Prognostic Value of Late Gadolinium Enhancement on Cardiac Magnetic Resonance Imaging in Japanese Hypertrophic Cardiomyopathy Patients

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Background: The prognostic value of late gadolinium enhancement (LGE) on contrast-enhanced cardiovascular magnetic resonance (CMR) in Japanese hypertrophic cardiomyopathy (HCM) patients in a large, single-center cohort was investigated.

Methods and Results: A total of 345 HCM patients (mean age, 59±17 years; 214 male) underwent CMR with gadolinium enhancement, and were followed (mean duration, 21.8 months) for cardiovascular events. Patients were divided into event-positive and event-negative groups. The clinical and CMR characteristics were compared between the 2 groups, and predictors of cardiovascular events assessed on multivariate analysis. LGE was positive in 252 patients (73%). The annual cardiovascular events rate was significantly higher in patients with LGE than in those without (6.2%/year vs. 0.6%/year, $P=0.003$). On multivariate analysis, LGE (hazard ratio [HR], 7.436; 95% confidence interval [CI]: 1.001–55.228, $P=0.050$), increased myocardial mass index (HR, 1.013; 95% CI: 1.002–1.023, $P=0.018$), reduced left ventricular ejection fraction (HR, 0.965; 95% CI: 0.945–0.985, $P=0.001$), and atrial fibrillation (HR, 2.257; 95% CI: 1.024–4.976, $P=0.043$) were significantly associated with cardiovascular events.

Conclusions: The presence of LGE, increased myocardial mass index, reduced left ventricular ejection fraction and atrial fibrillation were independent predictors of adverse prognosis in Japanese HCM patients. (*Circ J* 2014; **78**: 929–937)

Key Words: Cardiac magnetic resonance; Hypertrophic cardiomyopathy; Independent predictor; Late gadolinium enhancement

Cardiovascular events such as sudden death, admission for heart failure, heart failure death, and stroke are known complications of hypertrophic cardiomyopathy (HCM).¹ Implantable cardioverter defibrillator (ICD) therapy has been reported to be effective, especially in preventing sudden death.^{2,3} Although multiple conventional risk factors associated with sudden death are not adequate for risk assessment of sudden death,⁴ they continue to be applied to clinical care.⁵

follow-up period, definition of LGE, and endpoints. Hence, no conclusion has been reached so far. Furthermore, although there are several reports from Europe and the USA, no large-scale study has been reported from Japan. A definitive conclusion awaits further prospective long-term studies in multiple countries including Japan.

We conducted a retrospective study in a large number of HCM patients on the usefulness of LGE in predicting cardiovascular events.

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Recently, several studies of large cohorts have indicated that late gadolinium enhancement (LGE) observed on contrast-enhanced cardiac magnetic resonance (CMR) imaging is a prognostic factor of sudden death and cardiovascular events,^{6–10} suggesting the potential clinical usefulness of this method. These studies, however, varied widely in the number of cases studied,

Methods

Patient Selection

We conducted a retrospective study on 345 HCM patients who underwent gadolinium contrast-enhanced CMR between 7 January 2006 and 31 December 2010. First, we explained to all the patients that their clinical data were to be used in a retrospec-

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Table 1. Subject Characteristics vs. Presence of CV Events

	All (n=345)	Events (+) (n=29)	Events (-) (n=316)	P-value
Age (years)	59±17	59±16	58±19	0.542
Male gender	214 (62.0)	20 (69.0)	194 (61.4)	0.421
Family history of HCM	39 (11.3)	3 (10.3)	36 (11.4)	1.000
Family history of SCD	37 (10.7)	4 (13.8)	33 (10.4)	0.533
History of syncope	44 (12.8)	4 (13.8)	40 (12.7)	0.775
DM	46 (13.3)	4 (13.8)	42 (13.3)	1.000
AF	65 (18.8)	16 (55.2)	49 (15.5)	0.000
NYHA III or IV	42 (12.2)	10 (34.5)	32 (10.1)	0.001
Medications				
β-blocker	236 (68.4)	23 (79.3)	213 (67.4)	0.187
Calcium antagonist	97 (28.1)	7 (24.1)	90 (28.5)	0.619

Data given as mean±SD or n (%).

AF, atrial fibrillation; CV, cardiovascular; DM, diabetes mellitus; HCM, hypertrophic cardiomyopathy; NYHA, New York Heart Association; SCD, sudden cardiac death

tive study, and then obtained patient consent in writing. This study was approved by the Ethics Committee of Sakakibara Heart Institute. HCM was defined as left ventricular (LV) wall thickness ≥ 15 mm on echocardiography and/or CMR, in the absence of other cardiac or systemic diseases that could account for the hypertrophy. Patients who were already diagnosed with HCM before undergoing CMR were recruited into this study even though their LV wall thickness was <15 mm. To investigate the prognosis of HCM, patients with old myocardial infarction, those who had concurrent congenital heart disease, those with severe valvular disease (including those who had undergone surgery for valvular diseases), and those who had undergone percutaneous transluminal septal myocardial ablation (PTSDA) or septal myectomy before CMR were excluded. Furthermore, we also excluded patients with renal dysfunction (estimated glomerular filtration rate <30 ml·min⁻¹·1.73 m⁻²).

CMR Protocols and Image Analysis

CMR was performed with a 1.5-T MR scanner (Magnetom Sonata; Siemens Medical Solutions, Erlangen, Germany) using a 6-channel phased-array body and spine coil. All images were acquired using the electrocardiography (ECG)-gated breath-hold technique. First, steady-state free-precession cine images were acquired in 3 long-axis (2-, 3-, and 4-chamber) and 5 short-axis views covering the LV from base to apex (TR=56.8 ms, TE=1.2 ms). Subsequently, LGE images were acquired 10 min after i.v. gadodiamide hydrate 0.1 mmol/kg (Omniscan; Daiichi Sankyo, Tokyo, Japan), using the inversion recovery technique in the identical views (TR=600 ms, TE=1.26 ms; TI was individually optimized to null normal myocardial signal using a TI-scout sequence).

Experienced radiology technicians performed LV function analysis with dedicated software (Argus Function VA30; Siemens Medical Solutions). Epicardial and endocardial borders of the LV myocardium were manually traced during the whole cardiac phase on each cine short-axis image to obtain LV end-diastolic volume (EDV), end-systolic volume (ESV), ejection fraction (EF), and myocardial mass. The EDV index (EDVI) was calculated as EDV divided by the body surface area, and ESV index (ESVI), the ESV divided by the body surface area. Myocardial mass was calculated by multiplying the volume of the myocardium measured at end-diastole with the specific gravity of the myocardium (1.05 g/ml). The LV mass index was calculated as myocardial mass divided by the body surface area of each patient.

Two cardiologists and 1 radiologist evaluated LGE images for the presence of LGE within the LV myocardium for each patient by consensus. The myocardial LGE areas were visually determined as those with higher signal intensity compared to the reference myocardium. The presence of any higher signal intensity area was defined as LGE positive. This spatial extension was assessed referring to the LV 17-segment model.¹¹ LGE was converted to scores on a scale of 0 to 17, as the sum of the segments in the 17-segment model showing LGE. The maximum LV wall thickness was determined by measuring the minimal thickness of the thickest LV myocardium in the cine image at end-diastole.

Clinical and CMR Status and Outcome

The clinical records of all 345 patients were reviewed, and the clinical findings and medications at the time of CMR were extracted. Non-sustained ventricular tachycardia (NSVT) was not included in analysis because only 165 of 345 patients (48%) underwent Holter ECG within 3 months of CMR. The same applied to low blood pressure during exercise, because the exercise test was performed in very few study patients. The CMR parameters analyzed were maximum LV wall thickness measured from cine-magnetic resonance imaging, as well as EDVI, ESVI, EF, and myocardial mass index calculated from LV functional analysis. In addition, the presence or absence of LGE was observed on gadolinium contrast-enhanced CMR.

In all 345 patients, the occurrence of cardiovascular events as of September 2011 was determined retrospectively from clinical records. Cardiovascular events were defined as cardiac death, sudden death, aborted sudden death, sustained ventricular tachycardia, appropriate ICD discharge, and unscheduled hospitalization for heart failure, stroke, or acute myocardial infarction. Cardiovascular events were subdivided into arrhythmic events defined as cardiac death due to incessant ventricular tachycardia/ventricular fibrillation (VT/VF), sudden death, aborted sudden death, sustained VT, appropriate ICD discharge; and cardiac failure events defined as cardiac death due to progression of heart failure and unscheduled hospitalization for heart failure. The length of follow-up was until the most recent follow-up or death. For patients who underwent de novo PTSDA, surgical septal myectomy, or valve replacement during the follow-up period, the time at which these alternative endpoints occurred was regarded as the end of follow-up. During a mean follow-up of 21.8±19.2 months, PTSDA was performed in 71 patients (21%), mitral valve replacement in 1 patient, and surgical sep-

Table 2. CMR Characteristics vs. Presence of CV Events

	Events (+) (n=29)	Events (-) (n=316)	P-value
LVEDVI (ml/m ²)	74.1±21.6	62.0±15.6	0.006
LVESVI (ml/m ²)	40.7±26.0	20.9±10.9	0.000
EF (%)	48.1±20.1	67.1±10.1	0.000
LV myocardial mass index (g/m ²)	93.8±41.2	71.4±27.9	0.008
Maximum LVWT (mm)	21.1±5.8	20.6±5.0	0.605
Maximum LVWT >30 mm	3 (10.3)	24 (7.6)	0.486
Presence of LGE	28 (96.6)	224 (70.9)	0.003
LGE score	6.0±4.1	3.1±3.0	0.001

Data given as mean±SD or n (%).

CMR, cardiac magnetic resonance; EF, ejection fraction; LGE, late gadolinium enhancement; LV, left ventricular; LVEDVI, left ventricular end-diastolic volume index; LVESVI, left ventricular end-systolic volume index; LVWT, left ventricular wall thickness. Other abbreviation as in Table 1.

Figure 1. Gadolinium contrast-enhanced cardiac magnetic resonance images showing (A) absence of late gadolinium enhancement (LGE) and (B) hyperintense signals due to LGE in the myocardium of the left ventricular wall. Upper, short-axis images; lower, long-axis images.

tal myectomy in 1 patient.

Statistical Analysis

Data are given as mean±SD for continuous variables and as frequency with percentage for categorical data. Differences between means were tested using unpaired Student's t-test. Frequencies were compared using chi-squared test or Fisher's exact test, as appropriate. Univariate analysis was performed using the clinical and CMR variables considered possibly related to cardiovascular events. Comparison of clinical and CMR characteristics in patients with or without LGE was done using logistic regression analysis. Furthermore, multivariate Cox regression analysis with stepwise variable selection was used to identify the predictors of cardiovascular events. $P \leq 0.05$ was considered to be statistically significant. Analysis was performed using SPSS version 20.0.

Results

Clinical and CMR Characteristics

Table 1 lists the clinical characteristics of 345 patients divided into cardiovascular event-positive and -negative groups. Compared to the event-negative group, the event-positive group had a significantly higher rate of atrial fibrillation (AF; 16/29, 55.2% vs. 49/316, 15.5%, $P=0.000$) and of New York Heart Association (NYHA) functional class III or IV (10/29, 34.5% vs. 32/316, 10.1%, $P=0.001$). The 2 groups did not differ significantly with respect to family history of sudden death or history of syncope, which are conventionally considered to be risk factors of sudden death.

Table 2 lists the CMR characteristics of 345 patients divided into cardiovascular event-positive and -negative groups. Compared to the event-negative group, the event-positive group had significantly larger EDVI (74.1±21.6 vs. 62.0±15.6 ml/m²,

Table 3. Subject Characteristics vs. Presence of LGE

	LGE (–) n =93	LGE (+) n=252	P-value	OR (95% CI)
Age (years)	65	57	0.000	0.964 (0.947–0.982)
Male gender	45.2 (42/93)	68.3 (172/252)	0.000	2.611 (1.604–4.249)
Family history of HCM	9.7 (9/93)	11.9 (30/252)	0.563	1.261 (0.575–2.768)
Family history of SCD	6.5 (6/93)	12.3 (31/252)	0.126	2.034 (0.820–5.046)
History of syncope	12.9 (12/93)	12.7 (32/252)	0.960	0.982 (0.482–1.998)
DM	12.9 (12/93)	13.5 (34/252)	0.886	1.053 (0.520–2.132)
AF	8.6 (8/93)	22.6 (57/252)	0.005	3.106 (1.420–6.793)
NYHA III or IV	8.6 (8/93)	13.5 (34/252)	0.222	1.657 (0.737–3.725)
Medications				
β-blocker	72.0 (67/93)	67.1 (169/252)	0.378	0.790 (0.468–1.334)
Calcium antagonist	25.8 (24/93)	29.0 (73/252)	0.562	1.172 (0.684–2.009)
CMR				
LVEDVI (ml/m ²)	58.9	64.6	0.005	1.024 (1.007–1.042)
LVESVI (ml/m ²)	18.6	24.0	0.002	1.049 (1.018–1.081)
LVEF (%)	69.1	64.2	0.001	0.961 (0.938–0.985)
LV myocardial mass index (g/m ²)	59.8	78.3	0.000	1.029 (1.017–1.041)
Maximum LVWT (mm)	17.3	21.9	0.000	1.319 (1.216–1.430)

Data given as mean or as % (n).

CI, confidence interval; LVEF, left ventricular ejection fraction; OR, odds ratio. Other abbreviations as in Tables 1,2.

Table 4. Clinical Characteristics of CV Event-Positive Patients (n=29)

Patient	Events	Age (years)	Sex	Syncope	FH of SCD	FH of HCM	MWT>30mm
1	HF hospitalization	77	Male	–	–	–	–
2	Appropriate ICD discharge	52	Male	–	–	–	–
3	HF hospitalization	49	Female	–	–	–	–
4	Sudden death	65	Male	+	–	–	–
5	HF hospitalization	57	Male	–	–	–	–
6	HF hospitalization and appropriate ICD discharge	66	Male	–	–	–	–
7	Appropriate ICD discharge	59	Male	–	–	–	–
8	HF hospitalization	56	Female	–	–	+	–
9	HF hospitalization	45	Male	–	–	–	–
10	Stroke	48	Male	–	–	–	–
11	HF hospitalization	59	Male	–	–	–	–
12	HF hospitalization and incessant VT/VF	80	Female	–	–	–	–
13	Acute myocardial infarction	81	Female	–	–	–	–
14	HF hospitalization	80	Female	–	–	–	–
15	HF hospitalization	66	Female	+	+	–	–
16	Aborted sudden death	18	Female	–	+	–	–
17	Appropriate ICD discharge	76	Male	+	+	–	–
18	HF hospitalization	71	Male	–	–	–	–
19	Aborted sudden death	20	Male	–	–	+	+
20	Stroke	57	Male	–	–	–	–
21	HF hospitalization	41	Male	–	+	+	–
22	Appropriate ICD discharge	13	Female	+	–	–	–
23	Appropriate ICD discharge	39	Male	–	–	–	+
24	HF hospitalization	74	Female	–	–	–	–
25	Stroke	81	Male	–	–	–	–
26	HF hospitalization	66	Male	–	–	–	–
27	Appropriate ICD discharge	42	Male	–	–	–	+
28	HF hospitalization	68	Male	–	–	–	–
29	Appropriate ICD discharge	62	Male	–	–	–	–

(Table 4 continued the next page.)

$P=0.006$), ESVI (40.7 ± 26.0 vs. 20.9 ± 10.9 ml/m², $P=0.000$), and mass index (93.8 ± 41.2 vs. 71.4 ± 27.9 g/m², $P=0.008$). In contrast, EF was significantly smaller in the event-positive group compared to the event-negative group (48.1 ± 20.1 vs. 67.1 ± 10.1 %, $P=0.000$). On contrast-enhanced CMR, LGE was observed in 252 of 345 patients (73.0%). The prevalence of LGE was higher in the event-positive patients than in the event-negative patients (28/29, 96.6% vs. 224/316, 70.9%, $P=0.003$). LGE score was higher in the event-positive patients than in the event-negative patients (6.0 ± 4.1 vs. 3.1 ± 3.0 , $P=0.001$). **Figure 1** shows examples of the presence and absence of LGE in the LV myocardium.

Table 3 lists the clinical and CMR characteristics of 345 patients divided into LGE-positive and -negative groups. Compared to the LGE-negative group, the LGE-positive group had a significantly higher prevalence of male gender (172/253, 68.3% vs. 42/93, 45.2%, $P=0.000$) and AF (57/252, 22.6% vs. 8/93, 8.6%, $P=0.005$). Compared to the LGE-negative group, the LGE-positive group was significantly younger (57 vs. 65 years old, $P=0.000$), and had significantly larger EDVI (64.6 vs. 58.9 ml/m², $P=0.005$), ESVI (24.0 vs. 18.6 ml/m², $P=0.002$), mass index (78.3 vs. 59.8 g/m², $P=0.000$), and maximum LV wall thickness (21.9 vs. 17.3 mm, $P=0.000$). In contrast, EF was significantly smaller in the LGE-positive group compared to LGE-negative group (64.2 vs. 69.1 %, $P=0.000$).

Follow-up Results

During the follow-up period, cardiovascular events occurred in 28/252 patients with LGE (11%; sudden death in 1, aborted sudden death in 2, appropriate ICD discharge in 7, stroke in 3, acute myocardial infarction in 1, and unscheduled hospitalization for heart failure in 14) and 1/93 patients without LGE (1%; unscheduled hospitalization for heart failure). **Table 4** shows the clinical and CMR imaging characteristics of 29 patients with cardiovascular events. Kaplan-Meier survival curves for cardiovascular events with regard to the presence of LGE are shown in **Figure 2**. Compared to patients without LGE, those with LGE had a higher rate of cardiovascular events (annual events rate, 6.2%/year vs. 0.6%/year, $P=0.003$). Furthermore, outcome was compared with regard to the presence of LGE, focusing on arrhythmic events and heart failure events among cardiovascular events. One patient hospitalized for heart failure subsequently died due to incessant VT/VF. Another patient who was hospitalized had appropriate ICD discharge for VT during hospitalization. These 2 patients were analyzed and counted as having arrhythmic event. **Figure 2** shows Kaplan-Meier survival curves for arrhythmic events and heart failure events with regard to the presence of LGE. Arrhythmic events occurred at a higher rate in patients with LGE than in those without LGE (annual events rate, 2.5%/year vs. 0%/year, $P=0.037$), while the rate of heart failure events was not significantly different between the

Patient	NYHA	AF	Mean LVEDVI (ml/m ²)	Mean LVEF (%)	Mean LVMI (g/m ²)	Mean MWT (mm)	LGE	LGE score
1	4	–	35.0	47.5	140.5	25.0	+	4
2	1	–	61.6	52.5	153.4	21.0	+	5
3	3	+	107.4	25.8	102.5	16.0	+	6
4	3	–	114.4	12.5	168.0	18.0	+	17
5	3	+	83.2	20.8	81.2	9.0	+	4
6	3	+	115.5	28.9	158.8	21.0	+	9
7	2	+	46.7	62.0	87.2	26.0	+	9
8	3	–	59.9	67.6	79.8	24.0	+	3
9	3	+	68.4	39.0	90.8	24.5	+	6
10	1	+	56.3	45.0	55.7	19.9	+	3
11	1	+	78.1	18.0	112.6	14.4	–	0
12	2	+	61.8	54.0	129.0	25.0	+	10
13	1	+	63.8	77.0	88.9	18.9	+	2
14	4	–	101.5	23.0	63.9	21.5	+	7
15	2	+	62.6	55.0	57.7	19.1	+	4
16	2	–	75.9	67.0	66.1	15.2	+	1
17	1	–	55.9	53.2	67.9	21.3	+	4
18	2	+	59.4	32.0	44.3	17.0	+	12
19	2	–	92.8	43.0	177.2	32.0	+	7
20	2	–	63.7	66.0	67.4	20.0	+	2
21	3	+	114.0	21.8	58.7	14.0	+	6
22	1	–	56.9	79.6	44.1	25.0	+	2
23	2	–	82.1	49.3	155.5	32.0	+	11
24	2	+	68.3	64.1	57.0	19.0	+	1
25	1	+	87.0	73.4	81.0	22.0	+	4
26	2	+	76.4	67.7	102.7	23.0	+	10
27	1	–	51.5	66.0	131.8	35.0	+	8
28	3	+	92.4	19.0	47.3	12.0	+	14
29	1	–	55.6	63.0	47.9	22.0	+	4

FH, family history; HF, heart failure; ICD, implantable cardioverter defibrillator; LVMI, left ventricular mass index; MWT, maximum wall thickness; VT/VF, ventricular tachycardia/ventricular fibrillation. Other abbreviations as in Tables 1,2,3.

Figure 2. Kaplan-Meier curves of (A) cumulative cardiovascular, (B) arrhythmic and (C) heart failure event-free survival in late gadolinium enhancement (LGE)-positive and LGE-negative groups. Red, LGE positive; blue, LGE negative. CMR, cardiac magnetic resonance.

2 groups (annual events rate, 3.0%/year vs. 0.6%/year, $P=0.072$).

The patients were further divided into tertiles (no LGE, mild LGE, marked LGE) according to LGE score (first tertile, 0; second tertile, 1–3; third tertile, >4). Optimal cut off score was determined on receiver operating characteristic (ROC) curve.

Figure 3 shows Kaplan-Meier survival curves for cardiovascular events, arrhythmic events and heart failure events with regard to LGE score. The annual cardiovascular event rate in the marked LGE group exceeded that in the mild LGE and no LGE groups (8.4%/year vs. 3.5%/year vs. 0.6%/year, $P=0.001$). The annual arrhythmic event rate in the marked LGE group exceeded that in the mild LGE and no LGE groups (3.7%/year vs. 1.0%/year vs. 0%/year, $P=0.011$). The annual heart failure event rate in the marked LGE group exceeded that in the mild LGE and no LGE groups (4.6%/year vs. 1.0%/year vs. 0.6%/year, $P=0.008$).

Predictors of Cardiovascular Events

When the clinical characteristics were compared between patients with and those without cardiovascular events, presence of AF and NYHA functional class III or IV were significantly different between the 2 groups. Analysis of CMR characteristics showed that EDVI, ESVI, EF, mass index, and the presence of LGE were significantly different between the 2 groups. Pairwise associations (EDVI, ESVI, EF, and mass index) were investigated using Pearson's correlation coefficient test. A significant ($P<0.001$) and strong ($r=0.851$) correlation was observed between EF and ESVI. As a result, ESVI was omitted while EF

was selected for multivariate analysis. Finally, presence of AF; NYHA III or IV; EDVI; EF; mass index; and presence of LGE were included in the models, and multivariate Cox proportional hazards regression analysis was conducted after adjusting for age and sex. The results are listed in **Table 5**. On multivariate analysis, the presence of AF (hazard ratio [HR], 2.257; 95% confidence interval [CI]: 1.024–4.976, $P=0.043$), reduced LVEF (HR, 0.965; 95% CI: 0.945–0.985, $P=0.001$), increased myocardial mass index (HR, 1.013; 95% CI: 1.002–1.023, $P=0.018$), and the presence of LGE (HR, 7.436; 95% CI: 1.001–55.228, $P=0.050$) were identified as independent prognostic factors of cardiovascular events.

Discussion

Although patients with HCM are generally regarded to have good prognosis,¹² the occurrence of sudden death in some patients is an important issue. Moreover, other than sudden death, stroke death and heart failure death are also important causes of death in HCM patients.¹

The conventional risk factors reported for sudden cardiac death in HCM include family history of sudden death, history of syncope, LV wall thickness >30 mm, NSVT, and low blood pressure during exercise.⁴ Prognosis is poorer as the number of risk factors increases, but it is a clinical fact that some patients who do not have these conventional risk factors may also die of sudden death.^{13,14} Maron et al studied HCM patients im-

Figure 3. Kaplan-Meier curves of (A) cumulative cardiovascular, (B) arrhythmic and (C) heart failure event-free survival vs. extent of late gadolinium enhancement (LGE). Blue, no LGE (LGE score, 0); green, mild LGE (LGE score, 1–3); red, marked LGE (LGE score, >4). CMR, cardiac magnetic resonance

Table 5. Independent Prognostic Factors of CV Events

Variable	Univariate Analysis			Multivariate Analysis		
	Unadjusted HR	(95% CI)	P-value	Adjusted HR	(95% CI)	P-value
Presence of AF	4.166	2.002–8.67	0.000	2.257	1.024–4.976	0.043
NYHA III or IV	5.953	2.760–12.838	0.000			
LVEDVI (ml/m ²)	1.027	1.013–1.042	0.000			
LVESVI (ml/m ²)	1.034	1.022–1.046	0.000			
EF (%)	0.949	0.932–0.966	0.000	0.965	0.945–0.985	0.001
LV myocardial mass index (g/m ²)	1.020	1.010–1.030	0.000	1.013	1.002–1.023	0.018
Presence of LGE	11.309	1.532–83.462	0.017	7.436	1.001–55.228	0.050

HR, hazard ratio. Other abbreviations as in Tables 1,2,3.

planted with ICD and observed no difference in the number of ICD discharges even when patients were stratified according to the number of risk factors.¹⁵ The existence of new prognostic factors other than the conventional risk factors is expected.

LGE on CMR has been reported as a unique method of evaluating myocardial damage.^{16,17} Many reports on the presence of LGE on CMR in HCM patients have been published since the first report in 2002.¹⁸ This LGE is presumed to represent mainly fibrosis of the myocardium,^{19,20} and the presence of LGE has been expected to be a prognostic factor of cardiovascular events, especially sudden death. In recent years, the relationship between the presence of LGE and prognosis has been investigated in relatively large-scale studies recruiting hundreds of patients.^{5–10}

Maron et al suggested that there was no significant difference in the rate of combined cardiovascular events consisting of sudden death, appropriate ICD discharge, and progressive heart failure between patients with and those without LGE.⁶ Rubinshtein et al proposed that the presence of LGE may be a risk factor of sudden cardiac death,⁷ but the positive predictive value of LGE was low. Therefore, they commented that the absence of LGE does not mean that the risk is not present. Furthermore, O'Hanlon et al noted that the event rate was significantly higher in patients with fibrosis detected as LGE, and the risk of combined events increased with the increase in extent of fibrosis,⁸ but the extent of fibrosis was not a significant predictor for arrhythmic endpoint on multivariate analysis. Bruder et al reported that the presence of LGE was an independent prog-

nostic factor of cardiac mortality,⁹ but sudden cardiac death was not significantly different on Kaplan-Meier survival curve analysis.

As noted here, although several studies have been reported, the endpoint as well as the evaluation method and definition of LGE differed among studies. Consequently no consensus opinion has been achieved. Currently a prospective long-term follow-up study enrolling a large number of patients using standardized LGE evaluation methods is ongoing.²¹

All the reports so far have been from Europe or the USA. The present study is the first conducted in Japan examining a large number of subjects. Multivariate analysis identified 4 factors as independent predictors of cardiovascular events: lowered LVEF, increased myocardial mass index, presence of AF, and presence of LGE. This suggests that LGE is a prognostic factor of cardiovascular events in Japanese patients with HCM, as was reported in Western patients. A noteworthy finding in the present study is that in the group without LGE, there was only 1 case of unscheduled heart failure admission during follow-up and no other cardiovascular event.

HCM with decreased contractility is called end-stage HCM,²² and the prognosis of this is poor.²³ Therefore, EF is an important prognostic factor for cardiovascular events in HCM, as in other types of cardiac disease. Compared to maximum LV wall thickness, myocardial mass has been reported to have a higher correlation with outcome,²⁴ which would explain the relationship between abnormal increase in myocardial mass and event rate. In addition, HCM patients complicated with AF are known to have poorer outcome than those without AF.^{25,26} Thus, LVEF, myocardial mass index and AF are reasonable as independent risk factors of cardiovascular events. In addition to these 3 factors, the present study also identified the presence of LGE on contrast-enhanced CMR as an independent prognostic factor, but the P-value on multivariate analysis was 0.05; although this is considered significant, it cannot be interpreted as conclusive, as was the case in past studies. Several recent reports in a small number of patients, however, have indicated that the extent of LGE correlates with ventricular dysfunction and ventricular tachyarrhythmia.^{27–31} We classified the present patients not only into 2 groups with regard to presence of LGE, but into 3 groups on LGE score; the prognosis was then seen to change gradually with LGE score. Based on the present results, gadolinium contrast-enhanced CMR can be recommended for evaluating prognosis in HCM if there are no contraindications.

Study Limitations

There were several limitations in this study. First, the study was a retrospective, single-center study conducted in a tertiary hospital, and the subjects did not include patients already implanted with ICD. Second, LGE evaluation was conducted visually, and was semi-quantitative. Third, given that PTSMA is actively performed in HCM patients, the mean follow-up period was short. Fourth, NSVT and low blood pressure during exercise test, which are conventional risk factors for sudden death, were not included in analyses because few patients underwent Holter ECG and/or exercise test at around the same time as CMR. To resolve these limitations, it would be necessary to carry out a prospective follow-up study recruiting a large number of patients with a protocol to perform CMR and Holter ECG at the time of diagnosis, and quantitative, standardized, LGE evaluation.

Conclusions

In 345 Japanese patients with HCM, LVEF, LV myocardial mass index, presence of AF, and presence of LGE were inde-

pendent prognostic factors for cardiovascular events. In the absence of contraindications, CMR is recommended for prognosis evaluation in HCM patients.

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