

Cardiovascular Events in Patients With Fabry Disease

Natural History Data From the Fabry Registry

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Objectives	These analyses were designed to determine the incidence of major cardiovascular (CV) events and the natural history of CV complications in patients with Fabry disease.
Background	Fabry disease, a genetic disorder caused by deficiency of alpha-galactosidase A activity, is associated with CV dysfunction.
Methods	Major CV events (myocardial infarction, heart failure, or cardiac-related death) were analyzed in 2,869 Fabry Registry patients during the natural history period (i.e., before enzyme replacement therapy or among patients who never received therapy). Multivariate logistic regression analyses were performed to identify significant predictors of CV events.
Results	Eighty-three of 1,424 men (5.8%) and 54 of 1,445 women (3.7%) experienced CV events at mean ages of 45 and 54 years, respectively. Heart failure was the most common first CV event, reported by 50 men (3.5%) and 33 women (2.3%). Hypertension and left ventricular hypertrophy were the risk factors most strongly associated with CV events. When these parameters were used as covariates in logistic regression analyses, the odds ratio (OR) for hypertension in men was 7.8 (95% confidence interval [CI]: 2.1 to 28.6, $p = 0.0019$), and the OR for hypertension in women was 4.5 (95% CI: 1.6 to 12.3, $p = 0.0037$). The OR for left ventricular hypertrophy was 4.8 in men (95% CI: 1.03 to 22.2, $p = 0.0463$) and 8.2 in women (95% CI: 2.6 to 26.0, $p = 0.0003$).
Conclusions	Major CV events occurred in approximately 5% of Fabry Registry patients during the natural history period. All patients with Fabry disease should be monitored for possible CV risk factors, particularly hypertension and left ventricular hypertrophy. (J Am Coll Cardiol 2011;57:1093-9) © 2011 by the American College of Cardiology Foundation

Fabry disease is an X-linked lysosomal storage disorder, characterized by decreased or absent activity of lysosomal alpha-galactosidase A. As a result of this enzyme deficiency, globotriaosylceramide (GL-3) and other glycosphingolipids

accumulate within various tissues, including kidney, heart, and skin (1). The initial signs and symptoms of Fabry disease—including neuropathic pain in the extremities, hypohidrosis, angiokeratomas, and gastrointestinal discomfort—

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**Abbreviations
and Acronyms**

CI = confidence interval
CV = cardiovascular
ERT = enzyme replacement therapy
GL-3 = globotriaosylceramide
HF = heart failure
LVH = left ventricular hypertrophy
MI = myocardial infarction
OR = odds ratio

typically appear during childhood. Vital organ function progressively declines over time, putting patients with Fabry disease at risk of developing renal failure, cardiovascular (CV) dysfunction, and stroke (2–6).

The CV manifestations of Fabry disease include hypertension, left ventricular hypertrophy (LVH), rhythm and conduction abnormalities, increased intima-media thickness, valvular insufficiency, and ischemic heart disease (7–9). Over time, these

cardiac complications can progress to heart failure (HF), myocardial infarction (MI), and life-threatening arrhythmias (4,6,10). However, the incidence rate and predictors of CV events in patients with Fabry disease are not well known. Recent data suggest that women and, occasionally, pediatric patients experience CV manifestations and events (6,11). A better understanding of the CV complications of Fabry disease is essential for identifying patients for risk stratification and potential therapy. Therefore, we evaluated major CV events and the risk factors associated with these events in an international cohort of patients in the Fabry Registry.

Methods

The Fabry Registry is an ongoing, observational database that compiles clinical and laboratory data on an international cohort of patients with Fabry disease. All patients with Fabry disease are eligible to enroll, regardless of whether they are receiving enzyme replacement therapy (ERT) from any commercial source. Patients provide informed consent through local institutional review boards/ethics committees and may decline to participate or withdraw consent at any time. Independent boards of advisors recommend clinical and outcome variables that should be collected. Treating physicians determine the actual frequency of assessments according to the individualized needs of the patients. Given the voluntary nature of reporting data, some assessments of patients are not consistently reported to the Fabry Registry. In addition, patient ages at clinical assessments and time intervals between assessments are variable.

Data analyses and statistics. Only data from untreated Fabry Registry patients or data obtained before any ERT was initiated (among patients who received treatment) were included in these analyses. The period of data extended from date of birth until last available follow-up record before initiation of therapy for each patient. Cross-sectional data were analyzed with SAS statistical software version 9.1 (SAS Institute, Inc., Cary, North Carolina) and summarized with descriptive statistics.

Definition of CV, renal, and cerebrovascular events. CV events were defined as MI, HF, or cardiac-related death. Renal events were defined as renal dialysis or renal transplantation. Cerebrovascular events were defined as stroke. Clinical events were reported to the Fabry Registry by treating physicians, on the basis of their medical judgment, and were not independently adjudicated.

Analysis of risk factors. Clinical and medical history data in the Fabry Registry were analyzed to determine how many patients had reported various potential cardiac risk factors, including left posterior wall thickness, interval between each P- and R-wave (PR interval), hypertension, a history of smoking, hypercholesterolemia, estimated glomerular filtration rate, urinary protein to creatinine ratio, and diabetes. The Modification of Diet in Renal Disease equation was used to estimate glomerular filtration rate (12).

Risk factors for experiencing a CV event were analyzed through univariate and multivariate logistic regression models. For the multivariate model, the stepwise selection method was used to determine the covariates that best fit the model (13). Results of these analyses are expressed as odds ratios (ORs) and corresponding 95% confidence intervals (CIs). The Wald chi-square test was used to evaluate statistical significance with an alpha-level of $p < 0.05$. Age at CV events and age at diagnosis were compared between patient groups with the Student *t* test.

Results

As of October 3, 2008, the Fabry Registry had enrolled 2,869 patients. Among these, 137 patients (4.8%) had experienced a major CV event during the natural history period, including 83 of 1,424 men (5.8%) and 54 of 1,445 women (3.7%). As shown in Table 1, the mean age at first CV event was 45.2 years in men and 53.6 years in women ($p < 0.0001$). Among both sexes, Fabry Registry patients who had CV events were diagnosed at an older age than patients who did not: mean 40.9 years versus 26.4 years in men ($p < 0.0001$), and mean 48.3 years versus 32.8 years in women ($p < 0.0001$). As shown in Figure 1, most men (72%) experienced their first CV event between the ages of 35 and <55 years, whereas most women (72%) experienced their first CV event between the ages of 45 and <65 years. Five of 83 men (6.0%) and 1 of 54 women (1.9%) experienced a CV event before age 25.

Heart failure was the most common type of CV event among this cohort; 50 of 83 men (60%) and 33 of 54 women (61%) experienced HF. Thirty-eight of 83 men experienced MI (46%), and 22 of 54 women experienced MI (41%). Six patients had CV events before the age of 25 years: 3 men with HF, 2 men with MI, and 1 woman with HF.

The incidence rates of first CV events in the overall Fabry Registry natural history population are shown in Table 2. Fabry men exhibited a higher incidence of CV events than Fabry women within each age category, with the greatest difference occurring between the ages of 45 and <55 years.

Table 1 Demographic and Clinical Characteristics of Fabry Registry Patients

Characteristics	Men With CV Events (n = 83)	Men Without CV Events (n = 1,341)	Women With CV Events (n = 54)	Women Without CV Events (n = 1,391)	All Patients (n = 2,869)
Age at first CV event (yrs)					
Mean (SD)	45.2 (11.15)*	—	53.6 (10.75)	—	48.5 (11.71)
Median (range)	46.9 (19.3-76.8)	—	54.7 (21.3-78.2)	—	48.8 (19.3-78.2)
Age at Fabry diagnosis (yrs)					
n	83	1,320	51	1,334	2,788
Mean (SD)	40.9 (15.92)*†	26.4 (15.67)	48.3 (16.81)‡	32.8 (17.70)	30.3 (17.26)
Median (range)	40.3 (7.3-81.0)	24.4 (0.0-79.8)	48.3 (13.9-78.2)	32.3 (0.0-80.6)	29.2 (0.0-81.0)
Hypertension, n (%)	47/82, 57.3%	320/1156, 27.7%	25/53, 47.2%	267/1205, 22.2%	659/2,496, 26.4%
Hypercholesterolemia, n (%)	6/14, 42.9%	129/637, 20.3%	7/17, 41.2%	361/879, 41.1%	503/1,547, 32.5%
History of smoking, n (%)	34/76, 44.7%	274/1057, 25.9%	17/44, 38.6%	222/1090, 20.4%	547/2,267, 24.1%
Estimated GFR, ml/min/1.73 m ² , mean ± SD (n)	66 ± 36.4 (36)	90 ± 47.5 (870)	72 ± 18.3 (30)	93 ± 31.2 (1005)	91 ± 39.54 (1,941)
Urinary protein to urinary creatinine ratio, g/g, mean ± SD (n)	3.4 ± 3.86 (15)	1.1 ± 1.93 (458)	2.6 ± 4.19 (9)	1.0 ± 1.96 (584)	1.1 ± 2.03 (1,066)
Left ventricular posterior wall thickness, mm, mean ± SD (n)	15.4 ± 3.58 (30)	11.6 ± 3.51 (559)	13.9 ± 3.15 (27)	10.0 ± 2.80 (777)	10.9 ± 3.32 (1,393)

Patients with cardiovascular (CV) events are patients for whom recorded CV events occurred during the natural history time period (i.e., before the start of enzyme replacement therapy). Percentages were calculated on the basis of the number of patients who had data available within each category. The date of diagnosis was not available for all patients. Normal values were defined as: left ventricular posterior wall thickness ≤12 mm; estimated glomerular filtration rate (GFR) ≥90 mg/ml/min/1.73 m²; urinary protein/urinary creatinine ratio ≤1 g/g. Hypertension was defined as having either a measured systolic BP ≥130 mm Hg or a measured diastolic BP ≥80 mm Hg or having reported a medical history of hypertension on the case report form. Hypercholesterolemia was defined as having either a measured total cholesterol level >200 mg/dl or low-density lipoprotein level >130 mg/dl or having reported a medical history of hypercholesterolemia on the case report form. Laboratory parameter values included the last natural history value obtained before first CV event of the patient or the last value available during the natural history period for patients who did not experience CV events. *p < 0.001 for men who had CV events versus women who had CV events, by Student t test. †p < 0.001 for men who had CV event versus men who did not have CV events, by Student t test. ‡p < 0.001 for women who had CV event versus women who did not have CV events, by Student t test.

Among both sexes, the incidence rates of CV events progressively increased with age, reaching a maximum in patients over the age of 65 years. Because there are relatively few Fabry Registry patients over the age of 65 years, the 95% CIs associated with these incidence rates are wide (Table 2).

Various cardiac and renal characteristics of the subset of Fabry Registry patients who experienced CV events are shown in Figure 2. The majority of these patients exhibited LVH (defined as left ventricular posterior wall thickness ≥12 mm) and hypertension (defined as systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥80 mm

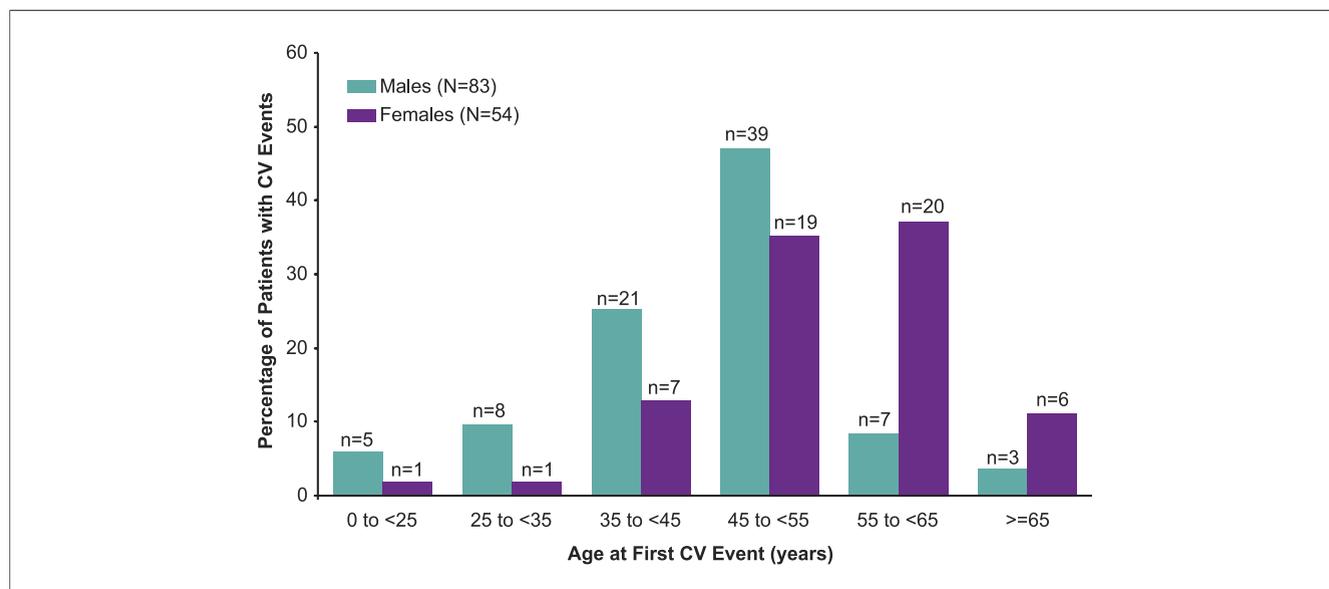


Figure 1 Age at First CV Event in Fabry Registry Patients

Percentages of patients experiencing their first cardiovascular (CV) event (heart failure, myocardial infarction, or cardiac-related death) during 6 age categories are shown. **Numbers above the bars** indicate the number of patients in each category. All data are from patients who had not been treated with enzyme replacement therapy at the time of their first CV event.

Table 2 Incidence Rates of CV Events in Fabry Registry Patients

	Age Categories (yrs)						All Ages
	0 to <25	25 to <35	35 to <45	45 to <55	55 to <65	≥65	
Men							
Patients ever in age category (n)	1,424	1,003	708	356	109	21	1,424
Patients with CV events, n (%)	5 (0.35)	8 (0.80)	21 (2.97)	39 (10.96)	7 (6.42)	3 (14.29)	83 (5.83)
Person-yrs of follow-up time	31,862	8,654	5,307	2,199	495	115	48,631
Incidence rate*	0.16	0.92	3.96	17.74	14.14	26.18	1.71
95% CI for incidence rate	0.1-0.4	0.4-1.8	2.4-6.0	12.6-24.2	5.7-29.1	5.4-76.5	1.4-2.1
Women							
Patients ever in age category (n)	1,445	1,119	892	590	312	90	1,445
Patients with CV events, n (%)	1 (0.07)	1 (0.09)	7 (0.78)	19 (3.22)	20 (6.41)	6 (6.67)	54 (3.74)
Person-yrs of follow-up time	33,306	10,088	7,433	4,420	1,806	522	57,575
Incidence rate*	0.03	0.10	0.94	4.30	11.08	11.49	0.94
95% CI for incidence rate	0.0-0.2	0.0-0.6	0.4-1.9	2.6-6.7	6.8-17.1	4.2-25.0	0.7-1.2

For Fabry Registry patients who experienced a cardiovascular (CV) event, person-years of follow-up were defined as the number of years from birth to the date of the first recorded CV event. For Fabry Registry patients who did not experience CV events, person-years of follow-up were defined as the last available follow-up date during the natural history period. Patients over the age of 25 years are included in multiple age categories, on the basis of their age at the last follow-up visit. *Incidence rate data are expressed as number of first CV events/1,000 person-years of follow-up time. CI = confidence interval.

Hg) at the time of their first CV event. At the time of their first CV event, 93% of men and 78% of women had LVH; 56% of men and 58% of women had hypertension at that time. Approximately one-third of the patients with LVH exhibited LVH in the absence of hypertension (25% of men and 10% of women, among the 40 patients who had both types of data available). A substantial proportion of patients had serious renal dysfunction at the time of their first CV event, including stage 3 or worse chronic kidney disease and proteinuria. A higher percentage of men exhibited renal abnormalities, compared with women, among patients for whom renal data were available (Fig. 2).

The majority of patients had ejection fraction and PR intervals within the normal range at the time of their first CV event, among those for whom data were available. Thirteen of 15 men (87%) and 12 of 19 women (63%) had PR intervals within the normal range at the time of their first CV event (defined as PR interval 120 to 200 ms). Twenty-one of 28 men (75%) and 22 of 25 women (88%) had ejection fractions within the normal range at the time of their first CV event (defined as estimated ejection fraction ≥55%).

The lower portion of Table 1 shows the distribution of various potential risk factors among Fabry Registry pa-

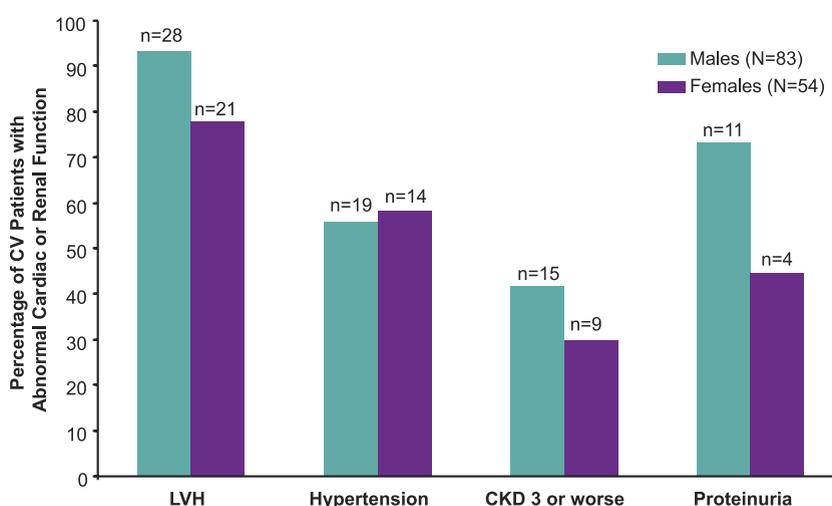


Figure 2 Cardiac and Renal Abnormalities Among Fabry Registry Patients Who Experienced CV Events

Percentages were calculated on the basis of the number of patients who had cardiac or renal data available within ± 12 months of the date of their first cardiovascular (CV) event. Clinical assessments designated as “abnormal” included: LVH = left ventricular posterior wall thickness ≥12 mm; hypertension = systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥80 mm Hg; chronic kidney disease (CKD) Stage 3 or worse = estimated glomerular filtration rate <60 ml/min/1.73 m²; proteinuria = urinary protein/urinary creatinine ratio ≥1 g/g. Numbers above the bars show the number of patients with abnormal cardiac or renal values in each group.

tients who experienced CV events and in those who did not. As in the general population, patients with Fabry disease who had CV events were more likely to have risk factors like hypertension, increased left ventricular posterior wall thickness, a history of smoking, and renal dysfunction, compared with Fabry patients who did not have CV events.

In Table 3, results of logistic regression analyses of these factors are shown as ORs expressing the association of each risk factor with the occurrence of CV events. Univariate analyses suggested that LVH, hypertension, older age at diagnosis, hypercholesterolemia (in men), a history of smoking, and renal dysfunction were associated with the occurrence of CV events (Table 3). A stepwise selection of covariates from the univariate analyses identified LVH and hypertension as the factors most strongly associated with the occurrence of CV events in each sex. Compared with patients who did not report hypertension, men with hypertension had a nearly 8-fold increase in the risk of experiencing a CV event (OR: 7.8, 95% CI: 2.1 to 28.6, $p = 0.0019$), and women with hypertension had a 4.5-fold risk of experiencing a CV event (OR: 4.5, 95% CI: 1.6 to 12.3, $p = 0.0037$). Left ventricular hypertrophy also significantly increased the odds of experiencing a CV event in the multivariate model. Compared with patients who did not have LVH, men with LVH were nearly 5 times more likely to experience a CV event (OR: 4.8, 95% CI: 1.0 to 22.2, $p = 0.0463$), and women with LVH were more than 8 times more likely to experience a CV event (OR: 8.2, 95% CI: 2.6 to 26.0, $p = 0.0003$). Other parameters that seemed to be associated with CV events in univariate analyses did not

emerge as significant risk factors in the stepwise selection of covariates for the multivariate model, in either sex.

The occurrence of other significant clinical events among this cohort was also analyzed. Twenty-five of 83 men (30%) and 3 of 54 women (5.6%) who had CV events also experienced a renal event (defined as renal transplant or chronic dialysis). Nine of 83 men who had CV events (11%) and 7 of 54 women who had CV events (13%) also experienced a stroke. The majority of patients who had CV events experienced a CV event as their first and/or only major clinical event during the natural history period (89% of men and 94% of women). Two of the 137 patients who experienced CV events were reported to have died: 1 man who had previously experienced HF, and 1 woman who had previously experienced MI.

In addition to major CV events (HF, MI, death), arrhythmias were reported by 281 of 2,869 patients (10%) during the natural history period (169 men and 112 women), although most of these patients did not have an arrhythmia type specified in their case report forms. Among those for whom this information was available, 74% reported atrial arrhythmias.

Discussion

We evaluated data obtained during the natural history period (i.e., before any ERT or from patients who never received therapy) in 2,869 Fabry Registry patients. One hundred thirty-seven patients (83 men and 54 women) experienced major CV events (i.e., MI, HF, or cardiac-related death) before any exposure to ERT. Although it is

Table 3 Univariate and Multivariate Analyses of Parameters Related to the Occurrence of CV Events

	Univariate Analyses		Multivariate Analyses	
	n (Events/No Events)	OR (95% CI)	n (Events/No Events)	OR (95% CI)
Men				
Hypertension (sBP ≥ 130 mm Hg or dBP ≥ 80 mm Hg or reported history)	1,239 (83/1,156)	6.82 (4.14-11.21)*	447 (19/428)	7.81 (2.14-26.56)†
LVH (left ventricular posterior wall thickness ≥ 12 mm)	590 (31/559)	12.05 (3.62-40.1)*	447 (19/428)	4.77 (1.03-22.22)†
Older age at Fabry diagnosis (≥ 40 yrs)	1,403 (83/1,320)	3.92 (2.50-6.15)*	—	—
Hypercholesterolemia (total cholesterol ≥ 20 mg/dl or LDL cholesterol ≥ 130 mg/dl)	651 (14/637)	2.95 (1.01-8.66)†	—	—
Smoking (reported history)	1,133 (76/1,057)	2.31 (1.44-3.71)†	—	—
Low eGFR (<60 ml/min/1.73 m ²)	909 (39/870)	2.33 (1.22-4.45)†	—	—
Women				
Hypertension (sBP ≥ 130 mm Hg or dBP ≥ 80 mm Hg or reported history)	1,258 (53/1,205)	4.95 (2.81-8.69)*	677 (22/650)	4.47 (1.63-12.27)†
LVH (left ventricular posterior wall thickness ≥ 12 mm)	805 (28/777)	11.17 (4.47-27.96)*	677 (22/650)	8.23 (2.61-26.01)†
Older age at Fabry diagnosis (≥ 40 yrs)	1,385 (51/1,334)	4.22 (2.28-7.78)*	—	—
Hypercholesterolemia (total cholesterol ≥ 20 mg/dl or LDL cholesterol ≥ 130 mg/dl)	896 (17/879)	1.00 (0.38-2.66)‡	—	—
Smoking (reported history)	1,134 (44/1,090)	2.46 (1.32-4.60)†	—	—
Low eGFR (<60 ml/min/1.73 m ²)	1,038 (33/1,005)	3.85 (1.78-8.32)*	—	—

n (events/no events) represents the total number of patients for whom each type of data were available, with the numbers in parentheses representing the number of these patients who had a CV event, followed by the number of these patients who did not have a CV event. * $p < 0.0001$; † $p < 0.05$; ‡not statistically significant by the Wald test.

CI = confidence interval; dBP = diastolic blood pressure; eGFR = glomerular filtration rate; LDL = low-density lipoprotein; LVH = left ventricular hypertrophy; OR = odds ratio; sBP = systolic blood pressure.

well-known that Fabry patients have a high risk of CV events, this is the first study to systematically analyze the rates and risk factors associated with such events in a large cohort of patients with Fabry disease. Not unexpectedly, the incidence rate of CV events was higher among men than women, because men generally experience higher penetrance and more severe manifestations of X-linked disorders (14). During the natural history period, 3.5% of men and 2.7% of women experienced HF, whereas 2.7% of men and 1.5% of women experienced MI. A recent retrospective chart review of 447 patients with Fabry disease reported very similar percentages of these events in untreated Fabry Registry patients (4).

This cohort of patients first experienced CV events at a mean age of 45 years in men and 54 years in women. Multivariate analyses indicated that the 2 risk factors most strongly associated with CV events in both sexes were hypertension and LVH. In fact, 86% of patients had LVH and 57% of patients had hypertension at the time of their first CV event, among those for whom such data were available. Left ventricular hypertrophy, myocardial fibrosis, and diminished regional left ventricular function have been identified as key markers of advanced Fabry cardiomyopathy (15). Although patients who had CV events were diagnosed at an older age than patients who did not have events, age at diagnosis was not a significant predictor of CV events in a stepwise selection of covariates. Key risk factors, including hypertension and LVH, would be expected to worsen with age in both Fabry and non-Fabry patients. The findings suggest that these parameters, particularly hypertension, should be closely monitored in Fabry patients and treated appropriately (16); untreated hypertension is known to lead to various types of more serious CV disease, including LVH (17).

The Fabry Registry also collects data on renal events (i.e., kidney transplants or chronic dialysis) and cerebrovascular events (i.e., strokes). The majority of patients in this cohort experienced a CV event as their first and/or only major clinical event during the natural history period (89% of men and 94% of women). However, a substantial proportion of patients exhibited chronic kidney disease stage 3 or worse and/or proteinuria at the time of their first CV event. Because renal disease itself can cause or exacerbate heart disease (18), renal dysfunction might also play an indirect role in the development of hypertension and Fabry cardiomyopathy.

Studies on patients with Fabry cardiomyopathy have demonstrated a significant increase in left ventricular mass and posterior lateral wall hyperenhancement on cardiac magnetic resonance imaging that correlates with fibrosis (19–21). As with other cardiomyopathies, this increase in left ventricular mass and myocardial fibrosis might be the substrate for cardiac events (22–24).

Enzyme replacement therapy has been shown to reduce left ventricular mass and improve myocardial function in some patients with Fabry disease (25–28); however, it seems

to be more effective in patients who are in the early stages of Fabry cardiomyopathy without evidence of myocardial fibrosis (29). Similarly, in terms of renal function, ERT has been shown to be most beneficial when initiated before the onset of advanced renal disease (30–32). Given the natural history of CV events in the patient population evaluated, future studies should focus on the effect of ERT on CV events. Fabry patients might benefit from general therapies used to control cardiac and renal disease, in addition to ERT, such as the use of angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers to control urinary protein excretion (33).

Study limitations. Observational data reported to registries are subject to various limitations. For example, a schedule of recommended clinical assessments is provided, but treating physicians determine the actual frequency of assessments according to individual patient needs. Similarly, the Fabry Registry case report form provides a standardized definition of clinical events; however, individual physicians are responsible for reporting their patient data. It is also important to note that not all patients who had CV events during the natural history period had complete sets of clinical data reported, which limited the number of patients who could be included in the logistic regression models of associations between CV events and specific risk factors. The numbers of patients who had CV events in the univariate analyses ranged from 14 to 83 for men and from 17 to 53 for women. The multivariate analyses included data from 19 men and 22 women who had CV events and who also had both echocardiographic and blood pressure data available. These numbers are relatively small compared with the total number of patients in this cohort who had CV events (83 men and 53 women). Therefore, these patients might not be representative of the overall population of Fabry patients who experience CV events. In addition, these are cross-sectional analyses of patients at different ages and with a wide range of disease severity, and the temporal relationship between clinical or medical history characteristics (risk factors) and CV events was not established.

Conclusions

Patients with Fabry disease, particularly those with hypertension and/or LVH, have a high risk of experiencing HF and MI at a relatively young age. Many patients also experience various types of arrhythmias. The cardiac manifestations of Fabry disease are consistent with other forms of CV disease, which makes it difficult to identify the disease solely on the basis of cardiac assessments. The medical community in general, especially cardiologists, should be aware of Fabry disease as a possible cause of cardiac dysfunction. Earlier diagnosis of these patients, before the onset of end organ failure, will allow for prompt initiation of appropriate treatment.

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Key Words: cardiomyopathy ■ Fabry disease ■ hypertension ■ left ventricular hypertrophy ■ lysosomal storage diseases.