecting AV node conduction (beta-blockers, verapamil, disopyramide) should be used with caution. In addition, disopyramide requires dose adjustment according to renal function. Septal reduction therapies (both percutaneous and surgical) have been successfully performed in severely symptomatic FD patients resistant to medical therapy.[113,199,269,270]

Atrial fibrillation

In cross-sectional studies, approximately 5% of males and 3% of females have AF and the incidence of new AF is around 6% per annum.[14] AF and atrial flutter may be partly responsible for the increased incidence of stroke in FD.[63] In contrast, a low prevalence of AF is seen in young stroke patients (<30 years), reflecting the fact that cardiac involvement is usually mild or absent before the fourth decade.[271] However, prolonged ECG monitoring should still be considered in FD patients.

Rhythm control

Maintenance of sinus rhythm involves both pharmacological and interventional therapies,[272] but is often challenging in the presence of an evolving atrial substrate and significant limitations of available drugs. Amiodarone should be limited to the management of poorly tolerated acute episodes as chronic therapy may induce phospholipidosis and potentially reduce the effect of ERT.[273–275] Little is known about the effect of dronedarone on endosomal/lysosomal trafficking and function and it is contraindicated in New York Heart Association class III–IV heart failure patients and impaired renal function (estimated glomerular filtration rate <30 mL/min). Sotalol

is contraindicated in decompensated heart failure and when creatinine clearance is <10 mL/min[276] and flecainide should be used cautiously when estimated glomerular filtration rate is <35 mL/min.[277] Furthermore, flecainide and propafenone are both contraindicated in patients with depressed ventricular function and heart failure. Experience with catheter ablation of AF is sporadic in FD. Extrapolating from HCM patients, a high rate of AF relapse and need for repeat procedures is to be expected, particularly in older patients with left atrial dilatation.[278]

Anticoagulation

None of the available scoring systems for estimating stroke risk are validated in FD and extrapolation from HCM suggests that they should not be used in FD. The use of the HAS-BLED score for estimation of bleeding risk may be useful, although the age criterion is not appropriate particularly in male patients.[22]

Anticoagulation with vitamin K antagonists should be considered in all patients with any form of AF or atrial flutter. Systematic data on direct oral anticoagulants (DOACs) in FD are lacking. However, given reports of cerebral microbleeds in FD, DOACs could have a potential advantage over warfarin as they are associated with reduced risks of intracranial bleeding.[271,279] In addition, the use of DOACs may reduce the risk of warfarin-induced nephropathy and slow the progression of renal function decline.[280,281] Special attention should be paid to dose reduction and contraindications of DOACs in patients with impaired renal function, as well as drug interactions specific for each of these agents.[282] In patients unable to use anticoagulation, left atrial appendage closure may be considered.[21]

Rate control

Due to the tendency of FD patients to develop bradycardia and AV conduction abnormalities, repeated Holter monitoring is recommended to verify the adequacy of rate control. The administration of any bradycardia-inducing drugs should be done with extreme caution with regular ambulatory ECG monitoring (*Table 4*).[69,90,271,273,279–281,283–294]

Bradycardia and atrio-ventricular block

Symptomatic bradycardia caused by sinus node dysfunction and AV block is relatively common in FD. In a series of 204 patients, the 5-year cumulative incidence of anti-bradycardia pacing was 8%. The need for pacing was best predicted by QRS duration and PR interval.[105] Symptomatic bradycardia should be treated in accordance with the current ESC guidelines.[25,90] Due to the high risk of AV node dysfunction, dual chamber pacemakers should be implanted unless patients are in permanent AF. If AV block is caused by AV node blocking drugs, their indication and dose should be reviewed and the need for pacing re-evaluated after adjustment.

The benefit of rate-responsive pacing in treating exercise intolerance is uncertain. However, highly symptomatic patients with proven chronotropic incompetence may benefit. Although some data suggest that bi-ventricular pacing might be superior to right ventricular pacing in preserving systolic function and preventing LV remodelling,[266,295] this approach is not fully supported by current guidelines. Cardiac resynchronisation therapy with pacemaker implantation should be considered in symptomatic patients with ejection fraction <50% and QRS prolongation (QRS >120 ms).[90,296] In those who have progressed to LV dysfunction (ejection fraction ≤35%), cardiac resynchronisation therapy should be considered in accordance with the current ESC Guidelines (*Table 5*).[25,90,105,266,295–299]

Ventricular arrhythmia

Non-sustained ventricular tachycardia (NSVT; defined as three or more ventricular premature beats at a rate of ≥100 bpm and lasting <30 s) is a common finding on ambulatory ECG monitoring in FD.[189] Its prevalence increases with age and correlates with progression of late gadolinium enhancement on CMRI.[150] Asymptomatic runs of NSVT do not usually require anti-arrhythmic therapy. Unlike patients with idiopathic or sarcomeric HCM, the relation between NSVT and sudden cardiac death (SCD) risk is unknown. However, in the majority of myocardial diseases, fibrosis extent along with presence or rapid and repetitive NSVT are correlated to SCD occurrence and such association was also suggested in FD.[15]

Documented sustained monomorphic ventricular tachycardia (≥30 s) is rare and in some patients its origin may be associated with areas of myocardial scarring.[109,111] Coronary artery disease should be excluded in all patients with prolonged or symptomatic episodes. In patients with evidence of a focal origin, EPS and ablation may be considered. Patients with poorly tolerated ventricular tachycardia should receive implantable cardioverter-defibrillator (ICD) therapy.[20]

Prevention of sudden cardiac death

A recent meta-analysis of data from 13 studies suggests that cardiovascular mortality is now the major cause of mortality in patients with FD.[188] An ICD is recommended in patients who have survived a cardiac arrest due to ventricular tachycardia or fibrillation, or who have spontaneous sustained ventricular tachycardia causing syncope or haemodynamic compromise, and have a life expectancy of >1 year.[20]

At present, there are insufficient data to determine the prognostic value of clinical risk markers used in patients with idiopathic or sarcomeric HCM and so in patients with FD the recommended ESC risk tool (HCM RISK-SCD) should not be used.[300] Current data suggest that patients with advanced LVH and extensive (and rapidly progressing) fibrosis may be candidates for ICD implantation.[150,188,189,301] ICD implantation may also be considered in patients with significant LVH and unexplained syncope.

Decisions concerning the ICD in primary prevention should be made on an individual patient basis, guided by the age and general health of the patient, personal preference, socio-economic factors and the psychological impact of therapy.[18,188] EPS with programmed ventricular stimulation does not seem to contribute effectively to SCD risk stratification in FD and its routine use in patients with

Table 4 Recommendations for the management of atrial arrhythmia

Recommendations	Class	Level	Ref.
Maintenance of sinus rhythm rather than rate control is recommended for patients with FD and AF.	I	C	90,283,284
Regular 48 h Holter monitoring is recommended in patients with left atrial enlargement and in case of unexplained palpitations to detect AF.	I	C	69,90,285
The use of $CHADS_2$ and CHA_2DS_2-VASc scores is not recommended to assess the need for anticoagulation in patients with FD and AF.	III	C	90,286
All patients with AF and atrial flutter should receive anticoagulation with DOACs or VKAs unless contraindicated.	I	C	90,287–292
DOACs should be considered as the first-line choice in FD patients without contraindications resulting from renal function impairment.	IIa	C	271,279–281
The use of aspirin monotherapy is not recommended to protect against cardioembolic stroke.	III	C	90
Combination therapy with aspirin 75–100 mg plus clopidogrel 75 mg daily may be considered for stroke prevention in patients for whom OAC therapy is unacceptable or contraindicated and where there is a low risk of bleeding.	IIb	C	90,293
Left atrial appendage closure may be considered in patients unable to receive anticoagulation therapy.	IIb	C	90
Amiodarone may interfere with lysosomal metabolism and its chronic use should be considered only if other treatments are ineffective.	IIa	C	69,273,294
In patients with AF treated with rate control, Holter ECG monitoring should be used to assess rate response and to detect bradycardia.	I	C	90
Ablation therapy for AF may be considered as for the general population.	IIb	C	90

AF, atrial fibrillation; DOAC, direct oral anticoagulant; ECG, electrocardiogram; FD, Fabry disease; OAC, oral anticoagulation; VKA, vitamin K antagonists.

Table 5 Recommendations for cardiac pacing in Fabry disease

Recommendations	Class	Level	Ref.
Dual-chamber pacing may be considered in symptomatic patients with FD and proven chronotropic incompetence.	IIb	C	25,105
CRT-P implantation should be considered in symptomatic patients with a pacing indication and an LVEF <50% and QRS prolongation (QRS >120 ms).	IIa	C	25,90,296
CRT-P implantation may be considered in symptomatic patients with a pacing indication and an LVEF ≥50% irrespective of QRS duration.	IIb	C	266,295,298,299

CRT-P, cardiac resynchronisation therapy with pacemaker; FD, Fabry disease; LVEF, left ventricular ejection fraction.

syncope or symptoms suggestive of malignant arrhythmia is not recommended[20] (*Table 6*).[14,90,108,109,150,188–190,302–307]

Other measures

Angiotensin-converting enzyme inhibitors or ARBs (if ACE inhibitors are not tolerated) should be used in all patients with hypertension, significant microalbuminuria/proteinuria and LV systolic dysfunction.[308] Their use in patients with LV outflow tract obstruction should be avoided if possible.[90]

There is no evidence of statin efficacy in FD but in the absence of any other supporting data, statins should be used according to current consensus guidelines.[242,309] The use of low-dose aspirin is recommended in secondary prevention in patients with symptomatic atherosclerosis.

Drugs interfering with lysosomal function, and possibly with FD specific therapies, like amiodarone and hydroxychloroquine, should be avoided or used with caution for a short course.[171]

Routine follow-up

In general, patients with FD require lifelong follow-up to detect changes in symptoms, arrhythmia occurrence, and heart failure progression. Clinical evaluation should be performed at baseline and whenever new symptoms develop. Cardiological follow-up should be part of a multidisciplinary team approach involving other specialties and should be performed in centres with experience of FD.[2,69,310]

In children, the progression of cardiac disease is slow and cardiac manifestations rare.[100] Therefore, cardiological re-evaluation may be less frequent (every 2–3 years). However, in classic FD the follow-up should be more frequent since early disease-specific treatment therapy may be beneficial.[311,312]

In adult men over the age of 20 years and women aged over 30, clinical re-evaluation should be performed on an annual basis. As a minimum, evaluation should consist of a clinical assessment, ECG, echocardiography and Holter monitoring. CMRI evaluation may be

Table 6 Recommendations for implantable cardioverter-defibrillators

Recommendations	Class	Level	Ref.
ICD implantation is recommended in patients with FD who have survived a cardiac arrest due to VT or VF, or who have spontaneous sustained VT causing syncope or haemodynamic compromise, and have a life expectancy of >1 year.	I	C	90,108,302–306
ICD implantation should be considered in patients with advanced hypertrophy and fibrosis requiring pacemaker implantation, and a life expectancy of >1 year.	IIa	C	14,109,188,189
ICD may be considered in patients with advanced hypertrophy and fibrosis and/or rapidly progressing fibrosis, and a life expectancy of >1 year.	IIb	C	108,109,150,307
ICD may be considered in patients with severe LVH and unexplained syncope or NSVT on ambulatory ECG monitoring.	IIb	C	108,188,190

ECG, electrocardiogram; FD, Fabry disease; ICD, implantable cardioverter-defibrillator; LVH, left ventricular hypertrophy; NSVT, non-sustained ventricular tachycardia; VF, ventricular fibrillation; VT, ventricular tachycardia.

considered routinely every 2–5 years before the onset of cardiac features and then every 2–3 years in patients with progressive disease or earlier based on the clinical picture.

Conclusions

Cardiac disease is a major cause of mortality and morbidity in classical and variant FD. Specific treatment strategies including enzyme replacement or small pharmacological chaperone have limited efficacy in advanced cases with irreversible organ damage, so that it is not only important to diagnose FD early and avoid any delays in treatment initiation, but it is also vital that patients receive timely assessment and treatment of cardiac symptoms and complications.

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