

Executive summary of evidence-based clinical practice guideline for Fabry nephropathy

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The Academy of Fabry Disease in the Korean Society of Nephrology has developed evidence-based clinical practice guidelines to optimize the management and treatment of Fabry nephropathy. Although Fabry disease is a rare genetic disorder, the recent availability of effective therapeutic options, including enzyme replacement therapy and chaperone therapy, highlights the importance of early diagnosis and timely intervention. These guidelines were developed using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology, with support from methodology experts. Clinical recommendations were derived through a systematic literature review addressing 11 key questions. These guidelines are intended to assist healthcare professionals, including nephrologists, in making informed, evidence-based clinical decisions to improve patient outcomes.

Keywords: Chronic kidney failure, Evidence-based practice, Fabry disease, GRADE approach, Practice guideline

Introduction

Fabry disease (FD), a rare lysosomal storage disorder, is caused by mutations in the *GLA* gene on the long arm of the X chromosome (Xq22.1) [1], resulting in deficiency of the enzyme α -galactosidase A (α -Gal A). This leads to the progressive systemic accumulation of its substrate, globotriaosylceramide (Gb3 or GL3), and its metabolite, globotriaosylsphingosine (lyso-Gb3 or lyso-GL3) [2], within various cells and tissues, causing irreversible damage to major organs, including the kidneys, heart, and brain [1]. Patients with Fabry nephropathy typically progress from early stages of microalbuminuria and proteinuria to chronic kidney disease (CKD) [3]. Without appropriate therapeutic

intervention, patients are at a markedly increased risk of premature mortality, often occurring in the fourth or fifth decade of life [1,4].

The clinical manifestations of FD are categorized into classical and late-onset (or variant) phenotypes. In males, classical FD is characterized by near-absent α -Gal A activity and early-onset symptoms, including acroparesthesia, corneal verticillata, and angiokeratomas. Historically, the prevalence of classical FD was estimated at 1 in 40,000 males [5]; however, recent international newborn screening studies suggest that the actual prevalence is substantially higher [6,7]. In South Korea, the inclusion of FD in the national newborn screening program in 2024 is expected to shift the epidemiological landscape and increase diagnosis

Received: April 7, 2026; **Revised:** April 10, 2026; **Accepted:** April 18, 2026

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tic frequency.

The introduction of effective therapies, including enzyme replacement therapy (ERT) and chaperone therapy, has enabled stabilization or slowing of disease progression through early diagnosis and timely intervention [8,9]. While the traditionally recommended age to initiate treatment in pediatric patients was between 10 and 13 years, current international trends advocate earlier initiation—often between 7 and 10, or even 5–7 years of age—to prevent irreversible organ damage before reaching the “point of no return” [5]. Nephrologists are likely to encounter patients with late-onset FD, in which organ involvement may be the primary presenting feature. Given that diagnosis is often delayed or missed in these cases, unless FD is clinically suspected, systematic screening of high-risk CKD popula-

tions is essential.

Despite this clinical burden, standardized evidence-based clinical practice guidelines tailored to Fabry nephropathy are lacking in South Korea, leading to inconsistencies in clinical decision-making. To address this, the Clinical Practice Guideline Work Group of the Academy of Fabry Disease in the Korean Society of Nephrology (AFD-KSN) has developed these guidelines using the internationally recognized Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology. These guidelines aim to provide clinicians with standardized diagnostic and therapeutic pathways, facilitating safer, more effective management of patients with Fabry nephropathy. Twelve recommendations were formulated (Table 1), and the overall clinical algorithm is summarized

Table 1. Summary of recommendations

Key question	Recommendation	Strength	Certainty
Screening and diagnosis			
1	Recommend α -Gal A enzyme testing as a screening method for Fabry nephropathy in male patients with CKD of unknown etiology.	Strong	Very low
2	Suggest using lyso-Gb3 rather than α -Gal A enzyme activity testing to screen for Fabry nephropathy in female patients with CKD of unknown etiology, because α -Gal A enzyme testing has low diagnostic value in females.	Conditional	Very low
3	Suggest considering kidney biopsy to confirm Fabry nephropathy and support the interpretation of the pathogenicity of a previously unreported <i>GLA</i> variant in patients who screen positive and harbor such a variant.	Conditional	Very low
Treatment I: general treatment options			
4	Recommend ERT for patients diagnosed with FD to slow the progression of Fabry nephropathy, because ERT has been linked to a slower decline in kidney function and a lower incidence of ESKD compared with no ERT.	Strong	Low
5	Suggest chaperone therapy with migalastat for patients with Fabry nephropathy who have an amenable <i>GLA</i> variant, because migalastat can stabilize renal function in selected patients and provides an oral treatment option.	Conditional	Very low
6	Suggest prescribing an ARB or ACEi in patients with Fabry nephropathy and proteinuria to reduce proteinuria and potentially slow progression of Fabry nephropathy.	Conditional	Very low
Treatment II: ERT in specific clinical subgroups			
7-1	Recommend ERT in Fabry nephropathy patients with microalbuminuria to proteinuria <1 g/day because ERT may slow progression of Fabry nephropathy.	Strong	Very low
7-2	Recommend ERT in Fabry nephropathy patients with proteinuria ≥ 1 g/day because ERT may slow progression of Fabry nephropathy.	Strong	Very low
8	Recommend ERT for patients with Fabry nephropathy and reduced kidney function, because ERT may slow progression of Fabry nephropathy even in patients with impaired eGFR.	Strong	Very low
9	Suggest ERT for patients with FD receiving dialysis when cardiac involvement is confirmed, to potentially improve or stabilize clinically important extra-renal manifestations.	Conditional	Very low
Monitoring and long-term assessment			
10	Recommend that patients with Fabry nephropathy undergo regular evaluation for cardiac and neurologic involvement.	Strong	Very low
11	Suggest against using routine blood lyso-Gb3 measurements for treatment monitoring in patients with Fabry nephropathy, because evidence linking lyso-Gb3 changes to clinically meaningful renal outcomes is insufficient.	Conditional	Very low

α -Gal A, α -galactosidase A; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; ERT, enzyme replacement therapy; ESKD, end-stage kidney disease; FD, Fabry disease; eGFR, estimated glomerular filtration rate; lyso-Gb3, globotriaosylsphingosine.

in Fig. 1.

Methods

The guidelines were developed *de novo* using GRADE methodology. Eleven key questions were formulated using the PICO (Population, Intervention, Comparison, and Outcome) framework by a multidisciplinary panel of 17 experts, including nephrologists, pediatricians, cardiologists, laboratory medicine specialists, and methodological experts. Systematic literature searches were conducted using Ovid Medline, Ovid Embase, the Cochrane Library, and KMBase through August 2021, supplemented by manual searches. Study selection was independently performed by two authors per question, and disagreements were resolved by consensus. The risk of bias was assessed using RoB 2.0 for randomized controlled trials (Cochrane), ROBINS-I for non-randomized studies (Cochrane), and QUADAS-2 for diagnostic accuracy studies (University of Bristol). Meta-analyses were performed using random-effects models when quantitative synthesis was feasible, and substantial heterogeneity was present. For each recommendation, the certainty of evidence was classified as high, moderate, low, or very low, and the recommendation strength was graded as strong, conditional, against, or inconclusive according to the GRADE framework. A strong recommendation indicates that the benefits clearly outweigh the harms in most clinical situations, whereas a conditional recommendation indicates that the balance may vary based on clinical circumstances or patient preferences.

The GRADE evidence-to-decision framework was applied, considering the benefits, harms, certainty of evidence, patient values and preferences, resource use, feasibility, and health equity. Final recommendations were approved by committee vote, with a threshold of $\geq 70\%$ agreement required for adoption. All 12 recommendations across 11 key questions achieved $\geq 92\%$ agreement. The full guideline document, including detailed evidence tables, forest plots, risk-of-bias assessments, and Summary of Findings tables, is available as a companion to the publication. The guidelines were externally reviewed by the Korean Society of Nephrology and formally endorsed by the society.

1. Screening and diagnosis

Recommendation 1

We recommend α -Gal A enzyme testing as a screening method for Fabry nephropathy in male patients with CKD of unknown etiology.

(Strong recommendation, very low certainty of evidence)

Advice and tools for implementing the recommendation

- Patients with predialysis CKD may benefit from disease-specific therapy if diagnosed with Fabry nephropathy, potentially slowing disease progression. In patients receiving dialysis, a confirmed diagnosis can facilitate management of major extra-renal organ involvement and enable pedigree analysis/cascade screening to identify additional affected family members at an earlier stage. Therefore, in male CKD patients with unknown cause, we suggest performing α -Gal A enzyme testing, a noninvasive test, as a screening approach for Fabry nephropathy.
- The positive predictive value (PPV) of α -Gal A testing for Fabry nephropathy is low; therefore, clinicians should explain this limitation to patients when initiating screening.
- Even when kidney function decline is suspected to be attributable to underlying conditions (e.g., hypertension or diabetes) or other causes, α -Gal A testing may be considered if clinical features suggestive of FD are identified.

Summary of evidence

A systematic review of 25 studies encompassing 25,200 male patients with CKD identified 452 screening-positive cases and 60 confirmed diagnoses of Fabry nephropathy, yielding an estimated prevalence of 0.238%. Most studies have included patients receiving maintenance dialysis. Meta-analysis showed a PPV of 0.15 (95% confidence interval [CI], 0.11–0.20) across 19 studies with FD prevalence $>0\%$ and $<1\%$. When restricted to six studies with ≥ 20 enzyme-positive cases, the PPV was 0.05 (95% CI, 0.03–0.09). The sensitivity and specificity could not be determined since *GLA* genetic testing was performed only in enzyme-positive patients. The specimen types, assay methods, and cutoff values varied across the studies. Despite this low PPV, the potential benefits of early diagnosis, including treatment to slow CKD progression, management of extra-renal complications, and cascade screening to identify affected family members, support the use of this noninvasive screening approach, particularly when a kidney biopsy is not feasible (e.g., solitary kidney).

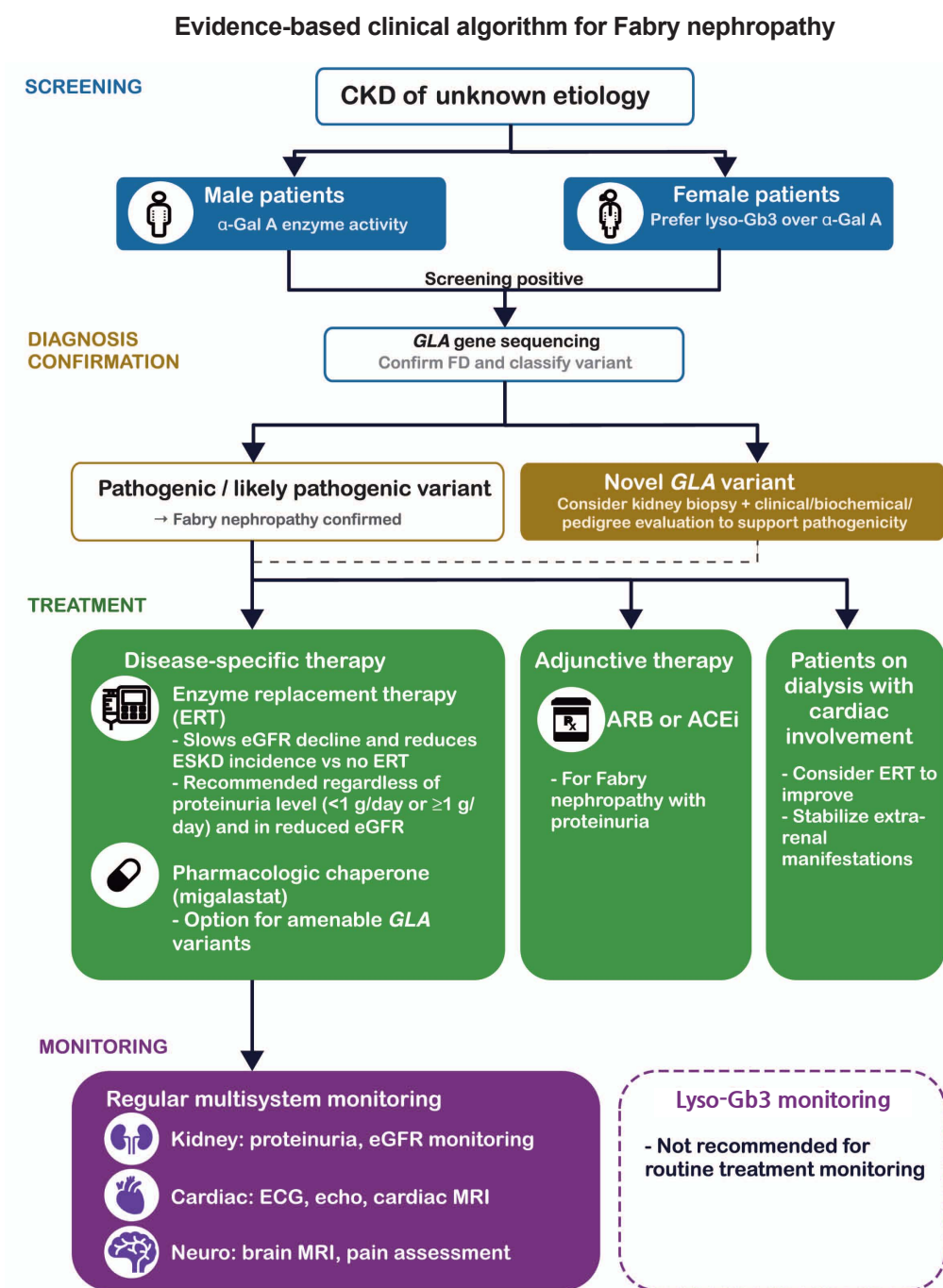


Figure 1. Evidence-based clinical algorithm for screening, diagnosis, treatment, and monitoring of Fabry nephropathy. CKD patients of unknown etiology undergo sex-specific screening (α-Gal A enzyme activity in males; lyso-Gb3 in females), followed by GLA gene sequencing for diagnostic confirmation. For previously unreported (novel) GLA variants, a kidney biopsy with clinical, biochemical, and pedigree evaluation is recommended. Treatment includes disease-specific therapy (enzyme replacement therapy and pharmacologic chaperone therapy with migalastat for amenable GLA variants), adjunctive therapy with ARB or ACEi for proteinuria, and consideration of ERT in dialysis patients with cardiac involvement to stabilize extra-renal manifestations. Monitoring consists of regular cardiac and neurologic evaluation; lyso-Gb3 is not recommended for routine treatment monitoring.

α-Gal A, α-galactosidase A; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; ECG, electrocardiography; eGFR, estimated glomerular filtration rate; ERT, enzyme replacement therapy; ESKD, end-stage kidney disease; FD, Fabry disease; lyso-Gb3, globotriaosylsphingosine; MRI, magnetic resonance imaging.

Recommendation 2

We suggest using lyso-Gb3 rather than α -Gal A enzyme activity testing to screen for Fabry nephropathy in female patients with CKD of unknown etiology, because α -Gal A enzyme testing has low diagnostic value in females.

(Conditional recommendation, very low certainty of evidence)

Advice and tools for implementing the recommendation

- Fabry nephropathy is rarer in females than males, and α -Gal A activity may be normal or only mildly reduced in a substantial proportion of affected females due to random X-chromosome inactivation, thereby limiting the diagnostic utility of α -Gal A enzyme testing in this population [10,11]. In this context, lyso-Gb3 may improve diagnostic yield compared with α -Gal A testing in females and can support the identification of FD when clinical suspicion exists.
- Lyso-Gb3 testing is not associated with direct harm; however, blood sampling is required, and test accessibility may be limited in South Korea, potentially posing practical barriers. Nevertheless, because a confirmed diagnosis may enable disease-specific therapy and potentially improve patient outcomes, clinicians should actively pursue diagnostic evaluation and referral to FD experts when Fabry nephropathy is suspected and/or when lyso-Gb3 testing is required.

Summary of evidence

Due to random X-chromosome inactivation, α -Gal A activity is normal or only slightly decreased in 40%–60% of affected female patients [10,11]. Meta-analysis demonstrated that when α -Gal A screening was positive in CKD populations, the probability of Fabry nephropathy diagnosis was 4.7% in males vs. 1.9% in females, suggesting a substantially lower diagnostic yield in females. In female CKD patients, lyso-Gb3 testing increased the diagnostic yield for Fabry nephropathy by 51% compared with α -Gal A testing. Ouyang et al. [12] have reported higher sensitivity for lyso-Gb3 than α -Gal A activity in diagnosing females with FD (82.4% vs. 23.5%). Since α -Gal A enzyme testing has limited diagnostic performance in females, lyso-Gb3 testing is the preferred screening method. However, given the practical barriers to access to tests in South Korea, clinicians should consider specialized referrals for patients with suspected FD.

Recommendation 3

We suggest considering a kidney biopsy to confirm Fabry nephropathy and support the interpretation of the pathogenicity of a previously unreported *GLA* variant in patients who screen positive and harbor such a variant.

(Conditional recommendation, very low certainty of evidence)

Advice and tools for implementing the recommendation

- When a novel *GLA* variant is detected in a patient with a positive screening result, clinicians should integrate clinical, biochemical, histopathological, and family history information to indirectly support interpretation of variant pathogenicity.
- Clinical evidence: Assess for classic Fabry manifestations (e.g., acroparesthesia, cornea verticillata, angiokeratomas) and evaluate organ involvement typical of FD, including renal, cardiac, and neurologic involvement.
- Biochemical evidence: Evaluate for elevated plasma and urine lyso-Gb3; however, additional evidence is still required to clarify the role of plasma and urine lyso-Gb3 as definitive biomarkers in this context.
- Practical caution in end-stage kidney disease (ESKD)/dialysis: In patients with ESKD already receiving dialysis, the bleeding risk associated with kidney biopsy can be substantial, and the diagnostic accuracy of biopsy may be reduced; therefore, alternative diagnostic approaches may be considered in selected cases.

Summary of evidence

With advances in diagnostic technology, previously unreported (novel) *GLA* variants have been increasingly identified in screening programs. In an analysis of 35 published screening studies, the prevalence of the novel *GLA* variant was 0.041%. The most robust method for determining pathogenicity is the *in vitro* *GLA* mutation expression assay [13], available only in specialized laboratories. Accordingly, indirect evidence, including clinical, biochemical, histopathological, and pedigree data, may support the assessment of pathogenicity. Clinicians should evaluate classic FD symptoms and assess renal, cardiac, and central nervous system involvement [14]. Among the 19 published case reports involving novel *GLA* variants, a kidney biopsy was performed in 13 cases to obtain histopathological evidence. Drug-related mimics (e.g., amiodarone and chloroquine) were also excluded.

2. Treatment I: general treatment options

Recommendation 4

We recommend ERT for patients diagnosed with FD to slow the progression of Fabry nephropathy, because ERT has been linked to a slower decline in kidney function and a lower incidence of ESKD compared with no ERT.

(Strong recommendation, low certainty of evidence)

Advice and tools for implementing the recommendation

- Although the renoprotective effect of ERT in Fabry nephropathy has not been conclusively demonstrated in large-scale, prospective randomized trials, available evidence—including randomized trials with limited sample size and follow-up, as well as multiple cohort studies—suggests clinically meaningful benefits, particularly in terms of attenuating estimated glomerular filtration rate (eGFR) decline and reducing ESKD events.
- Given the substantial financial cost of ERT and the practical burden of lifelong intravenous infusions (typically every 2 weeks), clinicians should carefully review the patient's GLA variant, baseline kidney status (including eGFR and proteinuria), and the overall likelihood of benefit before initiating therapy. Shared decision-making is recommended to align treatment decisions with the patient's values and preferences.

Summary of evidence

Thirty-five studies (four randomized trials and 31 cohort studies) have evaluated the effect of ERT on Fabry nephropathy. In a placebo-controlled trial by Eng et al. [15], agalsidase beta reduced Gb3 deposits in renal endothelial cells. In a trial by Banikazemi et al. [16], agalsidase beta reduced the risk of a composite renal outcome to 0.47 relative to placebo over a median of 18.5 months. Agalsidase alfa improved mesangial widening on renal biopsy and attenuated renal function decline [4]. However, these trials were limited by small sample sizes and short follow-up periods. Pooled analysis of cohort studies demonstrated annual estimated glomerular filtration rate (eGFR) change of $-1.99 \text{ mL/min/1.73 m}^2$ per year (95% CI, -2.85 to $-1.14 \text{ mL/min/1.73 m}^2$) with ERT ($n = 780$) vs. $-5.14 \text{ mL/min/1.73 m}^2$ per year (95% CI, -9.67 to $-0.61 \text{ mL/min/1.73 m}^2$) without ERT ($n = 359$) ($p = 0.082$). Across the 12 studies, the pooled ESKD incidence was 0.066 (95% CI, 0.045–0.097) in the ERT group vs. 0.278 (95% CI, 0.252–0.306) in the control group, supporting the association between ERT and attenuated

renal decline and a lower frequency of ESKD.

Recommendation 5

We suggest chaperone therapy with migalastat for patients with Fabry nephropathy who have an amenable GLA variant, because migalastat can stabilize renal function in selected patients and provides an oral treatment option.

(Conditional recommendation, very low certainty of evidence)

Advice and tools for implementing the recommendation

- Before initiating migalastat, clinicians should confirm whether the patient's GLA variant is amenable. Because many patients prefer oral therapy over biweekly intravenous infusions, clinicians should consider discussing migalastat as an option in eligible patients and incorporate patient preferences into shared decision-making.
- Differences between *in vitro* amenability and clinical responsiveness have been reported; therefore, ongoing monitoring is recommended. In particular, monitoring of major organ involvement is important, and for renal outcomes, periodic assessment of eGFR trajectory (GFR slope) is advised.

Summary of evidence

Seven studies evaluating chaperone therapy were identified, including two randomized trials. In the ATTRACT trial comparing migalastat with ERT, no marked differences were observed in the renal, cardiac, or neurological outcomes [9]. In a placebo-controlled study, migalastat significantly reduced plasma lyso-Gb3 (mean difference, -11.80 ; 95% CI, -14.72 to -8.88) [17]. Observational studies have also reported relative stability of kidney function during migalastat therapy, with annualized eGFR changes ranging from approximately -0.3 to $-2.6 \text{ mL/min/1.73 m}^2$ across subgroups. In the 30-month extension of the ATTRACT study, annualized eGFR changes were approximately $-1.7 \text{ mL/min/1.73 m}^2$ in those receiving migalastat throughout; 24-hour proteinuria did not change meaningfully [18]. Owing to the limited randomized evidence for hard renal endpoints, the certainty of the evidence remains very low.

Recommendation 6

We suggest prescribing an angiotensin receptor blocker (ARB) or angiotensin-converting enzyme inhibitor (ACEi) in patients with Fabry nephropathy and proteinuria to reduce proteinuria and potentially slow the progression of Fabry nephropathy. *(Conditional recommendation, very low certainty of evidence)*

Advice and tools for implementing the recommendation

- Kidney function and proteinuria should be assessed periodically in patients with FD.
- If proteinuria is present, clinicians should determine whether the patient has hypertension; ARB or ACEi should be considered first-line in hypertensive patients.
- In patients with proteinuria but without hypertension, ARB/ACEi may still be considered, although clinicians should balance potential benefit against risks such as hypotension and hyperkalemia and provide individualized counseling.

Summary of evidence

Although ARB/ACEi use is common as an adjunct to ERT in FD (reported in approximately 30%–45% of patients), no randomized controlled trials specific to Fabry nephropathy have been identified. Six cohort studies were evaluated; however, heterogeneity in outcome measures across the studies (e.g., annual eGFR change rate vs. pre-post eGFR slope difference) led to the exclusion of one study from the quantitative synthesis since it reported outcomes in monthly units. Direct Fabry-specific evidence showed no meaningful difference in eGFR slope between ARB/ACEi users and nonusers. Nevertheless, observational studies have supported the notion that the combination of ARB/ACEi with ERT may help control proteinuria and stabilize kidney function [19–21]. Given the limited Fabry-specific evidence, the panel also referenced broader CKD evidence: ARB/ACEi substantially reduced proteinuria (e.g., approximately 43% short-term and approximately 34% long-term) [22]. Proteinuria is common in Fabry nephropathy and requires active management [23]. Therefore, ARB/ACEi may be considered for reducing proteinuria in Fabry nephropathy, supported by direct observational data and indirect evidence from CKD, with the certainty of evidence assessed as very low.

3. Treatment II: enzyme replacement therapy in specific clinical subgroups

Recommendation 7

7-1. We recommend ERT in Fabry nephropathy patients with microalbuminuria to proteinuria <1 g/day because ERT may slow the progression of Fabry nephropathy. *(Strong recommendation, very low certainty of evidence)*

7-2. We recommend ERT in Fabry nephropathy patients with proteinuria ≥1 g/day because ERT may slow the progression of Fabry nephropathy. *(Strong recommendation, very low certainty of evidence)*

Advice and tools for implementing the recommendation

- Available evidence suggests that the renoprotective effect of ERT (in terms of eGFR decline) may occur regardless of proteinuria level. However, evidence is insufficient regarding whether proteinuria level modifies the effects of ERT on mortality and cardiovascular outcomes, necessitating further studies.

Summary of evidence

Six studies evaluated the effect of ERT on baseline proteinuria strata. The only randomized trial found no interaction between baseline proteinuria category (<1 g vs. ≥1 g) and the effect of ERT on renal outcomes ($p = 0.54$) [16]. In a panel-conducted meta-analytic comparison incorporating untreated historical cohorts [3,24], the annual eGFR slope in patients with proteinuria <1 g/day was $-2.22 \text{ mL/min/1.73 m}^2$ per year with ERT vs. $-3.38 \text{ mL/min/1.73 m}^2$ per year without ERT ($p = 0.41$). In patients with proteinuria ≥1 g/day, slopes were -5.53 with ERT vs. -7.88 without ERT ($p = 0.31$). Although statistical significance was not achieved, the direction of effect consistently favored ERT across proteinuria strata, suggesting an improvement of 1 to 2 mL/min/1.73 m² per year in eGFR slope.

Given the rarity of Fabry nephropathy and the limited statistical power of the available evidence, the certainty of evidence was rated very low; however, the panel considered the consistent direction of renal benefit sufficient to recommend ERT, regardless of proteinuria level, to slow renal progression.

Recommendation 8

We recommend ERT for patients with Fabry nephropathy and reduced kidney function, because ERT may slow progression of Fabry nephropathy even in patients with impaired eGFR. *(Strong recommendation, very low certainty of evidence)*

Advice and tools for implementing the recommendation

- Evidence remains insufficient regarding whether baseline kidney function modifies the effects of ERT on mortality and cardiovascular outcomes. In patients with reduced kidney function, ERT may be considered primarily to attenuate renal decline, and cardiovascular assessment is recommended to support monitoring of overall treatment impact.

Summary of evidence

Renal progression in Fabry nephropathy accelerates as baseline eGFR decreases; untreated male patients with eGFR <60 mL/min/1.73 m² showed an annual decline of approximately 6.8 mL/min/1.73 m² per year, compared with approximately 3 mL/min/1.73 m² per year in those with eGFR ≥60 mL/min/1.73 m² [24]. In comparative analyses, ERT-treated patients with eGFR <60 mL/min/1.73 m² showed a smaller decline in eGFR than controls (approximately -2.12 mL/min/1.73 m² vs. -4.46 mL/min/1.73 m²), whereas the difference was smaller in those with eGFR ≥60 mL/min/1.73 m² (-1.66 mL/min/1.73 m² vs. -1.95 mL/min/1.73 m²). Given the observational nature and limited sample size, certainty was assessed as very low; nonetheless, the available evidence supports recommending ERT to attenuate renal progression in patients with reduced kidney function.

Recommendation 9

We suggest ERT for patients with FD receiving dialysis when cardiac involvement is confirmed, to potentially improve or stabilize clinically important extra-renal manifestations. *(Conditional recommendation, very low certainty of evidence)*

Advice and tools for implementing the recommendation

- In Fabry patients on dialysis, clinicians should consider evaluation of extra-renal involvement through relevant specialists (e.g., cardiology, neurology).
- For suspected cardiac and neurologic complications, consider appropriate biomarkers and imaging.
- Evidence for the neurologic benefit of ERT in dialysis patients remains limited; additional research is needed.

Summary of evidence

Only two small studies have involved dialysis populations. Mignani et al. [25] reported that left ventricular mass index (LVMI) continued to increase in dialysis patients despite ERT, whereas it remained stable in transplant recipients. Pisani et al. [26] studied nine dialysis patients and reported complete resolution of pain by 6 months and improvement in gastrointestinal symptoms by 6–8 months; the LVMI slope showed a numerical improvement following ERT, although this change was modest. Given the small sample size and limited outcome data, the certainty was very low. Nevertheless, since cardiac disease is a major determinant of morbidity and mortality in patients with FD, ERT should be considered in patients undergoing dialysis with confirmed cardiac involvement.

4. Monitoring and long-term assessment

Recommendation 10

We recommend that patients with Fabry nephropathy undergo regular evaluation for cardiac and neurologic involvement. *(Strong recommendation, very low certainty of evidence)*

Advice and tools for implementing the recommendation

- Patients with FD require regular evaluation of extra-renal organ involvement.
- Neurologic involvement: pain indices, nerve conduction studies, and brain magnetic resonance imaging (MRI) as clinically indicated.
- Cardiac involvement: electrocardiography, cardiac biomarkers, Holter monitoring, echocardiography, and cardiac MRI as clinically indicated.
- Kidney status: proteinuria and eGFR monitoring.
- Multidisciplinary care: consider ophthalmology, dermatology, otolaryngology, gastroenterology, and psychiatry/behavioral health where appropriate.
- Follow-up intervals: should be individualized based on sex, phenotype, and baseline findings.

Summary of evidence

No study has directly evaluated the optimal screening intervals or outcomes of cardiac and neurological involvement. In a systematic review of 19 studies, cardiac involvement (defined as left ventricular hypertrophy) was reported in approximately 47% of males and 37% of females. Variably defined neurological involvement has been reported

in 25%–77% of patients. The summarized prevalence suggests that cardiac (approximately 43.6%) and neurological (approximately 51.2%) involvement may be as common as or more common than renal involvement (approximately 37.9%). Additional reports have described the involvement of the skin, ear/hearing, ocular, psychiatric, and gastrointestinal systems, supporting multidisciplinary evaluations [8,13].

Based on the clinical importance of preventing major complications (arrhythmia, heart failure, and stroke), the panel concluded that periodic evaluation was essential.

Recommendation 11

We suggest against using routine blood lyso-Gb3 measurements for treatment monitoring in patients with Fabry nephropathy, because evidence linking lyso-Gb3 changes to clinically meaningful renal outcomes is insufficient.

(Conditional recommendation, very low certainty of evidence)

Advice and tools for implementing the recommendation

- Blood lyso-Gb3 monitoring may be considered in selected cases, such as when anti-enzyme antibody development is suspected, and treatment response appears suboptimal. The role of lyso-Gb3 monitoring, including which patients to test and how frequently, warrants further research.

Summary of evidence

Lyso-Gb3 is a diagnostic and severity-associated biomarker of FD; however, evidence for its use in treatment monitoring remains limited. Only two studies evaluating lyso-Gb3 levels for monitoring treatment response were identified, both suggesting an association between ERT response and lyso-Gb3 levels. Some evidence indicates that lyso-Gb3 may reflect treatment resistance [27]. In contrast, other data suggest that changes in renal function after ERT may not correlate with changes in lyso-Gb3 [28]. Since clinically actionable thresholds and monitoring intervals were undefined, the panel did not support routine lyso-Gb3 monitoring for treatment follow-up.

Korean perspective

Several considerations are relevant to implementing these guidelines in South Korea. First, access to diagnostic testing varies: α -Gal A enzyme testing is available at hospital-level

institutions (approximate cost, 130,000 Korean won [KRW] in 2025), whereas *GLA* genetic testing (approximate cost: 625,000 KRW) is limited to specialized centers. Lyso-Gb3 testing, recommended for screening females (Recommendation 2), is currently not available domestically and may require referral to FD experts. Second, since 2024, FD has been included in the national newborn screening program, which is expected to increase the number of patients diagnosed and shift the epidemiological landscape in the coming years. Third, migalastat has been registered as a first-line treatment option in South Korea in 2025, thereby expanding the therapeutic armamentarium for patients with amenable *GLA* variants. Fourth, a survey of 33 CKD patients and 25 Fabry patients conducted during guideline development revealed important insights: only 24.2% of CKD patients initially wished to know whether they had a hereditary kidney disease, yet 54.5% agreed to blood-based screening once the possibility was explained; among Fabry patients, 96% preferred oral therapy over intravenous infusion, and 92% wished to pursue insurance coverage for ERT if not initially approved. These findings informed the panel's consideration of patient values and preferences within the GRADE evidence-to-decision framework.

Conclusion

These guidelines provide the first evidence-based clinical practice recommendations specifically tailored for Fabry nephropathy in South Korea. Given the rarity of FD, the certainty of evidence was rated as very low for most recommendations; however, the consistent direction of benefits across diagnostic and therapeutic interventions supported the panel's recommendations. With the expansion of newborn screening and the availability of new therapeutic options, nephrologists in South Korea are increasingly likely to encounter patients with Fabry nephropathy. These guidelines are intended to serve as a practical reference for informed clinical decision-making and to improve patient outcomes.

Additional information

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Conflicts of interest

All authors have no conflicts of interest to declare.

Funding

This study was supported by a cooperative research fund from the Korean Society of Nephrology (2021). The expenditures include consultation fees for the methodology expert and personnel costs for the research coordinator. Consulting fees were not paid to the committee chair, the secretary, the development committee members, or the external advisors. The funding organizations did not influence the content or development process of the guidelines.

Acknowledgments

We thank all members of the Clinical Practice Guideline Work Group of the Academy of Fabry Disease in the Korean Society of Nephrology (AFD-KSN) for their dedicated efforts and the patients with CKD and Fabry disease who participated in the preference surveys during guideline development.

These guidelines were developed to support clinical practice, research, and education related to the diagnosis, treatment, and prognosis of Fabry nephropathy based on a review of the best available evidence by experts convened by the AFD-KSN.

These guidelines were developed by the AFD-KSN with research funding support from the Korean Society of Nephrology. These guidelines may not be modified, adapted, or reproduced without prior permission from the AFD-KSN or the Korean Society of Nephrology.

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References

1. Germain DP. Fabry disease. *Orphanet J Rare Dis* 2010;5:30.
2. Aerts JM, Groener JE, Kuiper S, et al. Elevated globotriaosylsphingosine is a hallmark of Fabry disease. *Proc Natl Acad Sci U S A* 2008;105:2812–2817.
3. Branton M, Schiffmann R, Kopp JB. Natural history and treatment of renal involvement in Fabry disease. *J Am Soc Nephrol* 2002;13 Suppl 2:S139–S143.
4. Schiffmann R, Kopp JB, Austin HA, et al. Enzyme replacement therapy in Fabry disease: a randomized controlled trial. *JAMA* 2001;285:2743–2749.
5. 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.
6. Hwu WL, Chien YH, Lee NC, et al. Newborn screening for Fabry disease in Taiwan reveals a high incidence of the later-onset GLA mutation c.936+919G>A (IVS4+919G>A). *Hum Mutat* 2009;30:1397–1405.
7. Lin HY, Chong KW, Hsu JH, et al. High incidence of the cardiac variant of Fabry disease revealed by newborn screening in the Taiwan Chinese population. *Circ Cardiovasc Genet* 2009;2:450–456.
8. Biegstraaten M, Arngrímsson 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.
9. Hughes DA, Nicholls K, Shankar SP, et al. Oral pharmacological chaperone migalastat compared with enzyme replacement therapy in Fabry disease: 18-month results from the randomised phase III ATTRACT study. *J Med Genet* 2017;54:288–296.
10. Baydakova GV, Ilyushkina AA, Moiseev S, et al. A-galactosidase A/lysoGb3 ratio as a potential marker for Fabry disease in females. *Clin Chim Acta* 2020;501:27–32.
11. Nowak A, Mechtler TP, Desnick RJ, Kasper DC. Plasma lysoGb3: a useful biomarker for the diagnosis and treatment of Fabry disease heterozygotes. *Mol Genet Metab* 2017;120:57–61.
12. Ouyang Y, Chen B, Pan X, et al. Clinical significance of plasma globotriaosylsphingosine levels in Chinese patients with Fabry disease. *Exp Ther Med* 2018;15:3733–3742.
13. Ortiz A, Germain DP, Desnick RJ, et al. Fabry disease revisited: management and treatment recommendations for adult patients. *Mol Genet Metab* 2018;123:416–427.
14. van der Tol L, Smid BE, Poorthuis BJ, et al. A systematic review on screening for Fabry disease: prevalence of individuals with genetic variants of unknown significance. *J Med Genet* 2014;51:1–9.
15. Eng CM, Guffon N, Wilcox WR, et al. Safety and efficacy of recombinant human alpha-galactosidase A replacement therapy in Fabry's disease. *N Engl J Med* 2001;345:9–16.
16. 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.
17. 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.
18. Feldt-Rasmussen U, Hughes D, Sunder-Plassmann G, et al. Long-term efficacy and safety of migalastat treatment in Fabry disease: 30-month results from the open-label extension of the randomized, phase 3 ATTRACT study. *Mol Genet Metab* 2020;131:219–228.
19. Wanner C, Feldt-Rasmussen U, Jovanovic A, et al. Cardiomyopathy and kidney function in agalsidase beta-treated female Fabry patients: a pre-treatment vs. post-treatment analysis. *ESC Heart Fail* 2020;7:825–834.
20. Schiffmann R, Askari H, Timmons M, et al. Weekly enzyme replacement therapy may slow decline of renal function in patients with Fabry disease who are on long-term biweekly dosing. *J Am Soc Nephrol* 2007;18:1576–1583.
21. Feriozzi S, Torras J, Cybulla M, et al. The effectiveness of long-term agalsidase alfa therapy in the treatment of Fabry nephropathy. *Clin J Am Soc Nephrol* 2012;7:60–69.
22. Kunz R, Friedrich C, Wolbers M, Mann JF. Meta-analysis: effect of monotherapy and combination therapy with inhibitors of the renin angiotensin system on proteinuria in renal disease. *Ann Intern Med* 2008;148:30–48.
23. 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.
24. 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.

25. Mignani R, Feriozzi S, Pisani A, et al. Agalsidase therapy in patients with Fabry disease on renal replacement therapy: a nationwide study in Italy. *Nephrol Dial Transplant* 2008;23:1628–1635.
26. Pisani A, Spinelli L, Sabbatini M, et al. Enzyme replacement therapy in Fabry disease patients undergoing dialysis: effects on quality of life and organ involvement. *Am J Kidney Dis* 2005;46:120–127.
27. Rombach SM, Aerts JM, Poorthuis BJ, et al. Long-term effect of antibodies against infused alpha-galactosidase A in Fabry disease on plasma and urinary (lyso)Gb3 reduction and treatment outcome. *PLoS One* 2012;7:e47805.
28. Bichet DG, Aerts JM, Auray-Blais C, et al. Assessment of plasma lyso-Gb3 for clinical monitoring of treatment response in migalastat-treated patients with Fabry disease. *Genet Med* 2021;23:192–201.