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Cardiac Imaging

High-Intensity Signals in Coronary Plaques on Noncontrast T1-Weighted Magnetic Resonance Imaging as a Novel Determinant of Coronary Events

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Objectives The aim of this study was to determine whether coronary high-intensity plaques (HIPs) visualized by noncontrast T1-weighted imaging can predict future coronary events.

Background Coronary HIPs are associated with characteristics of vulnerable plaques, including positive remodeling, lower Hounsfield units, and ultrasound attenuation. However, it remains unclear whether the presence of HIPs is associated with increased risk for coronary events.

Methods The signal intensity of coronary plaques was prospectively examined in 568 patients with suspected or known coronary artery disease (CAD) who underwent noncontrast T1-weighted imaging to determine the plaque-to-myocardium signal intensity ratio (PMR).

Results During the follow-up period (median 55 months), coronary events were observed in 55 patients. Receiver-operating characteristic curve analysis identified a PMR of 1.4 as the optimal cutoff for predicting prognosis. Multivariate Cox regression analysis identified the presence of plaques with PMRs $\geq$1.4 as the significant independent predictor of coronary events (hazard ratio: 3.96; 95% confidence interval: 1.92 to 8.17; $p < 0.001$) compared with the presence of CAD (hazard ratio: 3.56; 95% confidence interval: 1.76 to 7.20; $p < 0.001$) and other traditional risk factors. Among the 4 groups based on PMR cutoff and the presence of CAD, coronary event–free survival was lowest in the group with PMRs $\geq$1.4 and CAD and highest in the group with PMRs <1.4 but no CAD. Importantly, the group with PMRs $\geq$1.4 and no CAD had an intermediate rate of coronary events, similar to the group with PMRs <1.4 and CAD.

Conclusions HIPs identified in a noninvasive, quantitative manner are significantly associated with coronary events and may thus represent a novel predictive factor. (J Am Coll Cardiol 2014;63:989–99) © 2014 by the American College of Cardiology Foundation

Recently, T1-weighted imaging (T1WI) of coronary plaques with or without contrast enhancement using cardiac magnetic resonance (CMR) has been successfully demonstrated (1–4). Because magnetic resonance (MR) imaging generates images without ionizing radiation, it can be repeated sequentially over time. Moreover, MR imaging allows the characterization of plaque composition in addition to morphologic evaluation (5). We have previously shown that the presence of coronary high-intensity plaques (HIPs) detected by noncontrast T1WI is associated with positive coronary artery remodeling, low density on computed tomographic angiography (CTA), and ultrasound attenuation (6). In addition, HIPs can be uniquely assessed using the plaque-to-myocardium signal intensity ratio (PMR) (6). Although our previous findings suggest that coronary HIPs may represent vulnerable lesions, there have been no studies evaluating the relationship between HIPs and subsequent coronary events. Therefore, we designed a prospective study

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Abbreviations and Acronyms

ACS = acute coronary syndrome(s)
CAD = coronary artery disease
CI = confidence interval
CMR = cardiac magnetic resonance
CTA = computed tomographic angiography
cTnT = cardiac troponin T
HIP = high-intensity plaque
MI = myocardial infarction
MR = magnetic resonance
PCI = percutaneous coronary intervention
PMR = plaque-to-myocardium signal intensity ratio
ROC = receiver-operating characteristic
T1WI = T1-weighted imaging
UAP = unstable angina pectoris

to determine the prognostic significance of HIPs and to identify the optimal PMR cutoff value for predicting coronary events.

Methods

Patients. Between December 2006 and September 2010, a total of 650 consecutive patients with suspected or known coronary artery disease (CAD) were initially screened with CTA and then underwent CMR examinations. Proven CAD was defined as: 1) a history of myocardial infarction (MI) or percutaneous coronary intervention (PCI); 2) ischemia-proven angina pectoris or silent myocardial ischemia diagnosed with stress myocardial scintigraphy; or 3) coronary arteriography–proven coronary artery stenosis ≥50%. We excluded patients with acute MIs (n = 13), unstable angina pectoris (UAP) (n = 7), left ventricular dysfunction (ejection fraction <40%) (n = 4), scheduled coronary artery bypass grafting (n = 1) or PCI (n = 29), and CMR images of poor quality (n = 28). Thus, 82 patients were excluded, and a total of 568 patients (mean age 62 ± 10 years; 435 men, 133 women) were ultimately enrolled in this study. This study was approved by the institutional review board of the National Cerebral and Cardiovascular Center and the ethics committee of Shin-Koga Hospital.

Coronary CTA. Coronary CTA was performed using a LightSpeed VCT (GE Healthcare, Milwaukee, Wisconsin). Computed tomographic procedures used in this study have been described previously (6).

CMR coronary plaque imaging. CMR imaging consisted of MR angiography and T1WI of plaque using a commercially available 1.5-T MR imager (Intera, Philips Medical Systems, Best, the Netherlands) with 5-element cardiac coils. The procedures used to acquire MR images in this study have been previously described (6). Briefly, coronary plaque images were obtained using a 3-dimensional T1-weighted turbo field echo sequence with inversion recovery (inversion time delay 500 ms) and fat suppression (repetition time 4.7 ms, echo time 1.37 ms, flip angle 20°, sensitivity encoding factor 2.5, number of signals acquired 2, navigator gating window ±1.5 to 2.5 mm, field of view 300 × 270 × 112 mm, acquisition matrices 224 × 200, acquisition slice number 70, reconstruction matrices 512 × 512, reconstruction slice number 140, acquired spatial resolution 1.34 × 1.35 × 1.60 mm, reconstructed to 0.59 × 0.53 × 0.80 mm). The mean acquisition time was 15 ± 3 min for plaque imaging. The average navigator efficiency was 50.5%.

Plaque analysis on CMR. On CMR images, the coronary vascular tree was subdivided into 8 segments (3). For segment identification, segments were pre-defined according to the distance from the vessel origin. The right coronary artery was analyzed in 3 segments (segments 1, 2, and 3). The left coronary artery was analyzed as the left main, left anterior descending (segments 6 and 7), and circumflex (segments 11 and 13) arteries. To confirm that the location of an observed HIP (Fig. 1A) corresponded to the presence of a coronary plaque, we used both cross-sectional (Fig. 1B) and curved multiplanar reformation computed tomographic angiographic images. In addition, for plaque detection, we used coregistration images (Fig. 1C) to facilitate confirmation of the anatomical position of high-intensity lesions on T1-weighted images (Fig. 1A) and the coronary vessel on MR angiography (Fig. 1D) using commercially available software (Virtual Place Raijin workstation, AZE, Tokyo, Japan).

The methods used to evaluate plaque images have been described previously (6). Briefly, an experienced technician and a cardiologist both blinded to patient data used the T1-weighted images to calculate the PMR, defined as the signal intensity of the coronary plaque divided by that of nearby left ventricular myocardium, measured using a free-hand region of interest on a standard console of the clinical MR system. We used left ventricular myocardium located the same distance from the surface coil as the plaque to determine plaque signal intensity. To avoid abnormal myocardial T1 measurements, we did not use areas of MI for reference. The highest signal intensity detected in each plaque was considered the PMR value for that plaque in segment-based analysis. In patient-based analysis, the highest PMR among the coronary plaques was assigned to be the PMR for that subject.

Intraclass correlation coefficients with 95% confidence intervals (CIs) were calculated to assess intrareader and interreader agreement for PMR. The intrareader intraclass correlation coefficient was 0.94 (95% CI: 0.80 to 0.98). The inter-reader intraclass correlation coefficient was 0.88 (95% CI: 0.73 to 0.95). All correlation coefficients for PMR were >0.8, with narrow CIs, indicating good intraobserver and interobserver agreement.

Follow-up study. After CMR data were obtained, study patients were followed at 3, 6, and 12 months and annually thereafter until the occurrence of 1 of the following coronary events: cardiac death, nonfatal ST-segment elevation MI, high-sensitivity cardiac troponin T (cTnT)–positive UAP or non–ST-segment elevation MI, or ischemia-driven PCI due to progressive angina pectoris. Cardiac death was defined as sudden death and death caused by acute MI or ventricular arrhythmias. Elevation of cTnT was defined as more than 2 times the upper limit of the normal range (0.010 ng/ml). Myocardial ischemia was diagnosed using stress myocardial scintigraphy before PCI. PCI-related restenosis and PCI

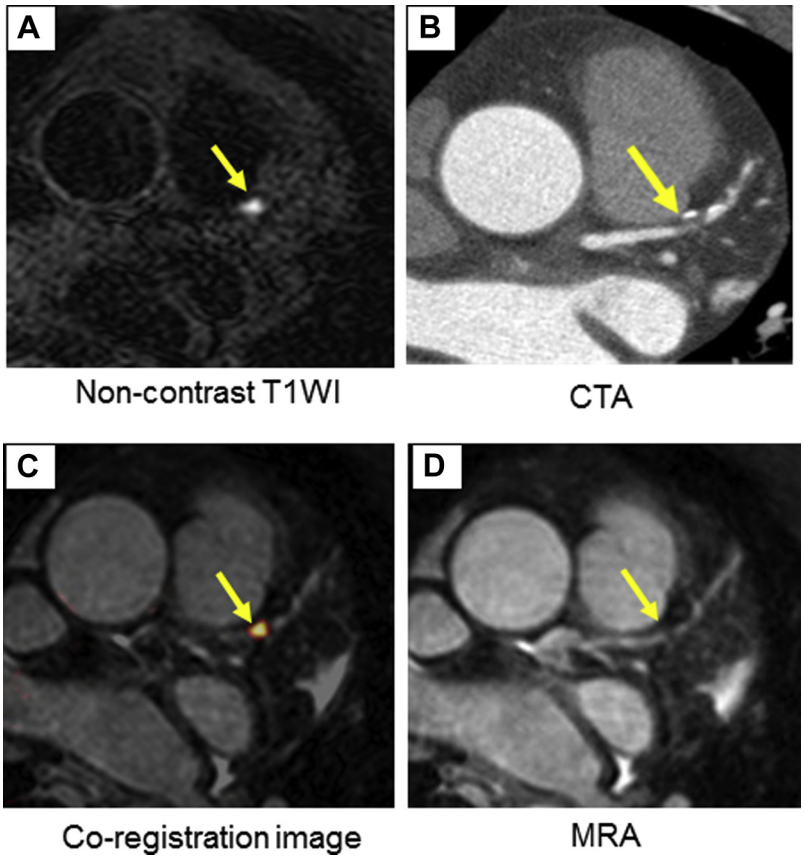


Figure 1 **Representative Images of High-Intensity Plaques on CMR**

The high-intensity signal on T1-weighted imaging (T1WI) **(A)** corresponds to the coronary plaque defined by computed tomographic angiography (CTA) **(B)**. Magnetic resonance images of coronary plaque **(yellow arrow)** in the proximal left anterior descending coronary artery coregistered **(C)** with noncontrast T1W1 **(A)** and magnetic resonance angiography (MRA) **(D)** showing that a high-intensity signal on T1WI **(A)** corresponds to the coronary artery wall on MRA **(D)**.

due to silent myocardial ischemia were not considered coronary events. Independent attending cardiologists reviewed charts to determine if hospitalizations and deaths qualified as coronary events. Chart review was blinded with respect to the patient's HIP status.

Statistical analysis. Continuous, normally distributed baseline variables are expressed as mean ± SD and were compared using unpaired Student *t* tests. Categorical baseline variables were compared using Fisher exact tests or chi-square tests as appropriate. Analysis of variance was used to compare the means of the 3 groups on the basis of PMR. For any statistically significant differences, post-hoc pairwise comparisons for each pair were performed using the Tukey-Kramer test for continuous variables to determine which pair differed significantly. PMR cutoff values were determined on the basis of receiver-operating characteristic (ROC) curve analysis using the Youden index. Survival analysis was carried out using the Kaplan-Meier method with the log-rank test according to the PMR cutoff value. The data were analyzed initially using a univariate model to determine which risk factors had significant associations with future coronary events. For all variables, we assessed the assumption of proportional hazards by testing for a nonzero slope in a regression of scaled Schoenfeld residuals on time. We then evaluated the discriminatory ability of predictors by comparing the C-index for PMR with the C-indexes for other clinical risk factors using Newson's method (7). Multivariate Cox regression analysis was then performed using only the covariates that significantly predicted coronary events in the univariate analysis. Collinearity was evaluated using the correlation coefficients between all covariates. Stepwise selection with a p value of 0.10 for backward elimination was used to select the best predictive model. Analyses were conducted using SPSS (SPSS Japan Inc., Tokyo, Japan) and Stata version 12 (StataCorp LP, College Station, Texas). All p values <0.05 were considered statistically significant.

Results

PMR cutoff value for developing cardiac events. During a median follow-up period of 55 months (interquartile

Table 1 Comparison of the Clinical Profiles of Patients With or Without Coronary Events

Variable	Coronary Event (n = 55)	No Coronary Event (n = 513)	p Value
Age (yrs)	68 ± 10	61 ± 10	<0.001
Men	51 (93%)	384 (75%)	0.002
Hypertension	38 (69%)	242 (47%)	0.003
Current smokers	28 (51%)	278 (54%)	0.67
Hyperlipidemia	41 (75%)	261 (51%)	0.001
Diabetes mellitus	23 (43%)	124 (23%)	0.009
BMI (kg/m^2)	23 ± 3	24 ± 11	0.39
SBP (mm Hg)	141 ± 20	133 ± 18	0.012
Total cholesterol (mg/dl)	190 ± 42	203 ± 34	0.006
LDL (mg/dl)	108 ± 32	117 ± 28	0.018
HDL (mg/dl)	49 ± 14	55 ± 14	0.01
TG (mg/dl)	134 (95–204)	110 (74–164)	0.01
HbA_{1c} (%)	6.6 ± 2	5.7 ± 1	<0.001
PMR	1.49 (1.27–1.90)	0.94 (0.83–1.29)	<0.001
PMR >1.0	51 (93%)	202 (39%)	<0.001
Proven CAD	38 (69%)	105 (20%)	<0.001
Multivessel disease	18 (33%)	50 (10%)	<0.001
Previous MI	10 (18%)	18 (4%)	<0.001
Medications			
Aspirin	29 (53%)	97 (19%)	<0.001
Beta-blockers	10 (18%)	29 (6%)	0.002
Statins	21 (38%)	95 (19%)	0.001
ACE inhibitors or ARBs	26 (47%)	127 (25%)	0.001

Values are mean ± SD, n (%), or median (interquartile range).

ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; BMI = body mass index; CAD = coronary artery disease; HbA_{1c} = glycosylated hemoglobin; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MI = myocardial infarction; PMR = plaque-to-myocardium signal intensity ratio; SBP = systolic blood pressure; TG = triglycerides.

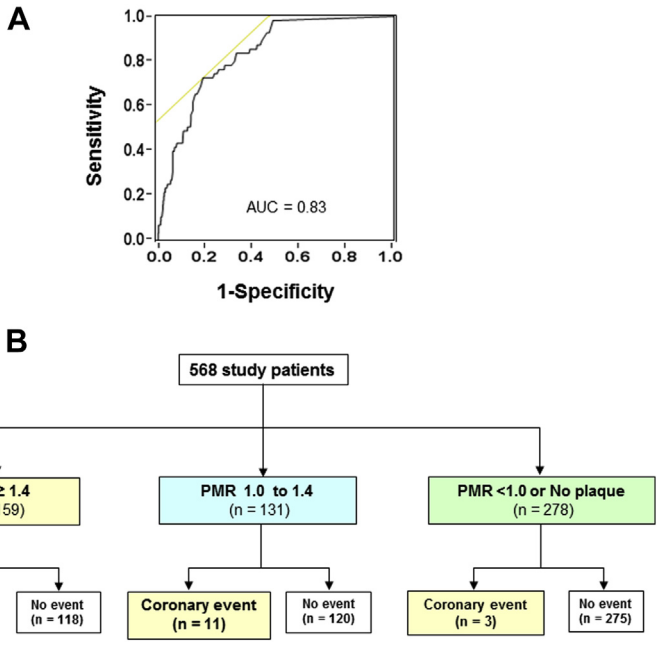


Figure 2 ROC Curve Analysis for Developing Coronary Events and Flowchart of Study Patients on the Basis of PMR

(A) From receiver-operating characteristic (ROC) curve analysis, a plaque-to-myocardium signal intensity ratio (PMR) of 1.4 was identified as the best cutoff value for predicting cardiac events, with 69.5% sensitivity and 82.3% specificity. The calculated area under the curve (AUC) was 0.83. **(B)** To stratify the analysis of coronary events, the 568 enrolled patients were divided into the following 3 groups: PMR ≥1.4 (n = 159), PMR 1.0 to 1.4 (n = 131), and PMR <1.0 or no plaque (n = 278).

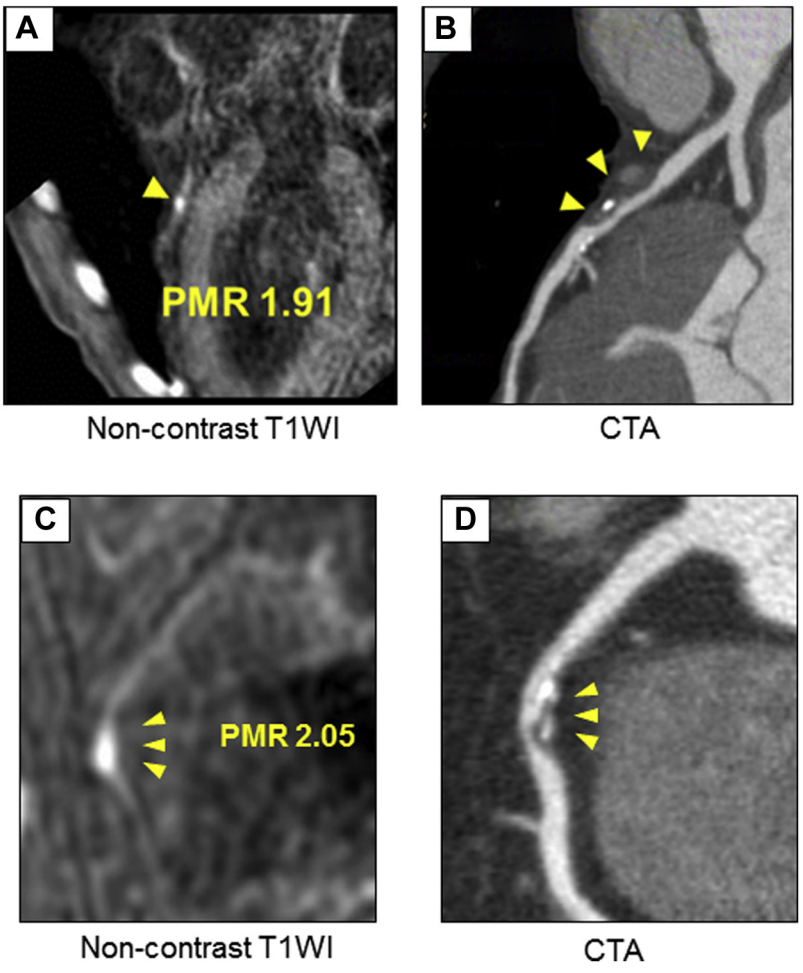


Figure 3 **Representative Images of HIPs With PMRs ≥1.4**

Representative noncontrast T1-weighted images of high-intensity plaques (HIPs) **(yellow arrowheads)** in the proximal left anterior descending coronary artery **(A)** and the right coronary artery **(C)**, in which plaque-to-myocardium signal intensity ratios (PMRs) were 1.91 and 2.05, respectively. These high-intensity signals each correspond to the left and right coronary plaques on computed tomographic angiography (CTA) (**yellow arrowheads** on curved multiplanar reformation images, **B and D**). T1WI = T1-weighted imaging.

range: 45 to 65 months), coronary events were observed in 55 of 568 study patients. Table 1 compares the clinical profiles of patients with and without subsequent development of coronary events; these groups differed significantly in terms of age, sex, hypertension, hyperlipidemia, diabetes mellitus, systolic blood pressure, lipid profile, glycosylated hemoglobin, multivessel CAD, previous MI, and medication use ($p < 0.05$). PMRs were significantly higher in patients who developed coronary events than those who did not (median 1.49 vs. 0.94; $p < 0.001$). Indeed, a higher proportion of patients with coronary events had PMRs >1.0 than those without ($p < 0.001$).

Based on ROC curve analysis, the optimal PMR cutoff value for developing cardiac events was 1.40, and the area under the ROC curve was 0.83 (Fig. 2A). At this value, the sensitivity and specificity for predicting a cardiac event were 69.5% and 82.3%, respectively.

Patient-based analysis. Because coronary plaque areas with PMRs >1.0 have been defined as HIPs in previous studies (6), we divided the study patients into 3 groups according to the new PMR cutoff value and the previous definition as follows: PMR ≥1.4 (n = 159), PMR 1.0 to 1.4 (n = 131), and PMR <1.0 or no plaque (n = 278) (Fig. 2B). Representative cases of plaques with PMRs ≥1.4 are shown in Figures 3A to 3D. Patients in the group with PMRs <1.0 either had coronary plaques without high-intensity signals or no plaques on CTA. Of the 159 patients with PMRs ≥1.4, 41 (25.8%) developed coronary events, whereas 11 events (8.4%) occurred in the group with PMRs of 1.0 to 1.4 (n = 131). Only 3 of the 278 patients (1.1%) with PMRs <1.0 developed coronary events.

Table 2 shows the baseline clinical characteristics of the 3 study groups. The group with PMRs ≥1.4 had a significantly higher mean age; higher proportions of men, current

Table 2 Comparison of Patients Characteristics Categorized by PMR Values

Variable	PMR ≥1.4 (n = 159)	PMR 1.0 to 1.4 (n = 131)	PMR <1.0 or No Plaque (n = 278)	p Value
Age (yrs)	66 ± 9	62 ± 10	59 ± 10	<0.001
Men	139 (87%)	97 (74%)	199 (72%)	0.001
Hypertension	106 (67%)	80 (61%)	95 (34%)	<0.001
Current smokers	98 (61%)	58 (45%)	152 (54%)	0.015
Hyperlipidemia	99 (62%)	75 (58%)	128 (46%)	0.002
Diabetes mellitus	57 (36%)	54 (41%)	36 (13%)	<0.001
BMI (kg/m^2)	23.8 ± 3	23.7 ± 3	24.4 ± 15	0.28
SBP (mm Hg)	138 ± 19	138 ± 19	130 ± 16	0.001
Total cholesterol (mg/dl)	192 ± 35	202 ± 32	205 ± 35	0.003
LDL (mg/dl)	112 ± 28	116 ± 28	118 ± 30	0.18
HDL (mg/dl)	50 ± 12	53 ± 14	57 ± 15	<0.001
TG (mg/dl)	147 ± 89	157 ± 123	118 ± 76	<0.001
HbA_{1c} (%)	6.0 ± 1.3	6.1 ± 1.5	5.6 ± 0.5	<0.001
PMR	1.75 ± 0.53	1.15 ± 0.10	0.86 ± 0.05	<0.001
Proven CAD	78 (49%)	42 (32%)	23 (8%)	<0.001
Multivessel disease	46 (29%)	21 (16%)	1 (0.4%)	<0.001
Previous MI	17 (11%)	7 (5%)	4 (1%)	<0.001
Medications				
Aspirin	58 (36%)	44 (34%)	24 (9%)	<0.001
Beta-blockers	17 (11%)	12 (9%)	10 (4%)	0.01
Statins	50 (31%)	24 (18%)	42 (15%)	<0.001
ACE inhibitors or ARBs	69 (43%)	41 (31%)	43 (15%)	<0.001

Values are mean ± SD or n (%).
Abbreviations as in Table 1.

smokers, and patients with hyperlipidemia, multivessel CAD, and previous MIs; and a lower mean level of high-density lipoprotein cholesterol. In contrast, the level of total cholesterol was lower in the group with PMRs ≥1.4, which also had higher rates of aspirin, beta-blocker, statin, angiotensin-converting enzyme inhibitor, and angiotensin II receptor blocker use. The median, 25th percentile, and 75th percentile PMR values were 1.56, 1.41, and 1.88, respectively, in the group with PMRs ≥1.4; 1.15, 1.07, and 1.21, respectively, in the group with PMRs of 1.0 to 1.4; and 0.83, 0.81, and 0.92, respectively, in the group with PMRs <1.0. Table 3 summarizes the coronary events that occurred during the follow-up period. The group with PMRs ≥1.4 had the highest incidence of all coronary events and acute coronary syndrome (ACS)–related events among the 3 groups ($p < 0.001$).

Univariate analysis of coronary risk factors, medications, and CMR analysis showed that age, male sex, systolic blood pressure, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, glycosylated hemoglobin, medications, multivessel CAD, previous MI, proven CAD, and the presence of plaques with PMRs ≥1.4 were all significant predictors of all coronary events (Table 4). All variables satisfied the assumption of proportionality. Table 5 summarizes the C-indexes of PMR and other risk factors. PMR had the highest C-index (0.81; 95% CI: 0.76 to 0.85), which was significantly different from those of the other risk factors evaluated. For the selection of the best predictive

Table 3 Coronary Events During the Follow-Up Period

Variable	PMR ≥1.4 (n = 159)	PMR 1.0 to 1.4 (n = 131)	PMR <1.0 or No Plaque (n = 278)	p Value
Composite endpoint				
All coronary events	41 (25.8%)	11 (8.4%)	3 (1.1%)	<0.001
ACS-related events	24 (15.1%)	5 (3.8%)	1 (0.4%)	<0.001
Coronary events				
Cardiac death	1 (0.6%)	0	0	0.280
STEMI	9 (5.7%)	1 (0.8%)	0	<0.001
cTnT-positive UAP/NSTEM	14 (8.8%)	4 (3.1%)	1 (0.4%)	<0.001
Ischemia-driven PCI	17 (10.7%)	6 (4.6%)	2 (0.7%)	<0.001

Values are n (%). ACS-related events include cardiac death, STEMI, and cTnT-positive UAP or NSTEMI.
ACS = acute coronary syndrome; cTnT = cardiac troponin T; NSTEMI, non–ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; PMR = plaque-to-myocardium signal intensity ratio; STEMI = ST-segment elevation myocardial infarction; UAP = unstable angina pectoris.

Table 4 Univariate Cox Regression Analysis of Risk Factors for All Coronary Events

	Univariate Analysis		
Variable	Hazard Ratio	p Value	95% CI
Age	1.07	<0.001	1.04–1.10
Male	2.69	0.022	1.15–6.27
Hypertension	2.44	0.002	1.37–4.32
Current smoking	0.84	0.517	0.49–1.43
Hyperlipidemia	2.70	0.001	1.47–4.96
Diabetes mellitus	2.29	0.002	1.34–3.92
BMI, kg/m^2	0.96	0.367	0.88–1.05
SBP	1.02	0.003	1.01–1.03
Total cholesterol	0.99	0.004	0.98–1.00
LDL	0.99	0.020	0.98–1.00
HDL	0.97	0.006	0.95–0.99
TG	1.00	0.001	1.00–1.00
HbA_{1c}	1.36	<0.001	1.20–1.54
PMR	2.70	<0.001	2.09–3.48
PMR ≥1.4	8.28	<0.001	4.56–15.00
Proven CAD	7.70	<0.001	4.34–13.70
Multivessel CAD	4.18	<0.001	2.37–7.36
Previous MI	5.06	<0.001	2.54–10.10
Medications			
Aspirin	4.57	<0.001	2.68–7.80
Beta-blockers	3.35	0.001	1.69–6.65
Statins	2.63	0.001	1.52–4.53
ACE inhibitors or ARBs	2.71	<0.001	1.59–4.61

CI = confidence interval; other abbreviations as in Table 1.

model, we started with the full model with all of the significant variables in Table 4. Age, male sex, glycosylated hemoglobin, proven CAD, and the presence of plaques with PMRs ≥1.4 remained in the final model. The presence of plaques with PMRs ≥1.4 in the coronary tree was found to be the most significant independent predictor for future coronary events (hazard ratio: 3.96; 95% CI: 1.92 to 8.17; p < 0.001) compared with proven CAD (hazard ratio: 3.56; 95% CI: 1.76 to 7.20; p < 0.001) (Table 5). Importantly, when we focused on ACS-related events (cardiac death, ST-segment elevation MI, and cTnT-positive UAP or non–ST-segment elevation MI), the presence of plaques with PMRs ≥1.4 remained a significant independent predictor (hazard ratio: 8.93; 95% CI: 3.23 to 24.7; p < 0.001). No collinearity was observed among the variables in the initial model.

Table 5 C-Index Analysis Demonstrating Discrimination for Prediction of All Coronary Events

Variable	C-Index	95% CI	p Values
PMR ≥1.4	0.81	0.76–0.85	Reference
Proven CAD	0.73	0.67–0.79	0.035
Multivessel disease	0.61	0.55–0.67	<0.001
Previous MI	0.57	0.52–0.62	<0.001
Age	0.67	0.60–0.74	<0.001
Male	0.52	0.50–0.54	<0.001
BMI	0.55	0.47–0.63	<0.001
LDL	0.60	0.52–0.68	<0.001
HDL	0.61	0.52–0.69	<0.001
TG	0.59	0.51–0.68	<0.001
HbA_{1c}	0.65	0.58–0.73	<0.001
SBP	0.59	0.51–0.67	<0.001

Abbreviations as in Tables 1 and 4.

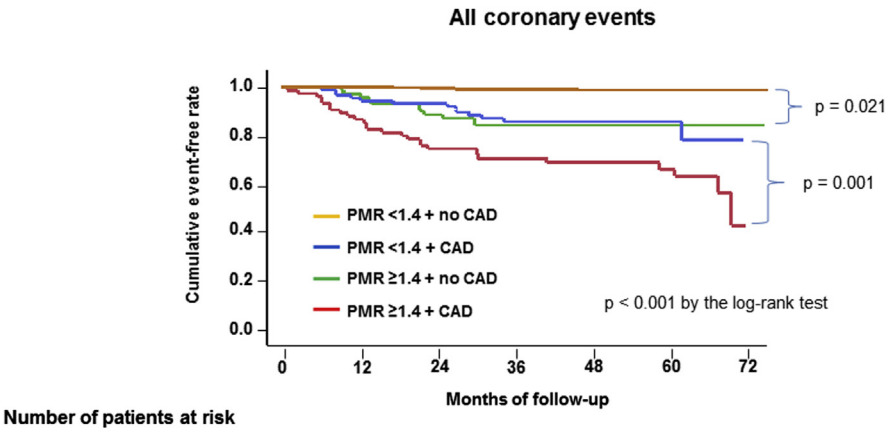
Because multivariate analysis for all coronary events showed that the presence of plaques with PMR ≥1.4 and proven CAD were both significant independent prognostic factors (Table 6), we subdivided the study patients into the following 4 groups according to the PMR cutoff value and the presence or absence of proven CAD: PMR ≥1.4 with CAD (n = 74), PMR ≥1.4 without CAD (n = 85), PMR <1.4 with CAD (n = 69), and PMR <1.4 without CAD (n = 340). On the basis of Kaplan-Meier analysis, the coronary event–free survival rate was lowest in the group with PMRs ≥1.4 with CAD and highest in the group with PMRs <1.4 without CAD. The rate in the group with PMRs ≥1.4 without CAD was intermediate but comparable with that in the group with PMRs <1.4 with CAD (Fig. 4). In addition, among patients without CAD, those with plaques with PMRs ≥1.4 had worse event-free survival than patients with plaques with PMRs <1.4 (p = 0.021). Furthermore, when we performed Kaplan-Meier analysis for ACS-related events, patients with PMRs ≥1.4 showed worse event-free survival than those with PMRs <1.4 (p < 0.001 by the log-rank test).

Segment-based analysis. Of the 4,544 segments (568 subjects) analyzed, 202 segments were excluded because they either contained lesions scheduled for PCI or they were previously treated with PCI using stents, leaving 4,342 segments that were analyzed (Fig. 5). Plaques with PMRs ≥1.4 were identified in 207 segments, those with PMRs of 1.0 to 1.4 were observed in 301 segments, and those with PMRs <1.0 or no plaque was seen in 3,834 segments. Of the 207 segments with plaques with PMRs ≥1.4, 35 (16.9%) segments were associated with coronary events, which developed in 18 segments (51.4%) in the first 12 months and in 9 segments (25.7%) during months 13 to 24. After 24 months, 8 of 35 segments (22.9%) were associated with coronary events. Among patients who had coronary events during the first 12 months, months 13 to 24, and after 24 months, there were significant differences in the median, 25th percentile, and 75th percentile PMR values (≤12 months: 2.23, 1.72, and 2.64;

Table 6 Best Predictive Model Selected by Stepwise Cox Regression Analysis of Risk Factors for All Coronary Events

	Multivariate Analysis		
Variable	Hazard Ratio	p Value	95% CI
Age	1.04	0.023	1.01–1.07
Male	2.61	0.071	0.92–7.39
HbA_{1c}	1.04	0.018	1.03–1.36
Proven CAD	3.56	<0.001	1.76–7.20
PMR ≥1.4	3.96	<0.001	1.92–8.17

Abbreviations as in Tables 1 and 4.



Number of patients at risk

PMR <1.4 + no CAD	340	340	327	145
PMR <1.4 + CAD	69	67	50	21
PMR ≥1.4 + no CAD	85	81	60	20
PMR ≥1.4 + CAD	74	60	51	24

Figure 4 Kaplan-Meier Curves Comparing the Probability of All Coronary Events

Coronary event–free survival was worst in the group with plaque-to-myocardium signal intensity ratios (PMRs) ≥1.4 and coronary artery disease (CAD) **(red line)** and best in the group with PMRs <1.4 but no CAD group **(orange line)**. The rate in the group with PMRs ≥1.4 and no CAD **(green line)** was intermediate but comparable with that in the group with PMRs <1.4 and CAD **(blue line)**.

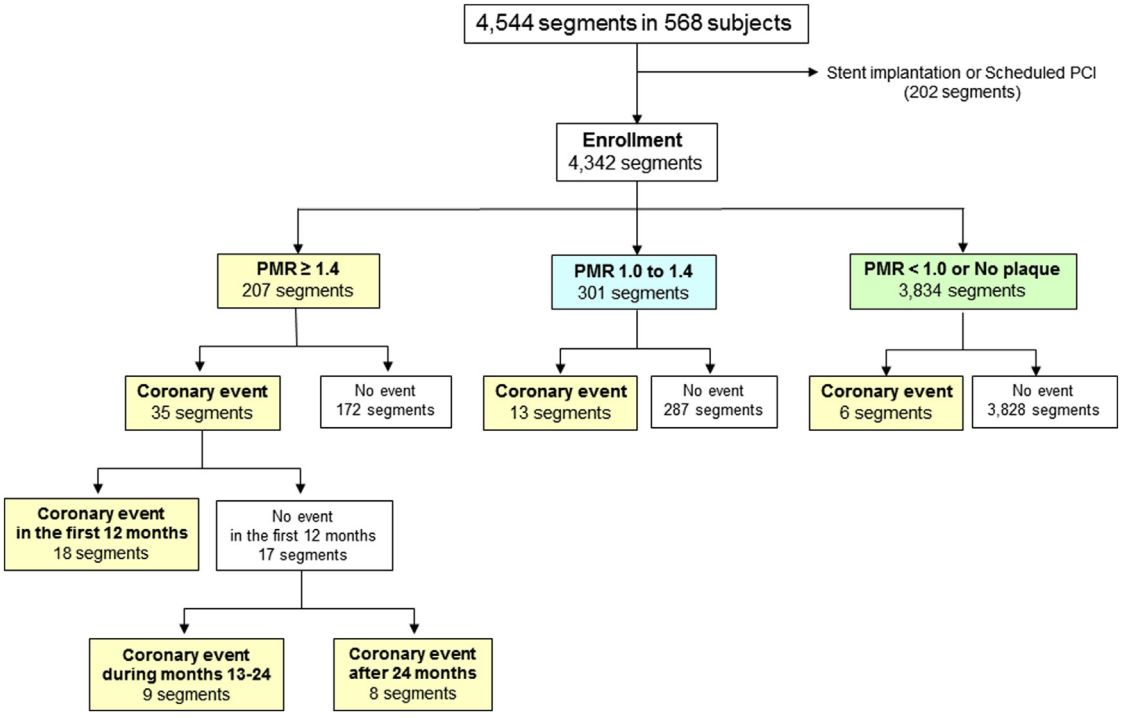


Figure 5 Incidence of Coronary Events in Segment-Based Analysis

A total of 4,342 segments were analyzed and divided into the following 3 groups: 207 segments with plaque-to-myocardium signal intensity ratios (PMRs) ≥1.4, 301 segments with plaques with PMRs of 1.0 to 1.4, and 3,834 segments with plaques with PMRs <1.0 or no plaque. Of the 207 segments with plaques with PMRs ≥1.4, 35 segments (16.9%) were associated with coronary events, which developed in 18 segments (51.4%) during the first 12 months, in 9 segments (25.7%) during months 13 to 24, and in 8 segments (22.9%) after 24 months of follow-up. PCI = percutaneous coronary intervention.

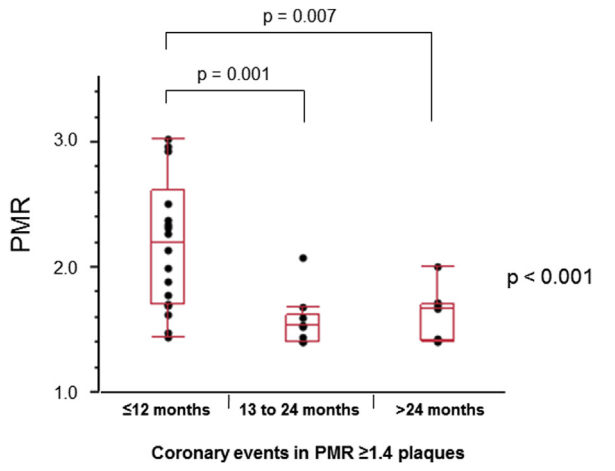


Figure 6 **PMR Values and the Timing of Coronary Events in 35 Segments With Plaques With PMRs ≥1.4**

Results are expressed as box-and-whisker plots; the central box covers the interquartile range, with the median indicated by the line within the box. The **whiskers** extend to the most extreme values within 1.5 interquartile range. More extreme values are plotted individually. PMR = plaque-to-myocardium signal intensity ratio.

13 to 24 months: 1.55, 1.42, and 1.63; >24 months: 1.69, 1.43, and 1.72; $p < 0.001$) (Fig. 6).

Figure 7 shows the event rates of coronary segments stratified by the PMR cutoff value of 1.4. In coronary segments with plaques with PMRs ≥1.4, 16.9% of all coronary events (35 of 207 segments) and 11.1% of ACS-related events (23 of 207 segments) developed from the same segment as the one containing a plaque with a PMR ≥1.4, whereas 0.5% of all coronary events (5 of 1,065 segments) and 0.3% of ACS-related events (3 of 1,065 segments) developed from segments containing plaques with PMRs <1.4 ($p < 0.001$, respectively). Similarly, event rates for ST-segment elevation MI, cTnT-positive UAP or non–ST-segment elevation MI, and ischemia-driven PCI arising from the same segment as the one containing a plaque with a PMR ≥1.4 were significantly higher than those from segments without plaques with PMRs ≥1.4 ($p < 0.001$). Thus, a higher incidence of coronary events occurred when the culprit lesion was in the same coronary segment as a plaque with a PMR ≥1.4.

Discussion

The major finding of this study is that the presence of plaques with PMRs ≥1.4 visualized by noncontrast T1WI is a significant and independent predictor of future coronary events in patients with CAD. To the best of our knowledge, this is the first clinical study that demonstrates HIP as a novel prognostic marker identified in a noninvasive and quantitative manner that does not involve radiation exposure.

Progress of HIP assessment in coronary arteries. Atherosclerotic plaque imaging using MR was originally developed for cerebrovascular disease. The presence of a high–signal intensity lesion on T1WI was considered to indicate intraplaque hemorrhage (8–10) and to be associated with a recent cerebrovascular event (9–12).

In contrast to carotid MR plaque imaging, coronary plaque imaging with CMR has been challenging because of the small sizes of coronary arteries, as well as cardiac and respiratory motion. Fayad et al. (13) were the first to demonstrate the feasibility of coronary plaque imaging in humans in vivo. In addition, Botnar et al. (14) and Stuber et al. (15) have described high-resolution coronary plaque imaging during free breathing using the combination of a real-time navigator for respiratory gating and real-time slice-position correction. We systematically evaluated the components of HIPs detected by noncontrast T1WI using CTA and intravascular ultrasound in a recent study showing that coronary HIPs are associated with ultrasound attenuation, positive vascular remodeling, and low computed tomographic density (6).

Assessment of HIPs and ROC curve analysis. We assessed HIPs by calculating PMR, defined as the signal intensity of the coronary plaque divided by that of neighboring left ventricular myocardium. In the previous study, we defined plaque areas with PMRs >1.0 as positive for HIP (6). Using this definition, the prevalence of HIPs was 60% to 70% in patients with stable angina pectoris and UAP, as reported in our previous study and others (6,16). In the present study, the median PMRs for patients with and without cardiac events were significantly different: 1.49 and 0.94, respectively (Table 1). The prevalence of PMR >1.0 was 93% in patients with cardiac events, but it should be noted that the prevalence of PMR >1.0 was also high (39%) in those without cardiac events. Therefore, we sought to re-evaluate the optimal PMR value for predicting coronary events. On ROC curve analysis, a PMR of 1.4 was identified as the best cutoff value for predicting prognosis. The sensitivity and specificity were 69.5% and 82.3%, respectively, fairly comparable with the use of the CTA index for detecting vulnerable plaques (17). Also, in the stratified analysis using PMR values of 1.0 and 1.4, the incidence of cardiac events was well differentiated, 25.8% for PMR ≥1.4, 8.4% for PMR of 1.0 to 1.4, and 1.1% for PMR <1.0 (Fig. 2B). These rates are comparable with those in patients with vulnerable coronary plaques detected by CTA (17). Moreover, we calculated the C-index for PMR ≥1.4 and other classic coronary risk factors. The C-index for PMR ≥1.4 was 0.81, higher than for any other risk factor (Table 5). Therefore, the new cutoff value for PMR in this study may be clinically useful for identifying vulnerable coronary plaques associated with future cardiac events.

The prognostic impact of HIP and its potential to detect plaque vulnerability. Multivariate analysis for all coronary events showed that the presence of plaques with PMRs ≥1.4 and proven CAD were both significant independent prognostic factors (Table 6). Therefore, we divided study patients into 4 groups according to high and low PMRs in patients with and without CAD. The coronary event–free survival

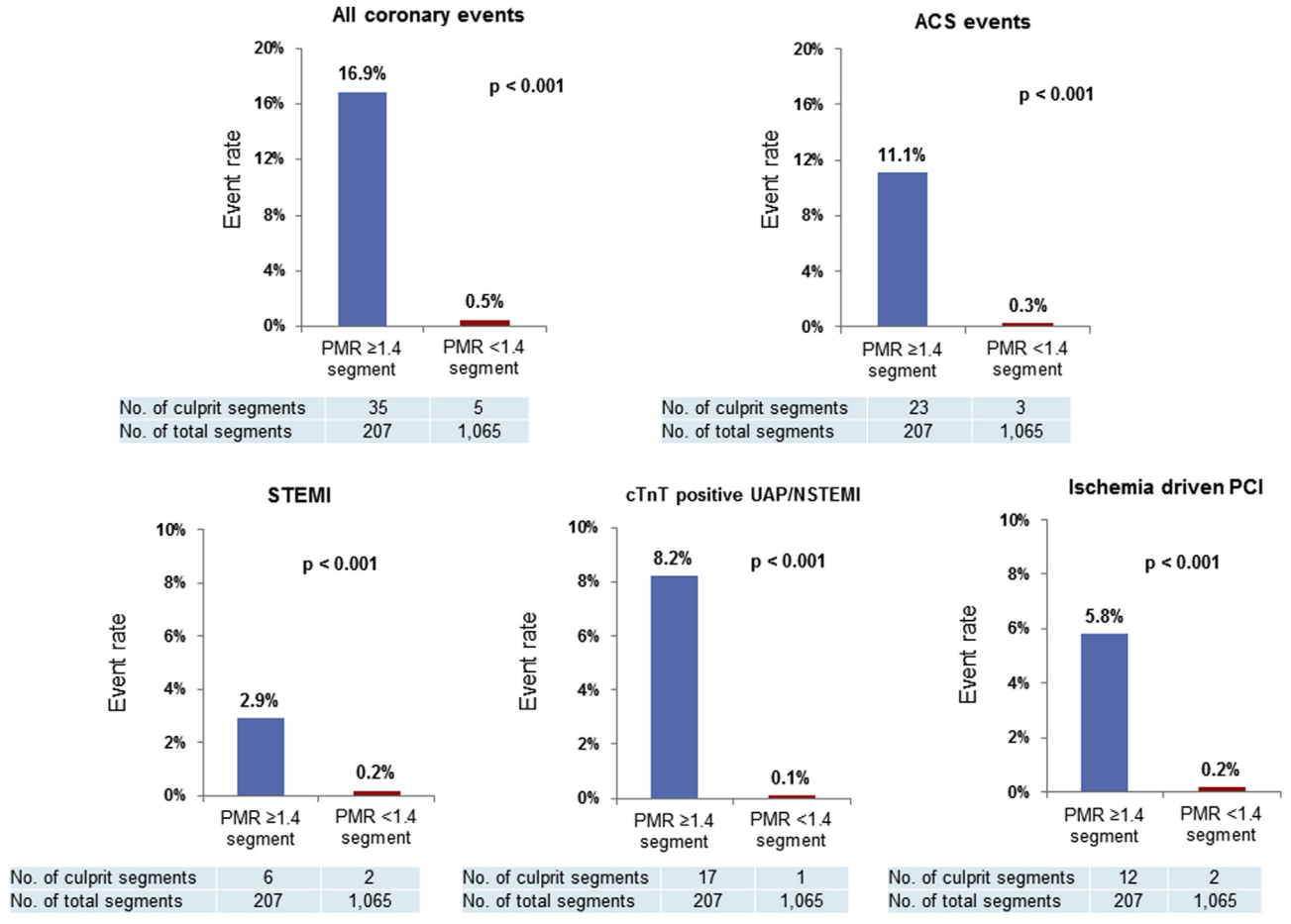


Figure 7 **Comparisons of Event Rates Between Coronary Segments With and Without Plaques With PMRs ≥1.4**

In the 1,272 coronary segments of 159 patients with plaques with plaque-to-myocardium signal intensity ratios (PMRs) ≥1.4, 207 segments contained plaques with PMRs ≥1.4, and the remaining 1,065 segments contained plaques with PMRs <1.4 or no plaque. The event rate for all coronary events was 16.9% (35 of 207 segments), and the acute coronary syndrome (ACS)–related event rate was 11.1% (23 of 207 segments) for events arising from the same segment as the one containing a plaque with a PMRs ≥1.4 **(blue bars)**, whereas 0.5% (5 of 1,065 segments) of all coronary events and 0.3% (3 of 1,065 segments) of ACS events arose from segments containing plaques with PMRs <1.4 ($p < 0.001$, respectively) **(red bars)**. Similarly, event rates for ST-segment elevation myocardial infarction (STEMI), cardiac troponin T (cTnT)–positive unstable angina pectoris (UAP) or non–ST-segment elevation myocardial infarction (NSTEMI), and ischemia-driven percutaneous coronary intervention (PCI) developing from the same segment as a plaque with a PMR ≥1.4 were significantly higher than event rates in segments with plaques with PMRs <1.4 ($p < 0.001$, respectively).

rate was lowest in the group with PMRs ≥1.4 and CAD and highest in the group with PMRs <1.4 but no CAD (Fig. 4). Importantly, the rate in the group with PMRs ≥1.4 and no CAD was intermediate but comparable with that in the group with PMRs <1.4 and CAD (Fig. 4). These findings demonstrate that coronary events can develop even when organic stenosis is not evident, confirming the concept of vulnerable patients in whom plaque destabilization occurs at multiple sites throughout systemic vascular beds (18,19). Indeed, as shown in Table 2, patients with plaques with PMRs ≥1.4 were characterized as a clinically high-risk population, with higher proportions of current smokers and patients with hyperlipidemia, proven CAD, multivessel CAD, previous MI, and low high-density lipoprotein cholesterol. Therefore, our results suggest that once a patient is identified to be at high risk for having an adverse cardiac event on the basis of traditional clinical and biochemical risk profiles, noncontrast T1WI may help identify those at greater risk for coronary events.

In addition to patient-based analysis, we also performed segment-based analysis, indicating that segments with especially high PMRs (median 2.23) developed coronary events within the first year of follow-up. Thus, such segments seem to be highly associated with disease vulnerability (Fig. 6). Figure 7 also shows that the prevalence of coronary events was higher in coronary artery segments with plaques with PMRs ≥1.4 than in segments with plaques with PMRs <1.4. Therefore, HIPs with high PMRs are likely to represent vulnerable plaques that develop into culprit lesions. CMR imaging–based evaluation of coronary plaques described herein provides clinically important information on the vulnerability of atherosclerotic coronary plaques.

Study limitations. First, this was a single-center study with a relatively small number of patients examined, and few reached the primary end point. A larger number of events is needed for adequate statistical power to fully evaluate whether a novel risk marker contributes additional prognostic information to an established set of risk factors in a multivariate model, as opposed to simply indicating whether the new marker is prognostic by itself (20). Therefore, although our data show that the presence of HIPs and a PMR ≥1.4 are risk factors for coronary events, the relative importance of HIPs and this PMR cutoff compared with other cardiac risk factors should be confirmed in a larger prospective study.

Second, during the follow-up period, medical therapy after diagnosis was individualized at the discretion of each attending physician on the basis of symptoms and risk factors. This may be relevant to the group with PMRs ≥1.4, which had a higher incidence of coronary events despite lower total plasma cholesterol levels than the other 2 groups. Because the group with PMRs ≥1.4 had higher rates of hyperlipidemia and proven CAD, it had a higher rate of statin use. Therefore, although HIPs may be associated with hyperlipidemia, the prognostic impact of HIPs may be due to more than the total cholesterol level.

Third, the results from the stepwise selection process were potentially biased by overfitting the derivation dataset. However, because the PMR cutoff value of 1.4 has been validated using a separate validation dataset (n = 175) (Online Appendix), we consider that the PMR cutoff value of 1.4 has been validated as a significant risk factor for coronary events.

Finally, although CMR is considered a safe alternative to ionizing radiation–based imaging techniques, Fiechter et al. (21) reported deoxyribonucleic acid double-strand breaks in human lymphocytes induced by routine 1.5-T CMR examination. Further studies are needed to evaluate the health risks associated with MR techniques.

Conclusions

The present study demonstrates that HIPs identified by noncontrast T1WI are significantly associated with coronary events and may thus be a promising predictive factor in patients at high risk.

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Key Words: coronary disease ■ magnetic resonance imaging ■ plaque ■ prognosis.

APPENDIX

For supplementary data and tables, please see the online version of this article.