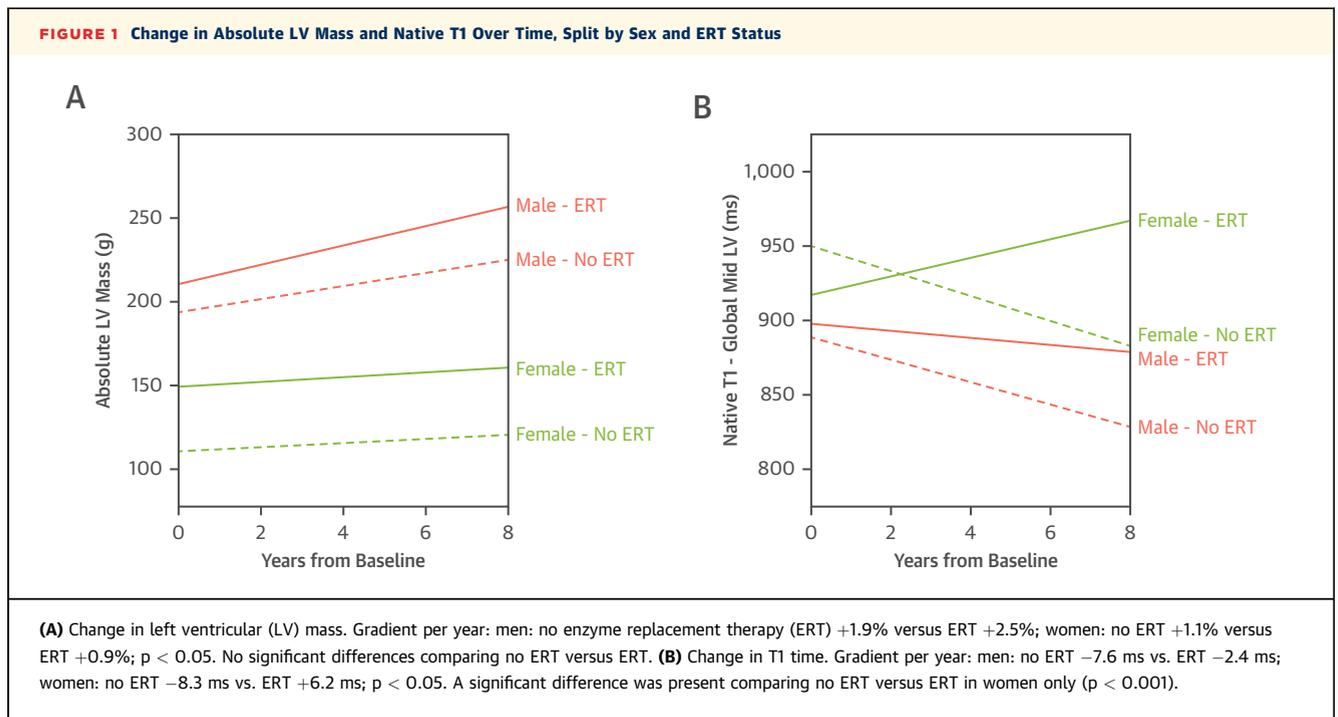


**Longitudinal Assessment of
Cardiac Involvement in Fabry Disease
Using Cardiovascular Magnetic
Resonance Imaging**



Fabry disease (FD) is an X-linked lysosomal storage disorder resulting in accumulation of sphingolipids in the heart, which leads to progressive left ventricular hypertrophy (LVH), fibrosis, and premature death (1). Although previous studies have tracked changes in mass using echocardiography (2), cardiovascular magnetic resonance (CMR) is the gold standard for reproducible measurement of mass and offers insight into the relationship between sphingolipid deposition, LVH, and fibrosis in FD over time, using T1 and T2 mapping, as well as late gadolinium enhancement (LGE). (3) The aim of this study was to define LV changes in FD over time and to consider use of enzyme replacement therapy (ERT).

This was a multicenter longitudinal study using CMR in 100 patients with FD (gene positive; 44% men; mean age 44 ± 14 years). Local clinical governance and ethical approval was obtained (NRES London 14/LO/1948, UHB clinical governance: RRK6621). Participants underwent 1.5-T CMR (Avanto, Siemens Healthcare, Erlangen, Germany) using a standard protocol that quantified LV mass and tissue characterization with T1 [Modified Look-Locker Inversion recovery sequence, 3(3)3(3)5 sampling scheme] and T2 mapping pre-contrast and inversion recovery imaging for LGE post-contrast. T1 maps were



analyzed using semi-automated segmentation at the mid-LV cavity, with a 20:20 percentage offset and an average of all segments taken (following artefactual segment exclusion), which gave global T1 mapping. LGE was quantified using a threshold of 6 SDs above the mean signal intensity of the reference myocardium.

The median duration of follow-up was 37 months (interquartile range [IQR]: 20 to 60 months), with a median of 2 follow-up visits per patient (range 2 to 6). Fifty percent of patients were on ERT at baseline (37 on agalsidase-alpha and 13 on agalsidase-beta). At baseline, men had higher indexed LV mass (LVMI) and maximum wall thickness (MWT) compared with women (median LVMI: 111.8 g/m² [IQR: 85.4 to 149.2 g/m²] vs. 62.7 g/m² [IQR: 56.7 to 82.5 g/m²]; MWT: 16 mm [IQR: 12 to 18 mm] vs. 10 mm [IQR: 9 to 12 mm]; $p < 0.001$ for both). Thirty-one patients (33%) had LGE at baseline (men: 49% vs. women: 21%; $p = 0.008$), with a similar mass of LGE seen (men 8.5 g [IQR: 3.2 to 19.6 g] vs. women: 7.4 g [IQR: 1.4 to 15.2 g]; $p = 0.359$).

There was an increase in absolute LVM over time ($n = 100$), with a gradient of 2.4% (95% confidence interval [CI]: 1.8% to 3.1%) per year in men ($p < 0.001$) and 1.0% (95% CI: 0.3 to 1.7%) per year in women ($p = 0.005$). Native T1 decreased over time in men (-3.4 ms per year; 95% CI: -6.4 to -0.4 ; $p = 0.029$), but no significant change was observed in women ($p = 0.831$). Mass of LGE increased by 36.6% (95% CI:

14.0% to 63.7%) per year in men ($p < 0.001$) and by 12.0% (95% CI: 2.0% to 23.0%) per year in women ($p = 0.011$). There were no changes in the proportions of male and female patients with chronic kidney disease, ischemic heart disease, or hypertension over the study period.

Five patients received ERT during follow-up and were excluded from subgroup analysis by ERT status (Figure 1). ERT usage differed by sex, with 32 of 41 (78%) men on ERT compared with 18 of 54 (33%) women ($p < 0.001$). The increase in LVM over time remained significant despite the use of ERT in both men (ERT: 2.5% per year; 95% CI: 1.9% to 3.0%; $p < 0.001$; no ERT: 1.9% per year; 95% CI: 0.3% to 3.6%; $p = 0.020$) and women (ERT: 0.9% per year; 95% CI: 0.1% to 1.8%; $p = 0.025$; no ERT: 1.1% per year; 95% CI: 0.3% to 1.9%; $p = 0.005$). T1 decreased over time in men not on ERT (-7.6 ms per year; 95% CI: -12.6 to -2.5 ; $p = 0.003$), although there was a tendency to a smaller reduction on ERT (-2.4 ms; 95% CI: -4.6 to -0.1 ; $p = 0.039$; between groups: $p = 0.064$). However, in women, T1 decreased over time in those not on ERT (-8.3 ms per year; 95% CI: -12.6 to -3.9 ; $p < 0.001$) but increased in the ERT group ($+6.2$ ms per year; 95% CI: 2.0 to 10.4; $p = 0.004$; between groups: $p < 0.001$).

This longitudinal CMR study was consistent with a sex-specific myocardial response in FD. Men had more advanced cardiac involvement at baseline and progressed at a greater rate than women, despite use

of disease-modifying therapy. During this study, these changes were less clear in women, and the impact of ERT was more pronounced. Although LV mass increased in women on ERT, T1 time increased, which could be consistent with either a sex-dependent response to therapy or a difference in myocardial response to storage. Limitations included the small sample size and lack of established prognostic T1 data, which made the relevance and importance of this parameter in disease progression unclear.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Cardiovascular Imaging* [author instructions page](#).

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