European Radiology (2019) 29:4593–4602
https://doi.org/10.1007/s00330-018-5951-8

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Clinical significance of evaluating coronary atherosclerosis in adult patients with hypertrophic cardiomyopathy who have chest pain

Yoon Joo Shin[1] · Jae Hwan Lee[2] · Jin Young Yoo[3] · Jeong A. Kim[4] · Yongho Jeon[5] · Yeonyee E. Yoon[6] · Eun Ju Chun[1]

Received: 6 September 2018 / Revised: 3 November 2018 / Accepted: 4 December 2018 / Published online: 22 February 2019

Abstract

Objective Chest pain is a common symptom in patients with hypertrophic cardiomyopathy (HCM), causing difficulty determining whether there is coexistent coronary artery disease (CAD). We investigated whether coronary computed tomography angiography (CCTA) can assess the prevalence and clinical significance of CAD in adult patients with HCM showing chest pain through longitudinal follow-up.

Methods In 238 adult patients with HCM, who underwent CCTA for chest pain, we analyzed the degree of stenosis and adverse plaque characteristics (APCs) as CCTA variables. Three prediction models for adverse cardiovascular events (ACEs: all-cause mortality, myocardial infarction, unstable angina, heart failure, implantable cardioverter-defibrillator implantation, and stroke) were assessed using the combination of clinical risk factors, echocardiographic parameters, and CCTA variables.

Results The prevalence of obstructive CAD (≥ 50% in luminal stenosis) and APC was 14.7% and 18.9%, respectively. During the follow-up period (median, 37 months; range, 2–108 months), there were 31 occurrences of ACEs (13.0%). Using multivariate Cox regression analysis, age, atrial fibrillation, low ejection fraction, obstructive CAD, and APCs were associated with ACEs (all $p < 0.05$). Among the prediction models for ACEs, the area under the curve (AUC) was higher (AUC = 0.92) when CCTA variables were added to the clinical (AUC = 0.84) and echocardiographic factors (AUC = 0.88) ($p < 0.001$).

Conclusions Using CCTA, about 20% of symptomatic HCM patients were associated with clinically significant atherosclerosis. Adding these CCTA variables to the clinical and echocardiographic variables may increase the predictions of ACEs; therefore, evaluating coronary atherosclerosis using CCTA may be helpful for symptomatic HCM patients.

Key Points

- *Chest pain in adult patients with hypertrophic cardiomyopathy (HCM) remains challenging to distinguish from coronary artery disease.*
- *Coronary computed tomography angiography (CCTA) can assess the severity and characteristics of coronary atherosclerosis in symptomatic HCM patients.*
- *Adding CCTA variables to clinical and echocardiographic factors may increase the predictions of adverse cardiac events in HCM patients, and thus evaluating coronary atherosclerosis using CCTA may be helpful for HCM patients with chest pain.*

Keywords Chest pain · Cardiomyopathy, hypertrophic · Coronary artery disease · Computed tomography angiography

Abbreviations

ACEs Adverse cardiovascular events
AF Atrial fibrillation
APCs Adverse plaque characteristics

✉ Eun Ju Chun
drejchun@hanmail.net

[1] Department of Radiology, Seoul National University Bundang Hospital, 82, Gumi-ro 173beon-gil, Bundang-gu, Seongnam, Gyeonggi-do 13620, South Korea

[2] Department of Radiology, National Cancer Center Hospital, Goyang, Gyeonggi-do, South Korea

[3] Department of Radiology, Chungbuk National University Hospital, Cheongju, South Korea

[4] Department of Radiology, Inje University Ilsan Paik Hospital, Goyang, Gyeonggi-do, South Korea

[5] Department of Applied Statistics, College of Commerce and Economics, Yonsei University, Seoul, South Korea

[6] Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam, Gyeonggi-do, South Korea

AUC	Area under the curves
CAD	Coronary artery disease
CCTA	Coronary computed tomography angiography
CI	Confidence interval
ECG	Electrocardiography
EF	Ejection fraction
HCM	Hypertrophic cardiomyopathy
HR	Hazard ratio
HU	Hounsfield units
ICD	Implantable cardioverter-defibrillator
LV	Left ventricle
MI	Myocardial infarction
ROC	Receiver-operator characteristic
UA	Unstable angina

Introduction

Although hypertrophic cardiomyopathy (HCM) has been known to be the most common cause of sudden cardiac death in young people [1, 2], a considerable number of adult patients with HCM remain clinically stable, with an annual mortality rate similar to the general population in the USA [3, 4]. A recent study reported that older patients (older than 60 years) with HCM are at low risk for disease-related morbidity and mortality. They suggested that other cardiac or non-cardiac comorbidities have a greater impact on survival than HCM in older patients [5]. Furthermore, the incidence of atherosclerotic coronary artery disease (CAD) increases with age. Therefore, with increased aged, the prognosis of HCM may be impacted by associated CAD.

In addition, chest pain is the most common symptom in patients with HCM [1]. Frequently, HCM-associated chest pain may be similar to angina in presentation, and the electrocardiography (ECG) can resemble that of myocardial infarction (MI) in the absence of CAD [6–8]. Therefore, it may be difficult to distinguish whether the cause of chest pain is solely from HCM, or with coexistent coronary atherosclerosis. Since the management of CAD is different from that of ventricular tachycardia or heart failure, investigating the presence of coexistent CAD might be needed in patients with HCM.

In this regard, ECG-gated coronary computed tomography angiography (CCTA) is an appealing noninvasive imaging tool for evaluating the myocardial hypertrophy and coronary artery atherosclerosis, concurrently [9, 10]. In addition, CCTA can further reveal not only the degree of vascular luminal stenosis but also the presence of adverse plaque characteristics (APCs) [11].

However, there is a paucity of data regarding the prevalence and clinical significance of coexistent CAD in patients with HCM through CCTA study. Therefore, we aimed to investigate whether CCTA can assess the prevalence and clinical significance of CAD in symptomatic patients with HCM in a longitudinal follow-up study.

Methods

Study population

This study was approved by the institutional review board, and informed consent was waived. Among the patients who were diagnosed with HCM between January 2008 and December 2013 at a single tertiary hospital, adult patients (over 30 years of age) who were referred for CCTA due to symptoms of angina or angina equivalent (shortness of breath, extreme fatigue, diaphoresis, nausea, or pain other than the chest pain) were retrospectively enrolled. The diagnosis of HCM was established by the presence of left ventricular (LV) hypertrophy (LV wall thickness ≥ 15 mm, or ≥ 13 mm in first-degree family members of an HCM patient) on echocardiography associated with a non-dilated LV chamber, in the absence of other cardiac or systemic diseases explaining the observed hypertrophy [12]. When other diseases that may contribute to the development of LV hypertrophy, such as hypertension and microvascular angina, including amyloidosis and Fabry disease, were suspected, we excluded those diseases by cardiac MR, myocardial biopsy, or clinical consensus [13, 14]. Subsequently, we excluded cardiovascular anomaly related to chest pain ($n = 34$) or aortic pathology ($n = 20$). Moreover, previous history of MI ($n = 4$), revascularization ($n = 10$), implantable cardioverter-defibrillator (ICD) implantation ($n = 3$), or stroke ($n = 3$) were also excluded. Therefore, a total of 266 patients were finally longitudinally observed for the occurrence of cardiac events.

Clinical risk factors

Basic demographic data and clinical risk factors were ascertained via interviews and medical records review. Clinical data—including body weight, height, blood pressure, and known risk factors of CAD, such as hypertension, diabetes, dyslipidemia, current smoking, presence of atrial fibrillation (AF), family history of HCM or premature CAD (CAD in male first-degree relative < 55 years; CAD in female first-degree relative < 65 years), and current medication—were assessed. We also calculated the Framingham risk score (FRS) for estimating 10-year risk of CAD [15].

Echocardiographic variables

For echocardiographic variables, the cardiologist calculated ejection fraction, LV mass, LV wall thickness, left atrium (LA) diameter, and volume as guidelines [12]. The presence of left ventricular outflow tract (LVOT) obstruction was

defined as a peak LVOT gradient > 30 mmHg at the resting state. Diastolic dysfunction was assessed with the mitral annulus velocity and classified into four grading categories [16].

CCTA scan protocol and image analysis

The cardiac CT examinations were performed using a 64-slice multi-detector CT scanner (Brilliance 64, Philips Medical Systems) with the following parameters: 64 × 0.625-mm section collimation, 420-ms rotation time, 120-kV tube voltage, and 800-mA tube current. Before CCTA imaging, intravenous esmolol 10–30 mg (Jeil Pharm. Co., Ltd) was injected to patients with a heart rate of over 70 beats/min. All scans were performed with ECG-gated dose modulation. A total bolus amount of 80 ml iomeprol (Iomeron 400; Bracco) was administered intravenously, at a rate of 4.0 ml/s, followed by a 50-ml saline chaser. Using the retrospective ECG gating, images were initially reconstructed at the mid-diastolic phase (75% of R-R interval) for coronary artery assessment, with additional reconstructions of the motion-free phase, when motion artifacts were present.

Two radiologists (EJC and JYY, with 10 and 4 years of experience in cardiac imaging, respectively) blindly assessed the CCTA images without clinical information. After an independent evaluation, the final diagnosis was made through consensus. The degree of luminal stenosis of the coronary arteries was evaluated on a per-segment basis according to a 16-segment model with three grades as follows: normal, non-obstructive CAD (< 50% luminal stenosis), and obstructive CAD (≥ 50% luminal stenosis). The maximal stenosis site was determined by comparing the mean value of the proximal and distal reference sites of the contrast-enhanced portion of the coronary artery. We defined myocardial bridging as when one of the vascular segment tunnels through the myocardium caused the segment to come in contact with the left ventricular myocardium, without intervening fat. For plaque characteristics, we defined the presence of APC as the plaque with at least two features out of the following characteristics [17, 18]: (1) low-density plaque which was defined as plaque density of < 30 Hounsfield units (HU), (2) positive remodeling which was defined as a remodeling index of > 1.1, (3) spotty calcification of < 3 mm in length, or (4) napkin-ring sign. To identify the presence of low-density plaque, at least three rounded regions of interest (0.5 mm2) were placed within the target lesions, and the lowest CT density value (in HU) was recorded as the plaque density [19]. The remodeling index was defined as the ratio of the vessel diameter at the plaque site to the average diameter of the proximal and distal reference segments of the vessel [20]. The napkin-ring sign, which was defined as a ring-like attenuation pattern of the coronary plaque with peripheral high attenuation tissue surrounding a central lower attenuation portion [17].

Cardiovascular events

During the median follow-up period of 37 months (range 2–108 months), clinical data were acquired by reviewing the medical records and data from the Korean National Statistical Office. The causes of mortality recorded with International Classification of Disease categories were reviewed by a single cardiologist (YYE, 8 years of experience).

The endpoints of this study were adverse cardiovascular events (ACEs), as follows: (1) all-cause mortality; (2) nonfatal MI with typical chest pain, elevated cardiac enzymes, and typical electrocardiographic changes; (3) unstable angina (UA) requiring hospital stay; (4) ICD or pacemaker implantation; (5) ongoing heart failure presenting with symptom aggravation based on the NYHA or CCS classes, or a decreased left ventricular ejection fraction (EF) < 50%; and (6) occurrence of a stroke.

Statistical analysis

To compare clinical characteristics and CCTA findings between the two groups (one with and one without ACE), Student's *t* test was used for continuous values and chi-square test was used for categorical values. Kaplan-Meier survival analysis was used to evaluate the cumulative survival based on the stenosis degree and plaque types. Independent predictors of ACE were analyzed by univariate and multivariate Cox proportional hazard regression models with the application of all variables, including clinical and CCTA findings. When multivariate Cox proportional hazard regression models were performed, the variables with at least a marginal univariate predictive value ($p < 0.05$) were applied.

To determine the incremental prognostic value of CCTA variables, including the degree of stenosis and APC, compared with the clinical risk factors and echocardiographic functional parameters, we developed three prediction models assessing the relationships between the potential predictors and endpoints, using a Cox proportional hazard regression. Model A included clinical risk factors, including age, gender, family history of previous CAD, and atrial fibrillation. Model B added the echocardiographic parameters, including ejection fraction and LA diameter to model A. Finally, model C added the CCTA variables, including the presence of obstructive CAD and APC to model B. To compare the predictive value for ACEs of each model, we used a logistic regression model to calculate the receiver-operator characteristic (ROC) curves and the area under the curves (AUC), including 95% confidence interval (CI).

P values of < 0.05 were considered statistically significant. All statistical analyses were performed using a statistical package R (version 2.10.1.).

Results

Study population and outcome results

Among the baseline total of 266 HCM patients with chest pain, 25 patients with missed follow-up were excluded. Three patients who underwent early revascularization within 1 year after the index CCTA were also excluded from the analysis to avoid biases correlated with the CCTA results.

Ultimately, a total of 238 patients were analyzed for our study. Table 1 lists the baseline demographic characteristics of the study population. The mean age was 62.0 ± 11.5 years and the prevalence of male gender was 73.1% ($n = 174$). The prevalence of hypertension, diabetes, current smoking, and hyperlipidemia was 30.7%, 23.1%, 22.7%, and 35.3%, respectively. The mean Framingham risk score was 12.0 ± 2.7 for males and 16.2 ± 5.4 for females. Among the various morphological phenotypes, there were 128 patients (53.8%) with septal-type HCM and 23 patients (9.7%) with left ventricular outflow tract obstruction.

Table 1 Clinical risk factors and echocardiographic characteristics of HCM in study population

	Total ($n = 238$)
Age (years)	62.0 ± 11.5 (range, 36–90)
Male gender	174 (73.1%)
Body mass index (kg/m2)	25.0 ± 3.2 (range, 15.3–39.8)
Clinical risk factors	
Hypertension	73 (30.7%)
Diabetes	55 (23.1%)
Current smoker	54 (22.7%)
Hyperlipidemia	84 (35.3%)
Family history of HCM	32 (13.4%)
Family history of premature CAD	24 (10.1%)
Atrial fibrillation	21 (8.8%)
Framingham risk score	12.0 ± 2.7 for males 16.2 ± 5.4 for females
Medication	
Statin	76 (31.9%)
Aspirin	90 (37.8%)
ACE inhibitor or ARB	73 (30.7%)
β-Blocker	52 (21.8%)
Echocardiographic parameters	
Ejection fraction (%)	64.5 ± 7.7 (30–84)
LV mass (g)	214.2 ± 66.5 (103.3–457.0)
LV wall thickness (mm)	18.4 ± 3.5 (13.5–31.0)
LA diameter	41.7 ± 7.0 (19.8–69.7)
LA volume	83.7 ± 36.7 (21.7–257.8)
Diastolic dysfunction	Grade I—20 (8.4%) Grade II—149 (66.0%) Grade III—35 (14.7%) Unclassified—26 (10.9%)
HCM	
Septal type	128 (53.8%)
Apical type	95 (39.9%)
Non-septal and non-apical type	15 (6.3%)
LVOT obstruction	23 (9.7%)

ACE, angiotensin-converting enzyme; *ARB*, angiotensin II receptor blocker; *CAD*, coronary artery disease; *HCM*, hypertrophic cardiomyopathy; *LA*, left atrium; *LV*, left ventricle; *LVOT*, left ventricular outflow obstruction

During a median follow-up period of 37 months (range 2–108 months), a total of 31 ACEs (13.0%) had occurred, including all-cause deaths ($n = 16$), MI ($n = 1$), UA ($n = 3$), ICD insertion ($n = 4$), ongoing heart failure ($n = 2$), and stroke ($n = 5$). The causes of death were as follows: sudden cardiac or tachycardia-induced cardiac death ($n = 4$), fatal MI ($n = 2$), fatal stroke ($n = 2$), cancer-related organ failure ($n = 3$), and unknown cause ($n = 5$). Therefore, clearly defined coronary-related mortality and morbidity, including 2 fatal MI, 2 non-fatal MI, and 3 UA, were developed in about 25% of events (Table 2).

CCTA imaging analysis

Table 3 summarizes the CCTA findings according to ACEs. In CCTA imaging analysis, the prevalence of subclinical atherosclerosis and obstructive CAD was 60.1% and 14.7%, respectively. With respect to the degree of stenosis, the prevalence of 50–69% stenosis and ≥ 70% stenosis was significantly higher in the event group than in the non-event group ($p < 0.001$). The prevalence of myocardial bridging was 25.2% in HCM patients. There was no significant difference in the prevalence of myocardial bridging between the ACE group and non-ACE group (25.8% vs. 25.1%; $p = 1.000$). Regarding plaque characteristics, APCs were observed in 45 patients (18.9%). All APCs, such as low attenuation, positive remodeling, napkin-

Table 2 Final events of HCM

Adverse cardiovascular events ($n = 31$)
All-cause of death ($n = 16$)
Cardiac death including tachycardia-induced, heart failure ($n = 4$)
Fatal MI ($n = 2$)*
Fatal stroke ($n = 2$)
Cancer-related organ failure ($n = 3$)
Unknown cause ($n = 5$)
Nonfatal MI ($n = 1$)*
Unstable angina with hospitalization ($n = 3$)*
ICD or pacemaker insertion ($n = 4$)
Ongoing heart failure ($n = 2$)
Stroke ($n = 5$)

ICD, implantable cardioverter-defibrillator; *MI*, myocardial infarction
*Clearly defined coronary-related mortality and morbidity

Table 3 CCTA findings according to the presence or absence of the adverse cardiac events

CCTA findings	Total ($n = 238$)	Non-ACE group ($n = 207$)	ACE group ($n = 31$)	p value
CACS	146.1 ± 401.2 (range, 0–3272.4)	100.5 ± 238.3	450.4 ± 878.4	
Stenosis degree				
0	95 (39.9%)	91 (44.0%)	4 (12.9%)	< 0.001*
1–49%	108 (45.4%)	93 (44.9%)	15 (48.4%)	
50–69%	20 (8.4%)	15 (7.2%)	5 (16.1%)	
≥ 70%	15 (6.3%)	8 (3.9%)	7 (22.6%)	
Myocardial bridging	60 (25.2%)	52 (25.1%)	8 (25.8%)	1.000
Plaque types				
Non-APC	87 (36.6%)	77 (37.2%)	10 (32.3%)	0.861
APC	45 (18.9%)	32 (15.5%)	13 (41.9%)	0.002*
Low attenuation	30 (12.6%)	19 (9.2%)	11 (35.5%)	0.001*
Positive remodeling	29 (12.2%)	17 (8.2%)	12 (38.7%)	< 0.001*
Napkin-ring sign	16 (6.7%)	10 (4.8%)	6 (19.4%)	0.012*
Spotty calcification	24 (10.1%)	16 (7.7%)	8 (25.8%)	0.020*

ACE, adverse cardiovascular event; *APC*, adverse plaque characteristic; *CCTA*, coronary computed tomography angiography

*$p < 0.05$

ring signs, and spotty calcifications, were more frequent in the event group than in the non-event group (all $p < 0.05$).

Kaplan-Meier curves showed that the cumulative survival rate decreased significantly with the extent of stenosis in patients with HCM (log-rank test, $p < 0.001$) (Fig. 1). Moreover, patients with APCs showed a gradual decrease in cumulative survival than patients without any APCs and patients with no plaque (log-rank test, $p < 0.001$) (Fig. 2).

Independent predictors for ACEs in patients with HCM

The independent predictors of ACEs in patients with HCM using univariate and multivariate Cox proportional hazard models are summarized in Table 4. In univariate analysis, age (hazard ratio (HR), 1.08; 95% confidence interval (CI), 1.04–1.12), body mass index (HR, 0.87; 95% CI, 0.78–0.97), family history of premature CAD (HR, 2.76; 95% CI, 1.19–6.40), AF (HR, 6.33; 95% CI, 2.97–13.46), and LA diameter (HR, 1.08; 95% CI, 1.04–1.13) were positively correlated with ACE and independent predictors (all $p < 0.05$). EF was reversely correlated with ACEs (HR, 0.93; 95% CI, 0.90–0.96). Among CCTA variables, any plaque (HR, 2.78; 95% CI, 1.20–6.46), obstructive CAD (HR, 5.22; 95% CI, 2.52–10.80), and the presence of APCs (HR, 3.49; 95% CI, 1.72–7.09) were independent predictors of ACEs (all $p < 0.05$).

Using multivariate analysis, age (HR, 1.07; 95% CI, 1.03–1.12), AF (HR, 4.20; 95% CI, 1.53–11.55), EF (HR, 0.94; 95% CI, 0.91–0.98), obstructive CAD (HR, 2.75; 95% CI, 1.07–7.05), and APCs (HR, 2.58; 95% CI, 1.11–6.00) were independent predictors of ACEs after adjusting for other clinical risk factors and echocardiographic variables (all $p < 0.05$).

Various predicting models and incremental prognostic value of CCTA

The prediction models were constructed with covariates of the clinical, echocardiographic, and CCTA variables, as well as their comparisons for ACEs. The ROC curve comparing the predictive power of ACEs between the models is shown in Fig. 3. As compared with the prediction model A (age + gender + clinical risk factors) (AUC 0.84 (95% CI, 0.76-0.91)), model B (added echocardiographic variables to model A) showed significant improvement with respect to the predictive power (AUC, 0.88; 95% CI, 0.81-0.95; $p < 0.001$). Furthermore, model C (adding CCTA variables to model B) led to further improvement of prediction ability (AUC 0.92; 95% CI, 0.88-0.97), compared with model B ($p < 0.001$).

Discussion

Our study investigated 238 HCM patients with chest pain and revealed the following: (1) the prevalence of subclinical atherosclerosis, obstructive CAD, and APC on CCTA was 60.1%, 14.7%, and 18.9%, respectively; (2) 31 patients (13.0%) had ACE during the follow-up period (median, 37 months), with age, AF, low EF, obstructive CAD, and APC being independent predictors; (3) the predictive power increased when CCTA-related variables, including obstructive CAD and APC, were added to the conventional clinical risk factors and echocardiographic variables in various prediction models for ACEs.

Pathophysiologically, when myocardium becomes thick, LV becomes stiff as a result of myocardial cellular changes.

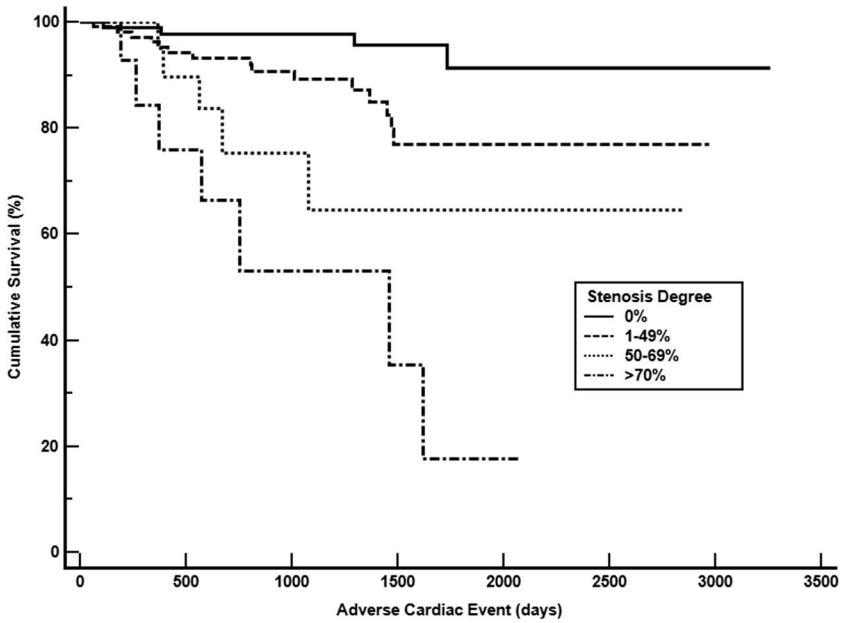

Fig. 1 Kaplan-Meier survival curves according to the stenosis degree. The cumulative survival rate was significantly decreased as the degree of stenosis was greater (log-rank test, $p < 0.001$)

The size of ventricle remains constant, but blood flow may be blocked from entering the ventricle by the thickening and increased pressure inside of the heart, causing chest pain in patients with HCM [21]. Moreover, myocardial bridging, which is more commonly associated with HCM than with non-HCM, may also cause chest pain [22]. Therefore, it is important to determine the cause of chest pain in patients with HCM for appropriate treatment.

Stress test using echocardiography or single-photon emission CT (SPECT) has traditionally been considered as the first-line test for detecting myocardial ischemia; however, a considerable false-positive ratio has been reported in HCM patients [23, 24]. Perfusion defects are caused by various pathologies such as myocardial bridging, small intramural coronary artery dysplasia, and increased oxygen demand due to LV hypertrophy and increased wall tension, even in the absence of significant stenosis of the coronary arteries [25, 26]. Therefore, the above methods have limitation in the diagnosis of coronary artery disease in HCM patients.

Traditionally, invasive coronary angiography (ICA) has been considered as the gold standard for the assessment of CAD or myocardial bridging. According to previous reports

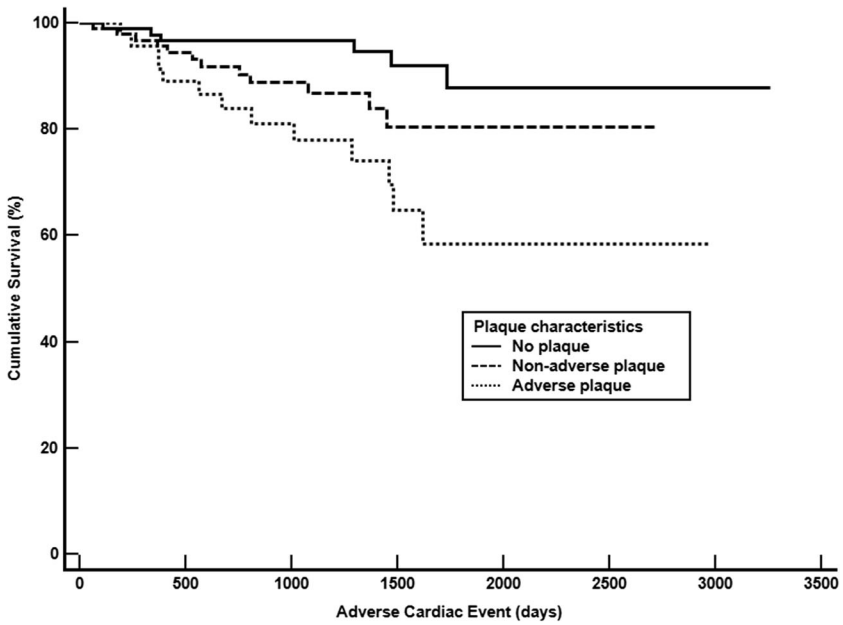

Fig. 2 Kaplan-Meier survival curves according to the plaque features. The patients who had adverse plaque characteristics (APCs) showed gradual decrease in cumulative survival compared to the patients with non-APC and patients with no plaque (log-rank test, $p < 0.001$)

Table 4 Univariate and multivariate Cox proportional hazard models for the total cardiovascular events in patients with HCM

	Univariate analysis			Multivariate analysis		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Age	1.08	1.04, 1.12	< 0.001*	1.07	1.03, 1.12	0.001*
Male gender	0.84	0.40, 1.78	0.650			
Body mass index	0.87	0.78, 0.97	0.010*	0.97	0.83, 1.12	0.650
Hypertension	1.71	0.74, 3.97	0.212	–	–	–
Diabetes	1.74	0.82, 3.70	0.149	–	–	–
Current smoker	0.43	0.13, 1.43	0.169	–	–	–
Hypercholesterolemia	0.89	0.42, 1.88	0.754	–	–	–
Family history of HCM	1.05	0.51, 2.16	0.898			
Family history of premature CAD	2.76	1.19, 6.40	0.018*	2.66	0.91, 7.81	0.074
Atrial fibrillation	6.33	2.97, 13.46	< 0.001*	4.20	1.53, 11.55	0.006*
Septal HCM	0.57	0.28, 1.17	0.127			
LVOT obstruction	0.56	0.13, 2.36	0.432			
EF	0.93	0.90, 0.96	< 0.001*	0.94	0.91, 0.98	0.003*
LV mass	1.00	0.99, 1.01	0.906	–	–	–
Maximal LV wall thickness	1.00	0.91, 1.10	0.988	–	–	–
LA diameter	1.08	1.04, 1.13	0.001*	1.04	0.98, 1.09	0.233
LA volume	1.00	0.99, 1.02	0.181			
Any plaque	2.78	1.20, 6.46	0.017*	0.81	0.27, 2.38	0.697
Myocardial bridging	1.16	0.52, 2.60	0.715			
Obstructive CAD	5.22	2.52, 10.80	< 0.001*	2.75	1.07, 7.05	0.035*
APC	3.49	1.72, 7.09	0.001	2.58	1.11, 6.00	0.027*

APC, adverse plaque characteristic; *CAD*, coronary artery disease; *CI*, confidence interval; *EF*, ejection fraction; *HCM*, hypertrophic cardiomyopathy; *HR*, hazard ratio; *LV*, left ventricle; *LVOT*, left ventricular outflow obstruction

*$p < 0.05$

using ICA, the prevalence of significant CAD (> 50% stenosis) varies from 11 to 26% in patients with HCM [27–29]. The prevalence of myocardial bridging has been reported with variable prevalence rates, ranging from 15 to 41%, which is higher than the incidence associated with the general population (1–3%) [22, 30].

In a recent CCTA study by Shariat et al [31], the prevalence of significant CAD diagnosed on CCTA was 6.6%, which was significantly lower in the HCM population than in the age-matched, gender-matched, and risk factor–matched control group. In our study, the prevalence of obstructive CAD in HCM patients was 14.7%, which is higher than that in the study by Shariat et al This is probably because the population of our study is older and the prevalence of some risk factors, such as diabetes, is higher. Although we did not compare the prevalence of CAD between HCM patients and normal controls, our study also revealed that patients with HCM, who have coexistent obstructive CAD, have more adverse outcomes compared with those without CAD [27, 28]. Several previous studies showed that myocardial bridging is not a significant risk factor in patients with HCM, despite the frequent prevalence of myocardial bridging in HCM patients [32]. This was similar to the results of our study. In our study, 25.2% of patients with HCM had myocardial bridging, and there was no significant difference with respect to the prevalence of myocardial bridging between the ACE group and non-ACE group.

The strength of our study is that we assessed the plaque characteristics in addition to evaluating the luminal stenosis as CCTA variables. Previous studies have evaluated CAD in HCM patients using ICA or CCTA; however, none of them included an assessment of the plaque characteristics in HCM patients. In our study, 18.9% of patients had APCs; furthermore, patients with APCs developed more adverse events than those with no plaque or non-APC. Most plaque ruptures are characterized in autopsy studies by a large lipid-rich core covered by a thin fibrous cap [33, 34]. CCTA has the advantage of detecting not only the degree of stenosis but also plaque characteristics. In fact, a large number of studies have reported that APCs evaluated with CCTA (low attenuation, positive remodeling, napkin-ring sign, or spotty calcification) are highly correlated with vulnerable plaque [17, 18], and that these features on CCTA predict acute coronary syndromes independently, regardless of the presence of significant stenosis [35]. Our

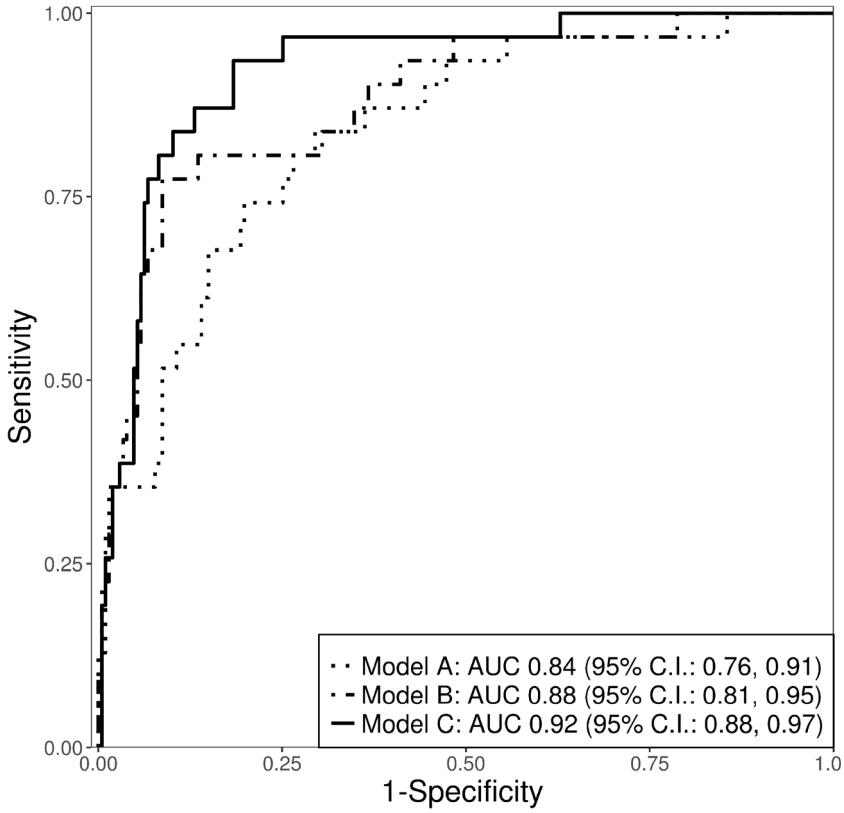

Fig. 3 ROC curve for comparing the prediction power of ACEs among prediction models

study also revealed that CCTA variables, including APCs and stenosis grade, might better predict ACE in HCM patients when it is added as part of the clinical risk factors and echocardiographic factors.

Many studies have shown that adult patients with HCM have a relatively benign prognosis and similar mortality to the general population [3, 36], while HCM is known to be the most common cause of sudden cardiac death in young people [2, 37]. Maron et al [38] reported that patients with HCM with age older than 60 years are at low risk for disease-related morbidity and mortality, including sudden death, suggesting that other cardiac or non-cardiac comorbidities may have a greater impact on survival than HCM in elderly patients. In our study evaluating an elderly population with a mean age of 62.0 ± 11.5 years, a clear coronary artery disease–related mortality or morbidity was about 30% among the cardiovascular events in HCM patients. Therefore, CCTA variables for the assessment of CAD are essential to the improvement of the prognosis of elderly HCM population. In addition, Asian population is more likely to have an apical HCM that is known to have a relatively favorable prognosis than other types of HCM [39]. Therefore, due to the benign prognosis of HCM, the evaluation of comorbidities, including age-related disease and coronary atherosclerotic changes, may be more important in adult HCM, especially in Asian populations.

Our study has several limitations. First, this was a retrospective analysis of HCM patients who underwent CCTA. CCTA was performed only in patients who had chest pain, and not all HCM patient population. This may explain why the prevalence of patients with ICD insertion or ongoing HF was lower in our study than in other previous studies. Therefore, the prediction model for ACEs was not validated in all HCM populations, although it was well validated in elderly HCM patients with chest pain who underwent CCTA. Second, this investigation was a single-center study, conducted on an entirely Asian population. As we mentioned earlier, since the prognosis of apical HCM is considered to be more benign than other forms of HCM, the contribution of HCM itself to the overall mortality could be lower than in the general population. Given that this study used the CCTA data between 2008 and 2013, there could be an intrinsic bias. Because CT technology has evolved in recent years, the prevalence of CAD or APC could be underestimated on some CT images—via conventional, non-updated techniques—that were unclear. Therefore, further prospective multinational, multicenter studies would be needed to draw more concrete clinical conclusions.

In conclusion, obstructive CAD and APCs were found in about 20% of adult HCM population with chest pain, and adding these variables to clinical and echocardiographic parameters increases the predictive power of ACEs in adult HCM population. In this regard, CCTA may play a role in the improvement of the prognosis of adult HCM because it provides comprehensive information on coronary artery

atherosclerosis, including vascular luminal stenosis, and plaque characteristics.

Funding This work was supported by the National Research Foundation grant NRF-2015R1D1A1A01059717 funded by the Korea government (MEST).

Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Kyung Won Lee.

Conflict of interest The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

Statistics and biometry Yongho Jeon, PhD (Department of Applied statistics, College of Commerce and Economics, Yonsei University), one of the authors, has contributed to the statistical analysis.

Informed consent Written informed consent was waived by the Institutional Review Board.

Ethical approval Institutional Review Board approval was obtained.

Methodology
- retrospective
- observational
- performed at one institution

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