BRIEF RESEARCH COMMUNICATION

Patterns of Left Ventricular Remodeling and Outcomes in Fabry Disease

To the Editor:

The development of progressive left ventricular hypertrophy (LVH) is the hallmark of Fabry cardiomyopathy. In patients with Fabry disease (FD), left ventricular mass index (LVMi) is a strong prognostic marker, and its regression or stability is one of the main targets of studies assessing the efficacy of disease-specific therapy at the cardiac level.[1,2]

In the present study, we aimed to investigate the prevalence of different patterns of left ventricular (LV) remodeling in a large population of patients with FD and to assess their prognostic implications.

Patients with FD consecutively evaluated between January 2011 and December 2023 at 5 Italian referral centers were retrospectively screened.[3] Patients with complete echocardiographic data and clinical follow-up of ≥12 months were included in the present analysis.

As currently recommended,[4] LV remodeling patterns were defined according to LVMi and relative wall thickness. The study end point was the composite of all-cause death, admission for heart failure, new-onset atrial fibrillation, major brady- or tachyarrhythmia, and ischemic stroke. Statistical methods are detailed in the Supplemental Appendix.

The population was composed of 347 patients with FD (mean age, 44 ± 17 years; 57% women). Normal geometry was found in 143 patients (41%), concentric remodeling in 43 (12%) patients, concentric LVH (cLVH) in 129 (36%) patients, and eccentric LVH (eLVH) in 32 (9%) patients.

Baseline features of the overall cohort and stratified by patterns of LV remodeling are listed in Table 1. Patients with normal geometry were younger than those with concentric remodeling, while patients with cLVH or eLVH were older compared with those with concentric remodeling. Patients with normal geometry and, interestingly, those with eLVH were more frequently women. Patients with cLVH and

Table Baseline characteristics of the overall population and according to the patterns of LV remodeling

	Overall (*n* = 347)	Normal geometry (*n* = 143)	Concentric remodeling (*n* = 43)	eLVH (*n* = 32)	cLVH (*n* = 129)	*P*
Clinical characteristics						
Age, y	44 ± 17	32 ± 13	40 ± 14	52 ± 15	56 ± 11	<.001
Sex, male	148 (43)	38 (27)	25 (58)	13 (42)	72 (56)	<.001
Variant, p. Asn215Ser	61 (18)	23 (16)	10 (23)	4 (13)	24 (19)	.629
eGFR,* mL/min/m^2	89 (69-106)	98 (85-115)	93 (77-110)	79 (52-108)	73 (51-92)	<.001
Hypertension	113 (33)	21 (15)	8 (19)	19 (61)	65 (50)	<.001
Atrial fibrillation	29 (8)	1 (1)	1 (2)	5 (16)	22 (17)	<.001
Ischemic stroke	8 (3)	1 (1)	0 (0)	3 (10)	4 (3)	.022
NYHA functional class II-IV	74 (21)	8 (6)	2 (5)	12 (39)	52 (40)	<.001
ERT/chaperone	130 (38)/11 (3)	37 (26)/5 (4)	17 (40)/1 (2)	13 (42)/1 (3)	63 (49)/4 (3)	.001
Electrocardiographic characteristics						
PR interval, ms	145 (130-160)	140 (130-157)	145 (130-160)	143 (131-166)	155 (134-175)	.007
QRS interval, ms	92 (80-108)	85 (80-92)	90 (84-100)	95 (80-114)	106 (102-132)	<.001
Right bundle branch block, ms	37 (14)	1 (1)	4 (12)	3 (13)	29 (30)	<.001
Left bundle branch block, ms	9 (4)	1 (1)	0 (0)	1 (4)	7 (8)	.053
Echocardiographic characteristics						
LVMWT, mm	11 (9-15)	8 (8-10)	11 (10-12)	12 (11-14)	15 (13-19)	<.001
LVMi, g/m^2	98 (73-133)	71 (61-83)	91 (73-100)	120 (103-139)	141 (119-200)	<.001
LVEDD, mm	46 (43-49)	45 (43-47)	43 (41-47)	52 (48-54)	46 (44-50)	<.001
LVEDVi, mL/m^2	51 (43-61)	49 (42-57)	50 (43-61)	61 (60-65)	51 (43-62)	.024
LVEF, %	63 (60-66)	63 (61-66)	64 (60-66)	62 (58-67)	63 (59-63)	.110
LAVi, mL/m^2	28 (20-38)	22 (17-28)	28 (20-32)	34 (27-50)	39 (26-51)	<.001
E/A ratio	1.2 (0.9-1.6)	1.5 (1.2-1.8)	1.3 (1.0-1.6)	1.2 (0.9-1.6)	0.9 (0.8-1.2)	<.001
E/e′ ratio	8 (6-10)	6 (5-7)	7 (6-8)	9 (6-12)	11 (9-14)	<.001
RVWT, mm	4 (4-6)	4 (3-4)	4 (4-5)	5 (4-8)	7 (4-9)	<.001
TAPSE, mm	22 (20-25)	24 (22-25)	22 (21-24)	21 (18-22)	20 (18-22)	<.001
PASP, mm Hg	26 (24-30)	25 (23-27)	25 (25-29)	30 (25-35)	30 (25-35)	<.001

eGFR, Estimated glomerular filtration rate; *ERT*, enzyme replacement therapy; *LAVi*, left atrial volume index; *LVEDD*, LV end-diastolic diameter; *LVEDVi*, LV end-diastolic volume index; *LVEF*, LV ejection fraction; *LVMWT*, LV maximal wall thickness; *NYHA*, New York Heart Association; *PASP*, pulmonary artery systolic pressure; *RVWT*, right ventricular wall thickness; *TAPSE*, tricuspid annular plane systolic excursion.

Data are expressed as mean ± SD, number (percentage), or median (interquartile range). The data comparison was performed using one-way analysis of variance, the Kruskal-Wallis test, or the Pearson χ^2 test, as appropriate.

*eGFR was calculated using the Modification of Diet in Renal Disease formula.

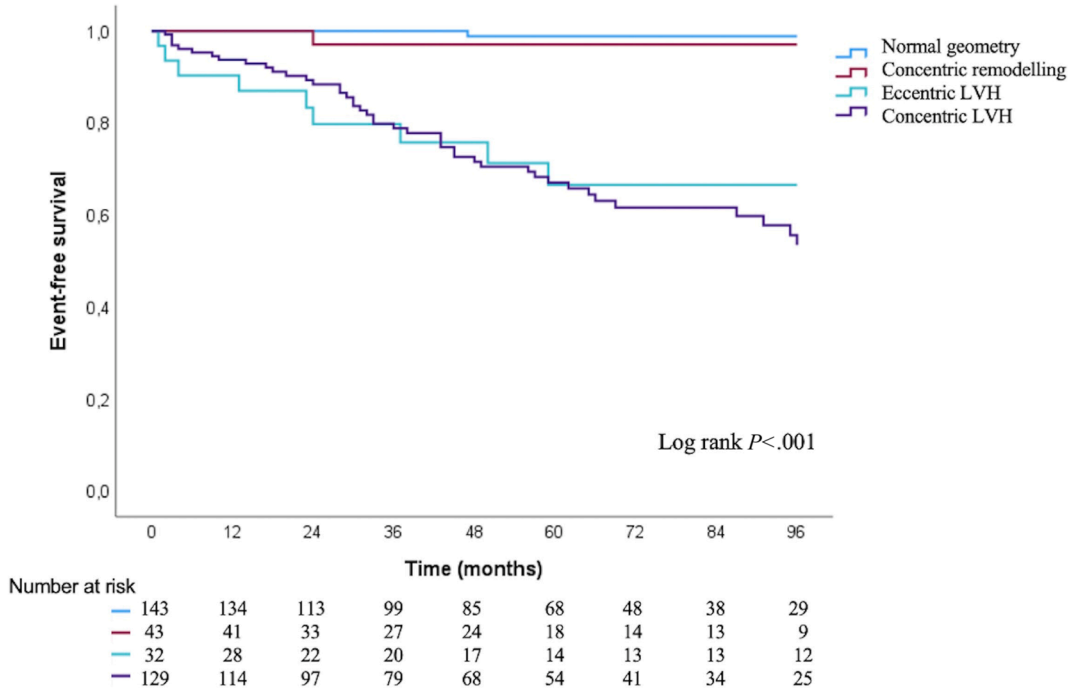

Figure Kaplan-Meier curves for the composite end point in patients with FD stratified by patterns of LV remodeling.

eLVH had higher prevalence of hypertension and atrial fibrillation and worse renal function in comparison with the other groups.

As expected, patients with normal geometry were more commonly naive to disease-specific therapy compared with other groups at baseline. Disease-specific treatment was started during follow-up in 80 patients (enzymatic replacement therapy and chaperone therapy in 58 and 22 patients, respectively), after a median of 12 months (interquartile range, 5-36 months). The rate of treatment initiation during follow-up was similar between LV remodeling groups ($P = .142$).

Regarding echocardiographic data, the highest values of LV maximum wall thickness and LVMi were found in the cLVH group, together with more prominent LV diastolic dysfunction and right ventricular hypertrophy. Conversely, patients with eLVH showed larger LV dimensions in comparison with the other groups.

A total of 64 patients (18%) reached the composite end point after a median of 53 months (interquartile range, 26-90 months). A breakdown of the composite outcome is provided in Supplemental Table 1. Kaplan-Meier survival curves showed significantly lower event-free survival at 4- and 8-year follow-up in patients with cLVH (80% and 54%, respectively) and eLVH (83% and 66%, respectively) in comparison with patients with concentric remodeling (97% and 97%, respectively) and those with normal geometry (100% and 99%, respectively) ($P < .001$; Figure 1). The study results were consistent in sex-stratified Kaplan-Meier analyses (data not shown).

The association of LV remodeling patterns and cardiovascular outcomes was further tested in multivariable Cox regression models. Both cLVH (hazard ratio [HR], 12.30; 95% CI, 1.51-97.23; $P = .017$) and eLVH (HR, 13.52; 95% CI, 1.64-111.38; $P = .016$) were independently associated with the study end point, after adjustment for age, sex, estimated glomerular filtration rate, New York Heart Association functional class, and exposure to disease-specific therapy. An alternative model built incorporating hypertension as covariate confirmed the study results (Supplemental Table 2). Increasing LVMi was associated with worse outcomes in patients with cLVH (crude HR, 1.007; 95% CI, 1.003-1.012; $P < .001$) and in those with eLVH (crude HR, 1.024; 95% CI, 1.009-1.039; $P = .001$).

When height-indexed LV mass thresholds were adopted,[5] the categorization of LV remodeling patterns was unchanged, except for three patients who were reclassified from having concentric remodeling to cLVH. In addition, the findings regarding the prognostic significance of LV remodeling patterns were confirmed (data not shown).

Fabry cardiomyopathy typically manifests as cLVH.[6] However, in the present study, a proportion of patients (9%) had eLVH, and they were mostly women, suggesting that sex might influence not only the degree[7] but also the pattern of LVH. Importantly, cLVH and eLVH were independently associated with cardiovascular outcomes, while concentric remodeling was associated with favorable long-term prognosis, similarly to normal LV geometry. This finding is novel, as previous outcome studies focused mainly on categorization according to the presence and degree of LVH,[1,2,6,7] rather than remodeling pattern.

We acknowledge that the number of events occurring for each group is relatively limited, but this is expected for a rare disease. Furthermore, remodeling patterns in these patients may not be completely attributable to cardiac involvement, as we cannot exclude an influence exerted by concomitant hypertension or renal disease. Nevertheless, the association with clinical outcomes was consistent controlling for these variables. Excellent interobserver agreement of echocardiographic measurements has already been reported for participating institution.[3] However, as linear dimensions are raised to the power of 3 in the formula for LV mass calculation, even small errors can have significant effects on the final value.

CONFLICTS OF INTEREST

Dr. Lillo has received advisory board fees from Amicus Therapeutics, Sanofi Genzyme, Takeda, and Shire. Dr. Biagini has received speaker fees from Amicus Therapeutics, Sanofi Genzyme, Takeda, and Bristol Myers Squibb. Dr. Cappelli has received speaker fees or honoraria from Pfizer, Alnylam, Novo Nordisk, BridgeBio, Bayer, and AstraZeneca. Dr. Pieroni has received speaker and/or advisory board fees from Sanofi Genzyme, Pfizer, and Bristol Myers Squibb. Dr Limongelli has received advisory board fees from Amicus Therapeutics; and has received an unrestricted grant from Sanofi. Dr Olivotto has received research grants from Bristol Myers Squibb, Cytokinetics, Sanofi Genzyme, Shire, Bayer, Amicus, Chiesi, and Menarini International; and has received speaker and/or advisory board fees from Bristol Myers Squibb, Cytokinetics, Sanofi Genzyme, Amicus, Shire, Tenaya, and Rocket Pharma. Dr. Graziani has research grants from Takeda and Pfizer; and has received advisory board fees from Amicus Therapeutics, Sanofi Genzyme, and Shire.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.1016/j.echo.2025.11.012.

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