SPECIAL REPORT

Enzyme replacement therapy in Fabry disease in Poland: a position statement

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Introduction Fabry disease (FD; Online Mendelian Inheritance in Man, OMIM #301500) is a rare inherited genetic lysosomal storage disease caused by mutations in the *GLA* gene on the X chromosome, which results in a lack or significant deficiency of the lysosomal enzyme α-galactosidase A (α-GAL A). This deficiency leads to the accumulation of glycosphingolipids (mainly globotriaosylceramide [GL-3] and its deacylated form, globotriaosylsphingosine [lyso-GL-3]) in numerous cells of the body as well as to the development of multisystem complications that impair the quality of life and result in premature death (TABLE 1).[1]

The clinical picture of FD is diverse and depends on the α-GAL A activity. A complete lack of or only trace α-GAL A activity (<5%) underlies the classic form of the disease, which mainly affects male patients. People with partially preserved enzymatic activity develop the nonclassic late-onset form of FD. The onset and severity of symptoms in women primarily depend on the random pattern of inactivation of one of the two X chromosomes.[2,3]

The first symptom of the classic form of FD, already seen in early childhood, is chronic or paroxysmal neuropathic pain in the hands and feet, defined as acroparesthesia. Later, other symptoms associated with thin nerve fiber involvement occur, such as impaired perspiration (hypohidrosis, anhidrosis), abdominal pain, and diarrhea. Characteristic symptoms of the classic form also include angiokeratoma-type cutaneous lesions and corneal opacities (cornea verticillata).[1] Even in childhood, clinically silent proteinuric chronic kidney disease (CKD) may occur with microalbuminuria or glomerulosclerosis. Multiorgan symptoms of the classic form of FD usually appear in young adults and may include CKD, left ventricular hypertrophy, myocardial fibrosis, arrhythmias and conduction abnormalities, transient ischemic attack, and stroke. People with late-onset FD typically experience cardiac symptoms, stroke, or CKD in the fourth or fifth decade of life.[1] The classic form is an early-onset multisystem disease that usually presents with cornea verticillata and angiokeratomas. In contrast, the nonclassic form has a later onset and usually affects a single organ, most often the heart; angiokeratomas or cornea verticillata is rare.

The progression of cellular and organ changes is observed in the course of FD. Metabolite accumulation begins as early as in the fetal period, leading to the involvement of numerous tissues and severe organ damage (FIGURE 1).[4] The life

TABLE 1 The most common renal, cardiac, neurologic, and other complications associated with Fabry disease (based on Ortiz et al)[11]

Renal complications	Cardiac complications	Neurologic complications	Other complications
Pathological albuminuria/ proteinuria	Left ventricular hypertrophy	Neuropathic pain (chronic, pain crises)	Angiokeratoma-type skin lesions
Reduced glomerular filtration rate	Heart arrhythmia (ventricular arrhythmia, atrial fibrillation, bradycardia)	Stroke, transient ischemic attack White matter lesions in the brain	Cornea verticillata, retinal/ conjunctival vascular changes
Chronic kidney disease leading to renal insufficiency	Myocardial fibrosis	Hearing loss	Cataract
Hypertension	Ischemia, myocardial infarction	Depression	Dyspnea, dry cough, sleep breathing disorders
Premature death	Valvular defects (mitral, aortic regurgitation)	Autonomic system disorders: gastrointestinal disorders (diarrhea, nausea, postprandial pain); sweating disorders	Moderate facial dysmorphia
	Reduced exercise tolerance	Premature death	Osteopenia, osteoporosis
	Heart failure		Lymphoedema
	Premature death		

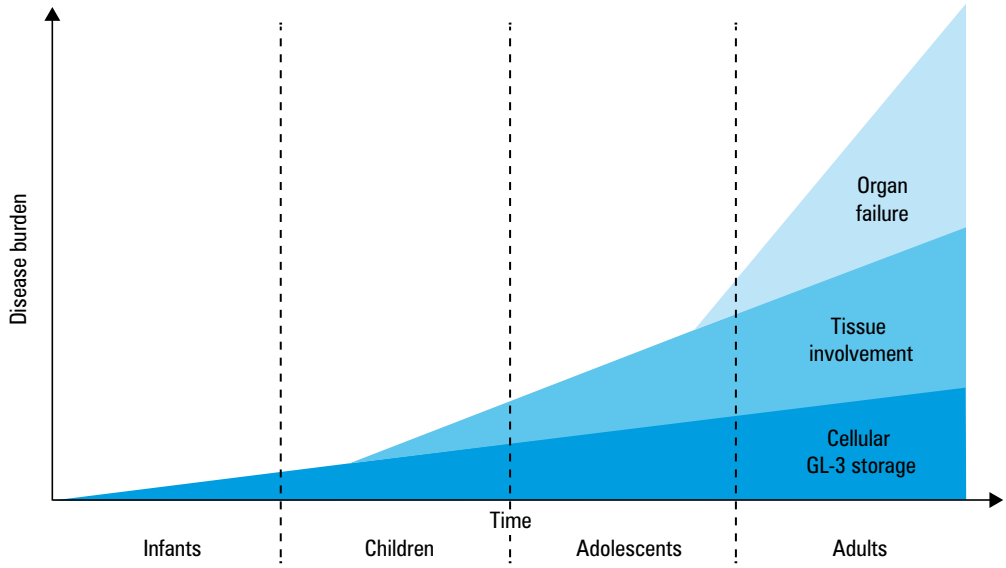

FIGURE 1 Progression of Fabry disease (modified from Clin Ther. Vol. 29 Suppl A, Wanner C, Fabry disease model: a rational approach to the management of Fabry disease: S2-5. © 2007 Excerpta Medica, Inc, with permission from Elsevier Inc. (Reuse must be cleared with Elsevier Inc.)[4]

expectancy of men with FD is shorter by 15 to 20 years, and that of women, by 6 to 10 years, as compared with the average life expectancy of the population.[5] It should be emphasized that even in the stage of late complications, the diagnosis of FD is difficult. Chronic kidney disease as well as cardiac and neurologic symptoms are widespread in the general population and are usually caused by common civilization diseases.

The estimated prevalence of FD in the general world population is 1/100 000. The prevalence of FD reported in Polish studies is 2.5/100 000 in the entire population: 1/40 000 in men and 0.85/100 000 (1/117 000) in women.[6-8] In men, the prevalence of the classic mutations that result in no detectable α-GAL A activity is about 1 in 20 000 to 45 000. The prevalence of the non-classic mutations, with some α-GAL A activity, is about 10-fold higher. In women, the prevalence of mutations is higher than in men (2:1 ratio) because FD is inherited with the X chromosome.

In Poland, there are no guidelines for the diagnosis and management of Fabry disease.[9] This position statement was prepared by an interdisciplinary group of experts and approved by the Boards of the Polish Cardiac Society, Polish Society of Inborn Errors of Metabolism, Polish Society of Internal Medicine, Polish Society of Nephrology, and Polish Society of Neurology. Although disease-specific treatments for FD include other treatments than enzyme replacement therapy (ERT; eg, migalastat), only ERT is currently reimbursed in Poland. This position paper aims to provide practical recommendations for physicians who treat patients with FD in Poland; therefore, the main focus is ERT.

Diagnosis of Fabry disease Due to the lack of specific symptoms indicating FD, the diagnostic process is difficult and can last many years. To diagnose FD, both the clinical picture and the results of enzymatic, biochemical, and genetic tests must be considered.[10,11] Most symptoms of FD, including hypertrophic cardiomyopathy, proteinuric CKD, and ischemic stroke, are nonspecific and have a wide differential diagnosis. The identification of certain symptoms such as cornea verticillata by a slit lamp or the histopathologic confirmation of angiokeratoma has greater diagnostic significance.[10,11]

To diagnose the disease, the α-GAL A activity is measured in whole blood (dried blood spot method), plasma, or leukocytes. An activity of less than 5%, usually found in men with the classic form of the disease or in homozygous women, definitely indicates FD. However, testing for α-Gal A activity

TABLE 2 Diagnostic confirmation of Fabry disease

Men	Women
Determination of α-GAL A activity (no / significant deficiency) in the dry blood spot test, plasma or peripheral blood leukocytes	Determination of lyso-GL-3 plasma levels in the dry blood spot test (plasma α-GAL A activity is usually within the reference range)
Genetic testing for the presence of a pathogenic mutation	
Determination of the type of mutation to confirm the disease phenotype, exclude benign polymorphisms, or enable family screening (for the variant of uncertain significance, determination of pathogenicity based on clinical, biochemical, or histopathologic parameters and family history)	

alone is diagnostic only in men. In women, the α-Gal A activity may be normal or only slightly decreased; therefore, a disease-causing mutation in the *GLA* gene must be found to confirm the diagnosis. Genetic testing should be offered also to men in order to determine the disease form, enable family screening, and exclude benign polymorphisms associated with reduced α-Gal A activity (TABLE 2).[11] Additional diagnostic information to assess the pathogenicity of mutations (variants of unknown significance [VUSs]) and disease severity (in heterozygous women) can be obtained by measuring disease biomarkers (especially plasma lyso-GL-3). Detection of GL-3 deposits by histopathologic examination (of the heart, kidneys, skin) indicates FD, but the results should be interpreted together with clinical, biochemical, and genetic data.

Renal complications Chronic kidney disease is a serious and frequent complication of FD. In the asymptomatic period, histopathologic examination may indicate the accumulation of glycosphingolipids in kidney cells, including podocytes as well as endothelial, mesangial, and renal tubular cells. Deposits of glycosphingolipids in the kidneys are present as early as in the fetal period.[12,13] Further progression of the disease leads to interstitial fibrosis, glomerulosclerosis, and renal tubular atrophy. These changes cause albuminuria and proteinuria as well as a progressive reduction of glomerular filtration followed by renal failure until the end stage is reached, requiring dialysis or renal transplant.[11]

The stage of CKD in FD should be assessed based on the glomerular filtration rate (GFR) and the severity of albuminuria. The Chronic Kidney Disease Epidemiology Collaboration equation is recommended to estimate the GFR.[14] In children, it should be determined with nuclear techniques before deciding on treatment. A kidney biopsy may be helpful in the case of diagnostic doubts or to evaluate the effectiveness of ERT. The assessment and treatment of CKD in adult patients with FD should follow the general Kidney Disease: Improving Global Outcomes 2012 recommendations.[14]

Cardiac complications Cardiac complications of FD are frequent, affect about 40% to 60% of patients, both men and women, and are a significant cause of premature mortality.[15-20] The accumulation of glycosphingolipids in cardiomyocytes, ischemic lesions associated with the involvement of small vessels, and inflammation contribute to the concentric left ventricular hypertrophy and subsequent fibrosis. Hypertrophy of the left ventricle, observed in about 50% of men and 30% of women, is most often diagnosed from the third decade of life onwards.[16] With disease progression, irreversible changes occur, including fibrosis.[21]

Cardiac hypertrophy can be assessed with electrocardiography, echocardiography, and cardiac magnetic resonance imaging (MRI), while left ventricular myocardial fibrosis can be evaluated by late gadolinium enhancement in MRI. The earliest cardiac manifestation of FD is the initial shortening and then prolongation of the PR interval, bradycardia, progressive atrioventricular and intraventricular conduction disorders, and cardiac hypertrophy. Many patients develop chronic heart failure with preserved ejection fraction that decreases with disease progression. Angina is also frequently reported. Epicardial coronary arteries are usually normal, but perfusion defects and slow coronary flow can be found on computed tomography angiography and myocardial perfusion. Endomyocardial biopsy shows lumen narrowing of intramyocardial arteries due to hypertrophy and hyperplasia of smooth muscle and endothelial cells. Fibrosis of the intimal and medial layer[22] and morphological lesions of the heart valves resulting in regurgitation are also frequent complications of FD.[22,23] In addition, myocardial fibrosis increases the risk of life-threatening arrhythmias. The use of cardiac MRI native T1 mapping allows assessment of myocardial involvement before left ventricular hypertrophy. The incidence of clinically significant ventricular arrhythmias is low, but there is a relatively high incidence of bradycardia and indications for pacing.[24] It is suspected that sudden cardiac death in FD is related to bradycardia.[24]

After the diagnosis of FD, 24- to 48-hour Holter monitoring is recommended.[24] Early detection of cardiac arrhythmias and conduction disorders allows the introduction of appropriate treatment in some cases, such as cardiac pacing or implantable cardioverter-defibrillator implantation or antithrombotic treatment in atrial fibrillation. Some forms of arrhythmia may also be treated with radiofrequency ablation.

Neurologic complications Fabry disease can affect both the peripheral and central nervous systems. The cause of damage to the peripheral nervous system is the accumulation of GL-3 deposits in the ganglia of the dorsal roots of the spinal cord. Along with small fiber neuropathy, it may manifest clinically as severe neuropathic pain in the hands and feet, both chronic and paroxysmal (pain crises). This is one of the first symptoms of the disease (red flag!), although it does not occur in all patients. Involvement of autonomic fibers may result in secretory problems (perspiration,

TABLE 3 Special indications for diagnostic testing for Fabry disease

Chronic kidney disease, proteinuria, or albuminuria of unknown origin
Unexplained left ventricular hypertrophic cardiomyopathy
Transient ischemic attack or stroke in young people
White matter lesions with an unclear cause
Unexplained neuropathy of thin nerve fibers
Angiokeratoma or cornea verticillata
Family history of Fabry disease (indication for active family screening of patients with diagnosed disease; inheritance related to the X chromosome)

TABLE 4 Effect of enzyme replacement therapy on clinical parameters in patients with Fabry disease (based on Germain et al,[38] Germain et al,[39] Banikazemi et al,[40] and El Dib et al)[41]

Elimination of GL-3 deposits in the kidneys, heart, neurons, and vascular endothelial cells
Reduction of disease severity shown on biochemical evaluation (plasma GL-3, lyso-GL-3, urinary GL-3)
Stabilization, limited progression, or improvement of albuminuria and proteinuria
Stabilization or limited progression of renal function (eGFR)
Limited progression of an increase in LV mass (LVM or LVMI, LVWT reduction)
Improvement of conduction disorders on electrocardiography
Improvement of sweat function and peripheral nervous system sensitivity
Reduction of neuropathic pain
Limited progression of white matter lesions in the brain
Reduction of clinically significant renal, cardiac, and neurologic endpoints (agalsidase beta)
Improvement in the quality of life

Abbreviations: eGFR, estimated glomerular filtration rate; GL-3, globotriaosylceramide; lyso-GL-3, globotriaosylsphingosine; LV, left ventricular; LVM, left ventricular mass; LVMI, left ventricular mass index; LVWT, left ventricular wall thickness

salivation, and secretion of tears), high temperature hypersensitivity, abdominal pain, hypotonia, and reduced exercise tolerability.[25-27] The diagnosis of neuropathy is usually hampered by normal electroneurographic results. More advanced tests that are not routinely performed (due to unavailability in most neurophysiological laboratories) are required, such as skin biopsy or laser-evoked potentials.

The mechanisms involved in central nervous system damage are not well understood, but changes in cerebral vessels and cardiac embolism are thought to contribute to ischemic lesions in the brain.[28] Fabry disease increases the risk of ischemic stroke (4.2-fold in the population of stroke patients aged 35–45 years), which usually occurs before the age of 50.[29] Stroke can be both ischemic and hemorrhagic. Ischemic stroke is most often found in the vertebrobasilar region. The pulvinar sign (hyperintense signal in the T1 MRI sequence) and enlargement of the basilar artery are sometimes observed. The distribution of ischemic lesions (white matter hyperintensities associated with small vessel disease) may be similar to those seen in multiple sclerosis or hypertensive encephalopathy.[30] Involvement of large vessels is usually secondary to heart disease (cardiogenic stroke). Early-onset stroke in the absence of other causes, as well as coexisting renal and cardiac disease with a history of burning pain in the feet and hands, should lead to the diagnostic workup for FD. Fabry disease is also associated with neuropsychiatric problems such as depression and cognitive decline; therefore, antidepressants may be helpful in symptomatic treatment.[31]

High-risk populations Published studies and guidelines indicate the need to perform diagnostic testing for FD in patients with conditions or symptoms that are classic and frequent complications of this disease (TABLE 3).[28,32-36]

Family screening and genetic counseling After establishing the diagnosis of FD, it is crucial to perform clinical and genetic screening of the patient's family members. Typically, such screening reveals FD in several family members, who can benefit from early diagnosis and treatment. The diagnosis of FD causes much distress and raises many questions among patients and their families. Thus, genetic counseling provided by a geneticist with expertise in FD must be offered to explain the X-linked pattern of inheritance and the available diagnostic and management options. Apart from the information on the medical aspects of the disease, patients should receive psychological support when needed. Information on the methods of prenatal diagnosis should be given to patients who are planning to have children.[11]

Enzyme replacement therapy in Fabry disease International standards and guidelines unequivocally accept the use of ERT as an optimal and specific treatment for patients with confirmed FD. The treatment was shown to stop the progression of organ changes and stabilize or improve organ function (TABLE 4).[11,37] Studies have confirmed the beneficial effect of ERT both on the removal of GL-3 deposits from organs and lowering the severity of the disease on biochemical evaluation (GL-3, lyso-GL-3 in plasma). The positive effect on intermediate endpoints, including reduction of albuminuria or proteinuria, estimated GFR, left ventricular mass, and pain severity, has also been confirmed.[38,39] In addition, ERT (agalsidase beta) led to significant reductions in the clinically significant composite renal, cardiac, and neurologic endpoint (–61%, $P = 0.034$, for the "per-protocol" population).[40,41]

Numerous clinical observations also indicated that the clinical effects depend on the stage of the disease in which ERT was initiated. The use of ERT in patients at a younger age, with less severe organ damage, without irreversible complications, or without previous serious cardiovascular events, resulted in more beneficial clinical effects.[40,42-46]

Currently, 2 human α-GAL A isoforms are available: agalsidase alfa (Replagal, Shire; European Medicines Agency [EMA] approval, in 2001) and agalsidase beta (Fabrazyme, Sanofi Genzyme; EMA approval in 2001, Food and Drug

TABLE 5 Enzyme replacement therapy in Fabry disease: contraindications, indications for therapy, and indications for therapy discontinuation (modified from Sirrs et al)[10]

Indications for ERT
Renal (1 major criterion or 2 minor ones required)
Major criteria:
• Fabry nephropathy with reduced GFR[a]
• Persistent proteinuria ≥500 mg/d/1.73 m^2 after excluding other causes
• High-risk pathology in kidney biopsy (glomerular sclerosis, tubular atrophy, vascular fibrosis or sclerosis)—only men
Minor criteria:
• Hyperfiltration
• Isolated proteinuria 300 mg/d/1.73 m^2 or higher than the norm for age and sex and persisting for at least 1 year, after excluding other causes
• Renal tubular dysfunction
• Hypertension lasting at least 1 year
• High-risk pathology in kidney biopsy (glomerulosclerosis, tubular atrophy, vascular fibrosis, or sclerosis) in the presence of indications—only women
Cardiac (2 criteria required)
• LVWT >12 mm in men and >11 mm in women
• LVMI on 2-dimensional echocardiography 20% above the norm for age
• LVM increase by at least 5 g/m^2 per year, with 3 measurements for a minimum of 1 year
• LV diastolic dysfunction in 2-dimensional + Doppler echocardiography (grade 2 or 3 according to the American Society of Echocardiography guidelines and/or the presence of abnormalities in the tracking of acoustic markers)
• Loss of LV base-to-apex circumferential strain gradient
• Increased left atrial size on 2-dimensional echocardiography; parasternal long-axis view of the LV >40 mm; left atrial volume index >34 ml/m^2
• Arrhythmia and conduction disorders: atrioventricular block, PR interval shortening, left bundle branch block, ventricular or atrial tachyarrhythmia, sinus bradycardia (without the use of drugs with negative chronotropic activity), or other causes
• Moderate to severe regurgitation of the main or mitral valve
• LGE of the LV myocardium on cardiac MRI
• Increase in NT-proBNP levels above the upper limit of the norm for age and sex or increase in high-sensitivity troponin levels (a replacement indicator of fibrosis) by more than twice the upper limit of normal
Neurologic (1 criterion required)
• Previous stroke or transient ischemic attack
• Severe neuropathic pain that is resistant to treatment
• Sudden 1-sided hearing loss when other possible causes have been excluded
• Acute ischemic optic neuropathy when other possible causes have been excluded
Gastrointestinal symptoms
• Significant gastrointestinal symptoms not responding to other treatments for at least 6 months or associated with delayed growth or significant reduction in the quality of life
Contraindications to ERT
• Pregnancy (relative contraindication) and lactation
• Serious comorbidities, with an estimated life expectancy below 1 year
• Severe cognitive impairment, regardless of the cause
• Serious complications in which the use of ERT will not significantly improve the quality of life
• Other diseases in which the benefit-to-risk ratio of using ERT is unfavorable
Indications for discontinuation of ERT
• Insufficient patient compliance
• Patient's request
• No clinical response to treatment after a reasonable (minimum 1 year) period of follow-up
• Estimated life expectancy of less than 1 year due to severe comorbidities or severe Fabry disease with end-stage heart failure if the patient is not a candidate for heart transplant
• Serious, permanent neurocognitive impairment
• Serious, life-threatening infusion-related adverse reactions despite prophylactic treatment

a For GFR <60 ml/min/1.73m^2, CKD grades 3–5: at least 2 concordant estimates or GFR measurements for a minimum of 3 months; for GFR 60–90 ml/min/1.73 m^2, CKD grade 2: at least 3 concordant estimates or GFR measurements for at least 6 months with a slope of the GFR curve greater than the age-related norm; for eGFR >135 ml/min /1.73 m^2: a 15% decrease in GFR or a slope of the GFR curve greater than the age-related norm measured by nuclear medicine techniques. The estimated GFR is not precise in this respect and therefore cannot be used.

Abbreviations: CKD, chronic kidney disease; ERT, enzyme replacement therapy; GFR, glomerular filtration rate; LGE, late gadolinium enhancement; MRI, magnetic resonance imaging; NT-proBNP, N-terminal fragment of the prohormone brain natriuretic peptide; others, see TABLE 4

Administration approval in 2003). Both drugs are administered every 2 weeks by intravenous infusion: agalsidase alfa at a dose of 0.2 mg /kg body weight (bw) and agalsidase beta at a dose of 1.0 mg/kg bw.[47,48] There have been no direct comparative studies assessing the long-term impact of these therapies on significant clinical parameters in a sufficiently large group of patients with a homogeneous phenotype. However, available observations indicate a relationship between the therapeutic effect and the dose of ERT (9-fold higher intracellular concentrations of agalsidase beta as compared with agalsidase alfa). This association is confirmed by the results of comparative assessments and studies in which agalsidase alfa was switched to agalsidase beta or vice versa.[49-52]

The most common adverse effects associated with ERT were postinfusion reactions (more frequent with agalsidase beta). Most of them were mild to moderate, were not a reason for discontinuation of therapy, and subsided with subsequent administrations. To minimize their severity, it is possible to reduce the rate of ERT administration and give premedication with antihistamines, analgesics, and/or corticosteroids. The ERT cannot be used simultaneously with chloroquine, amiodarone, benzoquinone, or gentamycin because these substances potentially inhibit the activity of intracellular α-GAL A.[47,48]

Since 2016, the oral drug migalastat (Galafold, Amicus) has also been available for use in the treatment of FD. Migalastat is a pharmacological chaperone that acts by stabilizing the mutated forms of α-GAL A and by increasing their availability in lysosomes. The drug is indicated for the treatment of adults and adolescents from 16 years of age, but only in patients with a mutation that makes them sensitive to its action.[53]

Enzyme replacement therapy: contraindications and indications for starting and stopping the therapy As mentioned above, early enzyme replacement is crucial to suppress the progression of FD. According to the European guidelines for the management of FD published in 2018, ERT should be initiated in all men with the classic form of the disease, regardless of symptoms, and in symptomatic women with the classic form. It should also be initiated in women who have positive laboratory, histologic, or imaging test results indicating kidney, heart, or central nervous system damage. Regarding the nonclassic form and a form in which VUSs are found, ERT is indicated in the presence of symptoms or kidney, heart, or central nervous system damage attributable to FD, which may require histologic or biochemical confirmation.[11] Moreover, in patients with VUSs, a geneticist with expertise in FD should provide advice on the pathogenicity of a given VUS.

In our opinion, in the context of clinical practice in Poland, the indications for starting ERT as presented in the 2017 Canadian Fabry Initiative Group guidelines should be followed.[52] These guidelines describe the clinical indications for starting and stopping ERT, as well as contraindications to the therapy, as summarized in TABLE 5.

Symptomatic treatment In addition to ERT, patients with FD should receive symptomatic treatment tailored to their individual needs in accordance with relevant clinical guidelines. Patients should be screened for modifiable risk factors such as diabetes, hypertension, arrhythmia, hyperlipidemia, smoking, sedentary lifestyle, depression, microalbuminuria, and renal failure. By early detection, risk factors can be controlled and the overall risk of complications reduced. Cardiovascular risk can be lowered by lifestyle modification as well as treatment of hypertension, hyperlipidemia, and heart failure. Heart arrhythmias may require implantation of an implantable cardioverter-defibrillator as part of sudden cardiac death prevention. In addition, patients with FD, regardless of sex and age, should receive anticoagulant therapy to prevent arterial embolism in the case of atrial fibrillation. Treatment of heart failure and CKD should be carried out according to general recommendations. Treatment of painful neuropathy requires the use of gabapentinoids (gabapentin, pregabalin). Carbamazepine is also recommended, as is venlafaxine or duloxetine in the case of coexisting neuropathic pain and depression.[4,10,11]

ARTICLE INFORMATION

CONFLICT OF INTEREST RG, JK, PP, AW, and DZ report consultation fees from Sanofi Genzyme; MN, ZO-S, KP, and JS report consultation/speaker fees from Sanofi Genzyme; SB-S, BB-H, and MK report consultation fees/speaker fees from Sanofi Genzyme and Shire. JI and JS-C report no conflict of interest.

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