Incidence and risk factors for development of left ventricular hypertrophy in Fabry disease

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Abstract

Background Left ventricular hypertrophy (LVH) is the principal cardiac manifestation of Fabry disease (FD). This study aimed to determine the incidence and predictors of LVH development in a contemporary cohort of patients with FD and no LVH at baseline evaluation.

Methods Consecutively referred adult (aged ≥16 years) patients with FD were enrolled into an observational cohort study. Patients were prospectively followed in a specialist cardiomyopathy centre and the primary endpoint was the first detection of LVH (left ventricular mass index (LVMi) ≥115 g/m^2 in men and ≥95 g/m^2 in women).

Results From a cohort of 393 patients, 214 (aged 35.8±13.8 years; 61 (29%) males) had no LVH at first evaluation. During a median follow-up of 9.4 years (IQR 4.7–12.7), 55 patients (24.6%) developed LVH. The estimated incidence of LVH was 11.3% (95% CI 6.5% to 16.1%) at 5 years, 29.1% (95% CI 21.5% to 36.7%) at 10 years and 45.0% (95% CI 33.8% to 62.4%) at 15 years of follow-up. On multivariable analysis, independent predictors for LVH development were age (HR 1.04 (95% CI 1.02 to 1.06) per 1-year increase, p<0.001), male sex (HR 2.90 (95% CI 1.66 to 5.09), p<0.001) and an abnormal ECG (HR 3.10 (95% CI 1.72 to 5.57), p<0.001). The annual rate of change in LVMi was +2.77 (IQR 1.45–4.62) g/m^2/year in males and +1.38 (IQR 0.09–2.85) g/m^2/year in females (p<0.001).

Conclusions Approximately one-quarter of patients with FD developed LVH during follow-up. Age, male sex and ECG abnormalities were associated with a higher risk of developing LVH in patients with FD.

Introduction

Fabry disease (FD) is an X linked genetic disorder caused by pathogenic variants in the *GLA* gene.[1] The age at onset and the clinical presentation of FD depend mainly on sex and type of *GLA* variant[1] with female heterozygotes typically developing disease later and in a milder form than males.[2]

Cascade genetic screening is usually offered to family members of patients with FD[3–5] and leads to the identification of individuals, especially females, with pathogenic *GLA* variants in the absence of an overt disease phenotype. Current recommendations suggest lifelong cardiovascular (CV) follow-up for these individuals, but evidence to support this strategy in FD is limited and mainly extrapolated from guideline recommendations applied to other inherited heart diseases.[6 7] Identifying patients at risk for disease progression is crucial, as they may benefit from early disease-modifying treatment.[8 9]

The primary aim of this study was to determine the incidence of left ventricular hypertrophy (LVH) development in patients with FD and to identify predictors of phenotype development. The secondary aim was to assess the incidence of adverse CV events in patients with FD but no LVH.

Methods

An observational, longitudinal, retrospective cohort design was used. The study adheres to the principles of the Helsinki Declaration. All patients provided written informed consent.

Eligibility criteria

The cohort included consecutive patients with FD aged ≥16 years, who were referred to a dedicated cardiomyopathy clinic between 1 January 1988 and 23 June 2022. To be eligible for enrolment, patients had to meet the following inclusion criteria: diagnosis of FD, defined by the presence of a pathogenic or likely pathogenic (P/LP) variant in the *GLA* gene; absence of LVH or diagnostic criteria for hypertrophic cardiomyopathy (HCM) at the baseline echocardiographic evaluation[10]; and a follow-up of at least 1 year. Patients with a clinical or biochemical diagnosis of FD without genetic confirmation or carrying a variant of uncertain significance (VUS), including p.A143T, p.D313Y, p.R118C and p.R227Q, and those without echocardiographic evaluations during follow-up were excluded.

Clinical investigations and data collection

Anonymised clinical data including non-identifiable demographics, family history, symptoms, medical therapy, resting 12-lead ECG, 2D, Doppler and colour transthoracic echocardiography, 24–48 ECG Holter monitoring and genetic testing results were collected. Patients underwent planned clinical reviews every 6–18 months. Data from the baseline evaluation were compared with the last clinical review. Hypertension was defined as a clinic systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg.

Recorded ECG parameters included rhythm, PR interval, QRS duration and repolarisation abnormalities. T-wave inversion (TWI) was defined as negative T-wave of ≥1 mm in depth in two or more contiguous leads, excluding leads aVR, III and V1.[11] An abnormal ECG was defined as the presence of one or more of the following criteria: PR interval ≥200 ms; QRS interval ≥110 ms; or the presence of TWI.

Echocardiographic measurements were made according to contemporary guidelines.[12] Offline readings and measurements were conducted by a single cardiologist. Recorded variables included left atrial diameter (LAD), left ventricular (LV) end-systolic diameter, LV end-diastolic diameter (LVEDD), LV ejection fraction (LVEF), maximal LV wall thickness (MLVWT), diastolic interventricular septal thickness (IVS), and diastolic posterior LV wall thickness (PW). LV mass (LVM) was calculated using the Cube formula [0.8 (1.04 [(LVEDD+PW+IVS)^3−(LVEDD)^3])+0.6 g] indexed to body surface area to obtain the LVM index (LVMi).[12] In accordance with the American Society of Echocardiography statement, 2D-guided M-mode measurements of LV wall thicknesses and diameters were conducted to enhance the accuracy of LVMi estimation. LVH was defined by an LVMi≥115 g/m^2 in men and ≥95 g/m^2 in women.[12]

MLVWT was defined as the greatest thickness in any single LV segment.[7] HCM was defined by the presence of an MLVWT≥15 mm not solely explained by haemodynamic overload.[7] Since the Cube formula estimates the LVM using septal and posterior wall thicknesses at the basal segment, and patients with FD may present with other patterns of LVH such as apical hypertrophy, patients meeting diagnostic criteria for HCM were excluded.

Genetic testing and variant classification

Variants were reclassified as P or LP using the American College of Medical Genetics and Genomics criteria.[13] Subjects with variants classified as VUS, likely benign or benign were excluded. Genetic testing was performed after obtaining informed written consent. *GLA* variants were classified as classic or late onset according to international databases (fabry-database.org /mutants/ and clinvarminer.genetics.utah.edu).

Outcomes

The primary endpoint was the first detection of LVH during follow-up. The secondary endpoint was a composite of CV death, appropriate implantable cardioverter-defibrillator (ICD) shock, bradyarrhythmias (second-degree or third-degree atrioventricular block or sinus node dysfunction (SND)) requiring pacemaker implantation, heart failure (HF)-related hospitalisation, stroke and atrial fibrillation (AF). CV death was stratified into sudden cardiac death (SCD) and HF-related death. Major adverse cardiovascular event (MACE) was defined as the composite of CV death, appropriate ICD shock, bradyarrhythmias requiring pacemaker implantation and HF-related hospitalisation. SCD was defined as witnessed sudden death with or without documented ventricular fibrillation or death within 1 hour of new symptoms or nocturnal deaths with no antecedent history of worsening symptoms.[14] SND was defined in the presence of symptomatic sinus bradycardia, sinoatrial block, sinus node arrest, tachycardia-bradycardia syndrome or chronotropic incompetence.[15]

Statistical analysis

Normally distributed continuous variables are described as mean±SD with two or three group comparisons using Student's t-test and analysis of variance, respectively. Changes in continuous echocardiographic parameters were assessed using the paired Student's t-test. Skewed data are described as median (IQR) with two or three-group comparisons performed using Wilcoxon rank-sum and Kruskal-Wallis tests, respectively. Categorical variables are listed as number (percentage) with group comparison conducted using χ^2 test or Fisher's exact test. A significance level (p value) of 0.05 (two-sided test) was used for all the comparisons.

To assess the intraobserver variability in the estimation of LVMi, the differences between the measurements (mean±SD) and the Pearson correlation coefficient were calculated.

Estimates of LVH development and freedom from the composite endpoint were obtained using the Kaplan-Meier product limit method. Log-rank tests were performed to compare patient survival between subgroups. Comparison between subgroups was performed after stratifying patients for sex, age at baseline (using tertiles) and type of *GLA* variant (classic vs late onset).

Univariate analysis of clinically relevant characteristics was performed. Specifically, clinical risk factors known to be associated with disease progression in FD (such as age, sex, *GLA* variant, New York Heart Association class, hypertension and ECG abnormalities) were included in the univariate analysis. Subsequently, a stepwise regression approach, incorporating variables with a univariate p value of ≤0.05, was used to build the multivariable model. Two different models were created: the first aimed at identifying risk factors associated with the development of LVH during follow-up, while the second aimed at identifying risk factors for the composite endpoint. Results are presented as HRs, 95% CIs and two-sided p values. Competing risk analysis was not conducted due to the low number of non-CV-related mortalities, which occurred in only one case. All statistical analyses were performed using IBM SPSS Statistics for Macintosh V.27.0 and GraphPad Prism V.9.5.1 for MacOs.

Results

Enrolment and baseline characteristics

From a total of 393 patients, we excluded 135 with LVH or HCM at the baseline evaluation, 32 with missing data and 12 carrying a *GLA* VUS. The remaining 214 patients with FD represent the final study cohort.

The clinical characteristics of the study population are shown in Table 1. The average age at the first evaluation was 35.8±13.8 years, and 61 (28.5%) were males. 133 patients (61.9%) carried a P/LP *GLA* variant associated with a classic phenotype, while 82 (38.1%) had a variant associated with a late-onset phenotype. 132 patients (61.7%) were treated with enzyme replacement therapy (ERT) or chaperone therapy at baseline evaluation. At baseline, male patients exhibited a

higher prevalence of non-sustained ventricular tachycardia (NSVT), AF and stroke; were more commonly on ERT or chaperone therapy; and had larger QRS interval, MLVWT, LAD and LVMi compared with females (Table 1).

Development of LVH during follow-up

During a median follow-up of 9.4 years (IQR 4.7–12.7), 55 patients (24.6%) developed LVH. The estimated incidence of LVH development was 11.3% (95% CI 6.5% to 16.1%) at 5 years, 29.1% (95% CI 21.5% to 36.7%) at 10 years and 45.0% (95% CI 33.8% to 62.4%) at 15 years of follow-up.

The development of LVH was more common in males than in females (26/61 (42.6%) vs 29/153 (18.9%), log-rank χ^2_1 15.0, p<0.001) (Figure 1). In males, the estimated incidence of LVH development was 21.3% (95% CI 9.9% to 30.1%) at 5 years, 49.5% (95% CI 34.3% to 64.5%) at 10 years and 63.5% (95% CI 44.7% to 82.3%) at 15 years of follow-up. In females, the estimated incidence of LVH development was 8.1% (95% CI 3.1% to 13.1%) at 5 years, 20.3% (95% CI 12.1% to 28.5%) at 10 years and 36.8% (95% CI 23.2% to 50.4%) at 15 years of follow-up.

At the baseline evaluation, patients developing LVH during follow-up were older (44.3±14.7 years vs 32.6±11.8 years, p<0.001), had higher prevalence of NSVT (16.4% vs 3.8%, p<0.001), hypertension (14.5% vs 3.8%, p=0.005), AF (5.4% vs 0.0%, p=0.003), and abnormal ECG (54.5% vs 17.0%, p<0.001), lower estimated glomerular filtration rate (88±19 mL/min/1.73 m^2 vs 100±24 mL/min/1.73 m^2, p=0.005), longer QRS interval (98±20 ms vs 87±13 ms, p<0.001), larger LAD (35±4 mm vs 32±4 mm, p<0.001) and LVMi (88±14 g/m^2 vs 69±15 g/m^2, p<0.001) compared with those who did not develop LVH (Table 2).

The estimated incidence of LVH development at 10 years was 15.1% (95% CI 3.3% to 26.9%) in patients <28 years, 23.4% (95% CI 11.2% to 35.6%) between 28 and 40 years, and 45.8% (95% CI 12.2% to 59.4%) >40 years (log-rank χ^2_1 16.3, p<0.001) at baseline evaluation (Figure 2A). This difference was significant in males (Figure 2B) but not in females (Figure 2C).

No significant difference was observed in the estimated incidence of LVH between patients with *GLA* variants associated with a classic disease phenotype and those with late-onset variants (online supplemental figure 1A). While no difference was present in males (online supplemental figure 1B), we observed that females with classic variants showed higher likelihood in LVH development during follow-up compared with those with late-onset variants (estimated incidence of LVH development at 10 years was 25.7% (95% CI 14.5% to 36.9%) in patients with classic variants versus 10.8% (95% CI 0.4% to 21.2%) in patients with late-onset variants (log-rank χ^2_1 4.5, p=0.019)) (online supplemental figure 1C).

On multivariable analysis, age (HR 1.04 (95% CI 1.02 to 1.06) per 1-year increase, p<0.001), male sex (HR 2.90 (95% CI 1.66 to 5.09), p<0.001) and abnormal ECG (HR 3.10 (95% CI 1.72 to 5.57), p<0.001) were independent predictors for LVH development during follow-up (Table 3). The presence of hypertension was a predictor for LVH development in the univariate analysis but was not an independent predictor when accounting for age, sex and ECG findings.

During a median follow-up of 9.4 years (IQR 4.7–12.7), significant changes in echocardiographic parameters were observed (online supplemental table 2). At the last echocardiographic evaluation, patients showed larger MLVWT (11±3 mm vs 9±2 mm, p<0.001), LAD (35±5 mm vs 32±5 mm, p<0.001), LVMi (92±34 g/m^2 vs 74±17 g/m^2, p<0.001) and lower LVEF (63±5% vs 66±5%, p<0.001) compared with the baseline evaluation. These results were observed in males and females.

Males showed a higher annual change rate in LVMi (+2.77 (IQR 1.45–4.62) g/m^2/year vs +1.38 (IQR 0.09–2.85) g/m^2/year, p<0.001) and in MLVWT (+0.21 (IQR 0.06–0.36) mm/year vs +0.10 (IQR 0.00–0.27) mm/year, p=0.017) than females. No difference was observed for LVEF (−0.22 (IQR −0.81 to 0.00) %/year vs 0.00 (IQR −0.60 to 0.00) mm/year, p=0.231) and LAD (+0.42 (IQR 0.00–0.72) mm/year vs +0.12 (IQR 0.00–0.38) mm/year, p=0.164) (online supplemental table 2, online supplemental figure 2).

Outcomes

During a median follow-up of 10.1 years (IQR 6.7–15.6), 23 (10.7%) experienced the composite endpoint (online supplemental table 3). No difference was observed in the

occurrence of the composite endpoint between male and female patients (Figure 3A). However, since the composite endpoint in females was fulfilled mainly due to the occurrence of non-cardioembolic stroke and AF, a significant difference was observed in the occurrence of MACE (Figure 3B).

The individual characteristics of patients suffering from an adverse event are shown in online supplemental table 4.

On multivariable analysis, age (HR 1.06 (95% CI 1.02 to 1.09) per 1-year increase, p<0.001) and abnormal ECG (HR 8.98 (95% CI 5.61 to 13.30), p<0.001) were independent predictors of composite endpoint during follow-up (online supplemental table 5).

Intraobserver variability in LVMi

Intraobserver variability was examined in 50 patients by reanalysing the echocardiographic measurements from the same patients. The repeated calculations of LVMi showed good consistency. The intraobserver variability in LVMi was −1.2±4.9 g/m² (95% CI −9.0 to 7.7; Pearson's r=0.973).

Discussion

This study describes the incidence and risk factors for LVH development in a single-centre cohort of patients with FD. The findings reveal that almost half of patients without LVH develop an increase in LVMi after 15 years, and that LVH development is associated with age at baseline evaluation, male sex and the presence of an abnormal ECG. Notably, the classification of *GLA* variant was unrelated to LVH development in males, but females carrying late-onset variants exhibited lower rates of LVH occurrence during follow-up than those with classical variants. Approximately 11% of patients experienced the composite endpoint but the type of events differed between males and females. Age and an abnormal ECG were independent predictors of the composite endpoint.

LVH development during follow-up

The identification of cardiac involvement in FD is crucial since it may determine eligibility for disease-modifying treatment and influences outcomes as patients with LVH have a higher risk of adverse events.[16 17] In addition, most evidence suggests

that the efficacy of ERT is less in the presence of LVH, especially in patients with advanced disease.[18–21]

Current recommendations suggest periodic re-evaluation for any signs or symptoms of cardiac disease.[3] Specifically, an ECG and Holter is recommended every 6–12 months and an echocardiographic evaluation every 12–24 months.[3] However, these recommendations are mostly extrapolated from guidelines for the diagnosis and management of patients with HCM,[7] a condition with a different natural history and disease penetrance.[22]

In this study, approximately 25% of patients developed LVH during a median follow-up of 9 years, with males, older patients and those with ECG abnormalities being more likely to develop LVH during follow-up. ECG abnormalities often represent the first clinical manifestation of cardiac involvement in FD[23] and are generally present in patients with overt FD cardiomyopathy.[24] In addition, ECG abnormalities are a risk factor for the occurrence of atrioventricular and sinus node disease requiring pacemaker implantation.[25 26] In our cohort, the presence of ECG abnormalities emerged as a robust predictor of LVH development and adverse events in patients with FD, regardless of age and sex. This observation confirms the pivotal role of the ECG as a screening tool for cardiac involvement in FD and highlights the need for long-term surveillance in individuals with an abnormal ECG.

Hypertension was observed in 6% of our cohort and was more common among patients with LVH than in those without. Although it was not an independent predictor for LVH development in the multivariable analysis, it may be as a disease modifier and contribute to LVH progression in FD.

LVH development and GLA variant

FD is a disease with heterogenous clinical manifestations, ranging from severe multiorgan phenotype to mild, single-organ involvement.[1] The main determinants of the disease phenotype are sex and the type of *GLA* variant. *GLA* variants are associated with variable residual α-galactosidase A enzyme function and patients with absent or severely reduced enzyme activity usually develop severe organ involvement (ie, classic disease). In contrast, those with residual enzyme activity tend to develop milder phenotypes, usually in advanced age (ie, late onset).[27] Recognising these two different natural histories is crucial since male

patients carrying classic variants are usually treated regardless of the disease phenotype. In contrast, treatment is often delayed in females and individuals of either sex carrying late-onset variants but without disease expression. In our study, we found that women carrying late-onset variants had a lower risk of disease progression, with an estimated incidence of developing LVH of 10% at 10 years of follow-up.

Outcomes

Many studies have shown that advanced age, disease severity (estimated by multiparametric scores) and LVMi are associated with the occurrence of CV events.[26] However, the long-term incidence of CV events in patients without LVH is less certain. In this study, during a median follow-up of approximately 10 years, 10% experienced the composite endpoint and no significant difference was observed between males and females. However, the occurrence of the composite endpoint in females was mainly driven by AF events. This observation is consistent with previous observations that AF can be observed in patients with FD with preserved LV function and in the absence of LVH,[28 29] showing a higher prevalence compared with the general population.[30] In contrast, MACE, including CV death, appropriate ICD shocks, bradyarrhythmias and HF-related hospitalisation, occurred almost exclusively in male patients. These results suggest that female patients without LVH at baseline evaluation have a low risk of developing MACE during medium term follow-up.

Clinical implications

This study suggests that the timing of follow-up should be individualised, taking into account factors such as age, sex, *GLA* variant and ECG findings. Since male patients exhibit a higher risk of disease development and adverse events, an annual CV re-evaluation is reasonable to identify disease progression and optimise management, especially in older patients and in those with ECG abnormalities. In contrast, female patients generally experience slower disease progression and a lower risk of MACE. In these patients, the timing of follow-up should be tailored according to the presence of risk factors for disease progression.

For patients without risk factors, such as those younger than 30 years old, with a late-onset *GLA* variant and no ECG abnormalities, a cardiological evaluation might

be performed every 3–5 years without consequence. Conversely, patients with a high risk for disease progression, such as those older than 40 years old, with a classic *GLA* variant and ECG abnormalities, should be evaluated annually irrespective of sex. Finally, in patients with one to two risk factors, such as those younger than 30 years old with a classic *GLA* variant and/or ECG abnormalities, the timing of follow-up should be decided on a case-by-case basis, with a cardiac evaluation performed every 1–3 years.

ERT and chaperone therapy have been demonstrated to reduce the progression of LVH and decrease CV outcome in patients with FD. The results of this study can assist physicians in predicting long-term disease progression and complications by using simple parameters, such as age, sex, ECG abnormalities and the specific gene variant. This risk assessment may enable the early introduction of disease-modifying therapies in individuals at a higher risk of disease progression.

Study limitations

This study has limitations inherent in retrospective analyses, including missing data and the potential for survival bias. Furthermore, patient evaluations lacked a standardised protocol. In our cohort, nearly all males and half of females were either on ERT or chaperone therapy at baseline evaluation or initiated treatment during follow-up for non-cardiological features associated with FD. The introduction of treatment, particularly in females, varied with age, *GLA* variant (classic or late onset) and systemic disease features, and evolved over time in accordance with contemporary expert recommendations. Furthermore, data on untreated patients are confined to a very small subgroup of females. Consequently, we deemed it inappropriate to model the potential impact of medical therapy on disease progression and outcome. Moreover, serial cardiac magnetic resonance data were not available for this study.

Larger prospective studies are needed to confirm our findings and establish the optimal timing of cardiac imaging following the diagnosis of FD.

Conclusion

Approximately one-quarter of patients with FD and no evidence for LVH developed LVH during follow-up. Age, male sex and ECG abnormalities were associated with a higher risk of developing LVH in patients with FD. This study suggests that the timing

of CV follow-up in patients without cardiac disease should be tailored to age, sex and ECG findings.

Data availability statement

Data are available upon reasonable request.

Ethics statements

Patient consent for publication

Consent obtained directly from patient(s).

Ethics approval

This study involves human participants and was approved by the University College London, UK (project ID 167619). Participants gave informed consent to participate in the study before taking part.

References

1. Germain DP. Fabry disease. Orphanet J Rare Dis 2010;5:30.

2. Wilcox WR, Oliveira JP, Hopkin RJ, et al. Females with Fabry disease frequently have major organ involvement: lessons from the Fabry Registry. Mol Genet Metab 2008;93:112–28.

3. Linhart A, Germain DP, Olivotto I, et al. An expert consensus document on the management of cardiovascular manifestations of Fabry disease. Eur J Heart Fail 2020;22:1076–96.

4. Limongelli G, Adorisio R, Baggio C, et al. Diagnosis and management of rare Cardiomyopathies in adult and Paediatric patients. A position paper of the Italian Society of Cardiology (SIC) and Italian Society of Paediatric Cardiology (SICP). Int J Cardiol 2022;357:55–71.

5. Wilde AAM, Semsarian C, Márquez MF, et al. European Heart Rhythm Association (EHRA)/Heart Rhythm Society (HRS)/Asia Pacific Heart Rhythm Society (APHRS)/Latin American Heart Rhythm Society (LAHRS) expert consensus statement on the state of genetic testing for cardiac diseases. Europace 2022;24:1307–67.

6. AHA/ACC guideline for the diagnosis and treatment of patients with hypertrophic cardiomyopathy: a report of the American college of cardiology/American Heart Association joint committee on clinical practice guidelines. Circulation 2020;142:e558–631.

7. Elliott PM, Anastasakis A, Borger MA, et al. 2014 ESC guidelines on diagnosis and management of hypertrophic cardiomyopathy: the task force for the diagnosis

and management of hypertrophic cardiomyopathy of the European Society of Cardiology (ESC). Eur Heart J 2014;35:2733–79.

8. Monda E, Bakalakos A, Rubino M, et al. Targeted therapies in pediatric and adult patients with hypertrophic heart disease: from molecular pathophysiology to personalized medicine. Circ Heart Fail 2023;16:e010687.

9. Monda E, Falco L, Palmiero G, et al. Cardiovascular involvement in Fabry's disease: new advances in diagnostic strategies. Card Fail Rev 2023;9:e12.

10. Arbelo E, Protonotarios A, Gimeno JR, et al. ESC guidelines for the management of cardiomyopathies. Eur Heart J 2023;44:3503–626.

11. Wilson MG, Sharma S, Carré F, et al. Significance of deep T-wave Inversions in asymptomatic athletes with normal cardiovascular examinations: practical solutions for managing the diagnostic conundrum. Br J Sports Med 2012;46 Suppl 1:i51–8.

12. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2015;28:1–39.

13. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 2015;17:405–24.

14. Zeppenfeld K, Tfelt-Hansen J, de Riva M, et al. ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. Eur Heart J 2022;43:3997–4126

15. Al-Khatib SM, Stevenson WG, Ackerman MJ, et al. AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American college of cardiology/American Heart Association task force on clinical practice guidelines and the Heart Rhythm Society. Circulation 2018;138:e272–391.

16. Meucci MC, Lillo R, Del Franco A, et al. Prognostic implications of the extent of cardiac damage in patients with Fabry disease. J Am Coll Cardiol 2023;82:1524–34.

17. Hopkin RJ, Cabrera G, Charrow J, et al. Risk factors for severe clinical events in male and female patients with Fabry disease treated with Agalsidase beta enzyme replacement therapy: data from the Fabry Registry. Mol Genet Metab 2016;119:151–9.

18. 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.

19. Weidemann F, Niemann M, Breunig F, et al. Long-term effects of enzyme replacement therapy on Fabry cardiomyopathy: evidence for a better outcome with early treatment. Circulation 2009;119:524–9.

20. Hughes DA, Elliott PM, Shah J, et al. Effects of enzyme replacement therapy on the cardiomyopathy of Anderson Fabry disease: a randomised, double-blind, placebocontrolled clinical trial of Agalsidase Alfa. Heart 2008;94:153–8.

21. Beer M, Weidemann F, Breunig F, et al. Impact of enzyme replacement therapy on cardiac morphology and function and late enhancement in Fabry's cardiomyopathy. Am J Cardiol 2006;97:1515–8.

22. Lorenzini M, Norrish G, Field E, et al. Penetrance of hypertrophic cardiomyopathy in sarcomere protein mutation carriers. J Am Coll Cardiol 2020;76:550–9.

23. Namdar M, Steffel J, Vidovic M, et al. Electrocardiographic changes in early recognition of Fabry disease. Heart 2011;97:485–90.

24. Niemann M, Hartmann T, Namdar M, et al. Cross-sectional baseline analysis of electrocardiography in a large cohort of patients with untreated Fabry disease. J Inherit Metab Dis 2013;36:873–9.

25. O'Mahony C, Coats C, Cardona M, et al. Incidence and predictors of anti-bradycardia pacing in patients with Anderson-Fabry disease. Europace 2011;13:1781–8.

26. Patel V, O'Mahony C, Hughes D, et al. Clinical and genetic predictors of major cardiac events in patients with Anderson–Fabry disease. Heart 2015;101:961–6.

27. Rubino M, Monda E, Lioncino M, et al. Diagnosis and management of cardiovascular involvement in Fabry disease. Heart Fail Clin 2022;18:39–49.

28. Pieroni M, Chimenti C, Ricci R, et al. Early detection of Fabry cardiomyopathy by tissue Doppler imaging. Circulation 2003;107:1978–84.

29. Frustaci A, Chimenti C. Cryptogenic ventricular arrhythmias and sudden death by Fabry disease: prominent infiltration of cardiac conduction tissue. Circulation 2007;116:e350–1.

30. Vijapurapu R, Roy A, Demetriades P, et al. Systematic review of the incidence and clinical risk predictors of atrial fibrillation and permanent pacemaker implantation for bradycardia in Fabry disease. Open Heart 2023;10:e002316.

Footnotes

- **Contributors** EMo and PME contributed to the conception or design of the work. EMo, AB, RL and PS contributed to the acquisition, analysis or interpretation of data for the work. EMo drafted the manuscript. AB, RL, PS, GL, EMu, DH and PME critically revised the manuscript. All authors gave final approval and agreed to be accountable for the overall content of the work, ensuring integrity and accuracy. EMo and PME act as guarantors.
- **Funding** The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.
- **Competing interests** None declared.
- **Patient and public involvement** Patients and/or the public were not involved

Table 1

Clinical characteristics of the study population

Clinical features	Overall cohort (n=214)	Males (n=61)	Females (n=153)
Age at baseline, years	35.8±13.8	33.9±15.2	36.3±12.9
Variants			
Classic	133 (61.9)	38 (62.3)	95 (62.1)
Late onset	82 (38.1)	23 (37.7)	58 (37.9)
FH SCD	9 (4.2)	4 (6.6)	5 (3.3)
Unexplained syncope	8 (3.7)	1 (1.6)	6 (3.9)
NYHA class			
I	195 (91.1)	53 (86.9)	142 (92.8)
II	19 (8.9)	8 (13.1)	11 (7.2)
NSVT	13 (6.1)	7 (11.85)	6 (3.9)
Hypertension	14 (6.5)	4 (6.6)	10 (6.5)
Diabetes mellitus	6 (2.8)	1 (1.6)	5 (3.3)
Atrial fibrillation	3 (1.4)	3 (4.9)	0 (0.0)
Previous stroke	6 (2.8)	5 (8.2)	1 (0.6)
eGFR, mL/min/1.73 m^2	96.1±23.5	99.2±28.2	94.6±20.6
ERT or chaperone therapy	132 (61.7)	55 (90.2)	77 (50.4)

Clinical features	Overall cohort (n=214)	Males (n=61)	Females (n=153)
Agalsidase alfa	92 (43.0)	40 (65.6)	52 (34.0)
Agalsidase beta	26 (12.1)	8 (13.1)	18 (11.7)
Migalastat	14 (6.5)	7 (11.4)	7 (4.6)
ECG data			
PR interval, ms	144±24	144±24	145±24
QRS interval, ms	91±13	100±15	87±11
TWI	45 (21.0)	16 (26.2)	29 (18.9)
Abnormal ECG	57 (26.6)	24 (39.3)	33 (21.6)
Echocardiographic data			
MLVWT, mm	9±2	10±3	8±2
LAD, mm	32±5	34±5	32±4
LVEF, %	66±5	65±5	66±5
LVMi, g/m^2	74±17	86±16	69±15
Echocardiographic follow-up, years	9.4 (4.7–12.7)	10.0 (4.6–13.3)	8.7 (4.7–12.4)
Follow-up, years	10.1 (6.7–15.6)	10.7 (6.6–16.8)	14.7 (6.7–14.7)

- Data are presented as mean±SD, median (IQR) or n (%).eGFR, estimated glomerular filtration rate; ERT, enzyme replacement therapy; FH, family history; LAD, left atrial diameter; LVEF, left ventricular ejection fraction; LVMi, left ventricular mass index; MLVWT, maximal left ventricular wall thickness; NSVT, non-sustained ventricular tachycardia; NYHA, New York Heart Association; SCD, sudden cardiac death; TWI, T-wave inversion.

Table 2

Clinical characteristics of the patients with and without left ventricular hypertrophy development during follow-up

	Overall cohort (n=214)			Males (n=61)		
Clinical features	No LVH (n=159)	LVH (n=55)	P value	No LVH (n=35)	LVH (n=26)	P value
Age at baseline, years	32.6±11.8	44.3±14.7	<0.001	25.5±10.4	45.1±13.2	<0.001
Variants			0.558			0.088
Classic	97 (61.0)	36 (65.5)		25 (71.4)	13 (50.0)	
Late onset	62 (39.0)	19 (34.5)		10 (28.6)	13 (50.0)	
FH SCD	3 (1.9)	6 (10.9)	0.004	1 (2.9)	3 (11.5)	0.176
Unexplained syncope	4 (2.5)	3 (5.5)	0.291	0 (0.0)	1 (3.8)	0.242
NYHA class			0.086			0.223
I	148 (93.1)	47 (85.5)		32 (91.4)	21 (80.8)	
II	11 (6.9)	8 (14.5)		3 (8.6)	5 (19.2)	
NSVT	4 (2.5)	9 (16.4)	<0.001	1 (2.9)	6 (23.1)	0.014
Hypertension	6 (3.8)	8 (14.5)	0.005	1 (2.9)	3 (11.5)	0.176
Diabetes mellitus	4 (2.5)	2 (3.6)	0.664	1 (2.9)	0 (0.0)	0.385
Atrial fibrillation	0 (0.0)	3 (5.4)	0.003	0 (0.0)	3 (11.5)	0.039
Previous stroke	3 (1.9)	3 (5.4)	0.167	3 (8.6)	2 (7.7)	0.901

	Overall cohort (n=214)			Males (n=61)		
Clinical features	No LVH (n=159)	LVH (n=55)	P value	No LVH (n=35)	LVH (n=26)	P value
eGFR, mL/min/1.73 m^2	100±24	88±19	0.005	110±29	83±17	<0.001
ERT or chaperone therapy	86 (54.1)	46 (83.6)	<0.001	31 (88.6)	24 (92.3)	0.628
ECG data						
PR interval, ms	144±21	146±30	0.663	142±19	147±29	0.454
QRS interval, ms	88±11	98±17	<0.001	97±10	104±18	0.045
TWI	21 (13.2)	24 (43.6)	<0.001	3 (8.6)	13 (50.0)	<0.001
Abnormal ECG	27 (17.0)	30 (54.5)	<0.001	7 (20.0)	17 (65.4)	<0.001
Echocardiographic data						
MLVWT, mm	8±2	11±3	<0.001	9±1	12±3	<0.001
LAD, mm	32±4	35±4	<0.001	33±5	36±5	0.016
LVEF, %	66±6	66±5	0.303	65±5	67±5	0.063
LVMi, g/m^2	69±15	88±14	<0.001	78±15	97±11	<0.001
Echocardiographic follow-up, years	8.2 (3.8–11.8)	10.6 (8.8–16.6)	<0.001	7.9 (3.2–11.8)	11.0 (9.6–16.8)	0.002
Follow-up, years	9.4 (6.0–13.9)	13.6 (9.7–17.6)	<0.001	9.2 (5.0–13.5)	14.8 (10.0–17.9)	0.003

- Data are presented as mean±SD, median (IQR) or n (%).

- eGFR, estimated glomerular filtration rate; ERT, enzyme replacement therapy; FH, family history; LAD, left atrial diameter; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; LVMi, left ventricular mass index; MLVWT, maximal left ventricular wall thickness; NSVT, non-sustained ventricular tachycardia; NYHA, New York Heart Association; SCD, sudden cardiac death; TWI, T-wave inversion.

Table 3

Univariate and multivariable analysis for LVH development predictors at α level of 0.05

	Univariate analysis		Multivariable analysis
Clinical parameters	HR (95% CI)	P value	HR (95% CI)
Age, per 1 year	1.05 (1.03 to 1.07)	<0.001	1.04 (1.02 to 1.06)
Male sex	2.73 (1.61 to 4.64)	<0.001	2.90 (1.66 to 5.09)
Late-onset variant	0.83 (0.47 to 1.45)	0.509	–
NYHA class II	1.87 (0.88 to 3.96)	0.102	–
Hypertension	2.17 (1.02 to 4.61)	0.043	0.93 (0.42 to 2.09)
Abnormal ECG	4.99 (2.92 to 8.51)	<0.001	3.10 (1.72 to 5.57)

- LVH, left ventricular hypertrophy; NYHA, New York Heart Association.

Figure legends

Figure 1

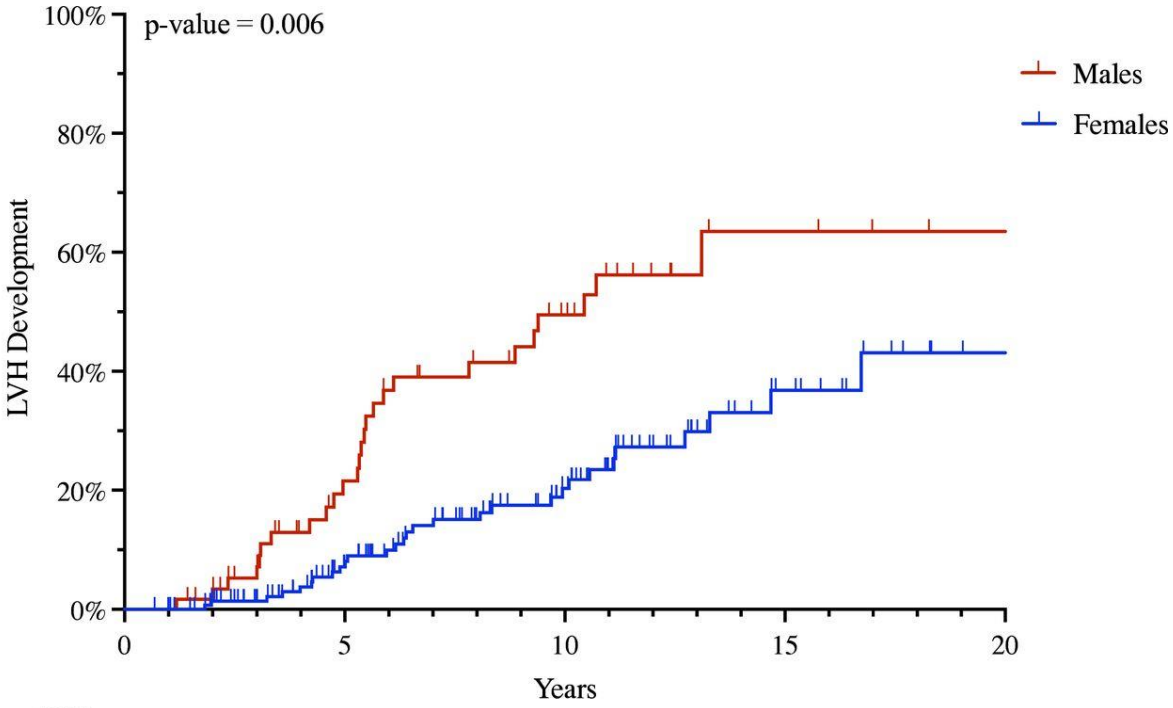
Left ventricular hypertrophy (LVH) development during follow-up according to sex.

Figure 2

Left ventricular hypertrophy (LVH) development during follow-up according to age at baseline evaluation. (A) Overall cohort. (B) Males. (C) Females.

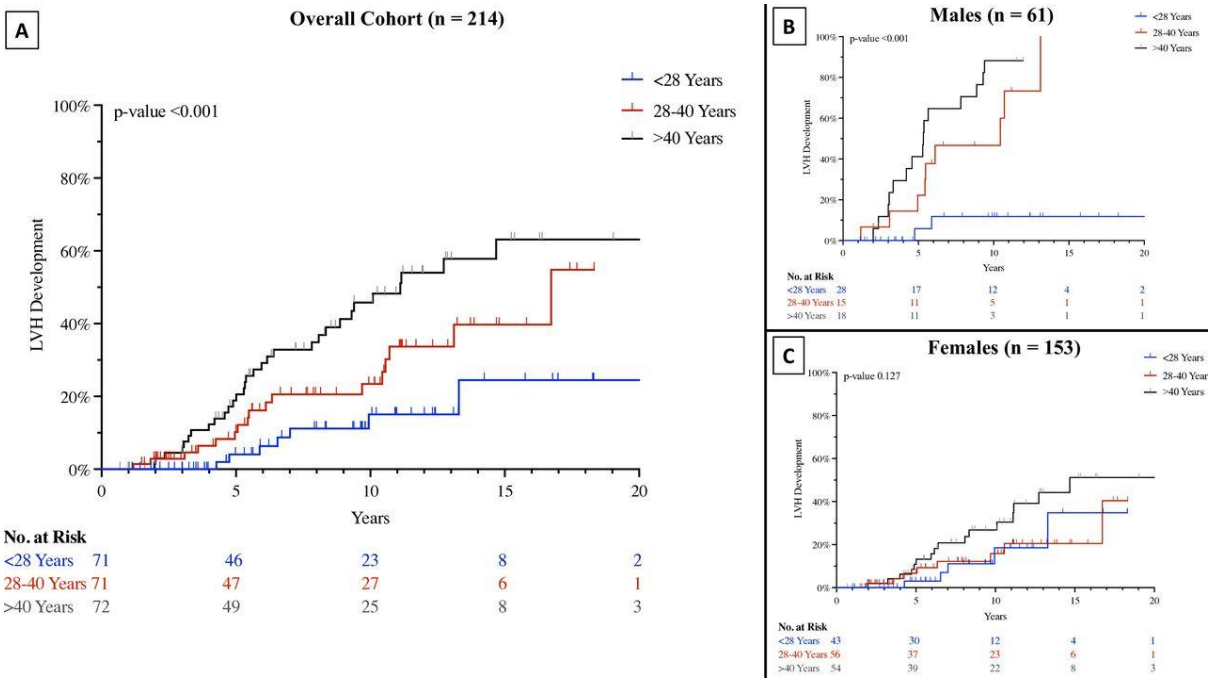
Figure 3

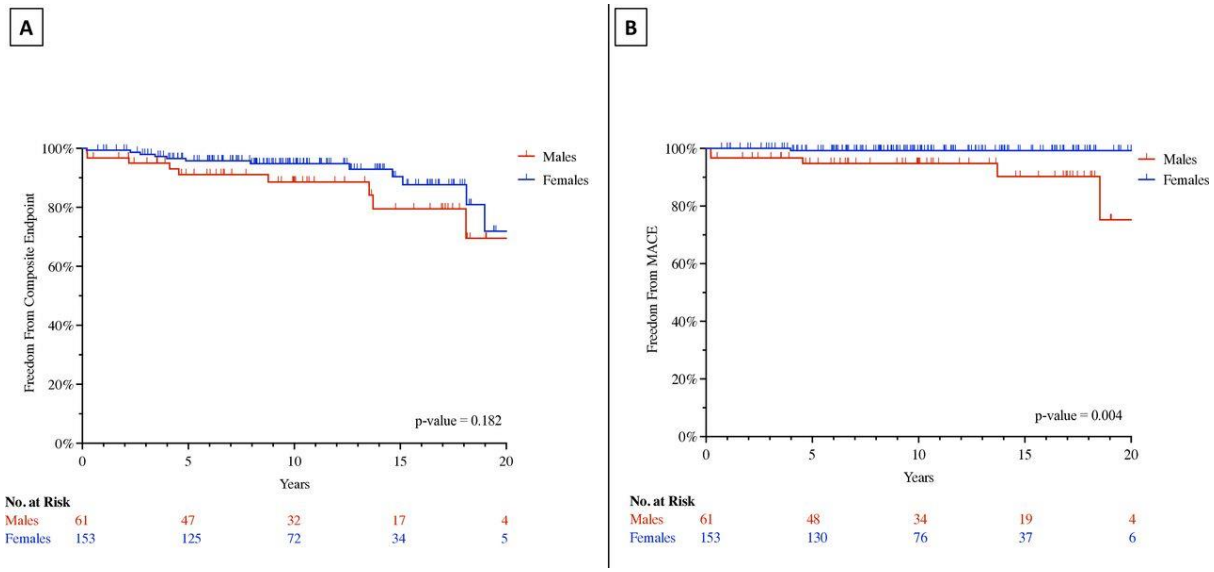
Freedom from composite endpoint (A) and major adverse cardiovascular events (MACE) (B) during follow-up according to sex.



No. at Risk

Males	61	37	18	5	2
Females	153	104	56	16	3


A
Overall Cohort (n = 214)
<28 Years
28-40 Years
>40 Years
p-value <0.001
LVH Development
100%
80%
60%
40%
20%
0%
0
5
10
15
20
Years
No. at Risk
<28 Years 71 46 23 8 2
28-40 Years 71 47 27 6 1
>40 Years 72 49 25 8 3
B
Males (n = 61)
<28 Years
28-40 Years
>40 Years
p-value <0.001
LVH Development
Years
No. at Risk
<28 Years 28 17 12 4 2
28-40 Years 15 11 5 1 1
>40 Years 18 11 3 1 1
C
Females (n = 153)
<28 Years
28-40 Year
>40 Years
p-value 0.127
LVH Development
Years
No. at Risk
<28 Years 43 30 12 4 1
28-40 Years 56 37 23 6 1
>40 Years 54 39 22 8 3


A
100%
80%
60%
40%
20%
0%
Freedom From Composite Endpoint
0
5
10
15
20
Years
Males
Females
p-value = 0.182
No. at Risk
Males 61 47 32 17 4
Females 153 125 72 34 5
B
100%
80%
60%
40%
20%
0%
Freedom From MACE
0
5
10
15
20
Years
Males
Females
p-value = 0.004
No. at Risk
Males 61 48 34 19 4
Females 153 130 76 37 6