

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

Aleš Linhart¹, Dominique P. Germain², Iacopo Olivetto³, Mohammed M. Akhtar⁴, Aris Anastasakis⁵, Derrallynn Hughes⁶, Mehdi Namdar⁷, Maurizio Pieroni⁸, Albert Hagège^{9,10,11}, Franco Cecchi^{3,12}, Juan R. Gimeno¹³, Giuseppe Limongelli¹⁴, and Perry Elliott^{4*}

¹Second Department of Internal Cardiovascular Medicine, First Faculty of Medicine, Charles University and General University Hospital in Prague, Prague, Czech Republic; ²Division of Medical Genetics, University of Versailles and AP-HP Paris-Saclay, Paris, France; ³Cardiomyopathy Unit, Careggi University Hospital, Florence, Italy; ⁴Institute of Cardiovascular Science, University College London and Barts Heart Centre, London, UK; ⁵Unit of Inherited and Rare Cardiovascular Diseases, Onassis Cardiac Surgery Center, Kallithea, Greece; ⁶Royal Free London NHS Foundation Trust and University College London, London, UK; ⁷Department of Internal Medicine Specialties, Cardiology, Electrophysiology, University Hospital of Geneva, Geneva, Switzerland; ⁸Cardiomyopathy Clinic, Cardiovascular Department, San Donato Hospital, Arezzo, Italy; ⁹Cardiology Department, Assistance Publique-Hôpitaux de Paris, Hôpital Européen Georges Pompidou, Paris, France; ¹⁰Université Paris Descartes, Sorbonne Paris Cité, Paris, France; ¹¹INSERM CMR970, Paris Cardiovascular Research Center PARCC, Paris, France; ¹²IRCCS, Istituto Auxologico Italiano, Department of Cardiovascular, Neural and Metabolic Sciences, San Luca Hospital, Milan, Italy; ¹³Hospital C. Universitario Virgen Arrixaca, Murcia, Spain; and ¹⁴Dipartimento di Scienze Mediche Traslazionali, Università della Campania "Luigi Vanvitelli", AORN Colli, Ospedale Monaldi, Naples, Italy

Received 17 May 2020; revised 4 July 2020; accepted 4 July 2020

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 (Gb₃), and its deacylated form globotriaosylsphingosine (lyso-Gb₃) 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 Gb₃ 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 variants⁶ 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

*Corresponding author. Institute of Cardiovascular Science, University College London and Barts Heart Centre, Gower Street, London WC1E 6BT, UK. Tel: +44 20 37658611, Email: perry.elliott@ucl.ac.uk

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}

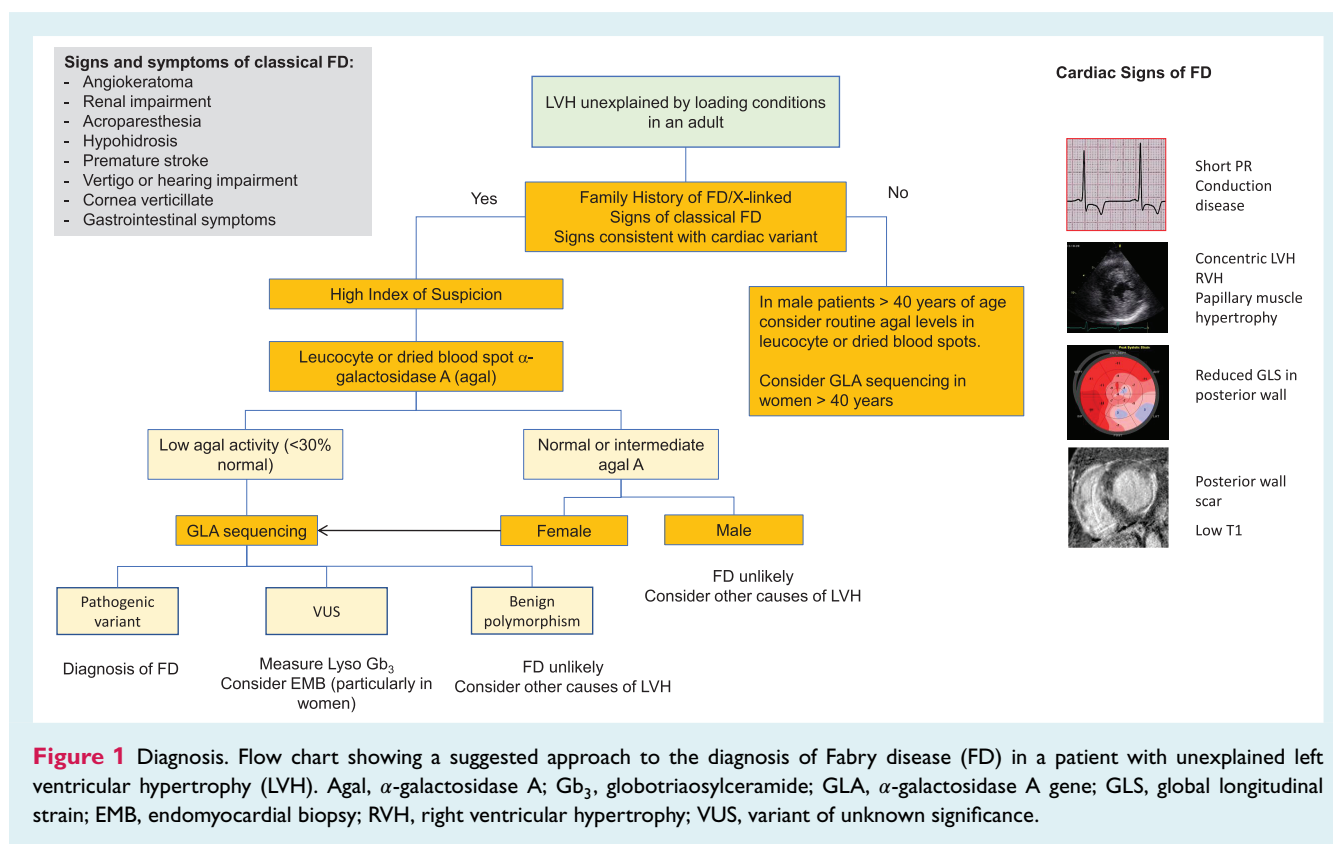
Most prevalence data are based on systematic screening of high-risk populations with manifestations typical for advanced FD such as HCM, cryptogenic stroke, or end-stage renal disease.^{46,47} The prevalence of FD in patients with unexplained LVH ranges from 0% to 12% in highly selected cohorts, but 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 Gb₃ 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 Gb₃ 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



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, Gb₃ is elevated in plasma or urine^{72,73} but may be normal in patients with isolated cardiac involvement.^{52,74} Recently, assessment of lyso-Gb₃ 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-Gb₃ levels as compared to later-onset variants, which may even be associated with normal lyso-Gb₃ levels.⁷⁸ Benign GLA variants are associated with normal lyso-Gb₃ 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) changes¹⁰⁰ 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 hypertrophy.

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 exceptional¹¹¹ and dynamic LV outflow tract obstruction caused by systolic anterior motion of the mitral valve can be provoked by exercise¹¹² 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 intra-ventricular septum, may be seen in FD¹¹⁹ 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

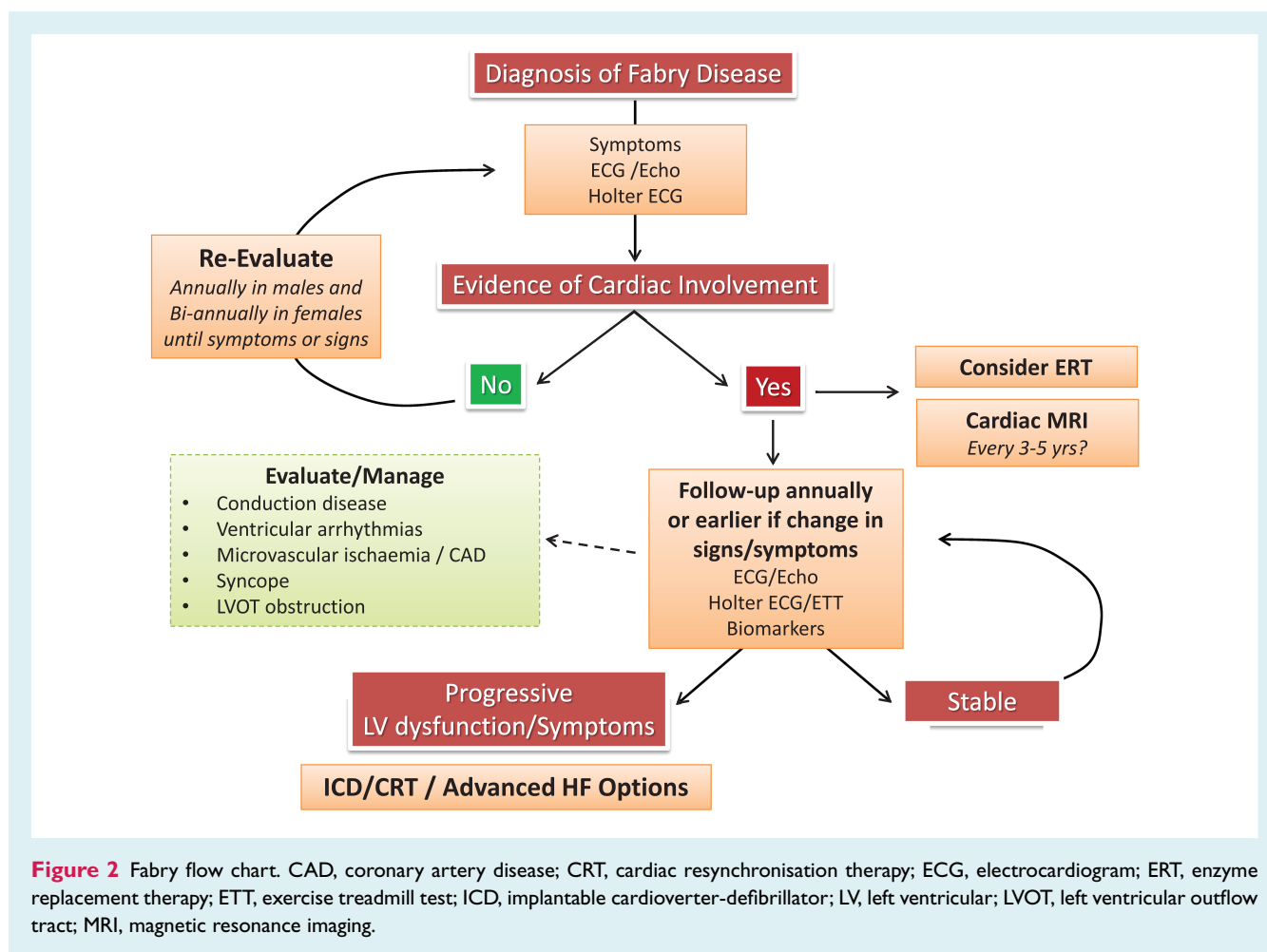


Figure 2 Fabry flow chart. CAD, coronary artery disease; CRT, cardiac resynchronisation therapy; ECG, electrocardiogram; ERT, enzyme replacement therapy; ETT, exercise treadmill test; ICD, implantable cardioverter-defibrillator; LV, left ventricular; LVOT, left ventricular outflow tract; MRI, magnetic 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 (³¹P spectroscopy).^{164–166}

Endomyocardial biopsy

Endomyocardial biopsy (EMB) may be considered in patients with VUS, high residual enzyme activity (>10%) and/or low lyso-Gb₃ 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 EPS¹⁷⁶ 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-Gb₃ 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-Gb₃ 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 prognosis¹⁸⁶ (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 registries⁶⁶ 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 provokable 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 provokable 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 <i>GLA</i> 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; Gb₃, 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 hypertrophy; NT-proBNP, N-terminal pro B-type natriuretic peptide.

have abnormal vessels due to endothelial and medial Gb₃ 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 changes²²⁸ 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 provokable 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 Gb₃ inclusions in the heart, but evidence for clearance of Gb₃ 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 data²⁵⁰ 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 patients¹⁶⁷ and one study has suggested that LVH may be prevented by early therapy.¹³ However, there are no data showing that ERT prevents myocardial fibrosis¹⁵⁰ 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 \geq 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 posterolateral 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/min²⁷⁶ 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 $\leq 35\%$), 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 ₂ DS 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 recommended²⁰ (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.

Funding

The meeting to formulate these recommendations was funded by an unrestricted grant from Sanofi Genzyme. Sanofi had no part in writing or editing the consensus recommendations.

Conflict of interest: A.L. received consultancy honoraria from Amicus Therapeutics, Sanofi Genzyme, Takeda, and speakers honoraria from Sanofi Genzyme and Takeda. D.P.G. is a consultant for Amicus Therapeutics, Sanofi Genzyme and Shire; has received research support from Sanofi Genzyme and Shire; and has received speaker honoraria and travel support from Amicus Therapeutics, Sanofi Genzyme, and Shire. I.O. has received research grants from Sanofi-Genzyme, Takeda-Shire, Amicus Therapeutics, Myokardia, Bayer, Menarini International, Boston Scientific; and has been a speaker and is on the advisory board of Sanofi-Genzyme, Takeda-Shire, Myokardia and Cytokinetics. D.H. has received honoraria for speaking and consulting, administered through UCL consultants, from Sanofi, Takeda, Protalix, amicus and freeline with a proportion of fees for UCL research. M.N. has received speaker fees/honoraria/travel grants by Bayer, Biosense Webster, Biotronik, Boston Scientific, Daiichi Sankyo, Medtronic, Sanofi Genzyme, Shire (now part of Takeda) and is on the advisory boards of Amicus, Bayer, Biotronik, Boston Scientific, Daiichi Sankyo, GBC, Sanofi Genzyme, Shire (now part of Takeda); has

investigatorship roles in Biotronik, Daiichi Sankyo, Biosense Webster, Boston-Scientific, Sanofi Genzyme; has research/fellowship grants from Abbott, Biotronik, Biosense Webster, Sanofi Genzyme and Shire (now part of Takeda); and Presidency of the CHAR (Swiss Arrhythmia Foundation). M.P. has received speaker and advisory board participation fees by Sanofi Genzyme, Takeda-Shire and Amicus Therapeutics. A.H. has served as an advisor to Amicus, Gilead, Myokardia, Sanofi Genzyme. F.C. was a consultant for Sanofi Genzyme in 2018. J.R.G. has speaker/teaching, advisory work for Sanofi and Amicus, and research projects participation for Sanofi and Shire. G.L. has served as an advisor to Amicus, Shire, Sanofi Genzyme. P.M.E. has received speaker honoraria from Sanofi Genzyme and Shire; and consultant and speaker honoraria from MyoKardia, Pfizer, Alnylam, and Sanofi Genzyme. All other authors have nothing to disclose.

References

1. Aerts JM, Groener JE, Kuiper S, Donker-Koopman WE, Strijland A, Ottenhoff R, van Roomen C, Mirzaian M, Wijburg FA, Linthorst GE, Vedder AC, Rombach SM, Cox-Brinkman J, Somerharju P, Boot RG, Hollak CE, Brady RO, Poorthuis BJ. Elevated globotriaosylsphingosine is a hallmark of Fabry disease. *Proc Natl Acad Sci U S A* 2008;**105**:2812–2817.
2. Germain DP. Fabry disease. *Orphanet J Rare Dis* 2010;**5**:30.
3. Banikazemi M, Bultas J, Waldek S, Wilcox WR, Whitley CB, McDonald M, Finkel R, Packman S, Bichet DG, Warnock DG, Desnick RJ; Fabry Disease Clinical Trial Study Group. Agalsidase-beta therapy for advanced Fabry disease: a randomized trial. *Ann Intern Med* 2007;**146**:77–86.
4. Eng CM, Guffon N, Wilcox WR, Germain DP, Lee P, Waldek S, Caplan L, Linthorst GE, Desnick RJ; International Collaborative Fabry Disease Study Group. Safety and efficacy of recombinant human alpha-galactosidase A replacement therapy in Fabry's disease. *N Engl J Med* 2001;**345**:9–16.
5. Schiffmann R, Kopp JB, Austin HA 3rd, Sabnis S, Moore DF, Weibel T, Balow JE, Brady RO. Enzyme replacement therapy in Fabry disease: a randomized controlled trial. *JAMA* 2001;**285**:2743–2749.
6. Germain DP, Hughes DA, Nicholls K, Bichet DG, Giugliani R, Wilcox WR, Feliciani C, Shankar SP, Ezgu F, Amartino H, Bratkovic D, Feldt-Rasmussen U, Nedd K, Sharaf El Din U, Lourenco CM, Banikazemi M, Charrow J, Dasouki M, Finegold D, Giraldo P, Goker-Alpan O, Longo N, Scott CR, Torra R, Tuffaha A, Jovanovic A, Waldek S, Packman S, Ludington E, Viereck C, Kirk J, Yu J, Benjamin ER, Johnson F, Lockhart DJ, Skuban N, Castelli J, Barth J, Barlow C, Schiffmann R. Treatment of Fabry's disease with the pharmacologic chaperone migalastat. *N Engl J Med* 2016;**375**:545–555.
7. Ashe KM, Budman E, Bangari DS, Siegel CS, Nietupski JB, Wang B, Desnick RJ, Scheule RK, Leonard JP, Cheng SH, Marshall J. Efficacy of enzyme and substrate reduction therapy with a novel antagonist of glucosylceramide synthase for Fabry disease. *Mol Med* 2015;**21**:389–399.

8. Simonetta I, Tuttolomondo A, Di Chiara T, Miceli S, Vogiatzis D, Corpora F, Pinto A. Genetics and gene therapy of Anderson-Fabry disease. *Curr Gene Ther* 2018;**18**:96–106.
9. Lee CJ, Fan X, Guo X, Medin JA. Promoter-specific lentivectors for long-term, cardiac-directed therapy of Fabry disease. *J Cardiol* 2011;**57**:115–122.
10. Shen JS, Busch A, Day TS, Meng XL, Yu CL, Dabrowska-Schlepp P, Fode B, Niederkruger H, Forni S, Chen S, Schiffmann R, Frischmuth T, Schaaf A. Mannose receptor-mediated delivery of moss-made alpha-galactosidase A efficiently corrects enzyme deficiency in Fabry mice. *J Inher Metab Dis* 2016;**39**:293–303.
11. Weidemann F, Breunig F, Beer M, Sandstede J, Turschner O, Voelker W, Ertl G, Knoll A, Wanner C, Strotmann JM. Improvement of cardiac function during enzyme replacement therapy in patients with Fabry disease: a prospective strain rate imaging study. *Circulation* 2003;**108**:1299–1301.
12. Hongo K, Ito K, Date T, Anan I, Inoue Y, Morimoto S, Ogawa K, Kawai M, Kobayashi H, Kobayashi M, Ida H, Ohashi T, Taniguchi I, Yoshimura M, Eto Y. The beneficial effects of long-term enzyme replacement therapy on cardiac involvement in Japanese Fabry patients. *Mol Genet Metab* 2018;**124**:143–151.
13. Weidemann F, Niemann M, Breunig F, Herrmann S, Beer M, Stork S, Voelker W, Ertl G, Wanner C, Strotmann JM. Long-term effects of enzyme replacement therapy on fabry cardiomyopathy: evidence for a better outcome with early treatment. *Circulation* 2009;**119**:524–529.
14. Patel V, O'Mahony C, Hughes D, Rahman MS, Coats C, Murphy E, Lachmann R, Mehta A, Elliott PM. Clinical and genetic predictors of major cardiac events in patients with Anderson-Fabry disease. *Heart* 2015;**101**:961–966.
15. Weidemann F, Niemann M, Stork S, Breunig F, Beer M, Sommer C, Herrmann S, Ertl G, Wanner C. Long-term outcome of enzyme-replacement therapy in advanced Fabry disease: evidence for disease progression towards serious complications. *J Intern Med* 2013;**274**:331–341.
16. Weidemann F, Breunig F, Beer M, Sandstede J, Stork S, Voelker W, Ertl G, Knoll A, Wanner C, Strotmann JM. The variation of morphological and functional cardiac manifestation in Fabry disease: potential implications for the time course of the disease. *Eur Heart J* 2005;**26**:1221–1227.
17. Patel MR, Cecchi F, Cizmarić M, Kantola I, Linhart A, Nicholls K, Strotmann J, Tallaj J, Tran TC, West ML, Beitner-Johnson D, Abiose A. Cardiovascular events in patients with Fabry disease: natural history data from the Fabry Registry. *J Am Coll Cardiol* 2011;**57**:1093–1099.
18. Mehta A, Clarke JT, Giugliani R, Elliott P, Linhart A, Beck M, Sunder-Plassmann G, FOS Investigators. Natural course of Fabry disease: changing pattern of causes of death in FOS - Fabry Outcome Survey. *J Med Genet* 2009;**46**:548–552.
19. Wann LS, Curtis AB, Ellenbogen KA, Estes NA, Ezekowitz MD, Jackman WM, January CT, Lowe JE, Page RL, Slotwimer DJ, Stevenson WG, Tracy CM, Fuster V, Ryden LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, Halperin JL, Heuzey J, Kay GN, Lowe JE, Olsson SB, Prystowsky EN, Tamargo JL, Wann LS. Management of patients with atrial fibrillation (compilation of 2006 ACCF/AHA/ESC and 2011 ACCF/AHA/HRS recommendations): a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 2013;**127**:1916–1926.
20. Priori SG, Blomstrom-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Camm J, Elliott PM, Fitzsimons D, Hatala R, Hindricks G, Kirchhof P, Kjeldsen S, Kuck KH, Hernandez-Madrid A, Nikolaou N, Norekval TM, Spaulding C, Van Veldhuisen DJ; Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC). 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: the Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPCC). *Europace* 2015;**17**:1601–1687.
21. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener HC, Heidbuchel H, Hendricks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Van Putte B, Vardas P; ESC Scientific Document Group. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J* 2016;**37**:2893–2962.
22. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Bohm M, Christiaens T, Cifkova R, De Backer G, Dominiczak A, Galderisi M, Grobbee DE, Jaarsma T, Kirchhof P, Kjeldsen SE, Laurent S, Manolis AJ, Nilsson PM, Ruilope LM, Schmieder RE, Sirnes PA, Sleight P, Viigimaa M, Waeber B, Zannad F, Redon J, Dominiczak A, Narkiewicz K, Nilsson PM, Burnier M, Viigimaa M, Ambrosioni E, Caulfield M, Coca A, Olsen MH, Schmieder RE, Tsoufis C, van de Borne P, Zamorano JL, Achenbach S, Baumgartner H, Bax JJ, Bueno H, Dean V, Deaton C, Erol C, Fagard R, Ferrari R, Hasdai D, Hoes AW, Kirchhof P, Knuuti J, Kolh P, Lancellotti P, Linhart A, Nihoyannopoulos P, Piepoli MF, Ponikowski P, Sirnes PA, Tamargo JL, Tendera M, Torbicki A, Wijns W, Windecker S, Clement DL, Coca A, Gillebert TC, Tendera M, Rosei EA, Ambrosioni E, Anker SD, Buaersachs J, Hitić JB, Caulfield M, De Buyere M, De Geest S, Derumeaux GA, Erdine S, Farsang C, Funck-Brentano C, Gerc V, Germano G, Gielen S, Haller H, Hoes AW, Jordan J, Kahan T, Komajda M, Lovic D, Mahrholdt H, Olsen MH, Ostergren J, Parati G, Perk J, Polonia J, Popescu BA, Reiner Z, Ryden L, Sirenko Y, Stanton A, Struijker-Boudier H, Tsoufis C, van de Borne P, Vlachopoulos C, Volpe M, Wood DA. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J* 2013;**34**:2159–2219.
23. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2016;**18**:891–975.
24. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, Jung B, Lancellotti P, Lansac E, Rodriguez Munoz D, Rosenhek R, Sjogren J, Tornos Mas P, Vahanian A, Walther T, Wendler O, Windecker S, Zamorano JL; ESC Scientific Document Group. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J* 2017;**38**:2739–2791.
25. Brignole M, Auricchio A, Baron-Esquivias G, Bordachar P, Boriani G, Breithardt OA, Cleland J, Deharo JC, Delgado V, Elliott PM, Gorenek B, Israel CW, Leclercq C, Linde C, Mont L, Padeletti L, Sutton R, Vardas PE. 2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy: the Task Force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). *Europace* 2013;**15**:1070–1118.
26. Gal A, Beck M, Hoppner W, Germain DP. Clinical utility gene card for: Fabry disease – update 2016. *Eur J Hum Genet* 2017;**25**:e1–e3.
27. Doheny D, Srinivasan R, Pagant S, Chen B, Yasuda M, Desnick RJ. Fabry disease: prevalence of affected males and heterozygotes with pathogenic GLA mutations identified by screening renal, cardiac and stroke clinics, 1995–2017. *J Med Genet* 2018;**55**:261–268.
28. Germain DP, Shabbeer J, Cotigny S, Desnick RJ. Fabry disease: twenty novel alpha-galactosidase A mutations and genotype-phenotype correlations in classical and variant phenotypes. *Mol Med* 2002;**8**:306–312.
29. Mogensen J, van Tintelen JP, Fokstuen S, Elliott P, van Langen IM, Meder B, Richard P, Syrris P, Caforio AL, Adler Y, Anastasakis A, Gimeno JR, Klingel K, Linhart A, Imazio M, Pinto Y, Newbery R, Schmidtke J, Charron P. The current role of next-generation DNA sequencing in routine care of patients with hereditary cardiovascular conditions: a viewpoint paper of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases and members of the European Society of Human Genetics. *Eur Heart J* 2015;**36**:1367–1370.
30. Smid BE, van der Tol L, Cecchi F, Elliott PM, Hughes DA, Linthorst GE, Timmermans J, Weidemann F, West ML, Biegtstraaten M, Lekanke Deprez RH, Florquin S, Postema PG, Tomberli B, van der Wal AC, van den Bergh Weerman MA, Hollak CE. Uncertain diagnosis of Fabry disease: consensus recommendation on diagnosis in adults with left ventricular hypertrophy and genetic variants of unknown significance. *Int J Cardiol* 2014;**177**:400–408.
31. Germain DP, Fouilhous A, Decramer S, Tardieu M, Pillet P, Fila M, Rivera S, Deschenes G, Lacombe D. Consensus recommendations for diagnosis, management and treatment of Fabry disease in paediatric patients. *Clin Genet* 2019;**96**:107–117.
32. Ferreira S, Ortiz A, Germain DP, Viana-Baptista M, Caldeira-Gomes A, Campreios M, Fenollar-Cortes M, Gallegos-Villalobos A, Garcia D, Garcia-Robles JA, Egido J, Gutierrez-Rivas E, Herrero JA, Mas S, Oancea R, Peres P, Salazar-Martin LM, Solera-Garcia J, Alves H, Garman SC, Oliveira JP. The alpha-galactosidase A p.Arg118Cys variant does not cause a Fabry disease phenotype: data from individual patients and family studies. *Mol Genet Metab* 2015;**114**:248–258.
33. Wilcox WR, Oliveira JP, Hopkin RJ, Ortiz A, Banikazemi M, Feldt-Rasmussen U, Sims K, Waldek S, Pastores GM, Lee P, Eng CM, Marodi L, Stanford KE, Breunig F, Wanner C, Warnock DG, Lemay RM, Germain DP, Fabry R. Females with Fabry disease frequently have major organ involvement: lessons from the Fabry Registry. *Mol Genet Metab* 2008;**93**:112–128.
34. Hopkin RJ, Cabrera G, Charrow J, Lemay R, Martins AM, Mauer M, Ortiz A, Patel MR, Sims K, Waldek S, Warnock DG, Wilcox WR. Risk factors for severe clinical events in male and female patients with Fabry disease treated with agalsidase beta enzyme replacement therapy: data from the Fabry Registry. *Mol Genet Metab* 2016;**119**:151–159.

35. Whybra C, Kampmann C, Willers I, Davies J, Winchester B, Kriegsmann J, Bruhl K, Gal A, Bunge S, Beck M. Anderson-Fabry disease: clinical manifestations of disease in female heterozygotes. *J Inher Metab Dis* 2001;**24**:715–724.
36. MacDermot KD, Holmes A, Miners AH. Anderson-Fabry disease: clinical manifestations and impact of disease in a cohort of 60 obligate carrier females. *J Med Genet* 2001;**38**:769–775.
37. Echevarria L, Benistan K, Toussaint A, Dubourg O, Hagege AA, Eladiri D, Jabbour F, Beldjord C, De Mazancourt P, Germain DP. X-chromosome inactivation in female patients with Fabry disease. *Clin Genet* 2016;**89**:44–54.
38. Dobrovolsky R, Dvorakova L, Ledvinova J, Magage S, Bultas J, Lubanda JC, Elleder M, Karetova D, Pavlikova M, Hrebicek M. Relationship between X-inactivation and clinical involvement in Fabry heterozygotes. Eleven novel mutations in the alpha-galactosidase A gene in the Czech and Slovak population. *J Mol Med (Berl)* 2005;**83**:647–654.
39. Lin HY, Chong KW, Hsu JH, Yu HC, Shih CC, Huang CH, Lin SJ, Chen CH, Chiang CC, Ho HJ, Lee PC, Kao CH, Cheng KH, Hsueh C, Niu DM. High incidence of the cardiac variant of Fabry disease revealed by newborn screening in the Taiwan Chinese population. *Circ Cardiovasc Genet* 2009;**2**:450–456.
40. Oliveira JP, Nowak A, Barbey F, Torres M, Nunes JP, Teixeira EC, Carvalho F, Sampaio S, Tavares I, Pereira O, Soares AL, Carmona C, Cardoso MT, Jurca-Simina IE, Spada M, Ferreira S, Germain DP. Fabry disease caused by the GLA p.Phe113Leu (p.F113L) variant: natural history in males. *Eur J Med Genet* 2020;**63**:103703.
41. Azevedo O, Gal A, Faria R, Gaspar P, Miltenberger-Miltenyi G, Gago MF, Dias F, Martins A, Rodrigues J, Reimao P, Pereira O, Simoes S, Lopes E, Guimaraes MJ, Sousa N, Cunha D. Founder effect of Fabry disease due to p.F113L mutation: clinical profile of a late-onset phenotype. *Mol Genet Metab* 2020;**129**:150–160.
42. Meikle PJ, Hopwood JJ, Clague AE, Carey WF. Prevalence of lysosomal storage disorders. *JAMA* 1999;**281**:249–254.
43. Spada M, Pagliardini S, Yasuda M, Tukul T, Thiagarajan G, Sakuraba H, Ponzone A, Desnick RJ. High incidence of later-onset Fabry disease revealed by newborn screening. *Am J Hum Genet* 2006;**79**:31–40.
44. Gelb MH, Turecek F, Scott CR, Chamoles NA. Direct multiplex assay of enzymes in dried blood spots by tandem mass spectrometry for the newborn screening of lysosomal storage disorders. *J Inher Metab Dis* 2006;**29**:397–404.
45. Scott CR, Elliott S, Buraker N, Thomas LI, Keutzer J, Glass M, Gelb MH, Turecek F. Identification of infants at risk for developing Fabry, Pompe, or mucopolysaccharidosis-I from newborn blood spots by tandem mass spectrometry. *J Pediatr* 2013;**163**:498–503.
46. Reuser AJ, Verheijen FW, Bali D, van Diggelen OP, Germain DP, Hwu WL, Lukacs Z, Muhl A, Olivova P, Piraud M, Wuyts B, Zhang K, Keutzer J. The use of dried blood spot samples in the diagnosis of lysosomal storage disorders – current status and perspectives. *Mol Genet Metab* 2011;**104**:144–148.
47. Linthorst GE, Bouwman MG, Wijburg FA, Aerts JM, Poorthuis BJ, Hollak CE. Screening for Fabry disease in high-risk populations: a systematic review. *J Med Genet* 2010;**47**:217–222.
48. Palecek T, Honzikova J, Poupetova H, Vlasikova H, Kuchynka P, Golan L, Magage S, Linhart A. Prevalence of Fabry disease in male patients with unexplained left ventricular hypertrophy in primary cardiology practice: prospective Fabry Cardiomyopathy Screening Study (FACSS). *J Inher Metab Dis* 2014;**37**:455–460.
49. Monserrat L, Gimeno-Blanes JR, Marin F, Hermida-Prieto M, Garcia-Honrubia A, Perez I, Fernandez X, de Nicolas R, de la Morena G, Paya E, Yague J, Egidio J. Prevalence of Fabry disease in a cohort of 508 unrelated patients with hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2007;**50**:2399–2403.
50. Sachdev B, Takenaka T, Teraguchi H, Tei C, Lee P, McKenna WJ, Elliott PM. Prevalence of Anderson-Fabry disease in male patients with late onset hypertrophic cardiomyopathy. *Circulation* 2002;**105**:1407–1411.
51. Elliott P, Baker R, Pasquale F, Quarta G, Ebrahim H, Mehta AB, Hughes DA; ACES Study Group. Prevalence of Anderson-Fabry disease in patients with hypertrophic cardiomyopathy: the European Anderson-Fabry Disease survey. *Heart* 2011;**97**:1957–1960.
52. Gagli M, Lajic N, Heinze G, Voigtlander T, Sunder-Plassmann R, Paschke E, Fauler G, Sunder-Plassmann G, Mundigler G. Screening for Fabry disease by urinary globotriaosylceramide isoforms measurement in patients with left ventricular hypertrophy. *Int J Med Sci* 2016;**13**:340–346.
53. Maron MS, Xin W, Sims KB, Butler R, Haas TS, Rowin EJ, Desnick RJ, Maron BJ. Identification of Fabry disease in a tertiary referral cohort of patients with hypertrophic cardiomyopathy. *Am J Med* 2018;**131**:200.e1–e8.
54. Kubo T, Ochi Y, Baba Y, Hirota T, Tanioka K, Yamasaki N, Yoshimitsu M, Higuchi K, Takenaka T, Nakajima K, Togawa T, Tsukimura T, Sano S, Tei C, Sakuraba H, Kitaoka H. Prevalence and clinical features of Fabry disease in Japanese male patients with diagnosis of hypertrophic cardiomyopathy. *J Cardiol* 2017;**69**:302–307.
55. Ommen SR, Nishimura RA, Edwards WD. Fabry disease: a mimic for obstructive hypertrophic cardiomyopathy? *Heart* 2003;**89**:929–930.
56. Nakao S, Takenaka T, Maeda M, Kodama C, Tanaka A, Tahara M, Yoshida A, Kuriyama M, Hayashibe H, Sakuraba H, Tanaka H. An atypical variant of Fabry's disease in men with left ventricular hypertrophy. *N Engl J Med* 1995;**333**:288–293.
57. Arad M, Maron BJ, Gorham JM, Johnson WH, Jr., Saul JP, Perez-Atayde AR, Spirito P, Wright GB, Kanter RJ, Seidman CE, Seidman JG. Glycogen storage diseases presenting as hypertrophic cardiomyopathy. *N Engl J Med* 2005;**352**:362–372.
58. Chimenti C, Pieroni M, Morgante E, Antuzzi D, Russo A, Russo MA, Maseri A, Frustaci A. Prevalence of Fabry disease in female patients with late-onset hypertrophic cardiomyopathy. *Circulation* 2004;**110**:1047–1053.
59. Havndrup O, Christiansen M, Stoevring B, Jensen M, Hoffman-Bang J, Andersen PS, Hasholt L, Norremolle A, Feldt-Rasmussen U, Kober L, Bundgaard H. Fabry disease mimicking hypertrophic cardiomyopathy: genetic screening needed for establishing the diagnosis in women. *Eur J Heart Fail* 2010;**12**:535–540.
60. Hagege AA, Caudron E, Damy T, Roudaut R, Millaire A, Etchecopar-Chevreuil C, Tran TC, Jabbour F, Boucly C, Prognon P, Charron P, Germain DP; FOCUS Study Investigators. Screening patients with hypertrophic cardiomyopathy for Fabry disease using a filter-paper test: the FOCUS study. *Heart* 2011;**97**:131–136.
61. Mawatari K, Yasukawa H, Oba T, Nagata T, Togawa T, Tsukimura T, Kyo-goku S, Ohshima H, Minami T, Sugi Y, Sakuraba H, Imaizumi T. Screening for Fabry disease in patients with left ventricular hypertrophy. *Int J Cardiol* 2013;**167**:1059–1061.
62. Terryn W, Deschoenmakers G, De Keyser J, Meersseman W, Van Biesen W, Wuyts B, Hemelsoet D, Pascale H, De Backer J, De Paepe A, Poppe B, Vanholder R. Prevalence of Fabry disease in a predominantly hypertensive population with left ventricular hypertrophy. *Int J Cardiol* 2013;**167**:2555–2560.
63. Mehta A, Ricci R, Widmer U, Dehout F, Garcia de Lorenzo A, Kampmann C, Linhart A, Sunder-Plassmann G, Ries M, Beck M. Fabry disease defined: baseline clinical manifestations of 366 patients in the Fabry Outcome Survey. *Eur J Clin Invest* 2004;**34**:236–242.
64. Eng CM, Germain DP, Banikazemi M, Warnock DG, Wanner C, Hopkin RJ, Bultas J, Lee P, Sims K, Brodie SE, Pastores GM, Strotmann JM, Wilcox WR. Fabry disease: guidelines for the evaluation and management of multi-organ system involvement. *Genet Med* 2006;**8**:539–548.
65. Germain DP, Brand E, Burlina A, Cecchi F, Garman SC, Kempf J, Laney DA, Linhart A, Marodi L, Nicholls K, Ortiz A, Pieruzzi F, Shankar SP, Waldek S, Wanner C, Jovanovic A. Phenotypic characteristics of the p.Asn215Ser (p.N215S) GLA mutation in male and female patients with Fabry disease: a multicenter Fabry Registry study. *Mol Genet Genomic Med* 2018;**6**:492–503.
66. Linhart A, Kampmann C, Zamorano JL, Sunder-Plassmann G, Beck M, Mehta A, Elliott PM; European FOS Investigators. Cardiac manifestations of Anderson-Fabry disease: results from the international Fabry Outcome Survey. *Eur Heart J* 2007;**28**:1228–1235.
67. Limongelli G, Monda E, Tramonte S, Gragnano F, Masarone D, Frisio G, Esposito A, Gravino R, Ammendola E, Salerno G, Rubino M, Caiazza M, Russo M, Calabrò P, Elliott PM, Pacileo G. Prevalence and clinical significance of red flags in patients with hypertrophic cardiomyopathy. *Int J Cardiol* 2020;**299**:186–191.
68. Oder D, Liu D, Hu K, Uceyler N, Salinger T, Muntze J, Lorenz K, Kandolf R, Grone HJ, Sommer C, Erdl G, Wanner C, Nordbeck P. Alpha-galactosidase A genotype N215S induces a specific cardiac variant of Fabry disease. *Circ Cardiovasc Genet* 2017;**10**:e001691.
69. Ortiz A, Germain DP, Desnick RJ, Politei J, Mauer M, Burlina A, Eng C, Hopkin RJ, Laney D, Linhart A, Waldek S, Wallace E, Weidemann F, Wilcox WR. Fabry disease revisited: management and treatment recommendations for adult patients. *Mol Genet Metab* 2018;**123**:416–427.
70. van der Tol L, Cassiman D, Houge G, Janssen MC, Lachmann RH, Linthorst GE, Ramaswami U, Sommer C, Tondel C, West ML, Weidemann F, Wijburg FA, Svarstad E, Hollak CE, Biegstraaten M. Uncertain diagnosis of Fabry disease in patients with neuropathic pain, angiokeratoma or cornea verticillata: consensus on the approach to diagnosis and follow-up. *JIMD Rep* 2014;**17**:83–90.
71. van der Tol L, Svarstad E, Ortiz A, Tondel C, Oliveira JP, Vogt L, Waldek S, Hughes DA, Lachmann RH, Terryn W, Hollak CE, Fournier S, van den Bergh Weerman MA, Wanner C, West ML, Biegstraaten M, Linthorst GE. Chronic kidney disease and an uncertain diagnosis of Fabry disease: approach to a correct diagnosis. *Mol Genet Metab* 2015;**114**:242–247.
72. Touboul D, Roy S, Germain DP, Baillet A, Brion F, Prognon P, Chaminade P, Laprevote O. Fast fingerprinting by MALDI-TOF mass spectrometry of urinary sediment glycosphingolipids in Fabry disease. *Anal Bioanal Chem* 2005;**382**:1209–1216.
73. Aury-Blais C, Blais CM, Ramaswami U, Boutin M, Germain DP, Dyack S, Bodamer O, Pintos-Morell G, Clarke JT, Bichet DG, Warnock DG, Echevarria L,

- West ML, Lavoie P. Urinary biomarker investigation in children with Fabry disease using tandem mass spectrometry. *Clin Chim Acta* 2015;**438**:195–204.
74. Ferreira S, Auray-Blais C, Boutin M, Lavoie P, Nunes JP, Martins E, Garman S, Oliveira JP. Variations in the GLA gene correlate with globotriaosylceramide and globotriaosylsphingosine analog levels in urine and plasma. *Clin Chim Acta* 2015;**447**:96–104.
 75. Gal A, Hughes DA, Winchester B. Toward a consensus in the laboratory diagnostics of Fabry disease - recommendations of a European expert group. *J Inher Metab Dis* 2011;**34**:509–514.
 76. Rombach SM, Dekker N, Bouwman MG, Linthorst GE, Zwinderman AH, Wijburg FA, Kuiper S, Vd Bergh Weerman MA, Groener JE, Poorthuis BJ, Hollak CE, Aerts JM. Plasma globotriaosylsphingosine: diagnostic value and relation to clinical manifestations of Fabry disease. *Biochim Biophys Acta* 2010;**1802**:741–748.
 77. Stiles AR, Zhang H, Dai J, McCaw P, Beasley J, Rehder C, Koeberl DD, McDonald M, Bali DS, Young SP. A comprehensive testing algorithm for the diagnosis of Fabry disease in males and females. *Mol Genet Metab* 2020;**130**:209–214.
 78. Maruyama H, Miyata K, Mikame M, Taguchi A, Guili C, Shimura M, Murayama K, Inoue T, Yamamoto S, Sugimura K, Tamita K, Kawasaki T, Kajihara J, Onishi A, Sugiyama H, Sakai T, Murata I, Oda T, Toyoda S, Hanawa K, Fujimura T, Ura S, Matsumura M, Takano H, Yamashita S, Matsukura G, Tazawa R, Shiga T, Ebato M, Satoh H, Ishii S. Effectiveness of plasma lyso-Gb3 as a biomarker for selecting high-risk patients with Fabry disease from multispecialty clinics for genetic analysis. *Genet Med* 2019;**21**:44–52.
 79. Auray-Blais C, Lavoie P, Boutin M, Ntwari A, Hsu TR, Huang CK, Niu DM. Biomarkers associated with clinical manifestations in Fabry disease patients with a late-onset cardiac variant mutation. *Clin Chim Acta* 2017;**466**:185–193.
 80. Kramer J, Weidemann F. Biomarkers for diagnosing and staging of Fabry disease. *Curr Med Chem* 2018;**25**:1530–1537.
 81. Nowak A, Mechtler T, Kasper DC, Desnick RJ. Correlation of Lyso-Gb3 levels in dried blood spots and sera from patients with classic and later-onset Fabry disease. *Mol Genet Metab* 2017;**121**:320–324.
 82. Kint JA. Fabry's disease: alpha-galactosidase deficiency. *Science* 1970;**167**:1268–1269.
 83. Desnick RJ, Allen KY, Desnick SJ, Raman MK, Bernlohr RW, Krivit W. Fabry's disease: enzymatic diagnosis of hemizygotes and heterozygotes. Alpha-galactosidase activities in plasma, serum, urine, and leukocytes. *J Lab Clin Med* 1973;**81**:157–171.
 84. Morrone A, Cavicchi C, Bardelli T, Antuzzi D, Parini R, Di Rocco M, Feriozzi S, Gabrielli O, Barone R, Pistone G, Spisni C, Ricci R, Zammarchi E. Fabry disease: molecular studies in Italian patients and X inactivation analysis in manifesting carriers. *J Med Genet* 2003;**40**:e103.
 85. Wang RY, Lelis A, Mirocha J, Wilcox WR. Heterozygous Fabry women are not just carriers, but have a significant burden of disease and impaired quality of life. *Genet Med* 2007;**9**:34–45.
 86. Weidemann F, Niemann M, Sommer C, Beer M, Breunig F, Wanner C. Interdisciplinary approach towards female patients with Fabry disease. *Eur J Clin Invest* 2012;**42**:455–462.
 87. Pasqualim G, Simon L, Sperb-Ludwig F, Burin MG, Michelin-Tirelli K, Giugliani R, Matte U. Fabry disease: a new approach for the screening of females in high-risk groups. *Clin Biochem* 2014;**47**:657–662.
 88. Zarate YA, Hopkin RJ. Fabry's disease. *Lancet* 2008;**372**:1427–1435.
 89. Miller EM, Wang Y, Ware SM. Uptake of cardiac screening and genetic testing among hypertrophic and dilated cardiomyopathy families. *J Genet Couns* 2013;**22**:258–267.
 90. Elliott PM, Anastakis A, Borger MA, Borggreve M, Cecchi F, Charron P, Hagege AA, Lafont A, Limongelli G, Mahrholdt H, McKenna WJ, Mogensen J, Nihoyannopoulos P, Nistri S, Pieper PG, Pieske B, Rapezzi C, Rutten FH, Tillmanns C, Watkins H. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). *Eur Heart J* 2014;**35**:2733–2779.
 91. Sunder-Plassmann G, Fodinger M. Diagnosis of Fabry disease: the role of screening and case-finding studies. In: Mehta A, Beck M, Sunder-Plassmann G, eds. *Fabry Disease: Perspectives from 5 Years of FOS*. Oxford: Oxford Pharmagenesis; 2006.
 92. Benjamin ER, Della Valle MC, Wu X, Katz E, Pruthi F, Bond S, Bronfin B, Williams H, Yu J, Bichet DG, Germain DP, Giugliani R, Hughes D, Schiffmann R, Wilcox WR, Desnick RJ, Kirk J, Barth J, Barlow C, Valenzano KJ, Castelli J, Lockhart DJ. The validation of pharmacogenetics for the identification of Fabry patients to be treated with migalastat. *Genet Med* 2017;**19**:430–438.
 93. Togawa T, Kodama T, Suzuki T, Sugawara K, Tsukimura T, Ohashi N, Suzuki K, Kitagawa T, Sakuraba H. Plasma globotriaosylsphingosine as a biomarker of Fabry disease. *Mol Genet Metab* 2010;**100**:257–261.
 94. Schiffmann R, Waldek S, Benigni A, Auray-Blais C. Biomarkers of Fabry disease nephropathy. *Clin J Am Soc Nephrol* 2010;**5**:360–364.
 95. Sueoka H, Ichihara J, Tsukimura T, Togawa T, Sakuraba H. Nano-LC-MS/MS for quantification of Lyso-Gb3 and its analogues reveals a useful biomarker for Fabry disease. *PLoS One* 2015;**10**:e0127048.
 96. Niemann M, Rolfs A, Stork S, Bijnens B, Breunig F, Beer M, Ertl G, Wanner C, Weidemann F. Gene mutations versus clinically relevant phenotypes: lyso-Gb3 defines Fabry disease. *Circ Cardiovasc Genet* 2014;**7**:8–16.
 97. Charron P, Arad M, Arbustini E, Basso C, Bilinska Z, Elliott P, Helio T, Keren A, McKenna WJ, Monserrat L, Pankuweit S, Perrot A, Rapezzi C, Ristic A, Seggewiss H, van Langen I, Tavazzi L; European Society of Cardiology Working Group on Myocardial and Pericardial Disease. Genetic counselling and testing in cardiomyopathies: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. *Eur Heart J* 2010;**31**:2715–2726.
 98. Ackerman MJ, Priori SG, Willems S, Berul C, Brugada R, Calkins H, Camm AJ, Ellinor PT, Gollob M, Hamilton R, Hershberger RE, Judge DP, Le Marec H, McKenna WJ, Schulze-Bahr E, Semsarian C, Towbin JA, Watkins H, Wilde A, Wolpert C, Zipes DP. HRS/EHRA Expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies: this document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA). *Europace* 2011;**13**:1077–1109.
 99. Girolami F, Frisso G, Benelli M, Crotti L, Iacone M, Mango R, Mazzaccara C, Pilichou K, Arbustini E, Tomberli B, Limongelli G, Basso C, Olivetto I. Contemporary genetic testing in inherited cardiac disease: tools, ethical issues, and clinical applications. *J Cardiovasc Med (Hagerstown)* 2018;**19**:1–11.
 100. Havranek S, Linhart A, Urbanova Z, Ramaswami U. Early cardiac changes in children with Anderson-Fabry disease. *JIMD Rep* 2013;**11**:53–64.
 101. Kampmann C, Wiethoff CM, Whybra C, Baehner FA, Mengel E, Beck M. Cardiac manifestations of Anderson-Fabry disease in children and adolescents. *Acta Paediatr* 2008;**97**:463–469.
 102. Hopkin RJ, Bissler J, Banikazemi M, Clarke L, Eng CM, Germain DP, Lemay R, Tylki-Szymanska A, Wilcox WR. Characterization of Fabry disease in 352 pediatric patients in the Fabry Registry. *Pediatr Res* 2008;**64**:550–555.
 103. Wijburg FA, Benichou B, Bichet DG, Clarke LA, Dostalova G, Fainboim A, Fellgiebel A, Forcelini C, An Haack K, Hopkin RJ, Mauer M, Najafian B, Scott CR, Shankar SP, Thurberg BL, Tondel C, Tylki-Szymanska A, Ramaswami U. Characterization of early disease status in treatment-naïve male paediatric patients with Fabry disease enrolled in a randomized clinical trial. *PLoS One* 2015;**10**:e0124987.
 104. Namdar M, Steffel J, Vidovic M, Brunckhorst CB, Holzmeister J, Luscher TF, Jenni R, Duru F. Electrocardiographic changes in early recognition of Fabry disease. *Heart* 2011;**97**:485–490.
 105. O'Mahony C, Coats C, Cardona M, Garcia A, Calcagnino M, Murphy E, Lachmann R, Mehta A, Hughes D, Elliott PM. Incidence and predictors of anti-bradycardia pacing in patients with Anderson-Fabry disease. *Europace* 2011;**13**:1781–1788.
 106. Niemann M, Hartmann T, Namdar M, Breunig F, Beer M, Machann W, Herrmann S, Ertl G, Wanner C, Weidemann F. Cross-sectional baseline analysis of electrocardiography in a large cohort of patients with untreated Fabry disease. *J Inher Metab Dis* 2013;**36**:873–879.
 107. Senechal M, Germain DP. Fabry disease: a functional and anatomical study of cardiac manifestations in 20 hemizygous male patients. *Clin Genet* 2003;**63**:46–52.
 108. Sene T, Lidove O, Sebbah J, Darondel JM, Picard H, Aaron L, Fain O, Zenone T, Joly D, Charron P, Ziza JM. Cardiac device implantation in Fabry disease: a retrospective monocentric study. *Medicine (Baltimore)* 2016;**95**:e4996.
 109. Weidemann F, Maier SK, Stork S, Brunner T, Liu D, Hu K, Seydelmann N, Schneider A, Becher J, Canan-Kuhl S, Blaschke D, Bijnens B, Ertl G, Wanner C, Nordbeck P. Usefulness of an implantable loop recorder to detect clinically relevant arrhythmias in patients with advanced Fabry cardiomyopathy. *Am J Cardiol* 2016;**118**:264–274.
 110. Wu JC, Ho CY, Skali H, Abichandani R, Wilcox WR, Banikazemi M, Packman S, Sims K, Solomon SD. Cardiovascular manifestations of Fabry disease: relationships between left ventricular hypertrophy, disease severity, and alpha-galactosidase A activity. *Eur Heart J* 2010;**31**:1088–1097.
 111. Deva DP, Hanneman K, Li Q, Ng MY, Wasim S, Morel C, Iwanochko RM, Thavendiranathan P, Crean AM. Cardiovascular magnetic resonance demonstration of the spectrum of morphological phenotypes and patterns of myocardial scarring in Anderson-Fabry disease. *J Cardiovasc Magn Reson* 2016;**18**:14.
 112. Calcagnino M, O'Mahony C, Coats C, Cardona M, Garcia A, Janagaran K, Mehta A, Hughes D, Murphy E, Lachmann R, Elliott PM. Exercise-induced left ventricular outflow tract obstruction in symptomatic patients with Anderson-Fabry disease. *J Am Coll Cardiol* 2011;**58**:88–89.

113. Cecchi F, Iascone M, Maurizi N, Pezzoli L, Binaco I, Biagini E, Fibbi ML, Olivetto I, Pieruzzi F, Frunzelata A, Dorobantu L, Rapezzi C, Ferrazzi P. Intraoperative diagnosis of Anderson-Fabry disease in patients with obstructive hypertrophic cardiomyopathy undergoing surgical myectomy. *JAMA Cardiol* 2017;**2**:1147–1151.
114. Niemann M, Liu D, Hu K, Herrmann S, Breunig F, Strotmann J, Stork S, Voelker W, Ertl G, Wanner C, Weidemann F. Prominent papillary muscles in Fabry disease: a diagnostic marker? *Ultrasound Med Biol* 2011;**37**:37–43.
115. Palecek T, Dostalova G, Kuchynka P, Karetova D, Bultas J, Elleder M, Linhart A. Right ventricular involvement in Fabry disease. *J Am Soc Echocardiogr* 2008;**21**:1265–1268.
116. Kampmann C, Baehner FA, Whybra C, Bajbouj M, Baron K, Knuf M, Wiethoff CM, Trubel H, Beck M. The right ventricle in Fabry disease. *Acta Paediatr Suppl* 2005;**94**:15–18; discussion 9–10.
117. Niemann M, Breunig F, Beer M, Herrmann S, Strotmann J, Hu K, Emmert A, Voelker W, Ertl G, Wanner C, Weidemann F. The right ventricle in Fabry disease: natural history and impact of enzyme replacement therapy. *Heart* 2010;**96**:1915–1919.
118. Graziani F, Laurito M, Pieroni M, Pennestri F, Lanza GA, Coluccia V, Camporeale A, Pedicino D, Verrecchia E, Manna R, Crea F. Right ventricular hypertrophy, systolic function, and disease severity in Anderson-Fabry disease: an echocardiographic study. *J Am Soc Echocardiogr* 2017;**30**:282–291.
119. Pieroni M, Chimenti C, De Cobelli F, Morgante E, Del Maschio A, Gaudio C, Russo MA, Frustaci A. Fabry's disease cardiomyopathy: echocardiographic detection of endomyocardial glycosphingolipid compartmentalization. *J Am Coll Cardiol* 2006;**47**:1663–1671.
120. Mundigler G, Gaggli M, Heinze G, Graf S, Zehetgruber M, Lajic N, Voigtlander T, Mannhalter C, Sunder-Plassmann R, Paschke E, Fauler G, Sunder-Plassmann G. The endocardial binary appearance ('binary sign') is an unreliable marker for echocardiographic detection of Fabry disease in patients with left ventricular hypertrophy. *Eur J Echocardiogr* 2011;**12**:744–749.
121. Koskenvuo JW, Engblom E, Kantola IM, Hartiala JJ, Saraste A, Kiviniemi TO, Mononen I, Saraste M. Echocardiography in Fabry disease: diagnostic value of endocardial border binary appearance. *Clin Physiol Funct Imaging* 2009;**29**:177–180.
122. Kounas S, Demetrescu C, Pantazis AA, Keren A, Lee PJ, Hughes D, Mehta A, Elliott PM. The binary endocardial appearance is a poor discriminator of Anderson-Fabry disease from familial hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2008;**51**:2058–2061.
123. Marek J, Palecek T, Magne J, Laverigne D, Boulogne C, Fadel BM, Jacard A, Linhart A, Mohty D. Comparison of echocardiographic parameters in Fabry cardiomyopathy and light-chain cardiac amyloidosis. *Echocardiography* 2018;**35**:1755–1763.
124. Toro R, Perez-Isla L, Doxastaquis G, Barba MA, Gallego AR, Pintos G, Barbados FJ, Mangas A, Zamorano JL. Clinical usefulness of tissue Doppler imaging in predicting preclinical Fabry cardiomyopathy. *Int J Cardiol* 2009;**132**:38–44.
125. Costanzo L, Buccheri S, Capranzano P, Di Pino L, Curatolo G, Rodolico M, Leggio S, Blundo A, Tamburino C, Monte I. Early cardiovascular remodelling in Fabry disease. *J Inherit Metab Dis* 2014;**37**:109–116.
126. Zamorano J, Serra V, Perez de Isla L, Feltes G, Calli A, Barbado FJ, Torras J, Hernandez S, Herrera J, Herrero JA, Pintos G. Usefulness of tissue Doppler on early detection of cardiac disease in Fabry patients and potential role of enzyme replacement therapy (ERT) for avoiding progression of disease. *Eur J Echocardiogr* 2011;**12**:671–677.
127. Pieroni M, Chimenti C, Ricci R, Sale P, Russo MA, Frustaci A. Early detection of Fabry cardiomyopathy by tissue Doppler imaging. *Circulation* 2003;**107**:1978–1984.
128. Niemann M, Herrmann S, Hu K, Breunig F, Strotmann J, Beer M, Machann W, Voelker W, Ertl G, Wanner C, Weidemann F. Differences in Fabry cardiomyopathy between female and male patients: consequences for diagnostic assessment. *JACC Cardiovasc Imaging* 2011;**4**:592–601.
129. Esposito R, Galderisi M, Santoro C, Imbriaco M, Riccio E, Maria Pellegrino A, Sorrentino R, Lembo M, Citro R, Angela Losi M, Spinelli L, Trimarco B, Pisani A. Prominent longitudinal strain reduction of left ventricular basal segments in treatment-naïve Anderson-Fabry disease patients. *Eur Heart J Cardiovasc Imaging* 2019;**20**:438–445.
130. Shanks M, Thompson RB, Paterson ID, Putko B, Khan A, Chan A, Becher H, Oudit GY. Systolic and diastolic function assessment in Fabry disease patients using speckle-tracking imaging and comparison with conventional echocardiographic measurements. *J Am Soc Echocardiogr* 2013;**26**:1407–1414.
131. Weidemann F, Niemann M, Herrmann S, Kung M, Stork S, Waller C, Beer M, Breunig F, Wanner C, Voelker W, Ertl G, Bijnens B, Strotmann JM. A new echocardiographic approach for the detection of non-ischaemic fibrosis in hypertrophic myocardium. *Eur Heart J* 2007;**28**:3020–3026.
132. Kramer J, Niemann M, Liu D, Hu K, Machann W, Beer M, Wanner C, Ertl G, Weidemann F. Two-dimensional speckle tracking as a non-invasive tool for identification of myocardial fibrosis in Fabry disease. *Eur Heart J* 2013;**34**:1587–1596.
133. Gruner C, Verocai F, Carasso S, Vannan MA, Jamorski M, Clarke JT, Care M, Iwanochko RM, Rakowski H. Systolic myocardial mechanics in patients with Anderson-Fabry disease with and without left ventricular hypertrophy and in comparison to nonobstructive hypertrophic cardiomyopathy. *Echocardiography* 2012;**29**:810–817.
134. Morris DA, Blaschke D, Cnaan-Kuhl S, Krebs A, Knobloch G, Walter TC, Haverkamp W. Global cardiac alterations detected by speckle-tracking echocardiography in Fabry disease: left ventricular, right ventricular, and left atrial dysfunction are common and linked to worse symptomatic status. *Int J Cardiovasc Imaging* 2015;**31**:301–313.
135. Niemann M, Breunig F, Beer M, Hu K, Liu D, Emmert A, Herrmann S, Ertl G, Wanner C, Takenaka T, Tei C, Weidemann F. Tei index in Fabry disease. *J Am Soc Echocardiogr* 2011;**24**:1026–1032.
136. Pieroni M, Chimenti C, Russo A, Russo MA, Maseri A, Frustaci A. Tissue Doppler imaging in Fabry disease. *Curr Opin Cardiol* 2004;**19**:452–457.
137. Boyd AC, Lo Q, Devine K, Tchan MC, Silence DO, Sadick N, Richards DA, Thomas L. Left atrial enlargement and reduced atrial compliance occurs early in Fabry cardiomyopathy. *J Am Soc Echocardiogr* 2013;**26**:1415–1423.
138. Linhart A, Cecchi F. Common presentation of rare diseases: left ventricular hypertrophy and diastolic dysfunction. *Int J Cardiol* 2018;**257**:344–350.
139. Talbot AS, Lewis NT, Nicholls KM. Cardiovascular outcomes in Fabry disease are linked to severity of chronic kidney disease. *Heart* 2015;**101**:287–293.
140. Linhart A, Palecek T, Bultas J, Ferguson JJ, Hrudova J, Karetova D, Zeman J, Ledvinova J, Poupetova H, Elleder M, Aschermann M. New insights in cardiac structural changes in patients with Fabry's disease. *Am Heart J* 2000;**139**:1101–1108.
141. Weidemann F, Strotmann JM, Niemann M, Herrmann S, Wilke M, Beer M, Voelker W, Ertl G, Emmert A, Wanner C, Breunig F. Heart valve involvement in Fabry cardiomyopathy. *Ultrasound Med Biol* 2009;**35**:730–735.
142. Barbey F, Qanadli SD, Juli C, Brakch N, Palecek T, Rizzo E, Jeanrenaud X, Eckhardt B, Linhart A. Aortic remodelling in Fabry disease. *Eur Heart J* 2010;**31**:347–353.
143. Kalliokoski RJ, Kalliokoski KK, Penttinen M, Kantola I, Leino A, Viikari JS, Simell O, Nuutila P, Raitakari OT. Structural and functional changes in peripheral vasculature of Fabry patients. *J Inherit Metab Dis* 2006;**29**:660–666.
144. Barbey F, Brakch N, Linhart A, Jeanrenaud X, Palecek T, Bultas J, Burnier M, Hayoz D. Increased carotid intima-media thickness in the absence of atherosclerotic plaques in an adult population with Fabry disease. *Acta Paediatr Suppl* 2006;**95**:63–68.
145. Barbey F, Brakch N, Linhart A, Rosenblatt-Velin N, Jeanrenaud X, Qanadli S, Steinmann B, Burnier M, Palecek T, Bultas J, Hayoz D. Cardiac and vascular hypertrophy in Fabry disease: evidence for a new mechanism independent of blood pressure and glycosphingolipid deposition. *Arterioscler Thromb Vasc Biol* 2006;**26**:839–844.
146. Collin C, Briet M, Tran TC, Beaussier H, Benistan K, Bensalah M, Mousseaux E, Froissart M, Bozec E, Laurent S, Boutouyrie P, Germain DP. Long-term changes in arterial structure and function and left ventricular geometry after enzyme replacement therapy in patients affected with Fabry disease. *Eur J Prev Cardiol* 2012;**19**:43–54.
147. Nicholls K. Increased arterial stiffness is associated with high cardiovascular mortality in male Fabry patients. *J Inherit Metab Dis* 2012;**35**:885–889.
148. Moon JC, Sachdev B, Elkington AG, McKenna WJ, Mehta A, Pennell DJ, Leed PJ, Elliott PM. Gadolinium enhanced cardiovascular magnetic resonance in Anderson-Fabry disease. Evidence for a disease specific abnormality of the myocardial interstitium. *Eur Heart J* 2003;**24**:2151–2155.
149. Moon JC, Sheppard M, Reed E, Lee P, Elliott PM, Pennell DJ. The histological basis of late gadolinium enhancement cardiovascular magnetic resonance in a patient with Anderson-Fabry disease. *J Cardiovasc Magn Reson* 2006;**8**:479–482.
150. Kramer J, Niemann M, Stork S, Frantz S, Beer M, Ertl G, Wanner C, Weidemann F. Relation of burden of myocardial fibrosis to malignant ventricular arrhythmias and outcomes in Fabry disease. *Am J Cardiol* 2014;**114**:895–900.
151. Hsu TR, Hung SC, Chang FP, Yu WC, Sung SH, Hsu CL, Dzhalgali I, Yang CF, Chu TH, Lee HJ, Lu YH, Chang SK, Liao HC, Lin HY, Liao TC, Lee PC, Li HY, Yang AH, Ho HC, Chiang CC, Lin CY, Desnick RJ, Niu DM. Later onset Fabry disease, cardiac damage progress in silence: experience with a highly prevalent mutation. *J Am Coll Cardiol* 2016;**68**:2554–2563.
152. Kozor R, Grieve SM, Tchan MC, Callaghan F, Hamilton-Craig C, Denaro C, Moon JC, Figtree GA. Cardiac involvement in genotype-positive Fabry disease patients assessed by cardiovascular MR. *Heart* 2016;**102**:298–302.
153. Kozor R, Callaghan F, Tchan M, Hamilton-Craig C, Figtree GA, Grieve SM. A disproportionate contribution of papillary muscles and trabeculations to total left ventricular mass makes choice of cardiovascular magnetic resonance analysis technique critical in Fabry disease. *J Cardiovasc Magn Reson* 2015;**17**:22.

154. Poulin MF, Shah A, Trohman RG, Madias C. Advanced Anderson-Fabry disease presenting with left ventricular apical aneurysm and ventricular tachycardia. *World J Clin Cases* 2015;3:519–524.
155. Sado DM, White SK, Piechnik SK, Banyersad SM, Treibel T, Captur G, Fontana M, Maestrini V, Flett AS, Robson MD, Lachmann RH, Murphy E, Mehta A, Hughes D, Neubauer S, Elliott PM, Moon JC. Identification and assessment of Anderson-Fabry disease by cardiovascular magnetic resonance noncontrast myocardial T1 mapping. *Circ Cardiovasc Imaging* 2013;6:392–398.
156. Pica S, Sado DM, Maestrini V, Fontana M, White SK, Treibel T, Captur G, Anderson S, Piechnik SK, Robson MD, Lachmann RH, Murphy E, Mehta A, Hughes D, Kellman P, Elliott PM, Herrey AS, Moon JC. Reproducibility of native myocardial T1 mapping in the assessment of Fabry disease and its role in early detection of cardiac involvement by cardiovascular magnetic resonance. *J Cardiovasc Magn Reson* 2014;16:99.
157. Thompson RB, Chow K, Khan A, Chan A, Shanks M, Paterson I, Oudit GY. T(1) mapping with cardiovascular MRI is highly sensitive for Fabry disease independent of hypertrophy and sex. *Circ Cardiovasc Imaging* 2013;6:637–645.
158. Mewton N, Liu CY, Croisille P, Bluemke D, Lima JA. Assessment of myocardial fibrosis with cardiovascular magnetic resonance. *J Am Coll Cardiol* 2011;57:891–903.
159. Moon JC, Messroghli DR, Kellman P, Piechnik SK, Robson MD, Ugander M, Gatehouse PD, Arai AE, Friedrich MG, Neubauer S, Schulz-Menger J, Schelbert EB; Society for Cardiovascular Magnetic Resonance Imaging; Cardiovascular Magnetic Resonance Working Group of the European Society of Cardiology. Myocardial T1 mapping and extracellular volume quantification: a Society for Cardiovascular Magnetic Resonance (SCMR) and CMR Working Group of the European Society of Cardiology consensus statement. *J Cardiovasc Magn Reson* 2013;15:92.
160. Pagano JJ, Chow K, Khan A, Michelakis E, Paterson I, Oudit GY, Thompson RB. Reduced right ventricular native myocardial T1 in Anderson-Fabry disease: comparison to pulmonary hypertension and healthy controls. *PLoS One* 2016;11:e0157565.
161. Nordin S, Kozor R, Baig S, Abdel-Gadir A, Medina-Menacho K, Rosmini S, Captur G, Tchan M, Geberhiwot T, Murphy E, Lachmann R, Ramaswami U, Edwards NC, Hughes D, Steeds RP, Moon JC. Cardiac phenotype of prehypertrophic Fabry disease. *Circ Cardiovasc Imaging* 2018;11:e007168.
162. Camporeale A, Pieroni M, Pieruzzi F, Lusardi P, Pica S, Spada M, Mignani R, Burlina A, Bandera F, Guazzi M, Graziani F, Crea F, Greiser A, Boveri S, Ambrogi F, Lombardi M. Predictors of clinical evolution in prehypertrophic Fabry disease. *Circ Cardiovasc Imaging* 2019;12:e008424.
163. Haaf P, Garg P, Messroghli DR, Broadbent DA, Greenwood JP, Plein S. Cardiac T1 mapping and extracellular volume (ECV) in clinical practice: a comprehensive review. *J Cardiovasc Magn Reson* 2016;18:89.
164. Nappi C, Altiero M, Imbriaco M, Nicolai E, Giudice CA, Aiello M, Diomaiuti CT, Pisani A, Spinelli L, Cuocolo A. First experience of simultaneous PET/MRI for the early detection of cardiac involvement in patients with Anderson-Fabry disease. *Eur J Nucl Med Mol Imaging* 2015;42:1025–1031.
165. Palecek T, Bultas J, Hajek M, Karetova D, Kuchynka P, Kautzner J, Elleder M, Linhart A. Association between cardiac energy metabolism and gain of left ventricular mass in Fabry disease. *Int J Cardiol* 2010;144:337–339.
166. Machann W, Breunig F, Weidemann F, Sandstede J, Hahn D, Kostler H, Neubauer S, Wanner C, Beer M. Cardiac energy metabolism is disturbed in Fabry disease and improves with enzyme replacement therapy using recombinant human galactosidase A. *Eur J Heart Fail* 2011;13:278–283.
167. Hsu TR, Sung SH, Chang FP, Yang CF, Liu HC, Lin HY, Huang CK, Gao HJ, Huang YH, Liao HC, Lee PC, Yang AH, Chiang CC, Lin CY, Yu WC, Niu DM. Endomyocardial biopsies in patients with left ventricular hypertrophy and a common Chinese later-onset Fabry mutation (IVS4 + 919G >A). *Orphanet J Rare Dis* 2014;9:96.
168. Thurberg BL, Fallon JT, Mitchell R, Aretz T, Gordon RE, O'Callaghan MW. Cardiac microvascular pathology in Fabry disease: evaluation of endomyocardial biopsies before and after enzyme replacement therapy. *Circulation* 2009;119:2561–2567.
169. Tschope C, Dominguez F, Canaan-Kuhl S, Blaschke D, Kuhl U, Pieske B, Haverkamp W. Endomyocardial biopsy in Anderson-Fabry disease: the key in uncertain cases. *Int J Cardiol* 2015;190:284–286.
170. Cooper LT, Baughman KL, Feldman AM, Frustaci A, Jessup M, Kuhl U, Levine GN, Narula J, Starling RC, Towbin J, Virmani R. The role of endomyocardial biopsy in the management of cardiovascular disease: a scientific statement from the American Heart Association, the American College of Cardiology, and the European Society of Cardiology. Endorsed by the Heart Failure Society of America and the Heart Failure Association of the European Society of Cardiology. *Eur Heart J* 2007;28:3076–3093.
171. Yogasundaram H, Hung W, Paterson ID, Sergi C, Oudit GY. Chloroquine-induced cardiomyopathy: a reversible cause of heart failure. *ESC Heart Fail* 2018;5:372–375.
172. Lip GY, Coca A, Kahan T, Boriani G, Manolis AS, Olsen MH, Oto A, Potpara TS, Steffel J, Marin F, de Oliveira Figueiredo MJ, de Simone G, Tzou WS, Chiang CE, Williams B. Hypertension and cardiac arrhythmias: a consensus document from the European Heart Rhythm Association (EHRA) and ESC Council on Hypertension, endorsed by the Heart Rhythm Society (HRS), Asia-Pacific Heart Rhythm Society (APHRS) and Sociedad Latinoamericana de Estimulacion Cardiaca y Electrofisiologia (SOLEACE). *Europace* 2017;19:891–911.
173. Al-Khatib SM, Arshad A, Balk EM, Das SR, Hsu JC, Joglar JA, Page RL. Risk stratification for arrhythmic events in patients with asymptomatic pre-excitation: a systematic review for the 2015 ACC/AHA/HRS guideline for the management of adult patients with supraventricular tachycardia: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol* 2016;67:1624–1638.
174. Katriotis DG, Boriani G, Cosio FG, Hindricks G, Jais P, Josephson ME, Keegan R, Kim YH, Knight BP, Kuck KH, Lane DA, Lip GY, Malmberg H, Oral H, Pappone C, Themistoclakis S, Wood KA, Blomstrom-Lundqvist C, Gorenek B, Dagres N, Dan GA, Vos MA, Kudaiberdieva G, Crijns H, Roberts-Thomson K, Lin YJ, Vanegas D, Caorsi WR, Cronin E, Rickard J. European Heart Rhythm Association (EHRA) consensus document on the management of supraventricular arrhythmias, endorsed by Heart Rhythm Society (HRS), Asia-Pacific Heart Rhythm Society (APHRS), and Sociedad Latinoamericana de Estimulacion Cardiaca y Electrofisiologia (SOLEACE). *Europace* 2017;19:465–511.
175. Zipes DP, Calkins H, Daubert JP, Ellenbogen KA, Field ME, Fisher JD, Fogel RI, Frankel DS, Gupta A, Indik JH, Kusumoto FM, Lindsay BD, Marine JE, Mehta LS, Mendes LA, Miller JM, Munger TM, Sauer WH, Shen WK, Stevenson WG, Su WW, Tracy CM, Tsipserfal A. 2015 ACC/AHA/HRS advanced training statement on clinical cardiac electrophysiology (a revision of the ACC/AHA 2006 update of the clinical competence statement on invasive electrophysiology studies, catheter ablation, and cardioversion). *Heart Rhythm* 2016;13:e3–e37.
176. Jastrzebski M, Baciur B, Dimitrow PP, Kawecka-Jaszcz K. Electrophysiological study in a patient with Fabry disease and a short PQ interval. *Europace* 2006;8:1045–1047.
177. Sugarman M, Choudhury J, Jovanovic A. An atypical p.N215S variant of Fabry disease with end-stage renal failure. *Mol Genet Metab Rep* 2018;15:43–45.
178. Yogasundaram H, Nikhanj A, Putko BN, Boutin M, Jain-Ghai S, Khan A, Auray-Blais C, West ML, Oudit GY. Elevated inflammatory plasma biomarkers in patients with Fabry disease: a critical link to heart failure with preserved ejection fraction. *J Am Heart Assoc* 2018;7:e009098.
179. Altarescu G, Chicco G, Whybra C, Delgado-Sanchez S, Sharon N, Beck M, Elstein D. Correlation between interleukin-6 promoter and C-reactive protein (CRP) polymorphisms and CRP levels with the Mainz severity score index for Fabry disease. *J Inher Metab Dis* 2008;31:117–123.
180. Goker-Alpan O, Gambello MJ, Maegawa GH, Nedd KJ, Gruskin DJ, Blankstein L, Weinreb NJ. Reduction of plasma globotriaosylsphingosine levels after switching from agalsidase alfa to agalsidase beta as enzyme replacement therapy for Fabry disease. *JIMD Rep* 2016;25:95–106.
181. Lenders M, Neusser LP, Rudnicki M, Nordbeck P, Canaan-Kuhl S, Nowak A, Cybulla M, Schmitz B, Lukas J, Wanner C, Brand SM, Brand E. Dose-dependent effect of enzyme replacement therapy on neutralizing antidrug antibody titers and clinical outcome in patients with Fabry disease. *J Am Soc Nephrol* 2018;29:2879–2889.
182. Stappers F, Scharnetzki D, Schmitz B, Manikowski D, Brand SM, Grobe K, Lenders M, Brand E. Neutralising anti-drug antibodies in Fabry disease can inhibit endothelial enzyme uptake and activity. *J Inher Metab Dis* 2020;43:334–347.
183. Liu D, Oder D, Salinger T, Hu K, Muntze J, Weidemann F, Herrmann S, Ertl G, Wanner C, Frantz S, Stork S, Nordbeck P. Association and diagnostic utility of diastolic dysfunction and myocardial fibrosis in patients with Fabry disease. *Open Heart* 2018;5:e000803.
184. Coats CJ, Parisi V, Ramos M, Janagarajan K, O'Mahony C, Dawney A, Lachmann RH, Murphy E, Mehta A, Hughes D, Elliott PM. Role of serum N-terminal pro-brain natriuretic peptide measurement in diagnosis of cardiac involvement in patients with Anderson-Fabry disease. *Am J Cardiol* 2013;111:111–117.
185. Nordin S, Kozor R, Medina-Menacho K, Abdel-Gadir A, Baig S, Sado DM, Lobascio I, Murphy E, Lachmann RH, Mehta A, Edwards NC, Ramaswami U, Steeds RP, Hughes D, Moon JC. Proposed stages of myocardial phenotype development in Fabry disease. *JACC Cardiovasc Imaging* 2019;12:1673–1683.
186. Seydelmann N, Liu D, Kramer J, Drechsler C, Hu K, Nordbeck P, Schneider A, Stork S, Bijnsens B, Ertl G, Wanner C, Weidemann F. High-sensitivity troponin: a clinical blood biomarker for staging cardiomyopathy in Fabry disease. *J Am Heart Assoc* 2016;5:e002839.

187. Rapezzi C, Arbustini E, Caforio AL, Charron P, Gimeno-Blanes J, Helio T, Linhart A, Mogensen J, Pinto Y, Ristic A, Seggewiss H, Sinagra G, Tavazzi L, Elliott PM. Diagnostic work-up in cardiomyopathies: bridging the gap between clinical phenotypes and final diagnosis. A position statement from the ESC Working Group on Myocardial and Pericardial Diseases. *Eur Heart J* 2013;**34**:1448–1458.
188. Baig S, Edward NC, Kotecha D, Liu B, Nordin S, Kozor R, Moon JC, Geberhiwot T, Steeds RP. Ventricular arrhythmia and sudden cardiac death in Fabry disease: a systematic review of risk factors in clinical practice. *Europace* 2018;**20**:f153–f161.
189. Shah JS, Hughes DA, Sachdev B, Tome M, Ward D, Lee P, Mehta AB, Elliott PM. Prevalence and clinical significance of cardiac arrhythmia in Anderson-Fabry disease. *Am J Cardiol* 2005;**96**:842–846.
190. Acharya D, Robertson P, Kay GN, Jackson L, Warnock DG, Plumb VJ, Tallaj JA. Arrhythmias in Fabry cardiomyopathy. *Clin Cardiol* 2012;**35**:738–740.
191. Kramer J, Nordbeck P, Stork S, Ritter C, Ertl G, Wanner C, Weidemann F. Electrical changes in resting, exercise, and Holter electrocardiography in Fabry cardiomyopathy. *JIMD Rep* 2015;**28**:19–28.
192. Elliott PM, Gimeno Blanes JR, Mahon NG, Poloniecki JD, McKenna WJ. Relation between severity of left-ventricular hypertrophy and prognosis in patients with hypertrophic cardiomyopathy. *Lancet* 2001;**357**:420–424.
193. Maron MS, Olivetto I, Betocchi S, Casey SA, Lesser JR, Losi MA, Cecchi F, Maron BJ. Effect of left ventricular outflow tract obstruction on clinical outcome in hypertrophic cardiomyopathy. *N Engl J Med* 2003;**348**:295–303.
194. Elliott P, Gimeno J, Tome M, McKenna W. Left ventricular outflow tract obstruction and sudden death in hypertrophic cardiomyopathy. *Eur Heart J* 2006;**27**:3073; author reply 3073–3074.
195. Shah JS, Esteban MT, Thaman R, Sharma R, Mist B, Pantazis A, Ward D, Kohli SK, Page SP, Demetrescu C, Sevdalis E, Keren A, Pellerin D, McKenna WJ, Elliott PM. Prevalence of exercise-induced left ventricular outflow tract obstruction in symptomatic patients with non-obstructive hypertrophic cardiomyopathy. *Heart* 2008;**94**:1288–1294.
196. Maron MS, Olivetto I, Zenovich AG, Link MS, Pandian NG, Kuvlin JT, Nistri S, Cecchi F, Udelson JE, Maron BJ. Hypertrophic cardiomyopathy is predominantly a disease of left ventricular outflow tract obstruction. *Circulation* 2006;**114**:2232–2239.
197. Dimitrow PP, Bober M, Michalowska J, Sorysz D. Left ventricular outflow tract gradient provoked by upright position or exercise in treated patients with hypertrophic cardiomyopathy without obstruction at rest. *Echocardiography* 2009;**26**:513–520.
198. Marwick TH, Nakatani S, Haluska B, Thomas JD, Lever HM. Provocation of latent left ventricular outflow tract gradients with amyl nitrite and exercise in hypertrophic cardiomyopathy. *Am J Cardiol* 1995;**75**:805–809.
199. Blount JR, Wu JK, Martinez MW. Fabry's disease with LVOT obstruction: diagnosis and management. *J Card Surg* 2013;**28**:695–698.
200. Olivetto I, Maron MS, Autore C, Lesser JR, Rega L, Casolo G, De Santis M, Quarta G, Nistri S, Cecchi F, Salton CJ, Udelson JE, Manning WJ, Maron BJ. Assessment and significance of left ventricular mass by cardiovascular magnetic resonance in hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2008;**52**:559–566.
201. Prinz C, Schwarz M, Illic I, Laser KT, Lehmann R, Prinz EM, Bitter T, Vogt J, van Buuren F, Bogunovic N, Horstkotte D, Faber L. Myocardial fibrosis severity on cardiac magnetic resonance imaging predicts sustained arrhythmic events in hypertrophic cardiomyopathy. *Can J Cardiol* 2013;**29**:358–363.
202. Bruder O, Wagner A, Jensen CJ, Schneider S, Ong P, Kispert EM, Nassenstein K, Schlosser T, Sabin GV, Sechtem U, Mahrholdt H. Myocardial scar visualized by cardiovascular magnetic resonance imaging predicts major adverse events in patients with hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2010;**56**:875–887.
203. O'Hanlon R, Grasso A, Roughton M, Moon JC, Clark S, Wage R, Webb J, Kulkarni M, Dawson D, Sulabeek L, Chandrasekaran B, Bucciarelli-Ducci C, Pasquale F, Cowie MR, McKenna WJ, Sheppard MN, Elliott PM, Pennell DJ, Prasad SK. Prognostic significance of myocardial fibrosis in hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2010;**56**:867–874.
204. Adabag AS, Maron BJ, Appelbaum E, Harrigan CJ, Buros JL, Gibson CM, Lesser JR, Hanna CA, Udelson JE, Manning WJ, Maron MS. Occurrence and frequency of arrhythmias in hypertrophic cardiomyopathy in relation to delayed enhancement on cardiovascular magnetic resonance. *J Am Coll Cardiol* 2008;**51**:1369–1374.
205. Nordin S, Kozor R, Bulluck H, Castelletti S, Rosmini S, Abdel-Gadir A, Baig S, Mehta A, Hughes D, Moon JC. Cardiac Fabry disease with late gadolinium enhancement is a chronic inflammatory cardiomyopathy. *J Am Coll Cardiol* 2016;**68**:1707–1708.
206. Karur GR, Robison S, Iwanochko RM, Morel CF, Crean AM, Thavandiranathan P, Nguyen ET, Mathur S, Wasim S, Hanneman K. Use of myocardial T1 mapping at 3.0 T to differentiate Anderson-Fabry disease from hypertrophic cardiomyopathy. *Radiology* 2018;**288**:398–406.
207. Mignani R, Preda P, Granata A, Maldini L, De Giovanni P, Montevocchi M, Rigotti A, Cagnoli L. Isolated microalbuminuria as the first clinical presentation of Fabry disease in an adult heterozygous female. *NDT Plus* 2009;**2**:455–457.
208. Schiffmann R, Hughes DA, Linthorst GE, Ortiz A, Svarstad E, Warnock DG, West ML, Wanner C. Screening, diagnosis, and management of patients with Fabry disease: conclusions from a "Kidney Disease: improving Global Outcomes" (KDIGO) controversies conference. *Kidney Int* 2017;**91**:284–293.
209. Madsen CV, Granqvist H, Petersen JH, Rasmussen AK, Lund AM, Oturai P, Sorensen SS, Feldt-Rasmussen U. Age-related renal function decline in Fabry disease patients on enzyme replacement therapy: a longitudinal cohort study. *Nephrol Dial Transplant* 2019;**34**:1525–1533.
210. Torralba-Cabeza MA, Olivera S, Hughes DA, Pastores GM, Mateo RN, Perez-Calvo JL. Cystatin C and NT-proBNP as prognostic biomarkers in Fabry disease. *Mol Genet Metab* 2011;**104**:301–307.
211. Masugata H, Senda S, Goda F, Yamagami A, Okuyama H, Kohno T, Hosomi N, Yukiiri K, Noma T, Murao K, Kohno M, Itoh S. Decline of plasma brain natriuretic peptide during enzyme replacement therapy in a female patient with heterozygous Fabry's disease. *Tohoku J Exp Med* 2009;**217**:169–174.
212. Feustel A, Hahn A, Schneider C, Sieweke N, Franzen W, Gunduz D, Rolfs A, Tanislav C. Continuous cardiac troponin I release in Fabry disease. *PLoS One* 2014;**9**:e91757.
213. Weidemann F, Beer M, Krawski M, Siwy J, Kampmann C. Early detection of organ involvement in Fabry disease by biomarker assessment in conjunction with LGE cardiac MRI: results from the SOPHIA study. *Mol Genet Metab* 2019;**126**:169–182.
214. Nowak A, Mechtler TP, Desnick RJ, Kasper DC. Plasma lysoGb3: a useful biomarker for the diagnosis and treatment of Fabry disease heterozygotes. *Mol Genet Metab* 2017;**120**:57–61.
215. Ouyang Y, Chen B, Pan X, Wang Z, Ren H, Xu Y, Ni L, Yu X, Yang L, Chen N. Clinical significance of plasma globotriaosylsphingosine levels in Chinese patients with Fabry disease. *Exp Ther Med* 2018;**15**:3733–3742.
216. Chimenti C, Padua L, Pazzaglia C, Morgante E, Centurion C, Antuzzi D, Russo MA, Frustaci A. Cardiac and skeletal myopathy in Fabry disease: a clinicopathologic correlative study. *Hum Pathol* 2012;**43**:1444–1452.
217. Magage S, Lubanda JC, Susa Z, Bultas J, Karetova D, Dobrovolsky R, Hrebicek M, Germain DP, Linhart A. Natural history of the respiratory involvement in Anderson-Fabry disease. *J Inher Metab Dis* 2007;**30**:790–799.
218. Brown LK, Miller A, Bhutani A, Sloane MF, Zimmerman MI, Schilero G, Eng CM, Desnick RJ. Pulmonary involvement in Fabry disease. *Am J Respir Crit Care Med* 1997;**155**:1004–1010.
219. Franzen D, Haile SR, Kasper DC, Mechtler TP, Flammar AJ, Krayenbuhl PA, Nowak A. Pulmonary involvement in Fabry disease: effect of plasma globotriaosylsphingosine and time to initiation of enzyme replacement therapy. *BMJ Open Respir Res* 2018;**5**:e000277.
220. Svensson CK, Feldt-Rasmussen U, Backer V. Fabry disease, respiratory symptoms, and airway limitation – a systematic review. *Eur Clin Respir J* 2015;**2**. <https://doi.org/10.3402/ecrj.v2.26721>.
221. Hilz MJ, Marthol H, Schwab S, Kolodny EH, Brys M, Stemper B. Enzyme replacement therapy improves cardiovascular responses to orthostatic challenge in Fabry patients. *J Hypertens* 2010;**28**:1438–1448.
222. Borlaug BA, Melenovsky V, Russell SD, Kessler K, Pacak K, Becker LC, Kass DA. Impaired chronotropic and vasodilator reserves limit exercise capacity in patients with heart failure and a preserved ejection fraction. *Circulation* 2006;**114**:2138–2147.
223. Lobo T, Morgan J, Bjorksten A, Nicholls K, Grigg L, Centra E, Becker G. Cardiovascular testing in Fabry disease: exercise capacity reduction, chronotropic incompetence and improved anaerobic threshold after enzyme replacement. *Intern Med J* 2008;**38**:407–414.
224. Powell AW, Jefferies JL, Hopkin RJ, Mays WA, Goa Z, Chin C. Cardiopulmonary fitness assessment on maximal and submaximal exercise testing in patients with Fabry disease. *Am J Med Genet A* 2018;**176**:1852–1857.
225. Schiffmann R, Rapkiewicz A, Abu-Asab M, Ries M, Askari H, Tsokos M, Quezado M. Pathological findings in a patient with Fabry disease who died after 2.5 years of enzyme replacement. *Virchows Arch* 2006;**448**:337–343.
226. Kovarnik T, Mintz GS, Karetova D, Horak J, Bultas J, Skulec R, Skalicka H, Aschermann M, Elleder M, Linhart A. Intravascular ultrasound assessment of coronary artery involvement in Fabry disease. *J Inher Metab Dis* 2008;**31**:753–760.
227. Elliott PM, Kindler H, Shah JS, Sachdev B, Rimoldi OE, Thaman R, Tome MT, McKenna WJ, Lee P, Camici PG. Coronary microvascular dysfunction in male patients with Anderson-Fabry disease and the effect of treatment with alpha galactosidase A. *Heart* 2006;**92**:357–360.
228. Chimenti C, Morgante E, Tanzili G, Mangieri E, Critelli G, Gaudio C, Russo MA, Frustaci A. Angina in Fabry disease reflects coronary small vessel disease. *Circ Heart Fail* 2008;**1**:161–169.

229. Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, Falk V, Filippatos G, Hamm C, Head SJ, Juni P, Kappetein AP, Kastrati A, Knuuti J, Landmesser U, Laufer G, Neumann FJ, Richter DJ, Schauerte P, Sousa Uva M, Stefanini GG, Taggart DP, Torracca L, Valgimigli M, Wijns W, Witkowski A. 2014 ESC/EACTS guidelines on myocardial revascularization: the Task Force on myocardial revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J* 2014;**35**:2541–2619.
230. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, Prescott E, Storey RF, Deaton C, Cuisset T, Agewall S, Dickstein K, Edvardsen T, Escaned J, Gersh BJ, Svitil P, Gilard M, Hasdai D, Hatala R, Mahfoud F, Masip J, Muneretto C, Valgimigli M, Achenbach S, Bax JJ; ESC Scientific Document Group. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J* 2020;**41**:407–477.
231. Tomberli B, Cecchi F, Sciagra R, Berti V, Lisi F, Torricelli F, Morrone A, Castelli G, Yacoub MH, Olivetto I. Coronary microvascular dysfunction is an early feature of cardiac involvement in patients with Anderson-Fabry disease. *Eur J Heart Fail* 2013;**15**:1363–1373.
232. Kallioikoski RJ, Kallioikoski KK, Sundell J, Engblom E, Penttinen M, Kantola I, Raitakari OT, Knuuti J, Nuutila P. Impaired myocardial perfusion reserve but preserved peripheral endothelial function in patients with Fabry disease. *J Inher Metab Dis* 2005;**28**:563–573.
233. Brignole M, Moya A, de Lange FJ, Deharo JC, Elliott PM, Fanciulli A, Fedorowski A, Furlan R, Kenny RA, Martin A, Probst V, Reed MJ, Rice CP, Sutton R, Ungar A, van Dijk JG; ESC Scientific Document Group. 2018 ESC Guidelines for the diagnosis and management of syncope. *Eur Heart J* 2018;**39**:1883–1948.
234. Koskenvuo JW, Kantola IM, Nuutila P, Knuuti J, Parkkola R, Mononen I, Hurme S, Kallioikoski R, Viikari JS, Wendelin-Saarenhovi M, Kiviniemi TO, Hartiala JJ. Cardiopulmonary involvement in Fabry's disease. *Acta Cardiol* 2010;**65**:185–192.
235. Fisher EA, Desnick RJ, Gordon RE, Eng CM, Griep R, Goldman ME. Fabry disease: an unusual cause of severe coronary disease in a young man. *Ann Intern Med* 1992;**117**:221–223.
236. Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, Byrne RA, Collet JP, Falk V, Head SJ, Juni P, Kastrati A, Koller A, Kristensen SD, Niebauer J, Richter DJ, Seferovic PM, Sibbing D, Stefanini GG, Windecker S, Yadav R, Zembala MO; ESC Scientific Document Group. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J* 2019;**40**:87–165.
237. Schroeder S, Achenbach S, Bengel F, Burgstahler C, Cademartiri F, de Feyter P, George R, Kaufmann P, Kopp AF, Knuuti J, Ropers D, Schuijff J, Tops LF, Bax JJ. Cardiac computed tomography: indications, applications, limitations, and training requirements: report of a Writing Group deployed by the Working Group Nuclear Cardiology and Cardiac CT of the European Society of Cardiology and the European Council of Nuclear Cardiology. *Eur Heart J* 2008;**29**:531–556.
238. Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, Budaj A, Bugiardini R, Crea F, Cuisset T, Di Mario C, Ferreira JR, Gersh BJ, Gitt AK, Hulot JS, Marx N, Opie LH, Pfisterer M, Prescott E, Ruschitzka F, Sabate M, Senior R, Taggart DP, van der Wall EE, Vrints CJ; ESC Committee for Practice Guidelines. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. *Eur Heart J* 2013;**34**:2949–3003.
239. Zipes DP, Camm AJ, Borggrefe M, Buxton AE, Chaitman B, Fromer M, Gregoratos G, Klein G, Moss AJ, Myerburg RJ, Priori SG, Quinones MA, Roden DM, Silka MJ, Tracy C, Priori SG, Blanc JJ, Budaj A, Camm AJ, Dean V, Deckers JW, Despres C, Dickstein K, Lekakis J, McGregor K, Metra M, Morais J, Osterspey A, Tamargo JL, Zamorano JL, Smith SC, Jr., Jacobs AK, Adams CD, Antman EM, Anderson JL, Hunt SA, Halperin JL, Nishimura R, Ornato JP, Page RL, Riegel B. ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death) developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Europace* 2006;**8**:746–837.
240. Raviele A, Giada F, Bergfeldt L, Blanc JJ, Blomstrom-Lundqvist C, Mont L, Morgan JM, Raatikainen MJ, Steinbeck G, Viskin S, Kirchhof P, Braunschweig F, Borggrefe M, Hocini M, Della Bella P, Shah DC; European Heart Rhythm Association. Management of patients with palpitations: a position paper from the European Heart Rhythm Association. *Europace* 2011;**13**:920–934.
241. Sakhi R, Theuns D, Bhagwandien RE, Michels M, Schinkel AFL, Szili-Torok T, Zijlstra F, Roos-Hesslink JW, Yap SC. Value of implantable loop recorders in patients with structural or electrical heart disease. *J Interv Card Electrophysiol* 2018;**52**:203–208.
242. Perk J, De Backer G, Gohlke H, Graham I, Reiner Z, Verschuren M, Albus C, Benlian P, Boysen G, Cifkova R, Deaton C, Ebrahim S, Fisher M, Germano G, Hobbs R, Hoes A, Karadeniz S, Mezzani A, Prescott E, Ryden L, Scherer M, Syvanne M, Scholte op Reimer WJ, Vrints C, Wood D, Zamorano JL, Zannad F; European Association for Cardiovascular Prevention & Rehabilitation (EACPR); ESC Committee for Practice Guidelines (CPG). European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). *Eur Heart J* 2012;**33**:1635–1701.
243. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, Clement DL, Coca A, de Simone G, Dominiczak A, Kahan T, Mahfoud F, Redon J, Rui-lope L, Zanchetti A, Kerins M, Kjeldsen SE, Kreutz R, Laurent S, Lip GYH, McManus R, Narkiewicz K, Ruschitzka F, Schmieder RE, Shlyakhto E, Tsioufis C, Aboyans V, Desormais I. 2018 ESC/ESH Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension. *J Hypertens* 2018;**36**:1953–2041.
244. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, Chapman MJ, De Backer GG, Delgado V, Ference BA, Graham IM, Halliday A, Landmesser U, Mihaylova B, Pedersen TR, Riccardi G, Richter DJ, Sabatine MS, Taskinen MR, Tokgozoglul O, Wiklund O; ESC Scientific Document Group. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J* 2020;**41**:111–188.
245. Politei JM, Bouhassira D, Germain DP, Goizet C, Guerrero-Sola A, Hilz MJ, Hutton EJ, Karaa A, Liguori R, Uceyler N, Zeltzer LK, Burlina A. Pain in Fabry disease: practical recommendations for diagnosis and treatment. *CNS Neurosci Ther* 2016;**22**:568–576.
246. Hughes DA, Elliott PM, Shah J, Zuckerman J, Coghlan G, Brookes J, Mehta AB. Effects of enzyme replacement therapy on the cardiomyopathy of Anderson-Fabry disease: a randomised, double-blind, placebo-controlled clinical trial of agalsidase alfa. *Heart* 2008;**94**:153–158.
247. Beer M, Weidemann F, Breunig F, Knoll A, Koeppel S, Machann W, Hahn D, Wanner C, Strotmann J, Sandstedt J. Impact of enzyme replacement therapy on cardiac morphology and function and late enhancement in Fabry's cardiomyopathy. *Am J Cardiol* 2006;**97**:1515–1518.
248. Germain DP, Charrow J, Desnick RJ, Guffon N, Kempf J, Lachmann RH, Lemay R, Linthorst GE, Packman S, Scott CR, Waldek S, Warnock DG, Weinreb NJ, Wilcox WR. Ten-year outcome of enzyme replacement therapy with agalsidase beta in patients with Fabry disease. *J Med Genet* 2015;**52**:353–358.
249. Germain DP, Waldek S, Banikazemi M, Bushinsky DA, Charrow J, Desnick RJ, Lee P, Loew T, Vedder AC, Abichandani R, Wilcox WR, Guffon N. Sustained, long-term renal stabilization after 54 months of agalsidase beta therapy in patients with Fabry disease. *J Am Soc Nephrol* 2007;**18**:1547–1557.
250. Ortiz A, Abiose A, Bichet DG, Cabrera G, Charrow J, Germain DP, Hopkin RJ, Jovanovic A, Linhart A, Maruti SS, Mauer M, Oliveira JP, Patel MR, Politei J, Waldek S, Wanner C, Yoo HW, Warnock DG. Time to treatment benefit for adult patients with Fabry disease receiving agalsidase beta: data from the Fabry Registry. *J Med Genet* 2016;**53**:495–502.
251. Wilcox WR, Linthorst GE, Germain DP, Feldt-Rasmussen U, Waldek S, Richards SM, Beitner-Johnson D, Cizmarik M, Cole JA, Kingma WW, Warnock DG. Anti-alpha-galactosidase A antibody response to agalsidase beta treatment: data from the Fabry Registry. *Mol Genet Metab* 2012;**105**:443–449.
252. Lenders M, Brand E. Effects of enzyme replacement therapy and antidrug antibodies in patients with Fabry disease. *J Am Soc Nephrol* 2018;**29**:2265–2278.
253. Liu HC, Lin HY, Yang CF, Liao HC, Hsu TR, Lo CW, Chang FP, Huang CK, Lu YH, Lin SP, Yu WC, Niu DM. Globotriaosylsphingosine (lyso-Gb3) might not be a reliable marker for monitoring the long-term therapeutic outcomes of enzyme replacement therapy for late-onset Fabry patients with the Chinese hotspot mutation (IVS4+919G>A). *Orphanet J Rare Dis* 2014;**9**:111.
254. Kampmann C, Linhart A, Devereux RB, Schiffmann R. Effect of agalsidase alfa replacement therapy on Fabry disease-related hypertrophic cardiomyopathy: a 12- to 36-month, retrospective, blinded echocardiographic pooled analysis. *Clin Ther* 2009;**31**:1966–1976.
255. Germain DP, Weidemann F, Abiose A, Patel MR, Cizmarik M, Cole JA, Beitner-Johnson D, Benistan K, Cabrera G, Charrow J, Kantola I, Linhart A, Nicholls K, Niemann M, Scott CR, Sims K, Waldek S, Warnock DG, Strotmann J, Fabry R. Analysis of left ventricular mass in untreated men and in men treated with agalsidase-beta: data from the Fabry Registry. *Genet Med* 2013;**15**:958–965.
256. Germain DP, Giugliani R, Hughes DA, Mehta A, Nicholls K, Barisoni L, Jennette CJ, Bragat A, Castelli J, Sitaraman S, Lockhart DJ, Boudes PF. Safety and pharmacodynamic effects of a pharmacological chaperone on alpha-galactosidase A activity and globotriaosylceramide clearance in Fabry disease: report from two phase 2 clinical studies. *Orphanet J Rare Dis* 2012;**7**:91.

257. Giugliani R, Waldek S, Germain DP, Nicholls K, Bichet DG, Simosky JK, Bragat AC, Castelli JP, Benjamin ER, Boudes PF. A phase 2 study of migalastat hydrochloride in females with Fabry disease: selection of population, safety and pharmacodynamic effects. *Mol Genet Metab* 2013;**109**:86–92.
258. Germain DP, Fan JQ. Pharmacological chaperone therapy by active-site-specific chaperones in Fabry disease: in vitro and preclinical studies. *Int J Clin Pharmacol Ther* 2009;**47**(Suppl 1):S111–S117.
259. Young-Gqamana B, Brignol N, Chang HH, Khanna R, Soska R, Fuller M, Sitaraman SA, Germain DP, Giugliani R, Hughes DA, Mehta A, Nicholls K, Boudes P, Lockhart DJ, Valenzano KJ, Benjamin ER. Migalastat HCl reduces globotriaosylsphingosine (lyso-Gb3) in Fabry transgenic mice and in the plasma of Fabry patients. *PLoS One* 2013;**8**:e57631.
260. Hughes DA, Nicholls K, Shankar SP, Sunder-Plassmann G, Koeller D, Nedd K, Vockley G, Hamazaki T, Lachmann R, Ohashi T, Olivetto I, Sakai N, Deegan P, Dimmock D, Eyskens F, Germain DP, Goker-Alpan O, Hachulla E, Jovanovic A, Lourenco CM, Narita I, Thomas M, Wilcox WR, Bichet DG, Schiffmann R, Ludington E, Viereck C, Kirk J, Yu J, Johnson F, Boudes P, Benjamin ER, Lockhart DJ, Barlow C, Skuban N, Castelli JP, Barth J, Feldt-Rasmussen U. Oral pharmacological chaperone migalastat compared with enzyme replacement therapy in Fabry disease: 18-month results from the randomised phase III ATTRACT study. *J Med Genet* 2017;**54**:288–296.
261. Lenders M, Nordbeck P, Kurschat C, Karabul N, Kaufeld J, Hennermann JB, Patten M, Cybulla M, Muntze J, Uceyler N, Liu D, Das AM, Sommer C, Pogoda C, Reiermann S, Duning T, Gaedeke J, Stumpfke K, Blaschke D, Brand SM, Mann WA, Kampmann C, Muschol N, Canaan-Kuhl S, Brand E. Treatment of Fabry's disease with migalastat: outcome from a Prospective Observational Multicenter Study (FAMOUS). *Clin Pharmacol Ther* 2020;**108**:326–337.
262. Pitt B, Pfeffer MA, Assmann SF, Boineau R, Anand IS, Claggett B, Clausell N, Desai AS, Diaz R, Fleg JL, Gordeev I, Hartley B, Heitner JF, Kenwood CT, Lewis EF, O'Meara E, Probstfield JL, Shaburishvili T, Shah SJ, Solomon SD, Sweitzer NK, Yang S, McKinlay SM; TOPCAT Investigators. Spironolactone for heart failure with preserved ejection fraction. *N Engl J Med* 2014;**370**:1383–1392.
263. Pfeffer MA, Claggett B, Assmann SF, Boineau R, Anand IS, Clausell N, Desai AS, Diaz R, Fleg JL, Gordeev I, Heitner JF, Lewis EF, O'Meara E, Rouleau JL, Probstfield JL, Shaburishvili T, Shah SJ, Solomon SD, Sweitzer NK, McKinlay SM, Pitt B. Regional variation in patients and outcomes in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) trial. *Circulation* 2015;**131**:34–42.
264. Ebert M, Jander N, Minners J, Blum T, Doering M, Bollmann A, Hindricks G, Arentz T, Kalusche D, Richter S. Long-term impact of right ventricular pacing on left ventricular systolic function in pacemaker recipients with preserved ejection fraction: results from a large single-center registry. *J Am Heart Assoc* 2016;**5**:e003485.
265. Angheloiu GO, Saul M, Edelman K, Shah H, Mezu UL, Saba S. Predictors of left ventricular function deterioration in patients with left bundle branch block and ejection fraction >50%. *Congest Heart Fail* 2013;**19**:E1–E4.
266. Chan JY, Fang F, Zhang Q, Fung JW, Razali O, Azlan H, Lam KH, Chan HC, Yu CM. Biventricular pacing is superior to right ventricular pacing in bradycardia patients with preserved systolic function: 2-year results of the PACE trial. *Eur Heart J* 2011;**32**:2533–2540.
267. Orteu CH, Jansen T, Lidove O, Jaussaud R, Hughes DA, Pintos-Morell G, Ramaswami U, Parini R, Sunder-Plassman G, Beck M, Mehta AB; FOS Investigators. Fabry disease and the skin: data from FOS, the Fabry Outcome Survey. *Br J Dermatol* 2007;**157**:331–337.
268. Lidove O, Zeller V, Chicheportiche V, Meyssonier V, Sene T, Godot S, Ziza JM. Musculoskeletal manifestations of Fabry disease: a retrospective study. *Joint Bone Spine* 2016;**83**:421–426.
269. Magage S, Linhart A, Bultas J, Wojacek J, Mates M, Palecek T, Popelova J, Tintera J, Aschermann M, Goldman ME, Desnick RJ. Fabry disease: percutaneous transluminal septal myocardial ablation markedly improved symptomatic left ventricular hypertrophy and outflow tract obstruction in a classically affected male. *Echocardiography* 2005;**22**:333–339.
270. Kunkala MR, Aubry MC, Ommen SR, Gersh BJ, Schaff HV. Outcome of septal myectomy in patients with Fabry's disease. *Ann Thorac Surg* 2013;**95**:335–337.
271. Sims K, Politei J, Banikazemi M, Lee P. Stroke in Fabry disease frequently occurs before diagnosis and in the absence of other clinical events: natural history data from the Fabry Registry. *Stroke* 2009;**40**:788–794.
272. Qian P, Ross D, Tchan M, Sadick N. A patient with recurrent disabling atrial fibrillation and Fabry cardiomyopathy successfully treated with single ring pulmonary vein isolation. *Int J Cardiol* 2015;**182**:375–376.
273. Reaser MJ, Kacew S. Drug-induced phospholipidosis: are there functional consequences? *Exp Biol Med* (Maywood) 2001;**226**:825–830.
274. Pintavorn P, Cook WJ. Progressive renal insufficiency associated with amiodarone-induced phospholipidosis. *Kidney Int* 2008;**74**:1354–1357.
275. Ikeda K, Hirayama M, Hirota Y, Asa E, Seki J, Tanaka Y. Drug-induced phospholipidosis is caused by blockade of mannose 6-phosphate receptor-mediated targeting of lysosomal enzymes. *Biochem Biophys Res Commun* 2008;**377**:268–274.
276. Electronic Medicines Compendium. Sotalol 80 mg tablets. <https://www.medicines.org.uk/emc/product/7038/smpc> (20 July 2020).
277. Electronic Medicines Compendium. Flecainide Acetate 50 mg tablets. <https://www.medicines.org.uk/emc/product/3087/smpc> (20 July 2020).
278. Di Donna P, Olivetto I, Delcroix SD, Caponi D, Scaglione M, Nault I, Montefusco A, Girolami F, Cecchi F, Haissaguerre M, Gaita F. Efficacy of catheter ablation for atrial fibrillation in hypertrophic cardiomyopathy: impact of age, atrial remodelling, and disease progression. *Europace* 2010;**12**:347–355.
279. Reisin RC, Romero C, Marchesoni C, Napoli G, Kisinovsky I, Caceres G, Sevlever G. Brain MRI findings in patients with Fabry disease. *J Neurol Sci* 2011;**305**:41–44.
280. Bohm M, Ezekowitz MD, Connolly SJ, Eikelboom JW, Hohnloser SH, Reilly PA, Schumacher H, Brueckmann M, Schirmer SH, Kratz MT, Yusuf S, Diener HC, Hijazi Z, Wallentin L. Changes in renal function in patients with atrial fibrillation: an analysis from the RE-LY trial. *J Am Coll Cardiol* 2015;**65**:2481–2493.
281. Brodsky SV, Nadasdy T, Rovin BH, Satoskar AA, Nadasdy GM, Wu HM, Bhatt UY, Hebert LA. Warfarin-related nephropathy occurs in patients with and without chronic kidney disease and is associated with an increased mortality rate. *Kidney Int* 2011;**80**:181–189.
282. Steffel J, Verhamme P, Potpara TS, Albaladejo P, Antz M, Desteghe L, Haessler KG, Oldgren J, Reinecke H, Roldan-Schilling V, Rowell N, Sinnaeve P, Collins R, Camm AJ, Heidbuchel H; ESC Scientific Document Group. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. *Eur Heart J* 2018;**39**:1330–1393.
283. Camm AJ, Lip GY, De Caterina R, Savelieva I, Atar D, Hohnloser SH, Hindricks G, Kirchhof P; ESC Committee for Practice Guidelines (CPG). 2012 Focused update of the ESC guidelines for the management of atrial fibrillation: an update of the 2010 ESC guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. *Eur Heart J* 2012;**33**:2719–2747.
284. Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S, Van Gelder IC, Al-Attar N, Hindricks G, Prendergast B, Heidbuchel H, Alfieri O, Angelini A, Atar D, Colonna P, De Caterina R, De Sutter J, Goette A, Gorennek B, Heldal M, Hohloser SH, Kolh P, Le Heuzey JY, Ponikowski P, Rutten FH; ESC Committee for Practice Guidelines. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Europace* 2010;**12**:1360–1420.
285. Guttmann OP, Rahman MS, O'Mahony C, Anastasakis A, Elliott PM. Atrial fibrillation and thromboembolism in patients with hypertrophic cardiomyopathy: systematic review. *Heart* 2014;**100**:465–472.
286. Liu D, Hu K, Schmidt M, Muntze J, Maniuc O, Gensler D, Oder D, Salinger T, Weidemann F, Ertl G, Frantz S, Wanner C, Nordbeck P. Value of the CHA₂DS₂-VASc score and Fabry-specific score for predicting new-onset or recurrent stroke/TIA in Fabry disease patients without atrial fibrillation. *Clin Res Cardiol* 2018;**107**:1111–1121.
287. Olivetto I, Cecchi F, Casey SA, Dolara A, Traverse JH, Maron BJ. Impact of atrial fibrillation on the clinical course of hypertrophic cardiomyopathy. *Circulation* 2001;**104**:2517–2524.
288. Maron BJ, Olivetto I, Bellone P, Conte MR, Cecchi F, Flygenring BP, Casey SA, Gohman TE, Bongioanni S, Spirito P. Clinical profile of stroke in 900 patients with hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2002;**39**:301–307.
289. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC, Joyner CD, Wallentin L; RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;**361**:1139–1151.
290. Gomez-Outes A, Terleira-Fernandez AI, Calvo-Rojas G, Suarez-Gea ML, Vargas-Castrillon E. Dabigatran, rivaroxaban, or apixaban versus warfarin in patients with nonvalvular atrial fibrillation: a systematic review and meta-analysis of subgroups. *Thrombosis* 2013;**2013**:640723.
291. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC, Jr., Conti JB, Ellorin PT, Ezekowitz MD, Field ME, Murray KT, Sacco RL, Stevenson WG, Tchou PJ, Tracy CM, Yancy CW. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *Circulation* 2014;**130**:2071–2104.
292. Yogasundaram H, Kim D, Oudit O, Thompson RB, Weidemann F, Oudit GY. Clinical features, diagnosis, and management of patients with Anderson-Fabry cardiomyopathy. *Can J Cardiol* 2017;**33**:883–897.

293. Connolly SJ, Pogue J, Hart RG, Hohnloser SH, Pfeffer M, Chrolavicius S, Yusuf S; ACTIVE Investigators. Effect of clopidogrel added to aspirin in patients with atrial fibrillation. *N Engl J Med* 2009;**360**:2066–2078.
294. Fine NM, Wang Y, Khan A. Acute decompensated heart failure after initiation of amiodarone in a patient with Anderson-Fabry disease. *Can J Cardiol* 2019;**35**e:104.e5–e7.
295. Yu CM, Fang F, Luo XX, Zhang Q, Azlan H, Razali O. Long-term follow-up results of the pacing to avoid cardiac enlargement (PACE) trial. *Eur J Heart Fail* 2014;**16**:1016–1025.
296. Rogers DP, Marazia S, Chow AW, Lambiasi PD, Lowe MD, Frenneaux M, McKenna WJ, Elliott PM. Effect of biventricular pacing on symptoms and cardiac remodelling in patients with end-stage hypertrophic cardiomyopathy. *Eur J Heart Fail* 2008;**10**:507–513.
297. Gu M, Jin H, Hua W, Fan XH, Niu HX, Tian T, Ding LG, Wang J, Xue C, Zhang S. Clinical outcome of cardiac resynchronization therapy in dilated-phase hypertrophic cardiomyopathy. *J Geriatr Cardiol* 2017;**14**:238–244.
298. Yu CM, Chan JY, Zhang Q, Omar R, Yip GW, Hussin A, Fang F, Lam KH, Chan HC, Fung JW. Biventricular pacing in patients with bradycardia and normal ejection fraction. *N Engl J Med* 2009;**361**:2123–2134.
299. Barold SS. Arrhythmias: changing indications for biventricular pacing in bradycardia. *Nat Rev Cardiol* 2013;**10**:436–438.
300. O'Mahony C, Jichi F, Pavlou M, Monserrat L, Anastasakis A, Rapezzi C, Biagini E, Gimeno JR, Limongelli G, McKenna WJ, Omar RZ, Elliott PM; Hypertrophic Cardiomyopathy Outcomes Investigators. A novel clinical risk prediction model for sudden cardiac death in hypertrophic cardiomyopathy (HCM risk-SCD). *Eur Heart J* 2014;**35**:2010–2020.
301. Takenaka T, Teraguchi H, Yoshida A, Taguchi S, Ninomiya K, Umekita Y, Yoshida H, Horinouchi M, Tabata K, Yonezawa S, Yoshimitsu M, Higuchi K, Nakao S, Anan R, Minagoe S, Tei C. Terminal stage cardiac findings in patients with cardiac Fabry disease: an electrocardiographic, echocardiographic, and autopsy study. *J Cardiol* 2008;**51**:50–59.
302. O'Mahony C, Lambiasi PD, Quarta G, Cardona M, Calcagnino M, Tsovolas K, Al-Shaikh S, Rahman SM, Arnous S, Jones S, McKenna WJ, Elliott P. The long-term survival and the risks and benefits of implantable cardioverter defibrillators in patients with hypertrophic cardiomyopathy. *Heart* 2012;**98**:116–125.
303. Elliott PM, Sharma S, Varnava A, Poloniecki J, Rowland E, McKenna WJ. Survival after cardiac arrest or sustained ventricular tachycardia in patients with hypertrophic cardiomyopathy. *J Am Coll Cardiol* 1999;**33**:1596–1601.
304. Cecchi F, Maron BJ, Epstein SE. Long-term outcome of patients with hypertrophic cardiomyopathy successfully resuscitated after cardiac arrest. *J Am Coll Cardiol* 1989;**13**:1283–1288.
305. Maron BJ, Spirito P, Shen WK, Haas TS, Formisano F, Link MS, Epstein AE, Almquist AK, Daubert JP, Lawrenz T, Boriani G, Estes NA 3rd, Favale S, Piccininno M, Winters SL, Santini M, Betocchi S, Arribas F, Sherrid MV, Buja G, Semsarian C, Bruzzi P. Implantable cardioverter-defibrillators and prevention of sudden cardiac death in hypertrophic cardiomyopathy. *JAMA* 2007;**298**:405–412.
306. Syska P, Przybylski A, Chojnowska L, Lewandowski M, Sterlinski M, Maciag A, Gepner K, Pytkowski M, Kowalik I, Maczynska-Mazuruk R, Ruzyllo W, Szwed H. Implantable cardioverter-defibrillator in patients with hypertrophic cardiomyopathy: efficacy and complications of the therapy in long-term follow-up. *J Cardiovasc Electrophysiol* 2010;**21**:883–889.
307. Iles L, Pfluger H, Lefkovits L, Butler MJ, Kistler PM, Kaye DM, Taylor AJ. Myocardial fibrosis predicts appropriate device therapy in patients with implantable cardioverter-defibrillators for primary prevention of sudden cardiac death. *J Am Coll Cardiol* 2011;**57**:821–828.
308. Warnock DG, Thomas CP, Vujkovic B, Campbell RC, Charrow J, Laney DA, Jackson LL, Wilcox WR, Wanner C. Antiproteinuric therapy and Fabry nephropathy: factors associated with preserved kidney function during agalsidase-beta therapy. *J Med Genet* 2015;**52**:860–866.
309. Reiner Z, Catapano AL, De Backer G, Graham I, Taskinen MR, Wiklund O, Agewall S, Alegria E, Chapman MJ, Durrington P, Erdine S, Halcox J, Hobbs R, Kjekshus J, Filardi PP, Riccardi G, Storey RF, Wood D; ESC Committee for Practice Guidelines (CPG) 2008-2010 and 2010-2012 Committees. ESC/EAS Guidelines for the management of dyslipidaemias: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). *Eur Heart J* 2011;**32**:1769–1818.
310. Wanner C, Arad M, Baron R, Burlina A, Elliott PM, Feldt-Rasmussen U, Fomin VV, Germain DP, Hughes DA, Jovanovic A, Kantola I, Linhart A, Mignani R, Monserrat L, Namdar M, Nowak A, Oliveira JP, Ortiz A, Pieroni M, Spada M, Tylki-Szymanska A, Tondel C, Viana-Baptista M, Weidemann F, Hilz MJ. European expert consensus statement on therapeutic goals in Fabry disease. *Mol Genet Metab* 2018;**124**:189–203.
311. Goker-Alpan O, Longo N, McDonald M, Shankar SP, Schiffmann R, Chang P, Shen Y, Pano A. An open-label clinical trial of agalsidase alfa enzyme replacement therapy in children with Fabry disease who are naive to enzyme replacement therapy. *Drug Des Devel Ther* 2016;**10**:1771–1781.
312. Schiffmann R, Pastores GM, Lien YH, Castaneda V, Chang P, Martin R, Wijatya A. Agalsidase alfa in pediatric patients with Fabry disease: a 6.5-year open-label follow-up study. *Orphanet J Rare Dis* 2014;**9**:169.