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

Aleš Linhart¹, Dominique P. Germain², Iacopo Olivotto³, Mohammed M. Akhtar⁴, Aris Anastasakis⁵, Derralynn Hughes⁶, Mehdi Namdar⁷, Maurizio Pieroni⁸, Albert Hagège⁹,¹⁰,¹¹, Franco Cecchi³,¹², Juan R. Gimeno¹³, Giuseppe Limongelli¹⁴, and Perry Elliott⁴*¹²

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 glycosphin-golipids, primarily globotriaosylceramide (Gb₃), and its deacylated form globotriaosylsphingosine (lyso-Gb₃) in cells throughout the body, including vascular endothelial and smooth muscle cells and cardiomyocytes.¹² 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.¹³–¹⁵ Novel therapy based on pharmacological chaperone is approved for FD patients carrying amenable pathogenic GLA gene variants 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 disease.
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.\textsuperscript{13–17} In these patients, the benefit of ERT may be attenuated. Consequently, cardiovascular complications now represent the predominant cause of FD-related mortality.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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).\textsuperscript{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%.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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\textsuperscript{26,31,32} and therefore reclassified.\textsuperscript{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.\textsuperscript{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.\textsuperscript{30,31}

Female carriers of GLA pathogenic variants may also develop disease, albeit in a delayed and generally milder form.\textsuperscript{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.\textsuperscript{37,38}

### Epidemiology

Fabry disease affects all ethnicities, with some geographical clusters based on founder mutations.\textsuperscript{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.\textsuperscript{42} In contrast, neonatal screening programmes have reported an unexpectedly high incidence of disease-causing variants, ranging from 1:1250 to 1:7800.\textsuperscript{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.\textsuperscript{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.\textsuperscript{27,48–62}

### Diagnosis of Fabry disease

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

Classic FD in males is characterized by onset of symptoms in childhood, absent or severely reduced (<1% of normal) AGAL-A enzyme activity and microvascular endothelial Gb\textsubscript{3} accumulation.\textsuperscript{127,63} Typical manifestations include cutaneous lesions (angiokeratoma), hypohidrosis, peripheral neuropathy (with acral pain and painful febrile crises), premature stroke, microalbuminuria and proteinuria, renal insufficiency, and cardiomyopathy (Figure 1).

A large number of patients have a late-onset phenotype manifesting mostly as LVH or HCM. This so-called ‘cardiac variant’ has slower progression due to residual AGAL-A enzyme activity and less vascular endothelial Gb\textsubscript{3} accumulation.\textsuperscript{51,64} However, the cardiac variant may occasionally present with some degree of extra-cardiac involvement including stroke and renal dysfunction, but the attribution of such complications to FD should be made with caution, and a kidney biopsy should be considered for differential diagnosis in all cases exhibiting albuminuria/proteinuria with
Figure 1 Diagnosis. Flow chart showing a suggested approach to the diagnosis of Fabry disease (FD) in a patient with unexplained left ventricular hypertrophy (LVH). Agal, α-galactosidase A; Gb3, globotriaosylceramide; GLA, α-galactosidase A gene; GLS, global longitudinal strain; EMB, endomyocardial biopsy; RVH, right ventricular hypertrophy; VUS, variant of unknown significance.

Diagnosis of cardiovascular involvement in Fabry disease

Electrocardiography

Children and adolescents may have subtle electrocardiographic (ECG) changes 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. In adults, the earliest clinical manifestations of Fabry-related cardiac disease are ECG abnormalities associated with slowly progressive LVH that deteriorate renal function, particularly in patients with concurrent risk factors for chronic kidney disease.

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.36,37,43,47–51,63,69,75–80,82–99

In many patients, Gb3 is elevated in plasma or urine 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).2,26,27,31,43,47–51,63,69,75–80,82–99

Diagnosis of cardiovascular involvement in Fabry disease

Electrocardiography

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Table 1 Recommendations for the diagnosis of Fabry disease

| Recommendations                                                                 | Class | Level | Ref.                          |
|--------------------------------------------------------------------------------|-------|-------|-------------------------------|
| Fabry disease should be considered in adults with unexplained LVH.             | Ila   | C     | 47–51                         |
| Assessment of AGAL-A activity is recommended as the first-line diagnostic     | I     | C     | 2,27,63,82,83                 |
| approach in men with clinically suspected FD.                                 |       |       |                               |
| Sequencing of the GLA gene is recommended as the first-line diagnostic        | I     | C     | 2,33,83–88                    |
| approach in women with clinically suspected FD.                               |       |       |                               |
| Sequencing of the GLA gene is recommended in all patients to: (i) identify and| I     | C     | 2,89–92                       |
| 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.                      |       |       |                               |
| Assessment of plasma lyso-Gb2 should be considered for assessment of disease   | Ila   | C     | 26,75–80,93–96                |
| severity in FD patients or in the diagnostic algorithm for patients with GLA  |       |       |                               |
| genetic variants of unknown significance.                                     |       |       |                               |
| Genetic counselling is recommended in all patients with FD, including those    | I     | B     | 2,43,69,97                    |
| with late-onset cardiac variants.                                             |       |       |                               |
| 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         | Ila   | C     | 97–99                         |
| evaluation of patients in centres with multidisciplinary teams that have      |       |       |                               |
| expertise in the diagnosis and management of FD.                             |       |       |                               |

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. 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. ST-segment depression and T-wave inversion may be associated with the presence of fibrosis.

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. 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.

The incidence of cardiac device implantation (pacemakers, defibrillators and loop recorders) in adult FD patients is between 1.07% and 1.9% per year. 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.

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. However, asymmetric thickening of the interventricular septum or apical hypertrophy is not exceptional and dynamic LV outflow tract obstruction caused by systolic anterior motion of the mitral valve can be provoked by exercise or be present at rest, mimicking classical HCM. 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. The ‘binary sign’, characterized by a bright endocardial layer and adjacent hypoechogenicity of the interventricular septum, may be seen in FD but similar findings occur in other types of LVH and the sensitivity and specificity of this feature are low.

Left ventricular ejection fraction is usually normal in FD, but can be reduced in patients with extensive fibrosis, coexisting coronary artery disease and ventricular dysynchrony induced by conduction disease. 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.

Myocardial strain and strain rate are usually abnormal in patients with LVH, particularly in the posterolateral basal LV segment, sometimes with post-systolic thickening. These findings may, in some cases, precede development of significant LVH and may correlate with functional limitation.

Myocardial performance (Tei) index is abnormal in patients with overt cardiomyopathy.
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. Left atrial dilatation is common. 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. Elevated LV filling pressures as assessed by E/e′ ratio are associated with unfavourable prognosis.

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.

Mild-to-moderate aortic dilatation involving the bulb and ascending aorta is frequently seen in advanced cases. 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.

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. The presence of extensive fibrosis is associated with reduced response to ERT and with an increased risk of arrhythmia. In some patients, particularly females, areas of replacement fibrosis are detectable before development of significant LVH. Thus, systematic use of CMRI may help to reclassify patients in whom standard echocardiography fails to detect relevant cardiac involvement.

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. Reduced T1 values are also reported within the right ventricular wall. 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 postero-lateral 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/CMR suggest an inflammatory process linked to fibrosis as well as disturbances of energy metabolism (\(^{131}\)P spectroscopy).\(^{164–166}\)

### Endomyocardial biopsy

Endomyocardial biopsy (EMB) may be considered in patients with VUS, high residual enzyme activity (>10%) and/or low lyso-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 EPS\(^ {176}\) and there is no evidence that the routine use of EPS to determine risk of ventricular arrhythmia in patients with FD provides clinical benefit.\(^ {20}\)

### Laboratory tests

Routine laboratory testing aids detection of non-cardiac conditions that cause or exacerbate ventricular dysfunction (e.g. thyroid disease and diabetes mellitus) and secondary organ dysfunction. Regular monitoring of renal function and detection of microalbuminuria or proteinuria should be part of routine assessment even in patients with known cardiac variant mutations, as renal dysfunction can occur both due to FD-related renal involvement and other causes.\(^ {55,177}\) 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 CMR imaging and myocardial fibrosis.\(^ {183–188}\) Elevated high sensitivity troponin indicates advanced disease and a worse prognosis (Table 2).\(^ {1,13,76,81,90,104,111,112,156,157,161,167,169,170,178,184,186–215}\)

### Assessment of cardiac symptoms

#### Heart failure

Heart failure symptoms are reported in up to a quarter of patients in FD registries\(^ {44}\) 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  | I      | B     | 90,104,187 |
| development of new symptoms, and every 6–12 months in adult patients.         |       |       |            |
| 24 h ambulatory ECG monitoring (or longer if available) should be considered  | Ia     | C     | 90,188–191 |
| at initial assessment and every 6–12 months in adult patients to document     |       |       |            |
| atrial and ventricular arrhythmias.                                            |       |       |            |
| **Cardiac imaging**                                                            |       |       |            |
| 2D and Doppler echocardiography is recommended in all patients at first       | I      | B     | 90,192     |
| clinical visit, with the development of new symptoms, and every 12 to 24     |       |       |            |
| months.                                                                        |       |       |            |
| In symptomatic patients with LVH, Doppler echocardiography during exercise   | I      | C     | 90,112,193–199 |
| in the standing, sitting or semi-supine position is recommended to detect     |       |       |            |
| provokable LV outflow obstruction and exercise-induced mitral regurgitation.  |       |       |            |
| In the absence of contraindications, contrast enhanced CMRI should be        | Ia     | C     | 90,111,157,161,200–205 |
| considered in all adult patients in order to assess cardiac anatomy,         |       |       |            |
| ventricular function and the presence of myocardial fibrosis at initial       |       |       |            |
| evaluation.                                                                   |       |       |            |
| In the absence of contraindications, contrast enhanced CMRI may be considered| Iib    | C     | 13,90     |
| every 5 years in adult patients in order to assess the progression of         |       |       |            |
| fibrosis and LV function depending on disease severity and CMRI availability. |       |       |            |
| Non-contrast T1 mapping may be considered in adult FD patients to detect     | Iib    | C     | 156,157,206 |
| early cardiac involvement or in the differential diagnosis from other causes  |       |       |            |
| of LVH.                                                                        |       |       |            |
| **Endomyocardial biopsy**                                                       |       |       |            |
| Endomyocardial biopsy with sample evaluation including electron microscopy    | Ia     | C     | 167,169,170 |
| should be considered in patients with LVH, genetic variants of unknown      |       |       |            |
| significance in the GLA gene, and significant residual AGAL-A activity        |       |       |            |
| (>10%) in order to confirm a diagnosis of FD.                                 |       |       |            |
| **Biomarkers**                                                                 |       |       |            |
| Regular assessment of renal function and urine analysis for                  | I      | C     | 207–209    |
| microalbuminuria/proteinuria is recommended in all patients.                 |       |       |            |
| Measurement of plasma BNP/NT-proBNP is recommended in symptomatic patients   | I      | B     | 178,184,210,211 |
| with suspected heart failure.                                                 |       |       |            |
| High-sensitivity cardiac troponin (hs-cTnT or hs-cTnI) may be considered for  | Iib    | C     | 186,212,213 |
| the assessment of disease severity.                                           |       |       |            |
| Measurement of lyso-Gb3 may be considered as a prognostic marker, particularly| Iib    | C     | 1,76,81,214,215 |
| in patients with genetic variants of unknown significance and/or late-onset  |       |       |            |
| genetic variants.                                                             |       |       |            |

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. In many patients, symptoms probably result from microvascular dysfunction. Stress testing is of limited value in patients with baseline ECG changes and coronary artery imaging should be considered in all patients with angina in accordance with the ESC guidelines on chronic coronary syndromes. 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. 

**Palpitations**

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

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. Special attention should be paid to the management of dyslipidaemia. 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.

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. Most evidence suggests that the heart responds less well to therapy when disease is advanced or postural syncope, to detect provocable LV outflow tract obstruction. In patients with unexplained syncope, an EPS and an ILR may be considered (Table 3).

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. 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. Exercise stress echocardiography should be considered, particularly in patients with exertional or postural syncope, to detect provocable LV outflow tract obstruction. In patients with unexplained syncope, an EPS and an ILR may be considered.

Management of cardiac complications

Chaperone therapy

Orally administered migalastat is an alternative treatment option 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. 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. The ability of migalastat to mitigate the glomerular filtration rate decline associated with some amenable GLA variants has recently been questioned.

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

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.113,119,269,270

### Atrial fibrillation

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

### Rhythm control

Maintenance of sinus rhythm involves both pharmacological and interventional therapies,272 but is often challenging in the presence of an evolving atrial substrate and significant limitations of available drugs. Amiodarone should be limited to the management of poorly tolerated acute episodes as chronic therapy may induce phospholipidosis and potentially reduce the effect of ERT.273–275 Little is known about the effect of dronedarone on endosomal/lysosomal trafficking and function and it is contraindicated in New York Heart Association class III–IV heart failure patients and impaired renal function (estimated glomerular filtration rate <30 mL/min). Sotalol
is contraindicated in decompensated heart failure and when creatinine clearance is <10 mL/min\(^2\) and flecainide should be used cautiously when estimated glomerular filtration rate is <35 mL/min\(^2\).

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\(^2\).

**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\(^2\).

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\(^2\). In addition, the use of DOACs may reduce the risk of warfarin-induced nephropathy and slow the progression of renal function decline\(^2\). 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\(^2\). In patients unable to use anticoagulation, left atrial appendage closure may be considered\(^2\).

**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)\(^8\).

**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\(^1\). Symptomatic bradycardia should be treated in accordance with the current ESC guidelines\(^5\). 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\(^5\), 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)\(^5\). In those who have progressed to LV dysfunction (ejection fraction ≤35%), cardiac resynchronisation therapy should be considered in accordance with the current ESC Guidelines (Table 5)\(^5\).

**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\(^1\). Its prevalence increases with age and correlates with progression of late gadolinium enhancement on CMR\(^1\).

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\(^1\).

Documented sustained monomorphic ventricular tachycardia (≥30 s) is rare and in some patients its origin may be associated with areas of myocardial scarring\(^1\). 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\(^2\).

**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\(^8\). 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\(^2\).

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\(^5\). Current data suggest that patients with advanced LVH and extensive (and rapidly progressing) fibrosis may be candidates for ICD implantation\(^1\). 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\(^1\). 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 CHADS2 and CHA2DS2-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. | Ila   | C     | 271,279–281 |
| The use of aspirin monotherapy is not recommended to protect against cardioembolic stroke. | III    | C     | 90,286 |
| 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     | 90,293 |
| Amiodarone may interfere with lysosomal metabolism and its chronic use should be considered only if other treatments are ineffective. | Ila   | 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     | 90,286 |
| Ablation therapy for AF may be considered as for the general population. | IIb   | C     | 90,286 |

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). | Ila   | 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.

**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. Their use in patients with LV outflow tract obstruction should be avoided if possible.

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. 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.

**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.

In children, the progression of cardiac disease is slow and cardiac manifestations rare. 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.

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...
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, and speakers honoraria from Sanofi Genzyme, Takeda, and Menarini International; Boston Scientific; and has been a speaker and is on the advisory board of Amicus Therapeutics, Sanofi Genzyme, and Takeda. M.N. has received speaker fees/honoraria/travel grants by Bayer, Biosense Webster, Biotronik, Boston Scientific, Daiichi Sankyo, Medtronic, 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, Ailyam, and Sanofi Genzyme. All other authors have nothing to disclose.

References
1. Aerts JM, Groenier JE, Kuiper S, Donker-Koopman WE, Strijland A, Ottenhoff R, van Rooijen C, Mirzaian M, Wijburg FA, Linhorst GE, Veddeler AC, Rombout SM, Cow-Brinkman J, Somerharju P, Boot RG, Hollak CE, Brady RG, 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, Baltas J, Waldek S, Wilcox WR, Whiteley CB, McDonald M, Finkel R, Packman S, Bichet DG, Warnock DG, Desnick Rj. Fabry Disease Clinical Trial Study Group. Agalsidase-bee therapy for advanced Fabry disease: a randomized trial. Am Intern Med 2007; 146: 77–86.
4. Eng CM, Guffon N, Wilcox WR, Germain DP, Lee P, Waldek S, Caplan L, Linhorst 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. Schiffrin R, Kopp Jb, Austin Ha 3rd, Sabnis S, Moore Df, Weibsel T, Balow Jc, Brady Rg. Enzyme replacement therapy in Fabry disease: a randomized controlled trial. JAMA 2001; 285: 2743–2749.
6. Germain DP, Hughes Da, Nichollis K, Bichet DG, Giugliani R, Wilcox Wr, Falciani C, Shankar Sp, Eguz F, Amartino H, Bratkovic D, Feldt-Rasmussen U, Nedd K, Sharaf El Din U, Lourenco Cm, Banikazemi M, Charron J, Dasouki M, Pnegold D, Giraldo P, Goker-Alpan O, Longo N, Scott Cr, Torra R, Tuffaha A, Jovanovic A, Waldek S, Packman S, Ludington E, Vierrebeck C, Kirk J, Yu J, Benjamin Er, Johnson F, Lockhart Dj, Sluban 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, Nietselski 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.
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113. Cecchi F, Iacono M, Maurizi N, Pezzoli L, Binacchi I, Bagi E, Fabbri ML, Olivotti L, Pieruzzi F, Fruntelta A, Dobranut L, Raperiz 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, Voeller 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, Dostovala G, Kuchynka P, Karetova D, Bultas J, Eldeder M, Linhart A. Right ventricular involvement in Fabry disease. J Am Soc Echocardiogr 2008;21:1265–1268.

116. Kampmann C, Baehner FA, Whybura C, Babjou M, Baron K, Knud M, Wiesthoff 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, Voeller 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, Pernissini 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 D, El Deschino A, Gaudio C, Russo MA, Frustaci A. Fabry’s disease cardiomyopathy: echocardiographic detection of endomyocardial glycosphingolipid compartmentalization. J Am Coll Cardiol 2004;47:1671–1677.

120. Mundigel G, Gaggi M, Heinze G, Graf S, Zehetgruber M, Lajic N, Voigtlander T, Mannhalter C, Sunder-Plassmann R, Paschke E, Fauter G, Sunder-Plassmann MG. 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, Vissner J, Voelker W, Ertl G, Wanner C, Weidemann F. Differences in Fabry cardiomyopathy in patients with obstructive hypertrophic cardiomyopathy. Circulation 2003;107:784–790.

122. Linhart A, Cecchi F. Common presentation of rare diseases: left ventricular hypertrophy and diabetic dysfunction. Int J Cardiol 2011;157:21–24.

123. Balbo AS, Lewis NT, Nicholls KM. Cardiovascular outcomes in Fabry disease are linked to severity of chronic kidney disease. Heart 2015;101:287–293.

124. Linhart A, Palecek T, Bultas J, Ferguson JJ, Hradova J, Karetova D, Zeman J, Ledinsky R, Breunig F, Weidemann F, Wanner C. Differences in cardiomyopathic changes in patients with Fabry disease. Am J Med 2000;109:1101–1108.

125. Weidemann F, Strotmann JM, Niemann M, Herrmann S, Wilke M, Beer M, Voeller W, Ertl G, Emmert A, Wanner C, Breunig F. Heart valve involvement in Fabry cardiomyopathy. Ultrasound Med Biol 2009;35:730–735.

126. Barbey F, Qaradli SD, Juli C, Brachk N, Placek T, Rizzo E, Jeaneux R, Eckhardt B, Linhart A. Aortic remodelling in Fabry disease. Eur J Heart 2010;31:347–353.

127. Kalliokoski RJ, Kalliokoski KK, Penttilä P, Kantola I, Leino A, Viikari JS, Urban CS, Mannhalter C, Gogala C. The right ventricle in Fabry disease. J Am Soc Echocardiogr 2006;19:47–53.

128. Linhart A, Palecek T, Bultas J, Placek T, Karetova D, Ertl G. Differences in Fabry cardiomyopathy and light-chain cardiac amyloidosis. J Inherit Med Dis 2011;34:347–353.

129. Barbey F, Brachk N, Linhart A, Kozar R, Callaghan F, Ciganek WJ, Tanaka K, Desnick RJ, Niu DM. Later onset Fabry disease: evidence for a new mechanism independent of genetic predisposition. J Inherit Med Dis 2010;33:347–353.

130. Collin C, Briet M, Tran TC, Beausseur H, Benistant K, Bensalah M, Mousseaux E, Froissart M, Bozec E, Laurent S, Boutouyrie P. Long-term changes in arterial structure and function and left ventricular geometry after enzyme replacement therapy in Fabry disease patients assessed by cardiovascular MR. J Cardiovasc Magn Reson 2010;12:587–596.

131. Kozar R, Ciganek WJ, Tanaka K, Desnick RJ, Niu DM. Later onset Fabry disease: evidence for a new mechanism independent of genetic predisposition. Arterioscler Thromb Vasc Biol 2006;26:839–844.

132. Courtin C, Bocci M, Tran TC, Beausseur H, Benistant K, Bensalah M, Mousseaux E, Froissart M, Bozec E, Laurent S, Boutouyrie P. Long-term changes in arterial structure and function and left ventricular geometry after enzyme replacement therapy in patients with Fabry disease. Eur J Prev Cardiol 2012;19:43–54.

133. Nicholls K. Increased arterial stiffness is associated with high cardiovascular mortality in male Fabry patients. J Inherit Metab Dis 2012;35:805–859.

134. Moon JC, Schadiev B, Elkington AG, McKenna WJ, Mehta A, Pennell DJ, Leed P, Elliott PM. Oxidation 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.

135. Moon JC, Sheppard M, Reed E, Lee P, Elliott PM, Pennell D. 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.

136. Kozar R, Niemann M, Herrmann S, Wilke M, Beer M, Emmert A, Wanner C, Weidemann F. Relation of burden of myocardial fibrosis to malignant ventricular arrhythmias and outcomes in Fabry disease. Am J Cardiol 2014;114:990–995.

137. Hsu TR, Hung SC, Chang FP, Yu WC, Sung SH, Hsu CL, Dzhangalow I, Yang CF, Chu TH, Lee HJ, Lyu 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.

138. Kozar R, Ciganek WJ, Tanaka K, Desnick RJ, Niu DM. Later onset Fabry disease: evidence for a new mechanism independent of genetic predisposition. J Inherit Med Dis 2010;33:347–353.

139. Kozar R, Ciganek WJ, Tanaka K, Hamilton-Craig C, Denaro C, Moon JC, Figtare GA, Griev 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, Banyaersad SM, Treibel T, Captur G, Fontana M, Maestri V, Piett AS, Robson MD, Lachmann RH, Murphy E, Mehta A, Hughes D, Neuberger S, Elliot PM, Moon JC. Identification and assessment of Anderson-Fabry disease using cardiovascular magnetic resonance: noncontrast myocardial T1 mapping. Circ Cardiovasc Imaging 2013;6:392–398.

156. Pica S, Sado DM, Maestri 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, Elliot 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. Circ 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;6:367–645.

158. Mewsow N, Liu CY, Croisille P, Bluemcke D, Lima JA. Assessment of myocardial fibrosis with cardiovascular magnetic resonance. J Am Coll Cardiol 2011;57:891–903.

159. Moon JC, Mercieri DR, Kellman P, Piechnik SK, Robson MD, Ugander M, Gatehouse PD, Arre AE, Friedrich MG, Neuberger S, Schultz-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 2012;14:92.

160. Pagano JJ, Chow K, Khan A, Michalakis 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-Menchaco K, Rosmini S, Captur G, Tchan M, Geberhiwot T, Murphy E, Lachmann R, Ramsawamy U, Edwards NC, Hughes D, Steeds RP, Moon JC. Cardiac phenotype of prehypertrophic Fabry disease. Circ Cardiovasc Imaging 2012;5:707–718.

162. Camponoreale A, Piroeni M, Pieruzzi F, Lusardi P, Pica S, Spada M, Mignani R, Burlina A, Banderla F, Guazzi M, Graziani F, Crea F, Greiber 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, Mesroghli 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, Altemore M, Imbrico M, Nicolai E, Giudice CA, Aiello M, Diomiaiuti CT, Pisani A, Spinelli L, Cuocolo A. First experience of simultaneous PET/MRI in the assessment of Fabry disease and its role in the clinical competence statement on invasive electrophysiology procedures in cardiovascular electrophysiology (a revision of the AHA/ACC/ES guidelines published by John Wiley & Sons Ltd on behalf of European Society of Cardiology). J Am Coll Cardiol Cardiovascular Imaging 2009;2:99–524.

165. Jastrzebski M, Bacior B, Dimitrow PP, Kawecka-Jaszcz K. Electroanatomic mapping and extracellular volume (ECV) in clinical practice: a comprehensive review. J Cardiovasc Magn Reson 2019;20:03.

166. Seydelmann N, Liu D, Kramer J, Drechsler C, Hu K, Nordbeck P, Schneider A, Stork S, Bjønnic B, Ertl G, Wanner C, Weidemann F. High-sensitivity troponin: a clinical blood biomarker for staging cardiomyopathy in Fabry disease. J Am Coll Cardiol 2016;67:256–2567.

167. Coats CJ, Parisi V, Ramos M, Janagarajan K, O’Mahony A, Dawney S, Aitzetmuller C, Brown D, Lenders M, Bran E. Neutralising anti-drug antibodies in Fabry disease can inhibit clinical blood biomarker for staging cardiomyopathy in Fabry disease. J Am Coll Cardiol Cardiovascular Imaging 2019;12:1673–1683.

168. Seydelmann N, Liu D, Kramer J, Drechsler C, Hu K, Nordbeck P, Schneider A, Stork S, Bjønnic 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.
Management of cardiovascular manifestations of Fabry disease

187. Ranezi C, Arbusini E, Caforio AL, Charron P, Gimeno-Blanes J, Helio T, Linhart A, Mogensen J, Pinto T, Ristic A, Seggewis 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 Hear J 2013;34:1448–1458.

188. Nordin S, Kozyr R, Bulluck H, Castlefieti 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;67:1707–1708.

189. Karur GR, Robison S, Iwanochko RM, Morrel CF, Crea AM, Thavendiranathan P, Nguyen ET, Mathur S, Waisim S, Hanneman K. Use of myocardial T1 mapping at 3.0 T to differentiate Anderson-Fabry disease from hypertrophic cardiomyopathy. Radiology 2018;288:396–406.

190. Mignani R, Preda P, Granata A, Maldini L, De Giovanni P, Montecucco 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.

191. Schüffmann 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 the “Kidney Disease: improving Global Outcomes” (KDIGO) controversies conference. Kidney Int 2017;91:284–293.

192. Madsen CV, Gravnhist V, 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.

193. Torralba-Cabeza MA, Oliveira S, Hughes D, Paxores GM, Mateo RN, Perez-Calo JJ, Cystatin C and NT-proBNP as prognostic biomarkers in Fabry disease. Mol Genet Metab 2011;104:301–307.

194. Masagut H, Senda S, Goda Y, Yamagami A, Ko hano T, Hosomi N, Yuki kiri K, Noma T, Muro koh K, Mioh S. Clinical presentation of plasma brain natriuretic peptide during enzyme replacement therapy in a female patient with heterozygous Fabry’s disease. Tsubu J Exp Med 2009;217:169–174.

195. Feutel A, Hahn A, Schneider C, Sieveke N, Franzen W, Gudzut D, Rolfs A, Tanisal C. Continuous cardiac troponin I release in Fabry disease. PLoS One 2014;9:e91757.

196. Weidemann F, Beer M, Krallewski 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 SOPHIMA study. Mol Genet Metab 2019;126:169–182.

197. Nowak A, Mechler TP, Desnich R, Kasper DC. Plasma lysoGb3: a useful biomarker for the diagnosis and treatment of Fabry disease heterozygotes. Mol Genet Metab 2017;120:57–61.

198. Ouyang Y, Chen B, Pan X, Wang Z, Ren H, Xu Y, Ni L, Xu Y, Yang L, Chen N. Clinical significance of plasma globotriaosylsphingosine levels in Chinese patients with Fabry disease. Exp Ther Med 2018;15:3733–3742.

199. Chimenti C, Paddus L, Pazzaglia C, Morgante C, Centurion C, Antuzzi D, Russo MA, Frustaci A. Cardiac and skeletal myopathy in Fabry disease: a clinicopathological case report. Pathol Int 2013;13:1444–1452.

200. Hagge S, Lubanda JC, Sua Z, Bultas J, Kereboda D, Dobrovolny R, Hrebicek M, Germain DP, Linhart A. Natural history of the respiratory involvement in Anderson-Fabry disease. J Inherit Metab Dis 2007;30:790–799.

201. Brown LK, Miller A, Bhuptani A, Sloane MF, Zimmerman MI, Schilero G, Eng CM, Desnich R. Pulmonary involvement in Fabry disease. Am J Resp Crit Care Med 1997;155:1004–1010.

202. Franzen D, Haile SR, Kasper DC, Mechler TP, Flammer AJ, Haykubin 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.

203. Svensson CK, Feldt-Rasmussen U, Backer V. Fabry disease, respiratory symptoms, and airway limitation – a systematic review. Eur Clin Respir J 2015. doi:10.3402/ecrj.v2i26721.

204. Hitz MJ, Marhoil TH, Schwab S, Kobold EH, Brys M, Steenber P. Enzyme replacement therapy improves cardiovascular responses to orthostatic challenge in Fabry patients. J Hypertrns 2018;40:1448–1448.

205. Borlaug BA, Melenovsky V, Russell SD, Kessler K, Pacak K, Becker LC, Kass DA. Impaired chronotropic and vasodilator reserves limit exercise capacity in Fabry patients with heart failure and a preserved ejection fraction. J Am Coll Cardiol 2011;57:2228–2236.

206. Bruder O, Wagner A, Jensen C, Schneider S, On K, Kispert EM, Nassenstein K, Schlösser T, Sabin GV, Sechtem U, Mahnholz H. Myocardial scar visualized by cardiovascular magnetic resonance imaging predicts major adverse events in patients with hypertrophic cardiomyopathy. Circulation 2013;129:358–363.

207. O’Hanlon R, Grassi A, Roughton M, Moon JC, Clark S, Wragh R, Webb J, Kulkarni M, Dawson D, Sulabekh L, Chandrasekhar B, Buccioni-Ducci C, Pasquale F, Cowie MR, McKenna WJ, Sheppard MN, Elliott PM, Pennell DJ. Prognostic significance of left ventricular mass by cardiovascular magnetic resonance in hypertrophic cardiomyopathy. J Am Coll Cardiol 2008;52:559–566.

208. Prinz C, Schwarz M, Iici L, Laser KT, Lehmann R, Prinz EM, Bitter T, Vogt J, van Buuren F, Bogunovic N, Horstkotte D, Faber L. Myocardial fibrosis severity in patients with hypertrophic cardiomyopathy. J Am Coll Cardiol 2009;53:513–520.

209. Marzwick TH, Nakatsu S, Halsaka B, Thomas JD, Lerner HM. Provocation of latent left ventricular outflow tract gradients with amyl nitrite and exercise in patients with hypertrophic cardiomyopathy. Lancet 1997;350:805–809.

210. Blount JR, Wu JK, Martinez MW. Fabry disease with LVOT obstruction: diagnosis and management. J Card Surg 2013;28:695–698.

211. Nowak A, Mechler TP, Flammer AJ, Haykubin 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.

212. Blount JR, Wu JK, Martinez MW. Fabry disease with LVOT obstruction: diagnosis and management. J Card Surg 2013;28:695–698.

213. Nowak A, Mechler TP, Flammer AJ, Haykubin 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.
Perk J, Jer Debacker G, Gohlke H, Graham I, Reiner Z, Verschuren M, Albus C, Benlian P, Boysen G, Clifton R, Deaton C, Ebrahim S, Fisher M, Germann G, Hobbs R, Hoes A, Karasendiz S, Mezzani A, Prescott E, Ryden L, Scherer M, Svanoe M, Scholte op Reimer WJ, Vrints C, Wood D, Zamaro ML, 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.

Williams B, Manca G, Spiering W, Agabiti Rosi E, Azizi M, Burnier M, Clement DL, Coca A, de Simone G, Dominiczak A, Kahan T, Maffoud F, Redon J, Rulicke I, Zanchetti A, Kerins M, Kjeldsen SE, Kreutz R, Laurent S, Lip GYH, McManus R, Narkiewicz K, Ruschitzka F, Schneider RE, Spyridakos E, Tsoufis C, Abayovs V, Desmarais JL. 2018 ESC/EAS 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.

Mae F, Baigent C, Caspano AL, Kaskin-KC, Casula M, Badimon L, Chapman MJ, De Backer GG, Delgado V, Ferencz BA, Graham IM, Halliday A, Landmesser U, Mihaylova B, Pedersen TR, Riccardi G, Richter DJ, Sabatine MS, Taskinen MR, Tokgozoglu L, Wiliuk D; ESC Scientific Document Group. 2018 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J 2020;41:111–188.

Politi JM, Bouloussas D, Germain DP, Gozit C, Guerrero-Sola A, Hilj M, Hoerl AJ, Karas A, Ligouri R, Uceyler N, Zeltzer LK, Burlina A. Pain in Fabry disease: practical recommendations for diagnosis and treatment. ONS Neurisci Ther 2016;22:568–576.

Hughes DA, Elliott PM, Shah J, Zuckerman J, Coghlan G, Brooksie 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.

Boer M, Weidemann F, Dierks J, Knoll A, Koepsell 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 disease. Acta Cardiol 2010;65:185–192.

Fisher EA, Desnick RJ, Gordon RE, Eng CM, Grieppe R, Goldman ME. Fabry disease: an unusual cause of severe coronary disease in a young man. J Interv Card Electrophys 2012;21:1363–1373.

Kalliokoski RJ, Kalliokoski KK, Sundell J, Engblom E, Penttinen M, Kantola I, Raitakari OT, Knutti J, Nuutila P, Impaired myocardial perfusion reserve but preserved peripheral endothelial function in patients with Fabry disease. J Hypertens Med 2005;28:563–573.

Brignole M, Moya A, de Lange FJ, Deharo JC, Elliott PM, Fanciulli A, Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, Budaj A, Gregoratos G, Klein G, Moss AJ, Myerburg RJ, Priori SG, Quinones MA, Zijlstra F, Roos-Hesselink JW, Yap SC. Value of implantable loop recorders in patients with Fabry disease: report of a Writing Group deployed by the Working Group on Cardiac morphology and function of the Task Force on the management of stable coronary artery disease of the Joint Task Force of the European Society of Cardiology and the European Council of Nuclear Cardiology. Eur Heart J 2008;29:511–536.
257. Giugliani R, Waldek S, Germain DP, Kirkman M, Davis-Geelen M, Piconi R, Boudes P, Lockhart DJ, Valenzano KJ, Samuel E, Benoit E, Hirshfeld JW. Risk factors for atrial fibrillation in Fabry disease: a prospective observational study. J Am Heart Assoc 2015;4(3):e002385.

258. Pfeffer MA, Claggett B, Assmann SF, Boineau R, Anand IS, Clausell N, Desai 262. Pitt B, Pfeffer MA, Assmann SF, Boineau R, Anand IS, Claggett B, Clausell N, 263. Reasor MJ, Kacew S. Drug-induced phospholipidosis: are there functional 259. Young-Gqamana B, Brignol N, Chang HH, Khanna R, Soska R, Fuller M, 257. Giugliani R, Waldek S, Germain DP, Kirkman M, Davis-Geelen M, Piconi R, Boudes P, Lockhart DJ, Valenzano KJ, Samuel E, Benoit E, Hirshfeld JW. Risk factors for atrial fibrillation in Fabry disease: a prospective observational study. J Am Heart Assoc 2015;4(3):e002385.

258. Pfeffer MA, Claggett B, Assmann SF, Boineau R, Anand IS, Clausell N, Desai 262. Pitt B, Pfeffer MA, Assmann SF, Boineau R, Anand IS, Claggett B, Clausell N, 263. Reasor MJ, Kacew S. Drug-induced phospholipidosis: are there functional 259. Young-Gqamana B, Brignol N, Chang HH, Khanna R, Soska R, Fuller M, 257. Giugliani R, Waldek S, Germain DP, Kirkman M, Davis-Geelen M, Piconi R, Boudes P, Lockhart DJ, Valenzano KJ, Samuel E, Benoit E, Hirshfeld JW. Risk factors for atrial fibrillation in Fabry disease: a prospective observational study. J Am Heart Assoc 2015;4(3):e002385.
303. O'Mahony C, Jichi F, Pavlova 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.

304. 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:e104.e5–e7.

305. 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.

306. Rogers DP, Marazia S, Chow AW, Lowe MD, Frenneaux M, Gu M, Jin H, Hua W, Fan XH, Niu HX, Tian T, Ding LG, Wang J, Xue C, Yu CM, Chan JY, Zhang Q, Omar R, Yip GW, Hussin A, Fang F, Lam KH. Implantable cardioverter-defibrillator in patients with hypertrophic cardiomyopathy: JAMA 2007:298:405–412.

307. Takenaka T, Teraguchi H, Yoshida A, Taguchi S, Ninomiya K, Umekita Y, A. Linhart et al.

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