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ORIGINAL ARTICLE

Cardiovascular Morbidity and Mortality in Fabry Disease

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BACKGROUND: Cardiac involvement is the main determinant of adverse outcomes in Fabry disease. The study aimed to investigate cardiovascular outcomes in patients with Fabry disease.

METHODS: This was a multicenter, retrospective, longitudinal study of consecutively referred adult patients with Fabry disease. The primary end point was the occurrence of major adverse cardiovascular events defined as a composite of cardiovascular death, major arrhythmic events, bradyarrhythmias requiring pacemaker implantation, and stroke.

RESULTS: A total of 680 patients (age, 42.3±15.9 years; 41.0% male; 68.7% on disease-specific therapy) were included. During a median follow-up of 7.1 (interquartile range, 3.9–11.6) years, 92 patients (13.5%) experienced a major adverse cardiovascular event. At 10 years, freedom from major adverse cardiovascular event was 85.1% (95% CI, 81.3–88.2) and was lower in males compared with females (76.1% [95% CI, 68.9–81.9] versus 91.3% [95% CI, 87.0–94.2]; log-rank χ^2=26.9; P<0.001). On multivariable analysis, age (hazard ratio, 1.04 [95% CI, 1.01–1.06] per 1 year; P<0.001), estimated glomerular filtration rate (hazard ratio, 0.99 [95% CI, 0.98–0.99] per 1 mL/min per 1.73 m^2; P<0.001), QRS interval (hazard ratio, 1.02 [95% CI, 1.01–1.03] per 1 ms; P=0.002), and left ventricular mass index (hazard ratio, 1.01 [95% CI, 1.00–1.01] per 1 g/m^2; P=0.032) were independent predictors of major adverse cardiovascular events during follow-up.

CONCLUSIONS: This study shows that the prevention and treatment of cardiovascular disease remain an unmet need for patients with Fabry disease.

Key Words: cardiovascular diseases ■ Fabry disease ■ hypertrophy, left ventricular ■ prognosis ■ sarcomeres

Fabry disease (FD) is a rare X-linked lysosomal storage disorder caused by pathogenic variants in the *GLA* gene, which encodes the enzyme α-Gal A (α-galactosidase A).[1] Reduced α-Gal A activity leads to the progressive accumulation of glycosphingolipids in various tissues[1] and a complex cellular pathophysiology that includes mitochondrial and sarcomere dysfunction, apoptosis, impaired autophagy, and inflammation.[2,3] These abnormalities translate into a wide spectrum of disease phenotypes.[1]

In individuals carrying classic *GLA* variants, symptoms typically emerge during childhood and include chronic neuropathic pain, hypohidrosis, angiokeratomas, gastrointestinal disturbances, sensorineural hearing loss, tinnitus, and cornea verticillata.[1] Progressive involvement of the kidneys, heart, and central nervous system generally occurs in adulthood.[1] Conversely, patients harboring late-onset *GLA* variants often remain underdiagnosed due to the absence of classic disease features and isolated organ involvement, most frequently

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Nonstandard Abbreviations and Acronyms

eGFR	estimated glomerular filtration rate
ERT	enzyme replacement therapy
FD	Fabry disease
HR	hazard ratio
LV	left ventricle
LVMi	left ventricular mass index
MACE	major adverse cardiovascular event
MLVWT	maximal left ventricular wall thickness
NSVT	nonsustained ventricular tachycardia
α-Gal A	α-galactosidase A

left ventricular (LV) hypertrophy.[2,4] In females, clinical expression could be influenced by both the specific *GLA* variant and the pattern of X-chromosome inactivation.[5] In addition, methylation and other genetic and nongenetic factors may further modulate phenotypic variability.[6]

Disease-specific therapy in the form of enzyme replacement and, more recently, oral pharmacological chaperone therapy has been available for >2 decades.[7–9] Recommendations for treatment initiation vary according to sex, clinical manifestations, and type of *GLA* variant.[10–12] Early initiation of treatment is associated with improved symptoms, as well as slowing and possibly preventing end-organ damage.[13] However, several studies report progression of cardiac manifestations in FD in spite of therapy.[14,15]

The aim of this multicenter collaboration was to investigate cardiovascular outcomes in patients with FD.

METHODS

This was a multicenter, retrospective, longitudinal study of consecutively referred patients diagnosed with FD between January 1, 1998, and December 2022. The participating centers were University College London/St. Bartholomew's Hospital, London, United Kingdom; Royal Free London NHS Foundation Trust, London; Inherited and Rare Cardiovascular Diseases, Department of Translational Medical Sciences, University of Campania Luigi Vanvitelli, Monaldi Hospital, Naples, Italy; Sant'Orsola Hospital, University of Bologna, Bologna, Italy; Careggi University Hospital, Florence, Italy; Catholic University of the Sacred Heart, Rome, Italy; and Federico II University, Naples. These centers maintain longitudinal databases that capture clinical, genetic, and outcome data. Internal review board approval was obtained at each participating site. The study adheres to the principles of Good Clinical Practice and the Declaration of Helsinki. The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure because of institutional and ethical restrictions.

Eligibility Criteria

Patients with a genetic diagnosis of FD, defined by the presence of a pathogenic or likely pathogenic variant in the *GLA* gene, were eligible for inclusion. Exclusion criteria included (1) patients with a clinical or biochemical diagnosis of FD without genetic confirmation or those carrying a variant of uncertain significance, (2) patients with a follow-up duration of <12 months, and (3) patients with missing data at baseline or during follow-up evaluations. Eligible patients were identified by the principal investigators at each site using multiple sources, including medical records and medical databases.

Clinical Investigations and Data Collection

Anonymized clinical data, including nonidentifiable demographics, family history, symptoms, resting 12-lead ECG, 2-dimensional, Doppler, and color transthoracic echocardiography, 24-48 ambulatory ECG monitoring, and genetic test results, were collected. Patients underwent planned clinical reviews every 6 to 18 months according to the center protocol and clinical need. Hypertension was defined as a clinic systolic blood pressure ≥140 mm Hg and a diastolic blood pressure ≥90 mm Hg.[16] Recorded 12-lead ECG parameters included rhythm, PR, and QRS interval. 2D and Doppler echocardiographic measurements were made according to contemporary guidelines.[17] Recorded variables included left atrial diameter, LV end-diastolic diameter, LV ejection fraction, maximal LV wall thickness (MLVWT), diastolic interventricular septal thickness, and diastolic posterior LV wall thickness. LV mass was calculated using the Cube formula (0.8[1.04([LV end-diastolic diameter+diastolic posterior LV wall thickness+diastolic interventricular septal thickness)3−[LV end-diastolic diameter]3)]+0.6 g) indexed to body surface area to obtain the LV mass index (LVMi).[17] In accordance with the American Society of Echocardiography statement, LV hypertrophy was defined as an LVMi ≥115 g/m^2 in men and ≥95 g/m^2 in women.[17] MLVWT was defined as the greatest thickness in any single LV segment.[18]

Genetic Testing and Variant Classification

Genetic testing was performed after obtaining informed written consent. Variants in *GLA* were reclassified as pathogenic or likely pathogenic using the American College of Medical Genetics and Genomics criteria.[19] Subjects with variants classified as variant of uncertain significance, likely benign, or benign were excluded. The reevaluation of variants was performed in January 2025. *GLA* variants were classified as classic or late-onset according to international databases (fabrydatabase.org/mutants/).

Outcomes

The primary end point was the occurrence of a major adverse cardiovascular event (MACE), defined as a composite of cardiovascular death, appropriate implantable cardioverter defibrillator shock, second- or third-degree atrioventricular block, or sinus node dysfunction requiring pacemaker implantation, and stroke.

The secondary end points were cardiovascular death, major arrhythmic events, defined as a composite of sudden cardiac

death, resuscitated ventricular fibrillation, and appropriate implantable cardioverter defibrillator shock, bradyarrhythmias requiring pacemaker implantation, and stroke.

Sudden cardiac death 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.[20] Sinus node dysfunction was defined in the presence of symptomatic sinus bradycardia, sinoatrial block, sinus node arrest, tachycardia-bradycardia syndrome, or chronotropic incompetence.[21]

All adverse events were adjudicated by experienced cardiologists at each center. Follow-up data to December 2022 were collected through the medical records of the last outpatient evaluation or hospital admission at the referral center or by telephone interview.

Statistical Analysis

Normally distributed continuous variables are presented as mean±SD; comparisons between groups were performed using an unpaired 2-tailed Student *t* test. Normality of continuous variables was assessed using graphical methods (ie, histograms) and the Shapiro-Wilk test. Skewed data are presented as median (interquartile range), with 2-group comparisons performed using the Wilcoxon rank-sum test. Categorical variables are reported as numbers (percentages), with group comparison performed using the χ^2 test. A significance level (*P* value) of 0.05 (2-sided test) was used for all the comparisons.

The time to end point was defined as the time to the first event or censored at the end of follow-up if no event occurred. Estimates of freedom from the primary end point 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 and type of *GLA* variant (classic versus late onset).

Univariable and multivariable Cox regression models were used to investigate the association between clinically relevant variables and the end point. For each model, a univariate analysis of clinically relevant characteristics was performed first. Then, a backward stepwise regression approach, incorporating variables with a univariate *P* value of ≤0.05 and the highest Wald test statistic, was used to build the multivariable model. Proportional hazards assumptions were verified by testing interactions with log(time). Results are presented as hazard ratios (HRs), 95% CIs, and 2-sided *P* values. All statistical analyses were performed using IBM SPSS Statistics for Macintosh, version 29.0, and GraphPad Prism, version 10.4.1, for macOS.

RESULTS

Enrollment and Baseline Characteristics

From a total of 712 individuals, we excluded 22 individuals who carried a *GLA* variant of uncertain significance or had no genetic confirmation and 10 patients with missing follow-up data. The remaining 680 patients with FD constituted the final study cohort. The clinical characteristics of the study population are shown in Table 1. The list of genetic variants for the study cohort is provided in Table S1.

Table 1. Clinical Characteristics of the Study Population. Data Are Presented as Mean±SD, Median (IQR), or n (%)

Clinical features	Overall cohort (n=680)	Males (n=279)	Females (n=401)	*P* value
Age at baseline, y	42.3±15.9	43.2±15.9	41.7±15.9	0.216
Age at diagnosis, y	41.7±15.9	42.1±15.9	41.4±15.8	0.545
Variants				0.940
Classic	452 (66.5)	185 (66.3)	267 (66.5)	
Late onset	228 (33.5)	94 (33.7)	134 (33.4)	
Unexplained syncope	39 (5.7)	16 (5.7)	23 (5.7)	0.885
NYHA class				<0.001*
I	544 (80.0)	204 (73.1)	340 (84.8)	
II	121 (17.8)	68 (24.3)	53 (13.2)	
III	15 (2.2)	7 (2.5)	8 (2.0)	
NSVT	49 (7.2)	35 (12.5)	14 (3.5)	<0.001*
Hypertension	158 (23.2)	83 (29.7)	75 (18.7)	<0.001*
Diabetes	25 (3.7)	11 (3.9)	14 (3.5)	0.758
Atrial fibrillation	53 (7.8)	30 (10.7)	23 (5.7)	0.016*
eGFR, mL/min per 1.73 m^2	95.5±29.8	91.1±35.3	98.9±24.3	0.003*
ERT or chaperone therapy	467 (68.7)	236 (84.6)	231 (57.6)	<0.001*
ERT	405 (59.6)	211 (75.6)	194 (48.4)	
Migalastat	62 (9.1)	25 (9.0)	37 (9.2)	
ECG data				
PR interval, ms	148±26	151±27	147±25	0.036*
QRS interval, ms	97±21	107±24	90±15	<0.001*
Echocardiographic data				
MLVWT, mm	12±4	14±5	10±3	<0.001*
LAD, mm	36±7	39±7	34±6	<0.001*
LVEF, %	64±6	63±7	65±6	<0.001*
LVMi, g/m^2	105±51	133±59	85±35	<0.001*
LVH	272 (40.0)	155 (55.6)	117 (29.2)	<0.001*
Follow-up, y	7.1 (3.9–11.6)	6.7 (3.5–11.8)	7.4 (4.2–11.5)	0.589

ECG indicates electrocardiography; eGFR, estimated glomerular filtration rate; ERT, enzyme replacement therapy; IQR, interquartile range; 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, nonsustained ventricular tachycardia; and NYHA, New York Heart Association.

*XXX.

The mean age at the first evaluation was 42.3±15.9 years; 279 (41.0%) patients were male. A total of 452 patients (66.5%) carried a pathogenic or likely pathogenic *GLA* variant associated with a classic phenotype, and 228 (33.5%) carried a variant associated with a late-onset phenotype. At baseline, 467 patients (68.7%) were receiving enzyme replacement therapy (ERT) or oral chaperone therapy. Compared with females, male patients had a higher prevalence of nonsustained ventricular tachycardia (NSVT), hypertension, and atrial fibrillation. Males had a lower estimated glomerular filtration rate (eGFR), were more frequently

on ERT or chaperone therapy, and had greater PR and QRS intervals, MLVWT, left atrial diameter, and LVMi. Males had a lower LV ejection fraction than females (Table 1).

Compared with male patients with a classic variant, those with a late-onset variant were older, had a higher prevalence of NSVT and diabetes, had a worse New York Heart Association class, and exhibited longer PR and QRS intervals, as well as greater MLVWT (Table 2). In contrast, females with classic and late-onset variants were similar in age and had comparable ECG characteristics at baseline. However, women with classic variants had greater MLVWT, left atrial diameter, and LVMi and were more often receiving ERT or chaperone therapy compared with those carrying late-onset variants (Table 2).

Primary End Point

During a median follow-up of 7.1 (interquartile range, 3.9–11.6) years, 92 patients (13.5%) experienced an MACE (Table S2). At 10 years, freedom from MACE was 85.1% (95% CI, 81.3%–88.2%) and was lower in males compared with females (males, 76.1% [95% CI, 68.9%–81.9%]; females, 91.3% [95% CI, 87.0%–94.2%]; log-rank χ^2=26.9; P<0.001; Figure 1).

When further stratified by sex and *GLA* variant, the 10-year freedom from MACE was 75.2% (95% CI, 66.4%–82.0%) in males with a classic variant, 78.2% (95% CI, 63.9%–87.4%) in males with a late-onset variant, 88.2% (95% CI, 82.2%–92.3%) in females with a classic variant, and 98.3% (95% CI, 93.2%–99.6%) in females with a late-onset variant (log-rank χ^2=30.2; P<0.001). No significant difference in the 10-year freedom from MACE was observed between males with a classic versus a late-onset variant (log-rank χ^2=0.5; P=0.486). In contrast, a difference emerged among females (log-rank χ^2=4.2; P=0.041).

At baseline, patients who later experienced an MACE were older, more likely to be male and carry classic *GLA* variants, and to have unexplained syncope, NSVT, and hypertension. They also had a lower eGFR, larger PR and QRS intervals, larger MLVWT, left atrial diameter, and LVMi, and a lower LV ejection fraction, and were more commonly receiving ERT or chaperone therapy compared with those who did not experience an MACE (Table S3).

On multivariable analysis, age (HR, 1.04 [95% CI, 1.01–1.06] per 1 year; P<0.001), eGFR (HR, 0.99 [95% CI, 0.98–0.99] per 1 mL/min per 1.73 m^2; P<0.001), QRS interval (HR, 1.02 [95% CI, 1.01–1.03] per 1 ms; P=0.002), and LVMi (HR, 1.01 [95% CI, 1.00–1.01] per 1 g/m^2; P=0.032) were independent predictors of MACEs during follow-up (Table 3).

A sensitivity analysis including patients with a follow-up between 5 and 10 years was performed, and the results are shown in Table S4.

Secondary End Points

During a median of 7.1 (interquartile range, 3.9–11.6) years of follow-up, 36 patients (5.3%) experienced a cardiovascular death (mean age at death, 62.7±14.2 years), 22 patients (3.2%) experienced a major arrhythmic event, 42 patients (6.2%) required pacemaker implantation for sinus node dysfunction or atrioventricular block, and 33 patients (4.9%) experienced a stroke (Figure 2). Noncardiovascular death occurred in 24 patients (3.5%; mean age at death, 60.7±14.9 years).

Clinical characteristics according to the occurrence of secondary end points are reported in Tables S5 through S8.

Results of the univariate analysis are reported in Tables S9 through S12. On multivariable analysis (Table 4; Figure 3), the following holds.

1. Age, LV ejection fraction, and LVMi were independent predictors for cardiovascular death.
2. NSVT and QRS interval were independent predictors of major arrhythmic events.
3. Age, eGFR, PR interval, and QRS interval were independent predictors of pacemaker implantation.
4. QRS interval and atrial fibrillation were independent predictors of stroke during follow-up.

DISCUSSION

This study describes the incidence of adverse cardiovascular events in a contemporary multicenter cohort of patients with FD. MACEs were more common in males and were associated with age at baseline evaluation, eGFR, QRS interval, and LVMi (Figure 3). The rate of MACEs was similar in men with classic and late-onset variants, but women carrying late-onset variants had lower rates of events than those with classic variants. These results show that the prevention and treatment of cardiovascular disease remain an unmet need for patients with FD.

Incidence and Risk Factors for Cardiovascular Events

In recent years, several studies have sought to determine risk factors for MACEs in patients with FD.[22–26] However, due to the rarity of the disease and the relatively low number of events during follow-up, designing a powered cohort capable of identifying risk factors for adverse events has been challenging. This has led to the use of composite outcomes, including mild adverse events, such as atrial fibrillation or NSVT. Here, we used a more stringent definition of MACE, including only hard events such as cardiovascular death, major arrhythmic events, bradyarrhythmias requiring pacemaker implantation, and stroke. This approach allows for a better assessment of the impact of cardiovascular complications and provides

Table 2. Clinical Characteristics of the Patients According to Sex and *GLA* Variant. Data Are Presented as Mean±SD, Median (IQR), or n (%)

	Overall cohort (n=680)			Males (n=279)			Females (n=401)		
Clinical features	Classic (n=452)	Late onset (n=228)	*P* value	Classic (n=185)	Late onset (n=94)	*P* value	Classic (n=267)	Late onset (n=134)	*P* value
Age at baseline, y	41.0±15.5	45.0±16.5	0.002*	39.9±14.1	49.8±17.3	<0.001*	41.7±16.4	41.8±15.1	0.972
Age at diagnosis, y	40.1±15.4	44.7±16.4	<0.001*	38.6±14.1	49.1±17.1	<0.001*	41.2±16.2	41.7±15.1	0.800
Unexplained syncope	24 (5.3)	15 (6.6)	0.783	8 (4.3)	8 (8.5)	0.248	16 (6.0)	7 (5.2)	0.545
NYHA class			0.513			0.044*			0.598
I	367 (81.2)	177 (77.6)		144 (77.8)	60 (63.8)		223 (83.5)	117 (87.3)	
II	75 (16.6)	46 (20.2)		37 (20.0)	31 (33.0)		38 (14.2)	15 (11.2)	
III	10 (2.2)	5 (2.2)		4 (2.2)	3 (3.2)		6 (2.2)	2 (1.5)	
NSVT	27 (5.9)	22 (9.7)	0.197	16 (8.6)	19 (20.2)	0.018*	11 (4.1)	3 (2.2)	0.237
Hypertension	112 (24.8)	46 (20.2)	0.180	55 (29.7)	28 (29.8)	0.992	57 (21.3)	18 (13.4)	0.055
Diabetes	12 (2.7)	13 (5.7)	0.046*	4 (2.2)	7 (7.4)	0.032*	8 (3.0)	6 (4.5)	0.446
Atrial fibrillation	36 (8.0)	17 (7.5)	0.815	18 (9.7)	12 (12.8)	0.439	18 (6.7)	5 (3.7)	0.221
eGFR, mL/min per 1.73 m^2	96.6±30.8	92.7±26.5	0.189	92.3±37.3	88.0±30.0	0.410	99.6±22.4	96.7±22.5	0.365
ERT or chaperone therapy	343 (75.9)	124 (54.4)	<0.001*	166 (89.7)	70 (74.5)	<0.001*	177 (66.3)	54 (40.3)	<0.001*
ERT	312 (69.0)	93 (40.8)		155 (83.8)	56 (59.6)		157 (58.8)	37 (27.6)	
Migalastat	31 (6.9)	31 (13.6)		11 (5.9)	14 (14.9)		20 (7.5)	17 (12.7)	
ECG data									
PR interval, ms	145±24	155±28	<0.001*	145±24	165±30	<0.001*	145±24	150±25	0.077
QRS interval, ms	97±20	98±22	0.343	105±23	111±26	0.029*	91±16	90±13	0.337
Echocardiographic data									
MLVWT, mm	12±4	12±5	0.249	13±4	15±5	<0.001*	10±3	9±3	0.010*
LAD, mm	36±7	36±7	0.953	38±8	40±7	0.060	34±6	33±5	0.047*
LVEF, %	64±6	64±6	0.820	63±7	64±6	0.249	65±6	64±5	0.146
LVMi, g/m^2	107±51	101±52	0.141	132±59	135±59	0.708	90±36	77±29	<0.001*
LVH	192 (42.5)	80 (35.1)	0.063	101 (54.6)	54 (57.4)	0.650	91 (34.1)	26 (19.4)	0.002*
Follow-up, y	7.6 (4.1–11.5)	6.4 (3.5–11.7)	0.241	6.8 (3.6–11.7)	6.2 (3.1–11.9)	0.623	8.2 (4.4–11.4)	6.4 (4.2–11.5)	0.256

ECG indicates electrocardiography; eGFR, estimated glomerular filtration rate; ERT, enzyme replacement therapy; IQR, interquartile range; 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, nonsustained ventricular tachycardia; and NYHA, New York Heart Association.

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a clearer picture of the true burden of cardiovascular disease in patients with FD.

In this study, the incidence of MACE was ≈15% at 10 years of follow-up, with significant differences between males and females. Specifically, males had a higher incidence of MACE (24% at 10 years) compared with females (9% at 10 years), highlighting a sex-specific difference in cardiovascular outcomes. Risk factors for MACEs were age, eGFR, QRS interval, and LVMi.

Due to the progressive nature of the disease, it is unsurprising that age per se is a risk factor for MACE, cardiovascular death, and bradyarrhythmias requiring pacemaker implantation.[22,27,28]

Renal involvement is common in FD, and kidney dysfunction often correlates with the severity of cardiovascular complications. In this study, it was an independent predictor for MACE and pacemaker implantation during follow-up. Similarly, QRS duration is a known predictor for pacemaker implantation in patients with FD[29] but was also a predictor of MACE, arrhythmic events, and stroke, suggesting that it serves as a useful surrogate for the severity of cardiovascular involvement.

LVMi is a widely used marker of cardiac involvement in FD[14,25] and is associated with a higher risk of cardiac events.[27] Both lower eGFR and higher LVMi have been associated with adverse cardiovascular outcomes in FD, suggesting a role of cardiorenal syndrome in the natural history of the disease. The presence of LV hypertrophy often precedes the development of more severe cardiac manifestations,[14] reinforcing the importance of monitoring this parameter in patients with FD. Indeed, a recent echocardiographic study on a large FD cohort showed that patients without LV hypertrophy exhibited a low rate of cardiovascular events.[27]

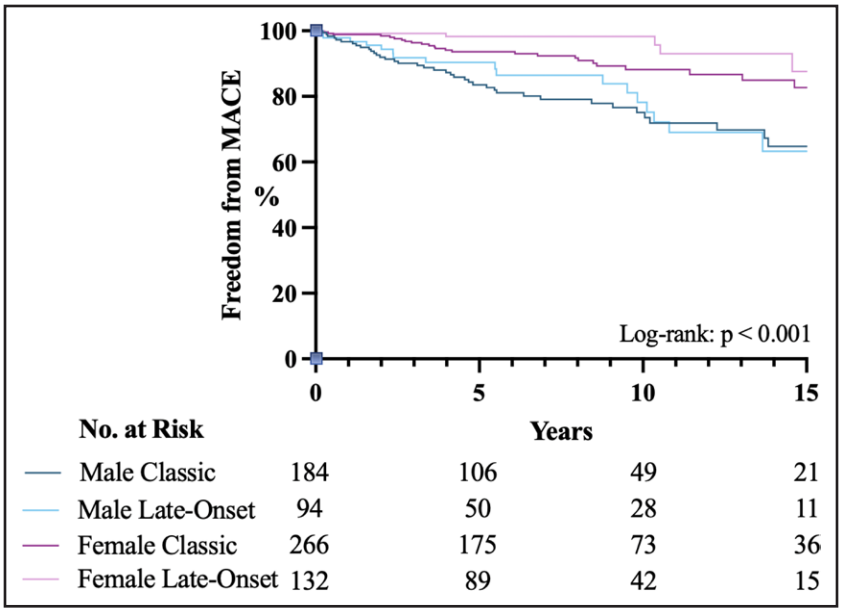

Figure 1. Freedom from the primary end point during follow-up according to sex and *GLA* variant.
At 10 years, freedom from major adverse cardiovascular event (MACE) was 85.1% (95% CI, 81.3–88.2) and was lower in males compared with females (males, 76.1% [95% CI, 68.9–81.9]; females, 91.3% [95% CI, 87.0–94.2]; log-rank χ^2=26.9; P<0.001).

Genetic Variants and Clinical Presentation and Outcome

In this study, we investigated variant-specific differences in clinical manifestations and outcomes. Males with late-onset *GLA* variants were, as expected, older at diagnosis, but they exhibited similar cardiac involvement at baseline as individuals with classic variants and experienced a similar rate of adverse events. This suggests that while genotype influences age of onset and associated organ manifestations, the long-term cardiovascular outcomes for men are ultimately the same. In contrast, females with classic and late-onset variants showed a similar age at baseline evaluation, but those carrying the classic variants had a higher LVMi and experienced a higher rate of MACEs. This sex-related difference in clinical presentation may be partly explained by different patterns of diagnosis, with males more often being probands, and females are more frequently diagnosed later through cascade screening. However, an ascertainment bias cannot be excluded, as females who are more severely affected are also more likely to be on disease-modifying therapy and to present earlier with symptoms.

Clinical Implications

Our data highlight the importance of early diagnosis and management of cardiovascular complications in classic

Table 3. Univariate and Multivariable Analysis for MACE Predictors at α Level of 0.05

	Univariate analysis		Multivariable analysis	
Clinical parameters	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age, y	1.07 (1.05–1.08)	<0.001*	1.04 (1.01–1.06)	0.003*
Male sex	2.96 (1.92–4.54)	<0.001*	1.41 (0.79–2.51)	0.239
Late-onset variant	0.79 (0.40–1.05)	0.079		
eGFR, mL/min per 1.73 m^2	0.88 (0.87–0.89)	<0.001*	0.99 (0.98–0.99)	<0.001*
Syncope	2.91 (1.61–5.27)	<0.001*	1.77 (0.79–3.51)	0.177
NSVT	3.66 (2.24–5.98)	<0.001*	0.98 (0.54–1.80)	0.961
Hypertension	2.30 (1.51–3.51)	<0.001*	0.71 (0.42–1.21)	0.209
Diabetes	1.61 (0.65–3.98)	0.299		
PR Interval, ms	1.01 (1.01–1.02)	<0.001*		
QRS Interval, ms	1.04 (1.03–1.05)	<0.001*	1.02 (1.01–1.03)	0.002*
LAD, mm	1.12 (1.10–1.12)	<0.001*		
LVEF, %	0.92 (0.89–0.95)	<0.001*	0.97 (0.94–1.01)	0.123
LVMi, g/m^2	1.01 (1.01–1.02)	<0.001*	1.01 (1.00–1.01)	0.032*

eGFR indicates estimated glomerular filtration rate; HR, hazard ratio; LAD, left atrial diameter; LVEF, left ventricular ejection fraction; LVMi, left ventricular mass index; MACE, major adverse cardiovascular event; and NSVT, nonsustained ventricular tachycardia.
*XXX.

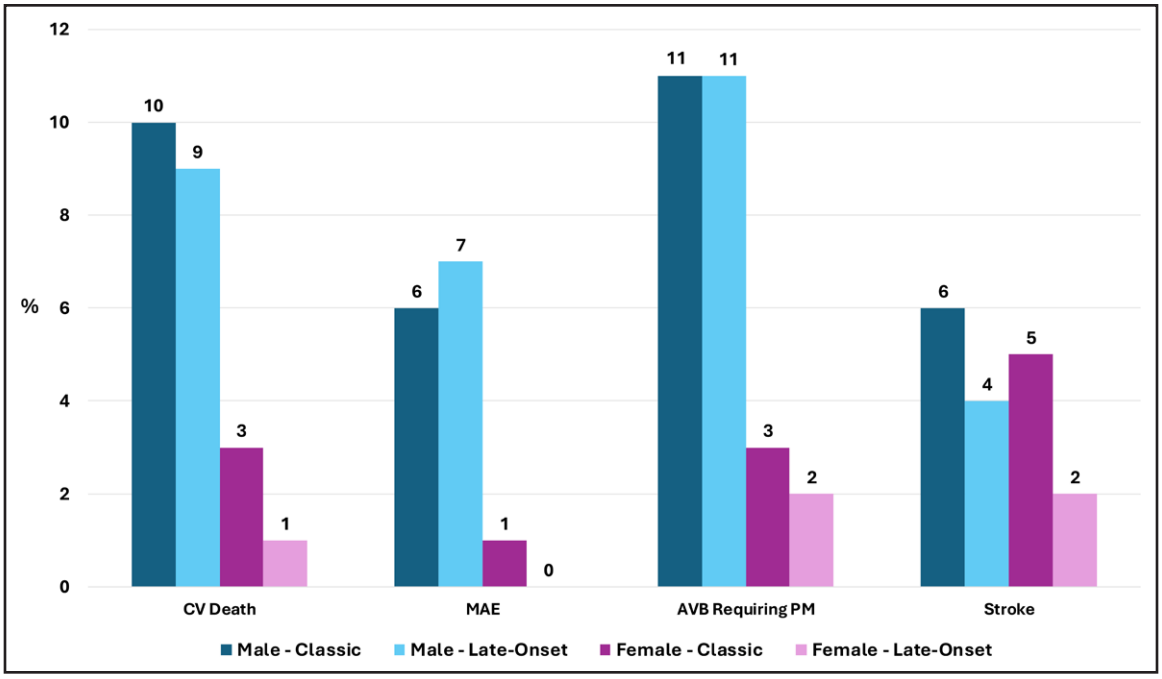

Figure 2. Rate of events during follow-up.
During a median of 7.1 (interquartile range, 3.9–11.6) years follow-up, 36 patients (5.3%) experienced a cardiovascular (CV) death (mean age at death, 62.7±14.2 years), 22 patients (3.2%) experienced a major arrhythmic event (MAE), 42 patients (6.2%) required pacemaker (PM) implantation for sinus node dysfunction or atrioventricular block (AVB), and 33 patients (4.9%) experienced a stroke.

and late-onset phenotypes. ECG parameters, in particular, are easily obtained predictive markers of overall and arrhythmic events, and standard ECG and dynamic Holter ECG should be regularly performed during follow-up to detect PR and QRS changes and the presence of NSVT. Interestingly, the number of bradyarrhythmias requiring pacemaker implantation exceeded the number of major arrhythmic events. This highlights the importance of conduction disease, with direct implications for patient management and follow-up strategies.

Table 4. Multivariable Analysis for Secondary End Point Predictors at α Level of 0.05

	Cardiovascular death		MAE		PM implantation		Stroke	
Clinical parameters	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age, y	1.06 (1.02–1.09)	<0.001*			1.04 (1.01–1.08)	0.009*		
Male sex								
Late-onset variant								
eGFR, mL/min per 1.73 m^2					0.98 (0.97–0.99)	0.004*		
Syncope								
NSVT			5.13 (2.03–12.97)	<0.001*				
Hypertension								
Diabetes								
PR interval, ms					1.01 (1.00–1.03)	0.046*		
QRS interval, ms			1.04 (1.02–1.05)	<0.001*	1.02 (1.01–1.03)	0.001*	1.03 (1.02–1.05)	<0.001*
LAD, mm								
LVEF, %	0.90 (0.86–0.95)	<0.001*						
LVMi, g/m^2	1.01 (1.01–1.02)	<0.001*						
Atrial fibrillation							3.98 (1.87–8.45)	<0.001*

eGFR indicates estimated glomerular filtration rate; HR, hazard ratio; LAD, left atrial diameter; LVEF, left ventricular ejection fraction; LVMi, left ventricular mass index; MACE, major adverse cardiovascular event; MAE, major arrhythmic event; NSVT, nonsustained ventricular tachycardia; and PM, pacemaker.
*XXX.

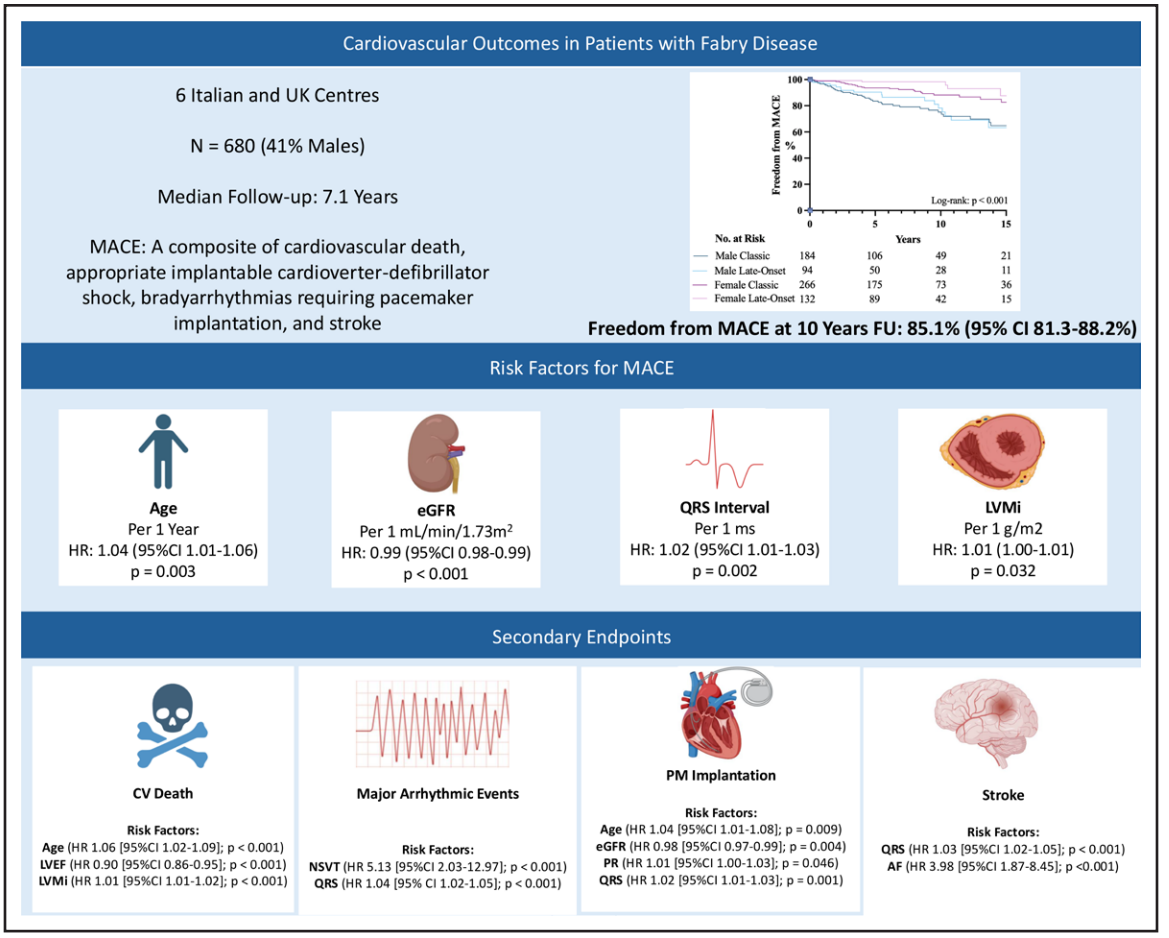

Figure 3. Summary of the study results.
The primary end point was the occurrence of a major adverse cardiovascular event (MACE) defined as a composite of cardiovascular (CV) death, major arrhythmic events, bradyarrhythmias requiring pacemaker (PM) implantation, and stroke. A total of 680 patients (age, 42.3±15.9 years; 41.0% males) constituted the study cohort. During a median follow-up of 7.1 (interquartile range, 3.9–11.6) years, 92 patients (13.5%) experienced an MACE. On multivariable analysis, age, estimated glomerular filtration rate, QRS interval, and left ventricular mass index were independent predictors of MACEs during follow-up. Risk factors for secondary end points (CV death, major arrhythmic events, PM implantation, and stroke) are also shown. AF indicates atrial fibrillation; eGFR, estimated glomerular filtration rate; HR, hazard ratio; LVEF, left ventricular ejection fraction; LVMi, left ventricular mass index; and NSVT, nonsustained ventricular tachycardia.

Limitations

This study has inherent limitations related to retrospective analyses, including missing data and the potential for survival bias. In our cohort, nearly all males and approximately half of the females were receiving ERT or chaperone therapy at baseline evaluation or initiated treatment during follow-up. The introduction of treatment, particularly in females, varied according to age, *GLA* variant (classic or late onset), and systemic disease features and evolved over time in accordance with contemporary expert recommendations. As a result, it was deemed inappropriate to model the potential impact of medical therapy on disease progression and outcomes. In addition, cardiac magnetic resonance imaging data were not available for this study. Previous studies reported the significance of cardiac magnetic resonance parameters (including late gadolinium enhancement, LVMi, and native T1 values) for predicting the risk of MACEs.[22] Furthermore, the role of biomarkers (including N-terminal pro-B-type natriuretic peptide, cardiac troponins, and lyso-Gb3) was not assessed.

Several potential confounders should also be acknowledged. Given the long enrollment period, advances in treatment and diagnostic approaches may have influenced outcomes. The increasing use of family screening may also have led to the enrollment of more asymptomatic relatives. Moreover, all participating centers were referral units, which may have introduced ascertainment bias. In addition, comorbidities such as hypertension and diabetes may have been underreported due to the reliance on retrospective medical records. Finally, no correction for multiple testing was applied.

Conclusions

This study provides an analysis of the incidence and risk factors for adverse cardiovascular events in patients

with FD. Despite important advances in therapy, cardiovascular disease continues to be a significant cause of disease-related morbidity and mortality.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Tables S1–S12

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