Targeted Literature Review Exploring Surrogacy Relationships Between eGFR/LVMI and Clinical Events in Fabry Disease

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Background

- Fabry disease (FD) is a rare, devastating and progressive condition associated with a range of clinical events and eventually premature death[1]
- Clinical trials in FD are often not powered to capture these clinical events, given the long-term nature of disease progression. Surrogate outcomes, such as estimated glomerular filtration rate (eGFR) and left ventricular mass index (LVMI), are often captured instead
- eGFR and LVMI are believed to be associated with long-term FD clinical events of interest, but precise surrogacy relationships are unclear[2]

Objective

- To identify published literature exploring the relationship between eGFR/LVMI and long-term clinical events in FD

Methods

- A comprehensive literature search was conducted in Embase® and MEDLINE® on 18 May 2021, and a targeted literature review was conducted. Table 1 shows the key inclusion criteria for this review
- Studies reporting a quantitative relationship between eGFR and/or LVMI and clinical events in FD were extracted, and narrative synthesis was conducted on these studies to understand these surrogate relationships

Table 1: Key criteria for study inclusion in the targeted literature review

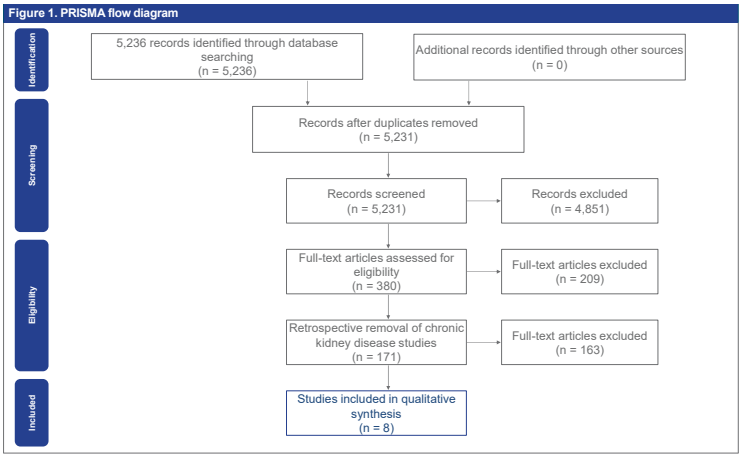
	Inclusion criteria	Exclusion criteria
Population	Patients with Fabry disease	Any other disease area
Outcomes	Surrogacy relationship values between eGFR or LVMI and the following clinical events: • Survival • Cardiac events (heart failure, atrial fibrillation, cardiac death, myocardial infarction, cardiac defibrillator or pacemaker implant, coronary artery bypass surgery, malignant ventricular tachycardia) • Renal events (end-stage renal disease) • Cerebrovascular events (stroke)	Studies that do not report surrogate outcomes for the outcomes of interest
Study design and publication types	Clinical studies reporting a surrogacy relationship	Exclude comments, letters, editorials, news articles, case reports, in vitro studies, studies focused on animals, and articles reporting design of a study but not reporting results

Key: eGFR, estimated glomerular filtration rate; LVMI, left ventricular mass index.

Results

- A total of 5,236 records were identified by the initial search. Five studies were removed as duplicates
- Following the screening of titles and abstracts, 4,851 records were excluded, with 380 included for secondary screening. After secondary screening of full texts, eight articles were included for data extraction (Figure 1)

Figure 1. PRISMA flow diagram



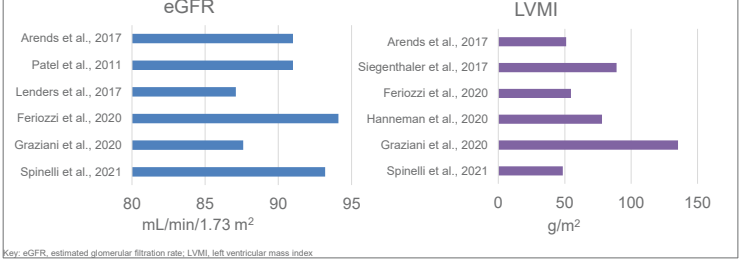
- The searches identified eight studies that investigated the relationship between one or more surrogate endpoints (eGFR and/or LVMI) and clinical events in patients with FD.[1,3-9] Five of these reported both eGFR and LVMI outcomes, two reported only eGFR outcomes and one reported only LVMI outcomes
- Table 2 shows the mean and range of key characteristics from the included studies. Figure 2 shows the range of baseline values for surrogate outcomes

Table 2: Patient characteristics of included studies

Characteristic	Number of studies	Mean	Range
Population size	N = 8	614	54–2,869
Age (years)	N = 8	45.85	41.8–52
Baseline eGFR (mL/min/1.73m²)	N = 6	90.67	87.1–94.1
Baseline LVMI (g/m²)	N = 8	76.1	48.5–135.2
Median follow-up (months)	N=6	69	43-103

Key: eGFR, estimated glomerular filtration rate; LVMI, left ventricular mass index.

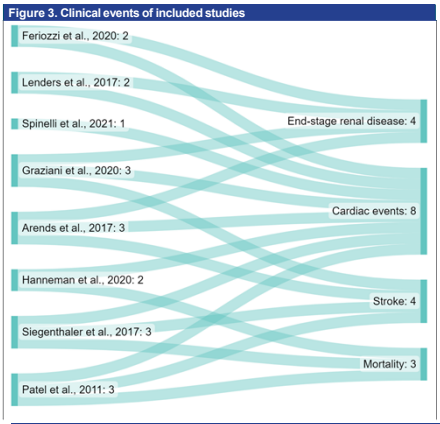
Figure 2: Baseline measurement for surrogate outcomes of interest in selected trials: eGFR and LVMI



Key: eGFR, estimated glomerular filtration rate; LVMI, left ventricular mass index

- All studies presented results for either a composite measure including a range of key FD clinical events, or a composite outcome that included at least one key FD clinical event. Cardiac complications were the most common event included in the composite measures (Figure 3)
- Patient treatment status varied among the included studies. Three studies included patients who had undergone enzyme replacement therapy (ERT) before baseline assessment; [1,5,6] two of these also included patients who initiated ERT in the follow-up period. [5,6] For three of the studies, all of the patients were treatment naïve at baseline, and none of them underwent any treatment during follow-up[7,8,3]

Figure 3. Clinical events of included studies



- To estimate hazard ratios (HRs) between eGFR and/or LVMI and clinical events of interest, all papers employed Cox proportional hazards survival modelling
- Seven of the eight included papers presented results for eGFR.[1,3,6-10] These generally showed a negative correlation between low or decreasing eGFR and the incidence of clinical events. Six of these studies presented results using an HR based on baseline eGFR, with one providing odds ratios (ORs) based on baseline eGFR[8].
- Six of the eight studies investigated LVMI as an explanatory variable of surrogate outcomes.[1,3,5,6,9,10] All six studies showed LVMI to be a predictor of FD clinical events, in univariate and/or multivariate analyses (Table 3).

Table 3: Models for eGFR and LVMI as a surrogate outcome for clinical events in FD

Reference	Method of analysis	eGFR	LVMI
		Outcome value (HR or OR)	
Spinelli et al., 2021	Univariate Cox analysis with predictor variable thresholds established by ROC curve analysis	**HR Predictors of events:** • eGFR ≤ 69: 0.978; CI (0.961, 0.996); p = 0.016	**Predictors of events:** • LVMI > 54.3: 1.022; CI (1.008, 1.036); p = 0.002
Graziani et al., 2020	Univariate and multivariate Cox regressions	**HR Predictors of events:** • eGFR: 0.97; CI (0.95, 0.99); p 0.008	**HR Predictors of events:** • LVMI (univariate): 1.01; CI (1.00, 1.01); p < 0.001 • LVMI (multivariate): 1.01; CI (1.00, 1.03); p = 0.03
Hanneman et al., 2020	Univariate and multivariate Cox regressions	N/A	**HR for 5 g/m² increase in LVMI:** 1.1; CI (1.1, 1.2); p < 0.001 (univariate) 1.1; CI (1.04, 1.2); p < 0.001 (multivariate)
Feriozzi et al., 2020	Multivariate Cox regression analysis	**HR for cardiovascular event** • eGFR at baseline (abnormal vs normal) 1.33; CI (1.04, 1.70); p = 0.021 **HR for renal event** • eGFR at baseline (abnormal vs normal) 5.88; CI (2.73, 12.68); p < 0.001 Abnormal eGFR defined as < 90 mL/min/1.73 m²	**HR for cardiovascular event** • LVMI at baseline (abnormal vs normal*) 1.57; CI (1.21, 2.05); p < 0.001 **HR for renal event** • LVMI at baseline (abnormal vs normal) 1.90; CI (0.94, 3.85); p = 0.074 * Abnormal LVMI defined as > 50 g/m$^{2.7}$ in males and > 48 g/m$^{2.7}$ in females
Lenders et al., 2017	Cox proportional hazards model	• HR for endpoint-free survival of patients receiving ERT with an eGFR = < 75 mL/min/1.73 m2: 4.77; CI (1.93, 11.81); p < 0.001 • HR for cardiovascular endpoints after ERT initiation end point free survival for patients with an eGFR ≤ 75 mL/min/1.73 m2: 3.59; CI (1.15, 11.18); p = 0.03	N/A
Siegenthaler et al., 2017	Univariate and multivariate Cox regressions	• HR for occurrence of primary endpoint according to baseline eGFR: **Crude** 0.42; CI: 0.28, 0.61; p < 0.001; **Model 1** 0.45; CI: 0.27,0.74; p = 0.002; **Model 2** 0.42; CI: 0.24, 0.74; p = 0.003; **Model 3** 0.45; CI: 0.25, 0.83; p = 0.01 Lower eGFR at baseline associated with a greater risk of developing an adverse clinical event HR: 0.41; CI (0.27, 0.62); p < 0.001 (per SD decrease in eGFR)	• HR for occurrence of primary endpoint according to baseline LVMI: **Crude** 2.14; CI: 1.52, 3.01; p < 0.001; **Model 1** 1.65; CI 1.06, 2.58; p = 0.03; **Model 2** 1.67; CI: 1.04, 2.73; p = 0.03; **Model 3** 1.67; CI: 1.04, 2.73; p = 0.03. Higher LVMMI associated with a greater risk of developing an adverse clinical event HR: 2.21; CI (1.43, 3.42); p < 0.001 for LVMMI (per SD increase in LVMMI)

Patel et al., 2011	Univariate logistic regression models. eGFR not considered in multivariate model as not selected during stepwise selection	• OR of experiencing a cardiovascular event for patients with low eGFR (< 60 ml/min/1.73 m²)
		  ▪ Men OR: 2.33; CI (1.22, 4.45), p < 0.05
		  ▪ Women OR: 3.85; CI (1.78, 8.32), p < 0.0001
			N/A

Arends et al., 2017	Univariate and multivariate Cox regressions	**HRs of the additional potential prognostic variables on the clinical event rate, adjusted for age at start of ERT, sex and phenotype** Mixed-effect models eGFR (per -10 ml/min/1.73 m²) HR: 1.19; CI (1.11, 1.27); p < 0.001 eGFR <60 ml/min/1.73 m² HR: 3.58; CI (2.21, 6.05); p < 0.001 Multivariate eGFR (per -10 ml/min/1.73 m²) HR: 1.12; CI (1.03, 1.22); p < 0.01 Multivariate analysis with eGFR as dichotomous variable eGFR (< 60 ml/min/1.73 m²) 2.66; CI (1.45, 4.90); p = 0.002 Multivariate analysis, excluding renal events eGFR (per -10 ml/min/1.73 m²) 1.01, CI (0.93, 1.10); p = 0.78	**HRs of the additional potential prognostic variables on the clinical event rate, adjusted for age at start of ERT, sex and phenotype** Mixed effect models LVMI (per 10 g/m$^{2.7}$) HR: 1.25; CI (1.08, 1.45); p < 0.01 Multivariate LVMI (per 10 g/m$^{2.7}$) HR: 1.16; CI (0.99, 1.36); p > 0.05 Multivariate analysis with eGFR as dichotomous variable LVMI (per 10 g/m$^{2.7}$) HR: 1.19; CI (1.02, 1.38); p = 0.028 Multivariate analysis, excluding renal events LVMI (per 10 g/m$^{2.7}$) HR: 1.19; CI (1.02, 1.38); p = 0.03

Key: eGFR, estimated glomerular filtration rate; LVMI, left ventricular mass index; HR, hazard ratio; OR, odds ratio

Discussion and Conclusions

- This review identified eight published studies that evaluated a quantitative relationship between eGFR and/or LVMI and key FD clinical events
- The evidence for using eGFR to model a surrogacy relationship in FD is largely supported by the literature identified in this review. This relationship was consistent in different types of analysis reported, such as assessment of eGFR as a continuous variable or differences between defined groups
- There was a clear consensus among the included studies that a low LVMI measurement in isolation was associated with an increased risk of patients experiencing a long-term clinical event. This held true for studies that used continuous or dichotomous definitions for LVMI
- Arends et al. 2017 was considered to be the most robust account for these relationships, as this study employed both mixed-effects and multivariate analyses and the use of both continuous and dichotomous modelling of LVMI and eGFR[3]
- While the direction of the relationship was unanimous among the included studies, its magnitude was not. Other aspects that remain unclear include which clinical events are predicted the most accurately, the level at which level eGFR and LVMI are predictive of events, and whether it is better to use a cut-off point or increments

Limitations

- Some analytical elements were absent from the identified studies. Few papers included the key driver variables in forms other than continuous. The studies only reported the impact of a patient's baseline eGFR/LVMI; none of the studies assessed the impact on patient outcomes of treatment-related changes in eGFR/LVMI
- The range in median follow-up was large (43-103 months) meaning some studies had more scope to capture long term Fabry outcomes
- Any interpretation of these findings should be considered with the caveat that these relationships are from baseline and across patients, rather than measuring the impact of within-patient changes.
- The most common form of regression analysis was univariate analysis, an approach that does not consider the impact of other variables that could also be driving the relationship
- The clinical events reported in the identified studies were all considered as part of composite outcomes. As such, the conclusions of this review are limited to the impact of eGFR and LVMI on clinical events when considered in general and within composite measures. Studies with isolated outcome variables may aid understanding of the surrogate relationship
- The heterogeneous nature of the included populations make it difficult to quantitatively establish a surrogate relationship as it is expected to vary between patient subgroups

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