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Long-term enzyme replacement therapy and renal outcomes in Fabry disease: a systematic review and meta-analysis

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ADMINISTRATIVE INFORMATION

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Review Stage at time of this submission - Completed but not published.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 9 October 2025 and was last updated on 9 October 2025.

INTRODUCTION

Review question / Objective To evaluate the long-term effects of enzyme replacement therapy (ERT) on renal outcomes in patients with Fabry disease, including renal function decline (eGFR slope), changes in proteinuria (UPCR), and risk of renal or systemic clinical events.
(PICOS framework)

Population: Patients with genetically or clinically confirmed Fabry disease

Intervention: Enzyme replacement therapy (ERT; agalsidase alfa or agalsidase beta)

Comparator: Non-ERT (untreated or natural history cohorts)

Outcomes: eGFR slope, UPCR change, composite renal/cardiovascular events

Study design: Prospective or retrospective cohort studies, RCTs.

Rationale Although ERT has been available for over two decades, its long-term effect on renal function remains uncertain. Existing studies vary in baseline renal function, proteinuria, and follow-up duration, leading to inconsistent conclusions. To our knowledge, no prior meta-analysis has specifically assessed the relationship between baseline eGFR, proteinuria, and the long-term renal benefits of ERT in Fabry disease. This systematic review aims to fill that gap and provide quantitative evidence to guide treatment timing and patient selection.

Condition being studied Fabry disease is a rare X-linked lysosomal storage disorder caused by

deficiency of α-galactosidase A (α-Gal A), leading to globotriaosylceramide accumulation in multiple organs, including kidneys, heart, and brain. Progressive renal damage is a major determinant of morbidity and mortality.

METHODS

Participant or population Patients with genetically or clinically confirmed Fabry disease, of any age or sex, who received or did not receive enzyme replacement therapy.

Intervention Enzyme replacement therapy (ERT) using agalsidase alfa (Replagal) or agalsidase beta (Fabrazyme), administered at standard doses and regimens as reported in the included studies.

Comparator Non-ERT group (natural history or untreated cohort), as reported in eligible studies.

Study designs to be included Randomized controlled trials (RCTs), prospective or retrospective cohort studies that report longitudinal renal outcomes (eGFR, UPCR, or clinical events).

Eligibility criteria Inclusion: Studies reporting renal outcomes (eGFR, UPCR, or clinical events) with ≥1-year follow-up.
Exclusion: Case reports, reviews, conference abstracts, duplicated data, or studies without quantitative outcomes.

Information sources Electronic databases, reference lists of included studies, and grey literature from Taiwan-based resources (Airiti Library, Index to Taiwan Periodical Literature System).

Main outcome(s) Primary outcome:

Annual rate of eGFR change (mL/min/1.73 m^2 per year).

Effect size measure: Standardized mean difference (SMD) or mean difference (MD) with 95% confidence intervals.

Additional outcome(s) Change in proteinuria (UPCR slope)

Incidence of major clinical events (renal replacement therapy, cardiovascular or cerebrovascular events).

Data management All extracted data were managed using Microsoft Excel and verified by two independent reviewers. Meta-analysis was performed using Comprehensive Meta-Analysis software (v3.0; Biostat, NJ, USA).

Quality assessment / Risk of bias analysis Study quality was assessed using the Quality in Prognosis Studies (QUIPS) tool, covering six domains: study participation, attrition, prognostic factor measurement, outcome measurement, confounding, and statistical reporting.

Strategy of data synthesis A random-effects meta-analysis model was used to pool effect sizes (SMD/MD) with 95% CIs. Heterogeneity was evaluated using I^2 statistics and Cochran's Q test. Funnel plots and Egger's test were applied to assess publication bias.

Subgroup analysis Subgroup analyses were performed by baseline renal function (eGFR ≥60 vs. <60 mL/min/1.73 m^2), baseline UPCR (<0.5 vs. ≥0.5 g/g), and sex (male vs. female).

Sensitivity analysis A leave-one-out sensitivity analysis was conducted to test the stability of the pooled results. Analyses were repeated after excluding studies with high risk of bias.

Language restriction English only.

Country(ies) involved Taiwan.

Keywords Fabry disease; enzyme replacement therapy; ERT; meta-analysis; renal function; eGFR; UPCR; proteinuria; kidney outcomes; clinical events.

Dissemination plans Results have been submitted to Biomedicines for peer review and publication. The dataset and materials will also be available in the INPLASY repository after registration approval.

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