

Screening, diagnosis, and management of patients with Fabry disease: conclusions from a “Kidney Disease: Improving Global Outcomes” (KDIGO) Controversies Conference



OPEN

Raphael Schiffmann¹, Derralynn A. Hughes², Gabor E. Linthorst³, Alberto Ortiz⁴, Einar Svarstad^{5,6}, David G. Warnock⁷, Michael L. West⁸ and Christoph Wanner⁹; for Conference Participants¹⁰

¹Institute of Metabolic Disease, Baylor Research Institute, Dallas, Texas, USA; ²Department of Haematology, Royal Free London NHS Foundation Trust, & University College London, UK; ³Department of Endocrinology and Metabolism, Academic Medical Center, Amsterdam, Netherlands; ⁴Unidad de Dialisis, IIS-Fundacion Jimenez Diaz/UAM, IRSIN, Madrid, Spain; ⁵Department of Clinical Medicine, University of Bergen, Bergen, Norway; ⁶Department of Medicine, Haukeland University Hospital, Bergen, Norway; ⁷Division of Nephrology, Department of Medicine, University of Alabama at Birmingham, Birmingham, Alabama, USA; ⁸Department of Medicine, Dalhousie University, Halifax, Canada; and ⁹Department of Medicine, Division of Nephrology, University Hospital of Würzburg, Würzburg, Germany

Patients with Fabry disease (FD) are at a high risk for developing chronic kidney disease and cardiovascular disease. The availability of specific but costly therapy has elevated the profile of this rare condition. This KDIGO conference addressed controversial areas in the diagnosis, screening, and management of FD, and included enzyme replacement therapy and nonspecific standard-of-care therapy for the various manifestations of FD. Despite marked advances in patient care and improved overall outlook, there is a need to better understand the pathogenesis of this glycosphingolipidosis and to determine the appropriate age to initiate therapy in all types of patients. The need to develop more effective specific therapies was also emphasized.

Kidney International (2017) **91**, 284–293; <http://dx.doi.org/10.1016/j.kint.2016.10.004>

KEYWORDS: chronic kidney disease; enzyme replacement therapy; Fabry disease; Fabry nephropathy; standard of care

Copyright © 2016, International Society of Nephrology. Published by Elsevier Inc. This is an open access article under the CC BY-NC-SA license (<http://creativecommons.org/licenses/by-nc-sa/4.0/>).

Correspondence: Raphael Schiffmann, Institute of Metabolic Disease, Baylor Research Institute, 3812 Elm Street, Dallas, TX 75226, USA. E-mail: raphael.schiffmann@baylorhealth.edu; and Christoph Wanner, University of Würzburg, University Hospital, Renal Division, 97080 Würzburg, Germany. E-mail: wanner_c@ukw.de

¹⁰See [Appendix](#) for list of other conference participants.

Received 13 September 2016; revised 8 October 2016; accepted 13 October 2016; published online 18 December 2016

Fabry disease (FD; OMIM entry number: 301500) is an X-linked lysosomal storage disorder caused by deficient activity of α -galactosidase A resulting in accumulation of glycosphingolipids with terminal α -D-galactosyl residue, particularly globotriaosylceramide (GL-3, Gb3, CTH) and globotriaosylsphingosine (Lyso-GL-3, lyso-Gb3).¹ These lipids progressively accumulate in the circulation and in virtually all cell types and organs, resulting in the development of a multisystem disorder. Affected patients are at high risk of developing a small-fiber neuropathy, progressive proteinuric kidney disease, fibrotic cardiac disease resulting in rhythm and conduction disturbances, progressive hypertrophic cardiomyopathy, and mostly ischemic cerebrovascular stroke.² Though this disease is X-linked, both males and females are affected by it.

Although diagnosis and management of FD have markedly improved over the years, the disease has no cure, and current therapy is suboptimal.³ Our goal was to summarize the current knowledge and knowledge gaps regarding screening, diagnosis, and therapy, and to propose a research agenda to resolve outstanding controversial issues.

SCREENING AND DIAGNOSIS

Clinical presentation and diagnostic testing

The clinical characteristics of FD are described in [Table 1](#). The diagnosis is established in males by α -galactosidase A-specific activity that is below 25% to 30% of mean control in peripheral white blood cells.^{2,4–7} Alpha-galactosidase A activity is somewhat predictive of classic or later-onset manifestations. Classically affected hemizygotes have undetectable or very low ($\leq 3\%$) enzymatic activity.² As with many genetic diseases, there is a wide phenotypic variability even among patients with the same *GLA* mutation. A late-onset phenotype of FD exists mainly with cardiac-variant disease forms.⁸ These patients present with typical disease in their fifth or sixth decade but often lack the early alerting clinical features of angio-keratoma, acroparesthesia, corneal opacities, and sweating abnormalities. Patients with milder variants typically have

Table 1 | Manifestations in Fabry disease**Childhood and adolescence (≤16 years)**

Acroparesthesia/pain crisis: chronic or episodic, burning sensation in the palms of hands or soles of feet, exacerbated by temperature changes, fever, stress, physical exercise, and alcohol

Angiokeratomas: small, raised, dark red spots that develop slowly and can be found on the buttocks, genitalia, inner thighs, back, and oral cavity

Ophthalmologic abnormalities: cornea verticillata (whorl-shaped opacity), posterior subcapsular cataracts, tortuous vascular lesions in the retina and conjunctiva, dilated vessels on upper lid margin

Sensorineural hearing loss

Hypohidrosis or anhidrosis

Increased albuminuria

History of nonspecific bowel disturbances

History of lethargy and fatigue

Early adulthood (17–30 years)

More extensive angiokeratomas

High albuminuria (>1g/24 hours)

Edema or lymphedema

Fever

Hypohidrosis or anhidrosis

Lymphadenopathy

Heat sensitivity

Diarrhea, abdominal pain

Cardiac: bradycardia, short PR interval, left ventricular hypertrophy, conduction defects

Later adulthood (age > 30 years)

Heart disease: fibrotic, left and right ventricular hypertrophy, heart valve abnormalities and dysrhythmias, sudden cardiac death, angina, diastolic heart failure, cardiac transplantation

Chronic kidney disease: including end-stage renal disease requiring renal replacement therapy with dialysis or renal transplantation

Stroke or transient ischemic attacks

Deafness, of acute or chronic onset

missense *GLA* mutations and variable residual enzyme activity. For example, the N215S mutation may have residual enzyme activity in plasma and/or leucocytes close to the normal range. One exception is a splice mutation common in Taiwanese patients with FD who have 10% residual enzyme activity and develop left ventricular hypertrophy in their fourth or fifth decade of life.⁴

In heterozygous females, random X-inactivation may result in expression of α -galactosidase A activity in the plasma or leucocytes within the normal range in up to 60% of women.⁹ Sequencing of the *GLA* gene is necessary for a diagnosis of FD in most females. In addition to point mutations, frameshift mutations and small deletions within exons and exon-intron boundaries, large deletions, and intronic mutations have been described.² The finding of elevated globotriaosylceramide (Gb3) in relevant tissues should be the ultimate requirement when confronted with *GLA* variants of unknown significance.¹⁰ Erroneous attribution of pathogenicity to a mutation may lead to a costly and inappropriate use of specific therapy such as enzyme replacement therapy (ERT) and a missed opportunity to

make the correct diagnosis. Where enzyme activity is low and no mutation is found by Sanger sequencing of exons and exon-intron boundaries, further investigations including multiplex ligation-dependent probe amplification analysis and assessment of specific intronic mutations should be performed.¹¹

Substrate accumulation including Gb3 and lyso-Gb3 may occur in plasma and urine. While glycolipid urinalysis may be helpful in attributing pathogenicity or phenotype, it may be less useful in screening because increased urinary Gb3 has been described in cohorts of patients with cardiac disease or nephrotic syndrome without a diagnosis of FD.¹²

Screening strategies for Fabry disease

Based on recent newborn screening studies each including at least 30,000 newborns, the prevalence of FD was found to be markedly higher than previously expected with 1 in 3100 males reported in northwestern Italy,¹³ 1 in 3000 males in Austria, 1 in 1300 males in Taiwan, 1 in 7800 males in Washington state (USA), and 1 in 1500 males in Missouri (USA). Before these studies, the prevalence was expected to be much lower: 1 in 117,000 in Australia,¹⁴ 1 in 468,000 in the Netherlands,¹⁵ and only 1 in 833,000 in Portugal.¹⁶

High-risk screening. Screening for stroke in the young has shown definite FD in 0.5%,¹⁷ in 0.9% of the hypertensive population with left ventricular hypertrophy,¹⁸ in 0.5% to 1% of patients with idiopathic hypertrophic cardiomyopathy^{5,19} but 4% of males,²⁰ and in 0.11% to 0.17% of dialysis patients.^{21–23} Only 0.2% of unselected patients with common heart disease have FD.¹² Prevalence screening studies may inadvertently indicate falsely higher prevalence due to benign polymorphisms (e.g., D313Y).^{24,25}

FD should be considered and tested in patients with chronic kidney disease (CKD) with no definitive cause of nephropathy and when no biopsy has been performed, especially in familial cases. The difficulty in recognizing this condition due to a highly variable and nonspecific phenotype, lack of positive family history in at least 5% of cases, and a low prevalence rate in many regions of the world signifies that many patients are diagnosed late or never diagnosed.²⁶ This situation can only be reversed by the introduction of widespread screening of at-risk patients.

Family screening. The X-linked nature of FD inheritance renders cascade screening of families efficient and of high diagnostic yield over on average 3 generations surrounding an index case. All index patients should meet with a genetic counselor or a physician to produce an informative family tree and facilitate communication with predicted affected family members so they may be referred to a medical geneticist for genetic counseling and testing. Considering the privacy of the index case is important and must be weighed against the risk of delayed diagnosis in family members.²⁷

Many patients find it valuable to discuss implications of testing with a clinical geneticist and may wish to consider preconception genetic diagnosis, prenatal testing, or postnatal

diagnosis. Diagnosis in a Fabry male has particular diagnostic implications for his mother and daughters, who will all, in the absence of new mutations or nonpaternity, have positive test results. The risk of FD in any male or female offspring of a woman with FD is 50%.²⁷ Once a genetic diagnosis has been made, patients should undergo a full clinical evaluation and treatment as described in [Supplementary Table S1](#).

Knowledge gaps and research recommendations (Table 2). The true prevalence of FD is not known, but future systematic screening for the disease in the general population may help determine it. Another challenge is to predict the pathogenicity of some *GLA* variants. Because newborn screening for FD has effectively begun in certain jurisdictions, future research must evaluate the ethical and psychological ramifications of early diagnosis of a disorder that may or may not manifest itself until years or decades later.

ENZYM REPLACEMENT THERAPY

ERT with recombinant human α -galactosidase A (agalsidase) is the only currently available therapy aimed at the etiology of FD ([Supplementary Table S2](#)). Agalsidase- α and agalsidase- β have been studied in clinical trials with different primary endpoints, hampering comparison of effectiveness. However, surrogate endpoints were evaluated on both enzymes in placebo-controlled trials that led to regulatory approval ([Supplementary Table S3](#)). These trials have reported on short periods of ERT, with different clinical endpoints, predominantly in (male) typical patients. As FD is a rare chronic, slowly progressive disease with a 4-decade natural history and broad heterogeneous presentation, this evidence is incomplete. Extrapolating results to long-term patient management or other Fabry populations is challenging. Based on ethical and feasibility considerations, it is very unlikely that further evidence from placebo-controlled trials will become available. Additional knowledge is provided by case series and post-marketing surveillance databases that, despite their limitations, suggest that the earlier therapy is started, the better the outcome may be. This observation is in accordance with the hypothesis that glycolipid clearance is most therapeutically effective before secondary, irreversible tissue injury has occurred.

Initiation of ERT

Expert opinion-based recommendations on initiation and cessation of ERT are available.^{28,29} However, there is no scientific evidence as to the optimal age of ERT initiation. Therefore, there are no uniform guidelines, and conditions and age to start ERT differ in various countries. In general, development of signs or symptoms related to FD is an indication to start ERT. For the kidney, this implies the development of CKD (i.e., pathological albuminuria or decreased glomerular filtration rate [GFR]) or progressive decrease in GFR if ERT has not already been started earlier for nonrenal manifestations such as pain.³⁰ The benefits of early treatment, before irreversible tissue injury occurs, should be

Table 2 | Knowledge gaps and research recommendations

Screening and diagnosis

- Elucidate role of gene variants of uncertain significance
- Investigate potential genotype–phenotype relations
- Determine when to initiate specific treatment as a function of *GLA* mutation severity
- Ascertain response to specific therapy as a function of *GLA* mutation severity
- Establish an independent, transparent, and freely accessible registry of consenting FD patients including phenotype, genotype data, and full annotation of phenotypes
- Evaluate utility of cardiology screening of patients with a short PR interval
- Identify optimal screening tools
- Follow the outcome of FD newborn screening programs
- Elucidate role of skewed X-inactivation in heterozygotes
- Investigate the mechanism of organ injury in female patients
- Pursue the use of biomarkers for diagnosis
- Acquire better understanding of glycosphingolipid pathogenesis and basic cellular pathology

Initiation of therapy

- Determine when to start treatment in asymptomatic or paucisymptomatic patients, females, with nonclassic disease
- Obtain expanded information on the natural history of FD in classic female patients and nonclassic FD patients, and the effects of ERT in these groups
- Undertake X-linked inactivation studies and early initiation of therapy in females

Therapeutic regimens

- Establish criteria and biomarkers for dose individualization
- Evaluate combination therapy: substrate synthesis reduction combined with ERT or with a pharmacological chaperone
- Develop standardized assessment of neutralizing antibodies and evaluate impact on treatment regimens – utilize experience from Pompe disease interventions

Outcomes

- Define therapeutic failure. Does progression of FD while undergoing ERT indicate therapeutic failure?
- Define long-term outcomes of different dosing schemes in different patient populations
- Define very long-term outcomes of patients starting ERT in childhood, both on clinical manifestations and glycolipid burden (e.g., cardiomyocytes, podocytes, vascular smooth muscle cells)
- Ascertain impact of ERT on heart and central nervous system disease, valvular abnormalities and aortic root dilatation, and lymphedema
- Identify outcome of ERT in nonclassic FD
- Understand pathophysiology of lung involvement and treatment with ERT as well as the role of β_2 -agonists^{36,114}
- Provide uniform description and categorization of study populations in future reports on the efficacy of therapy, including genotype, phenotype, sex, and age at initiation of therapy
- Conduct long-term outcome studies of (pediatric) patients who started ERT when asymptomatic or paucisymptomatic
- Collect histologic evidence of ERT-induced clearance of Gb3 in long-lived cells: vascular smooth muscle cells, cardiomyocytes, podocytes
- Conduct studies on the pathophysiology and treatment of gastrointestinal involvement and lymphedema
- Develop more sensitive patient-reported outcome measures

ERT, enzyme replacement therapy; FD, Fabry disease.

balanced against the burden of biweekly infusions in very young individuals. In a recent pediatric randomized controlled trial (RCT), Fabry arteriopathy and segmental effacement of podocyte foot processes were found in all biopsied FD patients with normal GFR and urinary albumin-to-creatinine ratio (UACR) < 30 mg/g,³¹ suggesting early

renal involvement and by inference an indication for initiation of ERT before kidney injury, marked by proteinuria or reduced GFR, become clinically apparent. There is lack of agreement on cessation criteria.

Glycolipid deposits. Placebo-controlled RCTs in classic FD have consistently shown that within 6 months, ERT reduces plasma and urinary Gb3 and capillary endothelial Gb3 (Supplementary Table S3). Clearance of Gb3 in other slowly dividing cells may take years. In young patients, there is some limited evidence of a dose-dependent clearance of podocytes over 5 years of follow-up.³² This finding has not yet been established as an acceptable surrogate for beneficial renal therapeutic effect.

Kidney, cardiac, and cerebral disease. Overall, there is a suggestion that ERT slows the progression of kidney involvement in FD and results in reduction of hypertrophic cardiomyopathy, especially when started prior to established fibrosis. However, there is no reduction in the rate of stroke with ERT. Though there are limited data and only few comparative studies, it is suggested that dose may have an impact. Only 1 placebo-controlled study addressed the effect of ERT (1.0 mg/kg/2 weeks agalsidase- β) on severe renal, cardiac, or central nervous system events. A small decrease in clinical events was observed after a prespecified correction for imbalances at baseline (Supplementary Table S3).³³ One patient registry study shows a decline in clinical event rate after the first 6 months of agalsidase- β , but in general there is no indication that the event rate on ERT is lower than the natural history of the disease.^{34,35} The clinical event rate for patients taking agalsidase- α has not been published, although morbidity may be delayed in these patients.³⁶ The observed differences in ERT outcomes may be caused by the profound clinical heterogeneity of studied patients (Supplementary Table S3).

Proteinuria is a well-recognized factor associated with progressive loss of kidney function in many forms of CKD.³⁷ In the phase 3 trial with agalsidase- β , classic FD patients presenting with <1.0 g/day (d) of proteinuria had stabilization of their renal function during 5 years of follow-up.³⁸ In contrast, classic patients presenting with >1 g/d of proteinuria, usually associated with fibrosis and scarring in more than half of the glomeruli on baseline renal biopsies, had progressive loss of kidney function, many reaching CKD stage 5.³⁸ These results have been extended with 10 years of follow-up. The important factors related to progressive loss of kidney function were age at which ERT was initiated and averaged ratio of urinary protein to creatinine <0.5 g/g (<0.5 g/d, <50 mg/mmol) during the follow-up period.^{39,40} In those with uncontrolled proteinuria or a reduced GFR (<60 ml/min/ 1.73 m²), ERT alone does not seem to prevent further deterioration of renal function.

The phase 3 follow-up results have been incorporated into various treatment recommendations, with the suggestion that ERT be withheld if there is clinical evidence of more severe renal involvement as denoted by significant proteinuria or loss of kidney function. This recommendation does not

address the appreciable number of patients with FD who present with pathological levels of albuminuria (>30 mg/g albumin-to-creatinine ratio) and reduced kidney function at initial evaluation,⁴¹ or the opportunity to initiate ERT before overt organ damage develops.^{32,42,43} Renal biopsies are useful in such cases to determine the severity of cellular injury (e.g., podocyte effacement) and organ damage (e.g., glomerular sclerosis and fibrosis; vascular smooth muscle hypertrophy and arteriopathy) that can develop before clinical signs of kidney involvement become apparent.

ERT may improve left ventricular hypertrophy if no fibrosis is present at baseline,^{44,45} but cardiac fibrosis will progress during ERT, especially if severe (i.e., greater than 3 segments). Left ventricular hypertrophy reduction is not a proven surrogate for improved cardiovascular outcome. There is no evidence of reversal or prevention of electrocardiogram changes or clinical arrhythmia. In the absence of a proper control group, it is unknown whether the rate of deterioration is slowed in those patients with most advanced disease who continue to decline during ERT.^{35,46} Indeed, cardiac death is a more common cause of death in patients with FD than progression to end-stage renal disease.^{3,47}

It is estimated that, depending on the age-range cohort, FD patients have a 5.5- to 12.2-fold increased risk of stroke compared to the general population.⁴⁸ Strokes continue to occur in patients on ERT.^{39,49,50} A long-term study from the UK suggested that stroke occurred more often among patients older than late 40s undergoing ERT.⁴⁹ In that study, 19 of 212 patients who were undergoing ERT developed stroke or transient ischemic attacks, while only 1 of 76 who were not undergoing ERT developed such complications ($P = 0.01$, Fisher's exact test), possibly suggesting that those patients with more severe manifestations were receiving ERT. In a placebo controlled RCT, 2 of 31 patients (6.45%) in the placebo group and 0 of 51 (0%, $P = 0.14$) in the agalsidase- β group experienced a stroke.³³ *Post hoc* analysis of this trial suggested prevention of new white matter lesions following ERT compared to placebo.⁵¹

Other symptoms. In placebo-controlled RCTs, both agalsidase- α and agalsidase- β improved pain scores in adults,^{52,53} but improvement was also seen in the placebo groups. In general clinical experience, ERT is only mildly effective at best³⁵ in decreasing pain, and younger patients may respond better than do older patients. Improved school attendance has been reported with ERT.^{54–56} Patient-reported outcomes from patient representatives indicate an overall significant improvement of pain in adults and children. A postmarketing registry paper and other anecdotal evidence suggest improvement of gastrointestinal symptoms with ERT.^{57,58}

Two studies suggest a beneficial response of ERT on mild-to-moderate hearing loss,^{59,60} but a recent longitudinal analysis demonstrates that hearing loss present before initiation of therapy cannot be reversed.⁶¹ Several postmarketing registry studies suggest improvement of quality of life (QoL) with ERT. However, the outcome of QoL on ERT is inconclusive.⁶²

The issue of dose. The issue of dose has been confounded by the fact that the label-recommended dose of the 2 available agalsidase preparations has a 5-fold difference; thus, any discussion on dose must be interpreted in the context of the different enzyme preparations. In the absence of adequately powered RCTs directly comparing 0.2 to 1.0 mg/kg/2 weeks, individual physicians should evaluate the available placebo-controlled RCT, case-series, and Canadian FD Initiative clinical trial results for personalized decision-making (Supplementary Table S3).

A dose effect, at least in some patients, is suggested for podocyte Gb3 clearance and preservation of renal function in case series of repeat kidney biopsy in young patients. Doubling the frequency of 0.2 mg/kg agalsidase- α in patients with progressive kidney disease from biweekly to weekly is also suggested.^{32,63} The largest randomized, prospective head-to-head trial comparing agalsidase- α to agalsidase- β in adults is underpowered but has 5-year longitudinal data on 1.0 mg/kg/2 weeks agalsidase- β versus 0.2 mg/kg/2 weeks agalsidase- α with a primary outcome of severe clinical events. There was no significant difference in the event-free survival between the 2 treatment arms. While the hazard ratio of 1.46 favored agalsidase- β , perhaps reflecting differences in baseline characteristics among the 2 patients groups,⁶⁴ a more recent analysis of the 8-year data (presented at the Society for the Study of Inborn Errors of Metabolism meeting in September 2016) reports a hazard ratio of 1.17, which again is not statistically significant despite a patient sample size of 115. While there is some evidence that higher agalsidase dose results in better biochemical clearance,^{65,66} at present there is no evidence to base treatment decisions on biomarker levels that do not correlate with patient outcomes.⁶⁷

The limited effect of ERT is likely due to a combination of: (i) delayed treatment initiation after the onset of irreversible organ damage; (ii) intermittent administration leaving the patient with little functional enzyme every second week; (iii) incomplete tissue penetration of the infused protein; (iv) presence of anti-agalsidase antibodies; (v) lack of appropriately powered RCTs to detect a very small clinical effect; and (vi) incompletely understood mechanism of response to ERT.⁶⁸ Weekly infusions, a novel α -galactosidase A preparation with a longer half-life, or the use of small molecules, such as pharmacological chaperones⁶⁹ or substrate synthesis reduction, may address some of these limitations.

Follow-up of treatment. Follow-up recommendations are listed in Supplementary Table S1. Patients with FD should have access to coordinated care through expert designated centers, either through their local physician or by visiting such a center.

Antibodies develop in a substantial proportion of typical male FD patients and also in some females, and negatively influence known substrate-related biomarkers. Gb3 reaccumulation in skin biopsies and greater disease progression were noted in patients with high antibody titers.^{70,71}

Knowledge gaps and research recommendations (Table 2). We do not know when ERT should be initiated

and in particular at what age. Is there a cut-off age or disease stage beyond which benefit of ERT is minimal? These may be different for different organ systems. The net effect of ERT in females could also be better ascertained in clinical trials performed only in female FD patients.

NONSPECIFIC STANDARD OF CARE THERAPY

Cardiac and cerebrovascular disease: heart failure, coronary disease, arrhythmia, and stroke

Cardiac deaths account for the majority of deaths in FD in both sexes,^{72,73} and cardiomyopathy has been reported in up to 90% of patients.⁷⁴ Low blood pressure is typical.¹⁸ Heart failure may have multifactorial causes that need to be treated according to general principles beyond ERT. Many patients do not tolerate β -blockers and may need a pacemaker due to bradycardia.⁷⁵ Adjunctive treatment of the cardiac disease includes renin angiotensin system blockers, which in general have beneficial effects on regression of hypertrophy.^{76,77} The beneficial effect of these drugs is especially well documented when there is concomitant CKD and hypertension.⁷⁸ While chest pain and dyspnea may pose a diagnostic challenge, coronary disease should be diagnosed and treated similarly to treatment in non-FD patients.

Cardiac arrhythmias and conduction abnormalities are frequent, and bradycardia and atrial fibrillation are common findings.⁷⁵ The risk of stroke in patients with paroxysmal atrial fibrillation, which is often asymptomatic, may be underestimated, and anticoagulation is needed in many of these patients.⁶⁸ The indication is probably stronger than the general recommendations in the ESC guidelines,⁷⁹ although the risk for cerebral microbleeds must be recognized.⁸⁰ Because both small and large cerebral vessels are involved, effective antiplatelet agents are highly recommended to prevent stroke in enzyme-naïve patients and in those undergoing ERT for primary and secondary stroke prevention.⁸¹ Implantation of a pacemaker is necessary in cases with symptomatic and severe bradycardia.⁸² Malignant arrhythmias are usually associated with occurrence of replacement fibrosis in advanced hypertrophic cardiomyopathy in male patients, and may also be seen in females before they develop overt left ventricular hypertrophy.⁸³ Implantation of a cardioverter-defibrillator should be considered in these patients.^{84,85}

Pulmonary disease

Dyspnea is a frequent symptom in many patients, and differential diagnosis between disturbed systolic or diastolic cardiac function versus pulmonary or airway dysfunction may be difficult. A mixture of different etiologic mechanisms of obstructive and restrictive pulmonary symptoms has been reported in several small studies and case reports, and a recent systematic review could not identify consistent findings in the literature.⁸⁶ A registry study concluded that 23 of 67 patients had airway obstruction similar to chronic obstructive pulmonary disease, and obstructive lung disease has been

reported to be up to 10 times more prevalent in people with FD than in the general population.

Neuropathic pain (chronic pain and pain crisis)

Neuropathic pain associated with small fiber neuropathy is a key feature of FD from childhood or early adulthood (average age of onset is 9 years in males and 16 years in females, though onset as early as the age of 5 years has been reported).^{87,88} No RCT has been conducted in the treatment of neuropathic pain in FD. Tables 3 and 4 show recommended approaches to treatment of chronic neuropathic pain and pain crisis in FD.

The mechanisms of FD neuropathy are not fully understood, but evidence of substrate deposits in dorsal root ganglia, stenosis and occlusion of vasa nervorum, and up-regulation of ectopic and unstable sodium channels and TRPV channels as expressions of nerve damage have been hypothesized to contribute to acroparesthesias and pain crises.⁸⁹ Drugs generally have similar efficacy in various conditions, except in trigeminal neuralgia, chronic radiculopathy, and HIV neuropathy, with level A evidence in support of tricyclic antidepressants, pregabalin, gabapentin, tramadol, and opioids (in various conditions) and duloxetine, venlafaxine, topical lidocaine, and capsaicin patches (in restricted conditions). Combination therapy appears useful for tricyclic antidepressants, gabapentin, and gabapentin-opioids.⁹⁰ Sodium-channel blockers (carbamazepine) have been reported to have beneficial effect on gastrointestinal symptoms as well as emotional (depressive) symptoms.^{91,92}

Renal involvement

Gb3 deposits have been described in many renal cell types as early as 17 weeks of gestation⁹³ and in placental tissue of patients with FD.⁹⁴ Kidney biopsy studies have shown age-dependent progressive accumulation of Gb3 in podocytes, and correlations between early kidney damage and albuminuria.⁹⁵ Early treatment with ERT may help prevent progressive renal involvement during 5 years of treatment in children with normoalbuminuria or microalbuminuria.³² A correlation between the cumulative administered dose of ERT, podocyte clearance of Gb3, and improvement in albuminuria has been suggested.³² Importantly, the transition from Gb3 accumulation in podocytes to the earliest phases of injury denoted by podocyte foot process effacement occurs before there are clinically evident increases in urinary albumin or protein

excretion.⁴² Recently, increased urinary loss of podocytes has been described early in FD, again before the onset of clinically apparent proteinuria.^{43,96} The phases of tissue accumulation of Gb3, cellular injury, organ damage, and progressive loss of kidney function are represented in Figure 1.

Generally, the diagnosis of early decline of GFR in patients with FD and CKD is hampered by inaccuracy of creatinine-based GFR measurements. Overestimation of true GFR may be especially relevant in many male FD patients. A measured GFR (e.g., iohexol GFR) may therefore be helpful in the assessment of nephropathy.^{97,98} However, it should be emphasized that there may be significant renal involvement before any changes in GFR are measured or estimated (Figure 1).

The mainstay approach for reducing urinary protein and albumin excretion in all forms of CKD has been the use of renin angiotensin system blockade with angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers, which has also been associated with improved renal and cardiac outcomes.³⁷ Recognizing the trade-off of control of proteinuria and the associated reduction in blood pressure with these agents, the goal for proteinuria reduction is not clearly defined in any form of CKD. The best available evidence is based on a meta-analysis of nondiabetic CKD treated with angiotensin-converting enzyme inhibitors; there was a clear-cut benefit of ACE inhibition compared to other forms of hypertension control when urinary protein excretion exceeded 500 mg/d.⁹⁹ Renin angiotensin system blockade has been shown to prevent the transition from microalbuminuria to overt albuminuria in patients with diabetes, but this effect was reversed when the therapy was stopped and did not have a persistent beneficial effect on kidney function.^{100–102} The effects of angiotensin-receptor blocker therapy on albumin excretion can be dissociated from the primary effect on systemic blood pressure, and in *post hoc* analyses, changes in urinary albumin excretion have been independently associated with slowing of progressive loss of renal function.¹⁰³ Despite these promising findings, more recent efforts to prevent microalbuminuria or aggressively control proteinuria in diabetic kidney disease have been disappointing.¹⁰⁴

There is a direct relationship between loss of renal function and sex, and also with severity of proteinuria both before and after the initiation of ERT.^{105–107} A single-center study reported stabilization of renal function in 6 classic FD patients at high risk for progression to end-stage renal disease

Table 3 | Adjunctive therapy for chronic pain

Agent	Dose range	Cardiac restrictions	Renal restrictions
Carbamazepine ^{115,116}	250–800 mg/d	May interfere with activity of other drugs (e.g., warfarin)	None
Gabapentin ¹¹⁷	Slowly titrated from 100 to a max of 2400 mg/d	None	Caution with chronic kidney disease
Phenytoin ¹¹⁸	300 mg/d	None	None
Pregabalin ⁸⁹	75–300 mg/d	None	Caution with chronic kidney disease
Tricyclic antidepressants ¹¹⁹	25–150 mg/d	Arrhythmias	None
Duloxetine ¹²⁰	60–120 mg /d	None	None

Table 4 | Adjunctive therapy for pain crisis

Agent	Dose range	Experience in Fabry disease and side effects	Cardiac and renal restrictions
IV lidocaine ¹²¹	2–5 mg/kg	Good clinical response	Arrhythmias, no renal restrictions
Tramadol ¹²²	100–400 mg/d	Caution with concomitant use of SSRIs, SNRIs, or TCAs	Caution with chronic kidney disease and epilepsy
Morphine ¹²²	Titration of 30–120 mg every 12 h	Monitor for addiction; constipation	None
Oxycodone ⁹¹	Titration of 20–60 mg every 12 h	Monitor for addiction; constipation	None
Diclofenac ⁹¹	50–150 mg/d	Risk of GI bleeding	Caution with chronic kidney disease

GI, gastrointestinal; h, hours; IV, intravenous; SNRI, serotonin–norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

with control of proteinuria to a target of 0.5 g/d while receiving concurrent ERT at 1 mg/kg every 2 weeks.¹⁰⁶ This study was recognized in the European Renal Best Practice report, but was not incorporated into the overall recommendations pending confirmation of these findings in a larger group of classic FD patients.¹⁰⁸ A recent report on a larger series of 24 patients described successful titration and maintenance of urinary protein-to-creatinine ratio at 0.5 g/g with angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers in 18 of the 24 patients who completed the 24-month open-label protocol.¹⁰⁹ Despite successful control of proteinuria in these 18 patients, only 6 experienced stabilization of their kidney function, while the remaining 12 patients continued to lose renal function at the same rate as the 6 patients who could not achieve the target for control of proteinuria.¹⁰⁹ The only identified factor that distinguished the patients who achieved the proteinuria goal and had preserved renal function from those who did not have preserved renal function was the age at which ERT was initiated. Similarly, a 10-year follow-up of the phase 3 agalsidase- β trial³⁹ patients showed that those who started ERT at a younger age had a significantly more favorable response.

Individual FD patients should follow the general guidelines for management of CKD, including blood pressure optimization, smoking cessation, dietary salt restriction, and management of hyperlipidemia.³⁷ A kidney biopsy should definitely be considered to confirm the diagnosis of Fabry nephropathy, evaluate the severity of irreversible renal involvement,^{30,110} and diagnose superimposed kidney disease in cases of unexpected kidney findings.¹¹¹ Several other approaches have also been described, including decreasing the ERT dosing interval,⁶³ the addition of amiloride to the anti-proteinuric regimen,¹¹² and the addition of paricalcitol therapy to renin angiotensin system blockade.¹¹³ Prospective evaluations of these approaches with larger numbers of patients are needed to improve the renal outcomes of patients with FD.

Knowledge gaps and research recommendations (Table 2). The biggest challenge is to separate the net contribution of specific therapy such as ERT from the overall effect of the nonspecific but powerful standard of care interventions described above. Future research should focus on additional ways to protect the glomerular function of the kidneys and cardiac rhythm and conduction system. The latter has thus far not responded to any specific treatment.

CONCLUSION

FD is a complex multisystem disease with mostly nonspecific symptoms and signs. Diagnosis requires a high index of suspicion in symptomatic patients and screening of certain at-risk groups. Common standard-of-care therapies are highly effective in alleviating symptoms and treating disease complications. ERT is the first specific therapy developed that can slow kidney disease and alleviate symptoms but confers little benefit to cardiovascular and cerebrovascular outcomes. Additional specific therapeutic agents such as modified α -galactosidase A with a longer half-life and better tissue penetration, pharmacological chaperones, and substrate reduction therapy may further improve patient health.

DISCLOSURE

RS declared having received consultancy fees from Protalix (monies went to Baylor Research Institute), speaker honoraria from Sanofi Genzyme, and research support from Protalix. DAH declared having received consultancy fees from Amicus, Genzyme, Protalix and Shire; speaker honoraria from Genzyme and Shire; and research support from Shire. GEL declared having received travel support, consultancy

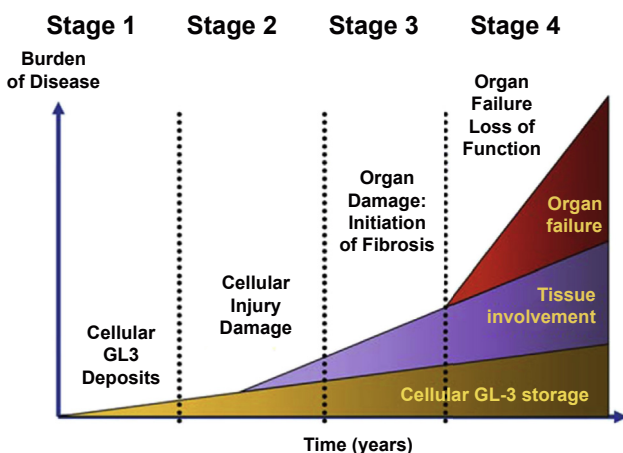


Figure 1 | Fabry nephropathy: GL3 accumulation, cellular injury, organ injury, and progressive loss of renal function. Adapted from Eng *et al.* with permission.¹²³ ACR, albumin-creatinine ratio; ESRD, end-stage renal disease; GFR, glomerular filtration rate.

fees, and educational grants from Actelion, Amicus, Protalix, Sanofi Genzyme, and Shire HGT; all financial arrangements are made through GEL's academic institution (AMC Medical Research BV). AO declared having received consultancy fees from Sanofi Genzyme; speaker honoraria from Sanofi Genzyme and Shire; and research support from Healthcare research fund (FIS, Spanish Government). ES declared having received consultancy fees from Genzyme and speaker honoraria from Genzyme and Shire. DGW declared having received consultancy fees from Actelion, Amicus, Genzyme and Protalix; and research support from the National Institutes of Health. MLW declared having received consultancy fees from Sanofi Genzyme; speaker honoraria from Excelsior Pharma, Sanofi Genzyme, and Shire; and research support from Sanofi Genzyme (Canada) and Shire. MLW has also served as an independent medical expert for medical legal cases. CW declared having received consultancy fees from Actelion, Protalix and Sanofi Genzyme; speaker honoraria from Actelion and Sanofi Genzyme; and research support from Sanofi Genzyme.

The conference was sponsored by Kidney Disease: Improving Global Outcomes (KDIGO) and supported in part by unrestricted educational grants from Amicus Therapeutics, Genzyme, Protalix Biotherapeutics, and Shire.

SUPPLEMENTARY MATERIAL

Table S1. Follow-up recommendations.

Table S2. Agalsidase preparations.

Table S3. Key phase 2 through phase 4 placebo-controlled agalsidase trials.

Supplementary material is linked to the online version of the paper at www.kidney-international.org.

REFERENCES

- Brady RO, Gal AE, Bradley RM, et al. Enzymatic defect in Fabry's disease. Ceramidetrihexosidase deficiency. *N Engl J Med.* 1967;276:1163–1167.
- Desnick RJ, Ioannou YA, Eng CM. Alpha-galactosidase A deficiency: Fabry disease. In: Valle D, Beaudet AL, Vogelstein B, Kinzler KW, et al. (eds). *The Online Metabolic and Molecular Bases of inherited disease.* McGraw-Hill: New York; 2014.
- Rombach SM, Smid BE, Linthorst GE, et al. Natural course of Fabry disease and the effectiveness of enzyme replacement therapy: a systematic review and meta-analysis: effectiveness of ERT in different disease stages. *J Inherit Metab Dis.* 2014;37:341–352.
- Chien YH, Lee NC, Chiang SC, et al. Fabry disease: incidence of the common later-onset alpha-galactosidase A IVS4+919G->A mutation in Taiwanese newborns—superiority of DNA-based to enzyme-based newborn screening for common mutations. *Mol Med.* 2012;18:780–784.
- Monserrat L, Gimeno-Blanes JR, Marin F, et al. Prevalence of fabry disease in a cohort of 508 unrelated patients with hypertrophic cardiomyopathy. *J Am Coll Cardiol.* 2007;50:2399–2403.
- Ferreira S, Ortiz A, Germain DP, et al. 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.
- Andrade J, Waters PJ, Singh RS, et al. Screening for Fabry disease in patients with chronic kidney disease: limitations of plasma alpha-galactosidase assay as a screening test. *Clin J Am Soc Nephrol.* 2008;3:139–145.
- Schiffmann R. Fabry disease. *Pharmacol Ther.* 2009;122:65–77.
- Gupta S, Ries M, Kotsopoulos S, et al. The relationship of vascular glycolipid storage to clinical manifestations of Fabry disease: a cross-sectional study of a large cohort of clinically affected heterozygous women. *Medicine (Baltimore).* 2005;84:261–268.
- Schiffmann R, Fuller M, Clarke LA, Aerts JM. Is it Fabry disease? *Genet Med.* 2016;18:1181–1185.
- Ferri L, Cavicchi C, Fiumara A, et al. Pitfalls in the detection of gross gene rearrangements using MLPA in Fabry disease. *Clin Chim Acta.* 2016;452:82–86.
- Schiffmann R, Forni S, Swift C, et al. Risk of death in heart disease is associated with elevated urinary globotriaosylceramide. *J Am Heart Assoc.* 2014;3:e000394.
- Spada M, Pagliardini S, Yasuda M, et al. High incidence of later-onset fabry disease revealed by newborn screening. *Am J Hum Genet.* 2006;79:31–40.
- Meikle PJ, Hopwood JJ, Clague AE, et al. Prevalence of lysosomal storage disorders. *JAMA.* 1999;281:249–254.
- Fuller M, Meikle PJ, Hopwood JJ. Epidemiology of lysosomal storage diseases: an overview. In: Mehta A, Beck M, Sunder-Plassmann G (eds). *Fabry Disease: Perspectives from 5 Years of FOS.* Oxford, UK: Oxford PharmaGenesis Ltd; 2006.
- Pinto R, Caseiro C, Lemos M, et al. Prevalence of lysosomal storage diseases in Portugal. *Eur J Hum Genet.* 2004;12:87–92.
- Rolfs A, Fazekas F, Grittner U, et al. Acute cerebrovascular disease in the young: the Stroke in Young Fabry Patients study. *Stroke.* 2013;44:340–349.
- Terry W, Deschoenmakere G, De Keyser J, et al. Prevalence of Fabry disease in a predominantly hypertensive population with left ventricular hypertrophy. *Int J Cardiol.* 2013;167:2555–2560.
- Elliott P, Baker R, Pasquale F, et al. Prevalence of Anderson-Fabry disease in patients with hypertrophic cardiomyopathy: the European Anderson-Fabry Disease survey. *Heart.* 2011;97:1957–1960.
- Palecek T, Honzikova J, Poupetova H, et al. Prevalence of Fabry disease in male patients with unexplained left ventricular hypertrophy in primary cardiology practice: prospective Fabry cardiomyopathy screening study (FACSS). *J Inherit Metab Dis.* 2014;37:455–460.
- Kotanko P, Kramar R, Devrnja D, et al. Results of a nationwide screening for Anderson-Fabry disease among dialysis patients. *J Am Soc Nephrol.* 2004;15:1323–1329.
- Nishino T, Obata Y, Furusu A, et al. Identification of a novel mutation and prevalence study for fabry disease in Japanese dialysis patients. *Ren Fail.* 2012;34:566–570.
- Okur I, Ezgu F, Biberoglu G, et al. Screening for Fabry disease in patients undergoing dialysis for chronic renal failure in Turkey: identification of new case with novel mutation. *Gene.* 2013;527:42–47.
- Froissart R, Guffon N, Vanier MT, et al. Fabry disease: D313Y is an alpha-galactosidase A sequence variant that causes pseudodeficient activity in plasma. *Mol Genet Metab.* 2003;80:307–314.
- Dubuc V, Moore DF, Gioia LC, et al. Prevalence of Fabry disease in young patients with cryptogenic ischemic stroke. *J Stroke Cerebrovasc Dis.* 2013;22:1288–1292.
- Pisani A, Daniele A, Di Domenico C, et al. Late diagnosis of Fabry disease caused by a de novo mutation in a patient with end stage renal disease. *BMC Res Notes.* 2015;8:711.
- Hughes DA, Evans S, Milligan A, et al. A multidisciplinary approach to the care of patients with Fabry disease. In: Mehta A, Beck M, Sunder-Plassmann G (eds). *Fabry Disease: Perspectives from 5 Years of FOS.* Oxford, UK: Oxford PharmaGenesis Ltd; 2006.
- Biegstraaten M, Arngrimsson R, Barbey F, et al. Recommendations for initiation and cessation of enzyme replacement therapy in patients with Fabry disease: the European Fabry Working Group consensus document. *Orphanet J Rare Dis.* 2015;10:36.
- Eng CM, Germain DP, Banikazemi M, et al. Fabry disease: guidelines for the evaluation and management of multi-organ system involvement. *Genet Med.* 2006;8:539–548.
- Ortiz A, Oliveira JP, Wanner C, et al. Recommendations and guidelines for the diagnosis and treatment of Fabry nephropathy in adults. *Nat Clin Pract Nephrol.* 2008;4:327–336.
- Wijburg FA, Benichou B, Bichet DG, et al. Characterization of early disease status in treatment-naive male paediatric patients with Fabry disease enrolled in a randomized clinical trial. *PLoS One.* 2015;10:e0124987.
- Tondel C, Bostad L, Larsen KK, et al. Agalsidase benefits renal histology in young patients with Fabry disease. *J Am Soc Nephrol.* 2013;24:137–148.
- Banikazemi M, Bultas J, Waldek S, et al. Agalsidase-beta therapy for advanced Fabry disease: a randomized trial. *Ann Intern Med.* 2007;146:77–86.
- Ortiz A, Abiose A, Bichet DG, et al. 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.
- Weidemann F, Niemann M, Stork S, et al. 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.

36. Beck M, Hughes D, Kampmann C, et al. Long-term effectiveness of agalsidase alfa enzyme replacement in Fabry disease: A Fabry Outcome Survey analysis. *Mol Genet Metab Rep.* 2015;3:21–27.
37. KDOQI clinical practice guidelines and clinical practice recommendations for diabetes and chronic kidney disease. *Am J Kidney Dis.* 2007;49:S12–S154.
38. Germain D, Waldek S, Banikazemi M, et al. 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.
39. Germain DP, Charrow J, Desnick RJ, et al. Ten-year outcome of enzyme replacement therapy with agalsidase beta in patients with Fabry disease. *J Med Genet.* 2015;52:353–358.
40. West M, Nicholls K, Mehta A, et al. Agalsidase alfa and kidney dysfunction in Fabry disease. *J Am Soc Nephrol.* 2009;20:1132–1139.
41. Ortiz A, Cianciaruso B, Cizmarik M, et al. End-stage renal disease in patients with Fabry disease: natural history data from the Fabry Registry. *Nephrol Dial Transplant.* 2010;25:769–775.
42. Tondel C, Kanai T, Larsen KK, et al. Foot process effacement is an early marker of nephropathy in young classic fabry patients without albuminuria. *Nephron Physiol.* 2015;129:16–21.
43. Trimarchi H, Canzonieri R, Schiel A, et al. Podocyturia is significantly elevated in untreated vs treated Fabry adult patients. *J Nephrol.* 2016;29:791–797.
44. Hughes DA, Elliott PM, Shah J, et al. 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.
45. Weidemann F, Niemann M, Breunig F, et al. Long-term effects of enzyme replacement therapy on fabry cardiomyopathy: evidence for a better outcome with early treatment. *Circulation.* 2009;119:524–529.
46. Rombach SM, Smid BE, Bouwman MG, et al. Long term enzyme replacement therapy for Fabry disease: effectiveness on kidney, heart and brain. *Orphanet J Rare Dis.* 2013;8:47.
47. El Dib RP, Gomaa H, Carvalho RP, et al. Enzyme replacement therapy for Anderson-Fabry disease. *Cochrane Database Syst Rev.* 2016;7:CD006663.
48. Sims K, Politei J, Banikazemi M, et al. 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.
49. Anderson LJ, Wyatt KM, Henley W, et al. Long-term effectiveness of enzyme replacement therapy in Fabry disease: results from the NCS-LSD cohort study. *J Inherit Metab Dis.* 2014;37:969–978.
50. Buechner S, Moretti M, Burlina AP, et al. Central nervous system involvement in Anderson-Fabry disease: a clinical and MRI retrospective study. *J Neurol Neurosurg Psychiatry.* 2008;79:1249–1254.
51. Fellgiebel A, Gartenschlager M, Wildberger K, et al. Enzyme replacement therapy stabilized white matter lesion progression in Fabry disease. *Cerebrovasc Dis.* 2014;38:448–456.
52. Eng CM, Banikazemi M, Gordon RE, et al. A phase 1/2 clinical trial of enzyme replacement in fabry disease: pharmacokinetic, substrate clearance, and safety studies. *Am J Hum Genet.* 2001;68:711–722.
53. Schiffmann R, Kopp JB, Austin HA 3rd, et al. Enzyme replacement therapy in Fabry disease: a randomized controlled trial. *JAMA.* 2001;285:2743–2749.
54. Ramaswami U, Stull DE, Parini R, et al. Measuring patient experiences in Fabry disease: validation of the Fabry-specific Pediatric Health and Pain Questionnaire (FPHQP). *Health Qual Life Outcomes.* 2012;10:116.
55. Ries M, Clarke JT, Whybra C, et al. Enzyme-replacement therapy with agalsidase alfa in children with Fabry disease. *Pediatrics.* 2006;118:924–932.
56. Wraith JE, Tylki-Szymanska A, Guffon N, et al. Safety and efficacy of enzyme replacement therapy with agalsidase beta: an international, open-label study in pediatric patients with Fabry disease. *J Pediatr.* 2008;152:563–570.
57. Banikazemi M, Ullman T, Desnick RJ. Gastrointestinal manifestations of Fabry disease: clinical response to enzyme replacement therapy. *Mol Genet Metab.* 2005;85:255–259.
58. Hoffmann B, Schwarz M, Mehta A, et al. Gastrointestinal symptoms in 342 patients with Fabry disease: prevalence and response to enzyme replacement therapy. *Clin Gastroenterol Hepatol.* 2007;5:1447–1453.
59. Hajioff D, Enever Y, Quiney R, et al. Hearing loss in Fabry disease: the effect of agalsidase alfa replacement therapy. *J Inherit Metab Dis.* 2003;26:787–794.
60. Hajioff D, Hegemann S, Conti G, et al. Agalsidase alpha and hearing in Fabry disease: data from the Fabry Outcome Survey. *Eur J Clin Invest.* 2006;36:663–667.
61. Suntjens EB, Smid BE, Biegstraaten M, et al. Hearing loss in adult patients with Fabry disease treated with enzyme replacement therapy. *J Inherit Metab Dis.* 2015;38:351–358.
62. Arends M, Hollak CE, Biegstraaten M. Quality of life in patients with Fabry disease: a systematic review of the literature. *Orphanet J Rare Dis.* 2015;10:77.
63. Schiffmann R, Swift C, Wang X, et al. A prospective 10-year study of individualized, intensified enzyme replacement therapy in advanced Fabry disease. *J Inherit Metab Dis.* 2015;38:1129–1136.
64. Sirrs SM, Bichet DG, Casey R, et al. Outcomes of patients treated through the Canadian Fabry disease initiative. *Mol Genet Metab.* 2014;111:499–506.
65. van Breemen MJ, Rombach SM, Dekker N, et al. Reduction of elevated plasma globotriaosylsphingosine in patients with classic Fabry disease following enzyme replacement therapy. *Biochim Biophys Acta.* 2011;1812:70–76.
66. Vedder AC, Breunig F, Donker-Koopman WE, et al. Treatment of Fabry disease with different dosing regimens of agalsidase: effects on antibody formation and GL-3. *Mol Genet Metab.* 2008;94:319–325.
67. Schiffmann R, Ries M, Blankenship D, et al. Changes in plasma and urine globotriaosylceramide levels do not predict Fabry disease progression over 1 year of agalsidase alfa. *Genet Med.* 2013;15:983–989.
68. Schiffmann R. Fabry disease. *Handb Clin Neurol.* 2015;132:231–248.
69. Germain DP, Hughes DA, Nicholls K, et al. Treatment of Fabry's disease with the pharmacologic chaperone migalastat. *N Engl J Med.* 2016;375:545–555.
70. Lubanda JC, Anijal E, Bzduch V, et al. Evaluation of a low dose, after a standard therapeutic dose, of agalsidase beta during enzyme replacement therapy in patients with Fabry disease. *Genet Med.* 2009;11:256–264.
71. Lenders M, Stypmann J, Duning T, et al. Serum-mediated inhibition of enzyme replacement therapy in Fabry disease. *J Am Soc Nephrol.* 2016;27:256–264.
72. Mehta A, Clarke JT, Giugliani R, et al. Natural course of Fabry disease: changing pattern of causes of death in FOS - Fabry Outcome Survey. *J Med Genet.* 2009;46:548–552.
73. Waldek S, Patel MR, Banikazemi M, et al. Life expectancy and cause of death in males and females with Fabry disease: findings from the Fabry Registry. *Genet Med.* 2009;11:790–796.
74. Linhart A, Kampmann C, Zamorano JL, et al. Cardiac manifestations of Anderson-Fabry disease: results from the international Fabry outcome survey. *Eur Heart J.* 2007;28:1228–1235.
75. Shah JS, Hughes DA, Sachdev B, et al. Prevalence and clinical significance of cardiac arrhythmia in Anderson-Fabry disease. *Am J Cardiol.* 2005;96:842–846.
76. Ferreira Filho C, Abreu LC, Valenti VE, et al. Anti-hypertensive drugs have different effects on ventricular hypertrophy regression. *Clinics (Sao Paulo).* 2010;65:723–728.
77. Lombardo M, Alli C, Broccolino M, et al. Long-term effects of angiotensin-converting enzyme inhibitors and calcium antagonists on the right and left ventricles in essential hypertension. *Am Heart J.* 1997;134:557–564.
78. K/DOQI clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease. *Am J Kidney Dis.* 2004;43:S1–S290.
79. Camm AJ, Lip GY, De Caterina R, et al. 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.
80. Kono Y, Wakabayashi T, Kobayashi M, et al. Characteristics of cerebral microbleeds in patients with Fabry disease. *J Stroke Cerebrovasc Dis.* 2016;25:1320–1325.
81. Kolodny E, Fellgiebel A, Hilz MJ, et al. Cerebrovascular involvement in Fabry disease: current status of knowledge. *Stroke.* 2015;46:302–313.
82. Weidemann F, Niemann M, Warnock DG, et al. The Fabry cardiomyopathy: models for the cardiologist. *Annu Rev Med.* 2011;62:59–67.
83. Niemann M, Herrmann S, Hu K, et al. Differences in Fabry cardiomyopathy between female and male patients: consequences for diagnostic assessment. *JACC Cardiovasc Imaging.* 2011;4:592–601.
84. Acharya D, Robertson P, Kay GN, et al. Arrhythmias in Fabry cardiomyopathy. *Clin Cardiol.* 2012;35:738–740.

85. Zipes DP, Camm AJ, Borggrefe M, et al. 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. *Circulation*. 2006;114:e385–e484.
86. Svensson CK, Feldt-Rasmussen U, Backer V. Fabry disease, respiratory symptoms, and airway limitation - a systematic review. *Eur Clin Respir J*. 2015;2.
87. Mehta A, Ricci R, Widmer U, et al. Fabry disease defined: baseline clinical manifestations of 366 patients in the Fabry Outcome Survey. *Eur J Clin Invest*. 2004;34:236–242.
88. Laney DA, Peck DS, Atherton AM, et al. Fabry disease in infancy and early childhood: a systematic literature review. *Genet Med*. 2015;17:323–330.
89. Burlina AP, Sims KB, Politei JM, et al. Early diagnosis of peripheral nervous system involvement in Fabry disease and treatment of neuropathic pain: the report of an expert panel. *BMC Neurol*. 2011;11:61.
90. Attal N, Cruccu G, Baron R, et al. EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. *Eur J Neurol*. 2010;17:1113–e1188.
91. Politei JM, Bouhassira D, Germain DP, et al. Pain in Fabry disease: practical recommendations for diagnosis and treatment. *CNS Neurosci Ther*. 2016;22:568–576.
92. Politei J, Thurberg BL, Wallace E, et al. Gastrointestinal involvement in Fabry disease. So important, yet often neglected. *Clinical Genetics*. 2016;89:5–9.
93. Brady RO, Uhlenendorf BW, Jacobson CB. Fabry's disease: antenatal detection. *Science*. 1971;172:174–175.
94. Vedder AC, Strijland A, vd Bergh Weerman MA, et al. Manifestations of Fabry disease in placental tissue. *J Inherit Metab Dis*. 2006;29:106–111.
95. Najafian B, Svarstad E, Bostad L, et al. Progressive podocyte injury and globotriaosylceramide (GL-3) accumulation in young patients with Fabry disease. *Kidney Int*. 2011;79:663–670.
96. Trimarchi H, Canzonieri R, Murvan A, et al. Copious podocyturia without proteinuria and with normal renal function in a young adult with Fabry disease. *Case Rep Nephrol*. 2015:257628.
97. Rombach SM, Baas MC, ten Berge IJ, et al. The value of estimated GFR in comparison to measured GFR for the assessment of renal function in adult patients with Fabry disease. *Nephrol Dial Transplant*. 2010;25:2549–2556.
98. Tondel C, Ramaswami U, Aakre KM, et al. Monitoring renal function in children with Fabry disease: comparisons of measured and creatinine-based estimated glomerular filtration rate. *Nephrol Dial Transplant*. 2010;25:1507–1513.
99. Kent DM, Jafar TH, Hayward RA, et al. Progression risk, urinary protein excretion, and treatment effects of Angiotensin-converting enzyme inhibitors in nondiabetic kidney disease. *J Am Soc Nephrol*. 2007;18:1959–1965.
100. Mathiesen ER, Hommel E, Hansen HP, et al. Randomised controlled trial of long term efficacy of captopril on preservation of kidney function in normotensive patients with insulin dependent diabetes and microalbuminuria. *BMJ*. 1999;319:24–25.
101. Mauer M, Zinman B, Gardiner R, et al. Renal and retinal effects of enalapril and losartan in type 1 diabetes. *N Engl J Med*. 2009;361:40–51.
102. Parving HH, Lehnert H, Brochner-Mortensen J, et al. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. *N Engl J Med*. 2001;345:870–878.
103. Hellemons ME, Persson F, Bakker SJ, et al. Initial angiotensin receptor blockade-induced decrease in albuminuria is associated with long-term renal outcome in type 2 diabetic patients with microalbuminuria: a post hoc analysis of the IRMA-2 trial. *Diabetes Care*. 2011;34:2078–2083.
104. Luft FC. Perspective on combination RAS blocking therapy: off-TARGET, dis-CORD, MAP-to-nowhere, low ALTITUDE, and NEPHRON-D. *Am J Nephrol*. 2014;39:46–49.
105. Schiffmann R, Warnock DG, Banikazemi M, et al. Fabry disease: progression of nephropathy, and prevalence of cardiac and cerebrovascular events before enzyme replacement therapy. *Nephrol Dial Transplant*. 2009;24:2102–2111.
106. Wanner C, Oliveira JP, Ortiz A, et al. Prognostic indicators of renal disease progression in adults with fabry disease: natural history data from the fabry registry. *Clin J Am Soc Nephrol*. 2010;5:2220–2228.
107. Warnock DG, Ortiz A, Mauer M, et al. Renal outcomes of agalsidase beta treatment for Fabry disease: role of proteinuria and timing of treatment initiation. *Nephrol Dial Transplant*. 2012;27:1042–1049.
108. Terryn W, Cochat P, Froissart R, et al. Fabry nephropathy: indications for screening and guidance for diagnosis and treatment by the European Renal Best Practice. *Nephrol Dial Transplant*. 2013;28:505–517.
109. Warnock DG, Thomas CP, Vujkovic B, et al. Antiproteinuric therapy and Fabry nephropathy: factors associated with preserved kidney function during agalsidase-beta therapy. *J Med Genet*. 2015;52:860–866.
110. van der Tol L, Svarstad E, Ortiz A, et al. Chronic kidney disease and an uncertain diagnosis of Fabry disease: approach to a correct diagnosis. *Mol Genet Metab*. 2015;114:242–247.
111. Skrunes R, Svarstad E, Kampevold Larsen K, et al. Reaccumulation of globotriaosylceramide in podocytes after agalsidase dose reduction in young Fabry patients [e-pub ahead of print]. *Nephrol Dial Transplant*. <http://dx.doi.org/10.1093/ndt/gfw094>.
112. Trimarchi H, Forrester M, Lombi F, et al. Amiloride as an alternate adjuvant antiproteinuric agent in Fabry disease: the potential roles of plasmin and uPAR. *Case Rep Nephrol*. 2014;2014:854521.
113. Pisani A, Sabbatini M, Duro G, et al. Antiproteinuric effect of add-on paricalcitol in Fabry disease patients: a prospective observational study. *Nephrol Dial Transplant*. 2015;30:661–666.
114. Franzen D, Krayenbuehl PA, Lidove O, et al. Pulmonary involvement in Fabry disease: overview and perspectives. *Eur J Intern Med*. 2013;24:707–713.
115. Filling-Katz MR, Merrick HF, Fink JK, et al. Carbamazepine in Fabry's disease: effective analgesia with dose-dependent exacerbation of autonomic dysfunction. *Neurology*. 1989;39:598–600.
116. Schuller Y, Linthorst GE, Hollak CE, et al. Pain management strategies for neuropathic pain in Fabry disease - a systematic review. *BMC Neurol*. 2016;16:25.
117. Ries M, Mengel E, Kutschke G, et al. Use of gabapentin to reduce chronic neuropathic pain in Fabry disease. *J Inherit Metab Dis*. 2003;26:413–414.
118. Lockman LA, Hunninghake DB, Krivit W, et al. Relief of pain of Fabry's disease by diphenylhydantoin. *Neurology*. 1973;23:871–875.
119. Mehta A, Beck M, Eyskens F, et al. Fabry disease: a review of current management strategies. *QJM*. 2010;103:641–659.
120. Sommer C, Üçeyler N, Duning T, et al. Pain therapy for Fabry's disease. *Der Internist*. 2012;54:121–130.
121. Politei JM. [Intravenous lidocaine as treatment for the painful episodes in Fabry's disease]. *Rev Neurol*. 2009;49:166–167.
122. O'Connor AB, Dworkin RH. Treatment of neuropathic pain: an overview of recent guidelines. *Am J Med*. 2009;122:522–532.
123. Eng CM, Fletcher J, Wilcox WR, et al. Fabry disease: baseline medical characteristics of a cohort of 1765 males and females in the Fabry Registry. *J Inherit Metab Dis*. 2007;30:184–192.

APPENDIX

Other Conference Participants

Daniel G. Bichet, Canada; Erik Ilsø Christensen, Denmark; Ricardo Correa-Rotter, Mexico; Perry M. Elliott, UK; Sandro Feriozzi, Italy; Agnes B. Fogo, USA; Dominique P. Germain, France; Carla E.M. Hollak, Netherlands; Robert J. Hopkin, USA; Jack Johnson, USA; Ilkka Kantola, Finland; Jeffrey B. Kopp, USA; Jürgen Kröner, Germany; Aleš Linhart, Czech Republic; Ana Maria Martins, Brazil; Dietrich Matern, USA; Atul B. Mehta, UK; Renzo Mignani, Italy; Behzad Najafian, USA; Ichiei Narita, Japan; Kathy Nicholls, Australia; Greg T. Obrador, Mexico; João Paulo Oliveira, Portugal; Antonio Pisani, Italy; Juan Politei, Argentina; Uma Ramaswami, UK; Markus Ries, Germany; Wim Terryn, Belgium; Camilla Tøndel, Norway; Roser Torra, Spain; Bojan Vujkovic, Slovenia; Stephen Waldek, UK; Jerry Walter, USA