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MINI FOCUS ISSUE: TRANSLATIONAL RESEARCH

Sarcomere Gene Mutations Are Associated With Increased Cardiovascular Events in Left Ventricular Hypertrophy

Results From Multicenter Registration in Japan

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Objectives This study investigated the occurrence of cardiovascular events in patients with hypertensive heart disease (HHD) or hypertrophic cardiomyopathy (HCM) with or without sarcomere gene mutations.

Background Although HHD and HCM are associated with left ventricular hypertrophy (LVH), few data exist regarding the difference in prognosis between them.

Methods We enrolled 256 patients with LVH (>13 mm) screened for sarcomere gene mutations. We divided them into 3 groups: the first had HHD without sarcomere gene mutations (group H), the second had sarcomere gene mutations (group G), and the third had neither sarcomere gene mutations nor HHD (group NG). We compared the occurrence of sudden cardiac death, ventricular tachycardia/fibrillation, admission for heart failure, and atrial fibrillation for 1 year.

Results Group G (n = 78, 36 men; mean age, 53.4 years) experienced more total cardiovascular events than group H (n = 45, 32 men; mean age, 67.4 years) (p = 0.042) after adjustments for age and sex, although there was no significant difference in total cardiovascular events between groups H and NG (n = 98, 66 men; mean age, 62.0 years). With Kaplan-Meier analysis, group G exhibited a significantly higher incidence of admission for heart failure (p = 0.017) and atrial fibrillation (p = 0.045) than group H in those 50 years of age and older. Additionally, there was a significant difference in total cardiovascular events between groups G and NG (p = 0.021).

Conclusions These results demonstrate that HCM with sarcomere gene mutations can be associated with increased cardiovascular events compared with HHD or HCM without sarcomere gene mutations. (J Am Coll Cardiol HF 2013;1:459–66) © 2013 by the American College of Cardiology Foundation

Left ventricular hypertrophy (LVH) is an independent predictor of the occurrence of cardiovascular events, even if left ventricular function is not impaired (1–3). The major causes of LVH include hypertrophic cardiomyopathy (HCM) and hypertensive heart disease (HHD) (4).

HCM is a primary myocardial disease, mainly caused by sarcomere gene mutations (5–9), that causes sudden cardiac death in the young or heart failure in the middle aged (3,10,11). Under these conditions, it is interesting to examine the differences in the prognosis of LVH between HCM and HHD. Therefore, in this multicenter, prospective trial, we investigated the difference in the occurrence of cardiovascular events between LVH patients with HCM with or without sarcomere gene mutations and with hypertension.

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Abbreviations and Acronyms

AF = atrial fibrillation
BNP = plasma B-type natriuretic peptide
BP = blood pressure
ECG = electrocardiographic
HCM = hypertrophic cardiomyopathy
HHD = hypertensive heart disease
ICD = implantable cardioverter-defibrillator
LVH = left ventricular hypertrophy
MR = mitral regurgitation
VF = ventricular fibrillation
VT = ventricular tachycardia

Methods

Study population. The Ethics Committee for Medical Research at our institutions approved the study protocol, and all patients provided written informed consent before participation. The study population comprised patients with suspected LVH by routine clinical examinations at 7 clinical institutions between September 2008 and March 2010. The follow-up survey was performed at the time of registration and after 1 year.

Clinical examinations. We performed echocardiography in all patients when the presence of LVH was suspected by routine clinical examinations. When LVH was confirmed by echocardiography, the patient was enrolled in this study. Plasma B-type natriuretic peptide (BNP) levels were also measured. The clinical diagnosis of HCM was based on the guidelines of the American College of Cardiology Foundation/European Society of Cardiology (12). The diagnosis of HHD was based on a history of long-term hypertension (systolic blood pressure [BP] ≥140 mm Hg and/or diastolic BP ≥90 mm Hg) and the absence of other cardiac or systemic diseases.

All of the patients continued appropriate medical treatment, such as beta-blockers, renin-angiotensin-aldosterone system inhibitors, calcium antagonists, and antiarrhythmic drugs. In addition, devices, such as a pacemaker and an implantable cardioverter-defibrillator, were also implanted if needed.

Echocardiographic examinations. Standard techniques were used for M-mode, 2-dimensional, and Doppler measurements. The severity and distribution of LVH were assessed by dividing the left ventricle into 5 regions: anterior, posterior, septal, and lateral segments in the parasternal short-axis view and the apical segment in the apical view. Wall thickness in the parasternal short-axis view was determined at the level of the mitral valve and the papillary muscles in each of the 4 segments. Maximal left ventricular wall thickness was defined as the greatest thickness within the chamber. The definition of LVH was based on a maximal left ventricular wall thickness >13 mm. Left ventricular outflow obstruction at rest was identified by a peak instantaneous left ventricular outflow tract pressure gradient ≥30 mm Hg. Other echocardiographic parameters were determined with methods recommended by the American Society of Echocardiography (13).

Genetic screening tests. Mutational analyses were performed using polymerase chain reaction and direct DNA sequencing for mutations in all translated exons of the 9 most common sarcomeric HCM genes: MYBPC3-encoded myosin binding protein C (*MYBPC3*), MYH7-encoded myosin heavy chain (*MYH7*), MYL2- and MYL3-encoded regulatory and essential myosin light chains (*MYL2* and *MYL3*, respectively), TNNI3-encoded troponin I (*TNNI3*), TNNT2-encoded cardiac troponin T (*TNNT2*), TPM1-encoded-tropomyosin (*TPM1*), TTN-encoded titin (*TTN*), and ACTC-encoded cardiac actin (*ACTC1*).

Evaluation of cardiovascular events. We investigated cardiovascular events such as sudden cardiac death,

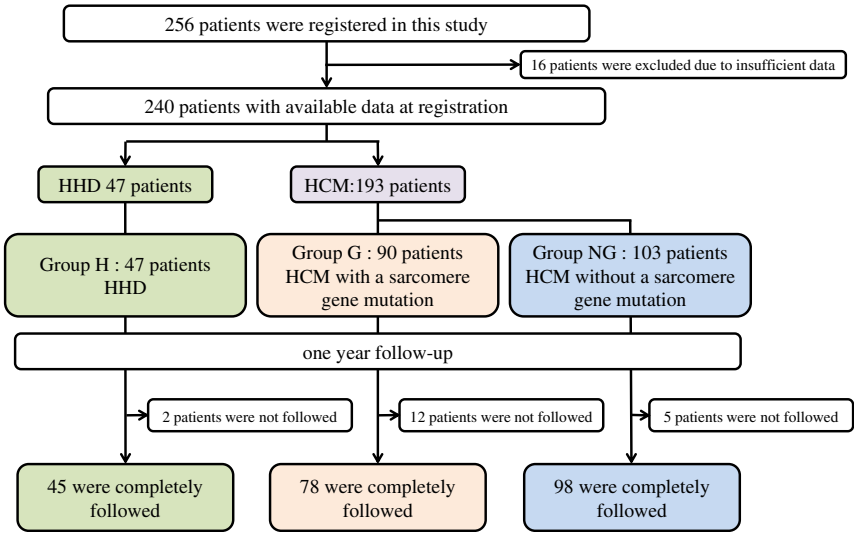

Figure 1 Study Enrollment and Flow of Patients

HCM = hypertrophic cardiomyopathy; HHD = hypertensive heart disease.

Table 1 Clinical Characteristics, Echocardiographic Data, Disease-Causing Gene, and Medication at Registration of All Patients

Variable	All Patients (N = 221)	Group H (n = 45)	All HCM (n = 176)	Group G (n = 78)	Group NG (n = 98)
Clinical characteristics					
Age, yrs	60.1 ± 17.0	67.4 ± 13.4	58.2 ± 17.4*	53.4 ± 20.0†	62.0 ± 13.9‡§
Male	134 (60.6)	32 (71.1)	102 (58.0)	36 (46.2)†	66 (67.3)§
Blood pressure, mm Hg					
Systolic	122.7 ± 18.6	135.4 ± 18.7	119.4 ± 17.1*	114.8 ± 16.9†	123.0 ± 16.5‡§
Diastolic	71.2 ± 11.6	76.1 ± 13.5	70.0 ± 10.8*	68.6 ± 11.6†	71.0 ± 10.0
Mean	88.0 ± 13.6	94.8 ± 13.6	86.4 ± 11.2*	84.0 ± 11.9†	88.3 ± 10.3‡§
Hypertension	61 (27.6)	45 (100.0)	16 (9.0)*	6 (7.7)†	10 (10.2)‡
Chronic AF	34 (15.4)	4 (8.9)	30 (17.0)	8 (10.3)	22 (22.4)§
ICD	25 (11.3)	1 (2.2)	19 (10.8)	9 (11.5)	10 (10.2)
BNP, pg/ml	274.0 ± 356.5	161.9 ± 233.5	285.4 ± 340.8*	288.0 ± 428.3†	283.4 ± 259.6‡
Echocardiography					
LAD, mm	44.2 ± 7.7	45.1 ± 6.1	44.0 ± 8.0	43.0 ± 8.6	44.8 ± 7.5
IVST, mm	16.0 ± 5.0	15.1 ± 3.9	16.2 ± 5.3	16.2 ± 5.7	16.3 ± 4.9
PLVWT, mm	10.8 ± 1.9	11.3 ± 1.6	10.6 ± 1.9*	10.1 ± 1.7†	11.1 ± 2.0§
MLVWT, mm	17.6 ± 4.7	16.0 ± 3.8	18.0 ± 4.9*	17.2 ± 5.5	18.6 ± 4.3‡
LVEDD, mm	46.7 ± 6.4	48.2 ± 5.3	46.3 ± 6.6*	46.2 ± 7.0†	46.4 ± 6.4
LVESD, mm	29.3 ± 7.4	30.1 ± 5.0	29.0 ± 7.9	29.9 ± 8.6	28.3 ± 7.1‡
LVEF, %	65.7 ± 12.3	65.6 ± 9.8	65.7 ± 12.9	64.3 ± 13.9	66.8 ± 12.0
LVOTPG >30 mm Hg	18 (8.1)	0 (0)	18 (10.2)*	5 (6.4)	13 (13.3)‡
Presence of MR	169 (76.5)	25 (55.6)	144 (81.8)*	58 (74.4)†	86 (87.8)‡§
Disease-causing gene					
MYBPC3				34 (43.6)	
TNNI3				23 (29.5)	
MYH7				15 (19.2)	
TNNT2				6 (7.7)	
Medication at registration					
Beta-blocker	101 (45.7)	20 (44.4)	81 (46.0)	31 (39.7)	50 (51.0)
Calcium antagonist	68 (30.8)	25 (55.6)	43 (24.4)*	20 (25.6)†	23 (23.5)‡
RAAS inhibitor	91 (41.2)	27 (60.0)	64 (36.4)*	32 (41.0)	32 (32.7)‡
Diuretic	48 (21.7)	12 (26.7)	36 (20.5)	19 (24.4)	17 (17.3)
Alpha-blocker	2 (0.9)	2 (4.4)	0 (0)*	0 (0)	0 (0)
Vitamin K antagonist	50 (22.6)	10 (22.2)	40 (22.7)	11 (14.1)	29 (29.6)§
Amiodarone	17 (7.7)	0 (0)	17 (9.7)*	9 (11.5)†	8 (8.2)

Values are mean ± SD or n (%). *$p < 0.05$, HHD vs. all HCM. †$p < 0.05$, group H vs. group G. ‡$p < 0.05$, group H vs. group NG. §$p < 0.05$, group G vs. group NG.

AF = atrial fibrillation; BNP = plasma B-type natriuretic peptide; ICD = implantable cardioverter-defibrillator; IVST = interventricular septum thickness; LAD = left atrial dimension; LVEDD = left ventricular end-diastolic dimension; LVESD = left ventricular end-systolic dimension; LVEF = left ventricular ejection fraction; LVOTPG = left ventricular outflow tract pressure gradient; MR = mitral regurgitation; MLVWT = maximal left ventricular wall thickness; PLVWT = posterior left ventricular wall thickness; RAAS = renin-angiotensin-aldosterone system. Group G = hypertrophic cardiomyopathy with sarcomere gene mutations; Group H = hypertensive heart disease; Group NG = hypertrophic cardiomyopathy without sarcomere gene mutations.

ventricular tachycardia (VT)/ventricular fibrillation (VF), admission for heart failure, and atrial fibrillation (AF) in all of the patients through a direct interview and with electrocardiography performed in the outpatient clinic or a telephone interview.

Documentation of AF was based on electrocardiographic (ECG) recordings obtained during provisional or routine medical examinations. Documentation of VT or VF was based on the occurrence of sudden cardiac death, records of VT/VF from an automated external defibrillator, or the use of an implantable cardioverter-defibrillator on Holter or continuous ECG monitoring. Nonsustained VT was defined as a minimum of 3 consecutive ventricular beats with a rate of >120 beats/min. The definition of admission caused by heart failure was that hospitalization was needed because of subjective or objective symptoms of heart failure.

Statistical analysis. Data are presented as the mean ± SD for continuous variables. Variables between the 2 groups were compared using the Mann-Whitney *U* test. Categorical frequencies were compared using the Fisher exact test, where appropriate. Survival estimates were calculated using Cox proportional hazards regression analysis or the Kaplan-Meier method, and their relationship was determined using the log-rank test for trend. A p value <0.05 was considered statistically significant. Data were analyzed using SPSS Statistics version 19.0 (SPSS Inc., Chicago, Illinois).

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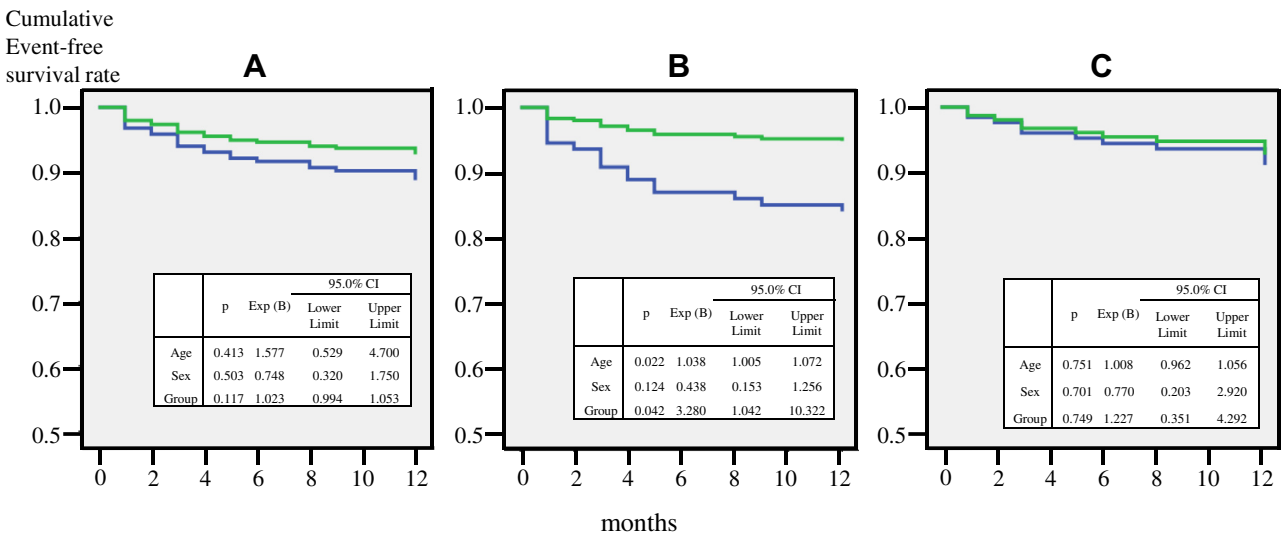

Figure 2 **Event-Free Survival in Total Cardiovascular Events With Cox Proportional Hazards Regression Analysis Adjusted for Age and Sex**

(A) All hypertrophic cardiomyopathy **(blue line)** and group H **(green line)**. **(B)** Groups G **(blue line)** and H **(green line)**. **(C)** Groups NG **(blue line)** and H **(green line)**. Group G = hypertrophic cardiomyopathy with sarcomere gene mutations; Group H = hypertensive heart disease; Group NG = hypertrophic cardiomyopathy without sarcomere gene mutations. CI = confidence interval.

Results

Over a period of 3 years, a total of 256 patients with LVH were enrolled. Sixteen patients were excluded because their data were insufficient at registration. Of the remaining 240 patients, 47 patients received a diagnosis of HHD and 193 patients HCM. Moreover, of the 193 patients with a diagnosis of HCM, 90 with a sarcomere gene mutation were registered in group G and 103 without a sarcomere gene mutation were registered in group NG (Fig. 1). Unfortunately, 2 patients in group H, 12 in group G, and 5 in group NG were excluded from the analysis because they changed their clinic after registration, interrupted their treatment, decided not to attend the follow-up of their own volition, or withdrew their consent. Therefore, no further information was obtained for these lost patients. Finally, a follow-up survey was completed in 45 patients in group H (32 men; mean age, 67.4 years), 78 in group G (36 men; mean age, 53.4 years), and 98 in group NG (66 men; mean age, 62.0 years) (Fig. 1).

First, we examined the difference in the prognosis of patients in group H and those with HCM (groups G and NG). The baseline characteristics of the 45 group H and 176 HCM patients are shown in Table 1. There were significant differences in age, BP, BNP levels, posterior wall thickness, maximal wall thickness, left ventricular end-diastolic dimension, left ventricular outflow tract pressure gradient, and presence of mitral regurgitation (MR) between both groups. It is important to note that, under these conditions, the imbalances of several potential confounders listed in Table 1 could mask differences between the groups as well as cause spurious associations. Even after adjusting for age and sex, there was no significant difference in total cardiovascular events between both groups with Cox proportional hazards regression analysis (hazard ratio: 1.023; 95% confidence interval: 0.994 to 1.053; p = 0.117) (Fig. 2A).

Next, we compared groups G and NG with group H. The baseline characteristics of groups G and NG are shown in Table 1. There were significant differences in age, sex, BP, BNP levels, posterior left ventricular wall thickness, left ventricular end-diastolic dimension, and the presence of MR between groups G and H, and significant differences in age, BP, BNP levels, maximal left ventricular wall thickness, left ventricular end-systolic dimension, left ventricular outflow tract pressure gradient, and presence of MR between groups NG and H. Six patients in group G and 10 in group NG also had high BP; however, these patients had no cardiovascular events, suggesting that this may have no impact on the present results. An ICD had been implanted in 1 patient in group H, 9 in group G, and 10 in group NG. Holter monitoring had been performed on 4 patients in group H, 23 in group G, and 30 in group NG. Under these conditions, for the identification of VT/VF, 6 patients were confirmed by Holter monitoring and 1 by checking their ICD, whereas 4 patients received shocks from an automated external defibrillator or ICD.

In group G, we identified 34 *MYBPC3* mutations, 23 *TNNI3* mutations, 15 *MYH7* mutations, and 6 *TNNT2* mutations (Table 1). The sarcomere gene mutation sites are

Table 2 Clinical Characteristics, Echocardiographic Data, Disease-Causing Gene, and Medication at Registration in Patients 50 Years of Age and Older in Groups G and H

Variable	All Patients (N = 86)	Group G (n = 45)	Group H (n = 41)
Clinical characteristics			
Age, yrs	69.0 ± 9.8	67.8 ± 10.5	70.5 ± 8.8
Male	53 (61.6)	24 (53.3)	29 (70.7)
Blood pressure, mm Hg			
Systolic	127.6 ± 19.4	120.3 ± 16.8	135.5 ± 19.0*
Diastolic	72.3 ± 12.2	70.0 ± 12.0	74.8 ± 12.2
Mean	90.7 ± 13.0	86.7 ± 11.9	95.0 ± 12.9*
Hypertension	46 (53.5)	5 (11.1)	41 (100.0)*
Chronic AF	11 (12.8)	7 (15.6)	4 (9.8)
ICD	6 (7.0)	5 (11.1)	1 (2.4)
BNP, pg/ml	213.8 ± 247.9	258.6 ± 251.5	171.3 ± 240.0*
Echocardiography			
LAD, mm	46.3 ± 6.5	47.6 ± 6.4	45.0 ± 6.3*
IVST, mm	15.5 ± 4.6	15.8 ± 5.2	15.1 ± 3.9
PLVWT, mm	10.9 ± 1.5	10.5 ± 1.4	11.2 ± 1.6*
MLVWT, mm	16.6 ± 4.3	17.1 ± 4.8	16.1 ± 3.8
LVEDD, mm	48.6 ± 6.3	49.2 ± 7.2	47.9 ± 5.2
LVESD, mm	31.8 ± 7.4	33.3 ± 9.0	30.2 ± 4.6
LVEF, %	62.3 ± 12.9	59.8 ± 15.1	65.1 ± 9.2
LVOTPG >30 mm Hg	3 (3.5)	3 (6.7)	0 (0)
Presence of MR	61 (70.9)	38 (84.4)	23 (56.1)*
Disease-causing gene			
MYBPC3		21 (46.7)	
TNNI3		11 (24.4)	
MYH7		9 (20.0)	
TNNT2		4 (8.9)	
Medication at registration			
Beta-blocker	37 (43.0)	19 (42.2)	18 (43.9)
Calcium antagonist	35 (40.7)	13 (28.9)	22 (53.7)*
RAAS inhibitor	52 (60.5)	28 (62.2)	24 (58.5)
Diuretic	28 (32.6)	17 (37.8)	11 (26.8)
Alpha-blocker	2 (2.3)	0 (0)	2 (4.9)
Vitamin K antagonist	19 (22.1)	9 (20.0)	10 (24.4)
Amiodarone	6 (7.0)	6 (13.3)	0 (0)*

*Values are mean ± SD or n (%). $p < 0.05$, group H vs. group G.
Abbreviations as in Table 1.

shown in Online Table 1. Most of these mutations have been identified and described elsewhere (7,9,14–19). Some novel mutations were presumed to be pathogenic by the standard criteria of the absence of the mutation in large numbers of normal controls, alteration of evolutionarily conserved residues, and/or predicted impact on protein structure. With respect to medication at registration, beta-blockers and renin-angiotensin-aldosterone system inhibitors were mainly used in these groups. Calcium antagonists were used more frequently in group H than in groups G and NG. Amiodarone was used in only 9 patients in group G and 8 in group NG.

Interestingly, Cox proportional hazards regression analysis, which was performed after adjusting for age and sex, demonstrated a significant difference in total cardiovascular events between groups H and G (hazard ratio: 3.28; 95% confidence interval: 1.042 to 10.322; p = 0.042) (Fig. 2B), although there was no significant difference in total cardiovascular events between groups H and NG (hazard ratio: 1.227; 95% confidence interval: 0.351 to 4.292; p = 0.749) (Fig. 2C).

With respect to groups H and G, when both groups were stratified in 10-year age groups and evaluated for the occurrence of cardiovascular events, few events were observed in patients younger than 50 years of age in both groups. Accordingly, both groups were re-evaluated for the occurrence of each cardiac event in a subgroup 50 years of age and older. There were 45 patients in group G and 41 in group H in this age group (Table 2). There were significant differences in BP, BNP levels, left atrial dimensions, posterior left ventricular wall thickness, and presence of MR between both groups in this age range. The sarcomere gene mutations sites of these patients in group G are shown in Online Table 2. Under these conditions, group G had significantly more admissions for heart failure (p = 0.017) and more AF (p = 0.045) than group H, although there was

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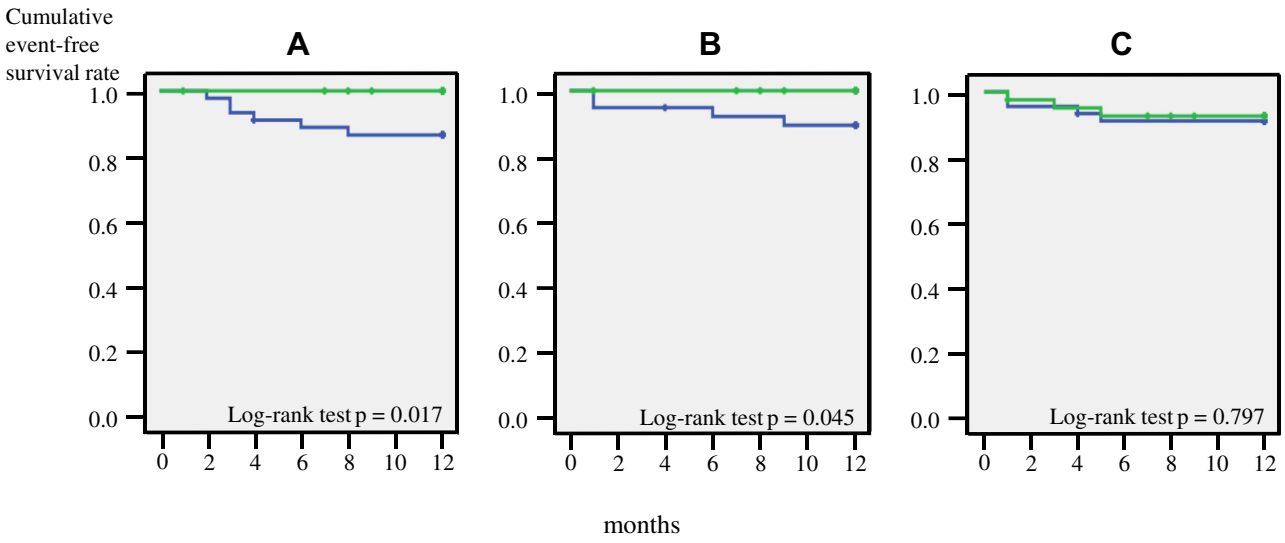

Figure 3 **Kaplan-Meier Analyses for Each Cardiovascular Event in Groups G and H in Patients 50 Years of Age and Older**

Group G = **blue line**; Group H = **green line**. **(A)** Rate of admission for heart failure. **(B)** Rate of atrial fibrillation. **(C)** Rate of ventricular tachycardia/ventricular fibrillation. Abbreviations as in Figure 2.

no significant difference in VT/VF (p = 0.797) between both groups (Fig. 3).

It is interesting to examine the relationship between disease-causing mutations and cardiovascular events. There were mutations in *TNNI3* in 2 patients, in *MYBPC3* in 2, in *TNNT2* in 1, and in *MYH7* in 1 of those admitted for heart failure, and there were mutations in *TNNI3* in 1 patient, in *MYBPC3* in 1, in *TNNT2* in 1, and in *MYH7* in 1 of those with AF. There was no significant relationship between the kind of disease-causing gene and the occurrence of cardiovascular events in this cohort. Additionally, when we divided group G according to the presence or absence of an *MYBPC3* mutation because of the high prevalence of *MYBPC3* in the present study, there was no significant difference in cardiovascular events between the subgroups.

It is intriguing to compare the occurrence of cardiovascular events between groups G and NG. Cox proportional hazards regression analysis, adjusting for age and sex, demonstrated a significant difference in total cardiovascular events between groups G and NG (hazard ratio: 3.031; 95% confidence interval: 1.183 to 7.764; p = 0.021) (Online Fig. 1). Also, there was a significant difference in AF (p = 0.036) between groups G and NG, although there was no significant difference in admission for heart failure (p = 0.172) and VT/VF (p = 0.288) between groups G and NG.

Discussion

The present study demonstrates that there are significantly more total cardiovascular events in 1 year in group G than in groups H and NG after adjusting for age and sex, although there was no significant difference in cardiovascular events between group H and group G with NG or between groups H and NG. This suggests that sarcomere gene mutations are associated with increased cardiovascular events in LVH, although HCM without sarcomere gene mutations did not increase the risk compared with HHD after 1 year. These results are consistent with previous reports in which HCM with a sarcomere gene mutation had an increased frequency of cardiovascular events over time (9,20–22).

In the subgroup 50 years of age and older, there was a higher occurrence of admission for heart failure and AF in group G than in group H. There was no admission for heart failure in group H, although BP was significantly higher in this group, even with the use of antihypertensive drugs. This suggests that if the target BP is achieved with antihypertensive treatment, the development of heart failure can be inhibited, thereby improving the survival rate of patients with HHD (1,23–25). Conversely, HCM with sarcomere gene mutation is a progressive disease; indeed, Ho et al. (26) demonstrated the early occurrence of myocardial fibrosis in HCM patients with sarcomere gene mutations. The initial medical therapy for HCM is negative inotropic agents, such as beta-blockers, verapamil, and disopyramide (12,27–29), as was also observed in the present study. However, these agents have not been shown to suppress or induce the regression of cardiac hypertrophy or myocardial fibrosis. Moreover, BNP levels were significantly higher in group G than in group H, although the left ventricular ejection fraction was not significantly

different between both groups. This suggests that left ventricular diastolic function was more highly impaired in group G than in group H. In groups G and NG, there were no significant differences in BNP levels and left ventricular ejection fraction. This may explain why there was no significant difference in admission for heart failure between groups G and NG in the present study.

It is important to note the impact of amiodarone on the occurrence of arrhythmias. With regard to AF, only 1 of 6 patients 50 years of age and older in group G taking amiodarone had AF. Therefore, amiodarone had little effect. The higher prevalence of MR and larger atrial dimensions in patients 50 years of age and older in group G than in group H might contribute to the higher occurrence of AF in group G, as described in a previous report (30).

Study limitations. First, the ratio of sarcomere gene mutations in this study was somewhat different from that generally reported, despite the multicenter nature of the present study (5,31). This mutation bias might affect the frequency of cardiovascular events. However, this bias could have little impact on the present results because there was no significant difference in the occurrence of cardiovascular events among the different sarcomere gene mutation carriers in the present cohort. Second, some cases of nonsustained VT could have been missed because Holter or continuous ECG monitoring was not performed in all patients. However, this disadvantage could be minimized by careful interview regarding the occurrence of arrhythmias. Third, there is no standard protocol for the use of therapeutic medicines, and each doctor's judgment was entrusted. However, they administered the therapeutic medications according to major guidelines (12,32,33). Actually, there was no major difference in the medications used among the participating facilities. Finally, LVH progresses slowly, and a long-term follow-up study is required. However, there was a significant difference in cardiovascular events even after a 1 year follow-up, suggesting the clinical significance of gene mutations in LVH patients.

Conclusions

The present study demonstrates that HCM with sarcomere gene mutations can be associated with increased cardiovascular events compared with HHD and HCM without sarcomere gene mutations. We suggest that the elucidation of the cause of LVH, particularly the identification of sarcomere gene mutations, is important for the determination of the prognosis in LVH patients.

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Key Words: heart failure ■ left ventricular hypertrophy ■ prognosis ■ sarcomere gene mutations.

APPENDIX

For supplemental tables and figure, please see the online version of this article.