The present study was designed to evaluate the prevalence, clinical characteristics, and initial management of CE, and early and late outcomes, as well, in a large consecutive series of patients. We also propose new diagnostic criteria for CE based on histological, angiographic, and other diagnostic imaging findings.

Methods

Study Population and PCI Procedure

We retrospectively analyzed a total of 2135 consecutive patients with AMI from January 2001 to December 2013 in the National Cerebral and Cardiovascular Center AMI database. We excluded 359 patients with a history of previous myocardial infarction (n=241), PCI (n=90), coronary artery bypass grafting (n=18), or both PCI and coronary artery bypass grafting (n=10), resulting in a total of 1776 patients with de novo AMI that were ultimately analyzed in this study (Figure 1). All study patients underwent invasive coronary arteriography and transthoracic echocardiography. The details of imaging modalities used to diagnose CE are presented in Table I in the online-only Data Supplement. This retrospective study was approved by the National Cerebral and Cardiovascular Center institutional review board.

AMI was defined by biomarker evidence of myocardial ischemia with symptoms of ischemia, ECG changes suggestive of new ischemia (new ST-T changes or new left bundle-branch block), or the development of pathological Q waves on ECG.[20] An ST-segment–elevation myocardial infarction (STEMI) was defined as an AMI with new ST elevation at the J point in 2 continuous leads with the following cutoff points: ≥ 0.2 mV in men or ≥ 0.15 mV in women in leads V_2 through V_3 and ≥ 0.1 mV in other leads.[20]

Based on recommendations from the American Heart Association,[21] coronary stenosis was assessed through visual inspection by attending cardiologists in the core laboratory who were blinded to the clinical data. PCI was performed as previously described.[22] In brief, PCI was performed after intravenous administration of 10 000 IU heparin using a 6F or 7F sheath and catheters. Antiplatelet therapy before PCI consisted of aspirin only between January 2001 and November 2007 and aspirin and clopidogrel between October 2007 and December 2013. After crossing the target lesion with the guide wire, coronary thrombus aspiration was performed depending on the operator's judgment. Aspiration was performed using the 6F or 7F Thrombuster (Kaneka, Osaka, Japan), Rescue PT system (Boston Scientific, Maple Grove, MN), TVAC (Nipro, Osaka, Japan), or Eliminate (Terumo, Tokyo, Japan). Some patients with suboptimal results after thrombus aspiration or balloon angioplasty received bare metal or drug-eluting stents.

National Cerebral and Cardiovascular Center Criteria for the Clinical Diagnosis of CE

The case definition of CE used in this study consisted of 3 major and 3 minor criteria (Table 1). Scores based on these criteria were used to distinguish between definite and probable cases of CE in patients with AMI. The 3 major criteria included (1) angiographic evidence of coronary artery embolism and thrombosis without atherosclerotic components, (2) concomitant multisite CE, and (3) concomitant systemic embolization excluding left ventricular thrombus attributable to AMI. The 3 minor criteria included (1) coronary angiography shows <25% stenosis, except for the culprit lesion; (2) evidence of an embolic source detected by any imaging modality; and (3) coexistence of a potential for thromboembolic disease, that is, AF, cardiomyopathy, rheumatic valvular disease, infective myocarditis, prosthetic valve implantation, recent cardiac surgery, hypercoagulable state, patent foramen ovale, or atrial septal defect. We propose that the diagnosis of definite CE be based on the presence of ≥2 major criteria, 1 major criterion plus ≥2 minor criteria, or 3 minor criteria. Patients were categorized as probable CE if they fulfilled 1 major criterion plus 1 minor criterion or 2 minor criteria. We excluded patients with the following findings: (1) pathological evidence of atherosclerotic thrombus, (2) coronary artery ectasia,[23] (3) plaque disruption or coronary erosion detected by intravascular ultrasound or optic coherence tomography on the proximal site of the culprit lesion, and (4) history of coronary revascularization defined as a history of myocardial infarction, PCI for angina pectoris with proven ischemia, or silent myocardial ischemia diagnosed with stress myocardial scintigraphy, or coronary artery bypass grafting. Patients with ≥25% coronary artery stenosis outside of the culprit lesion on coronary angiography after the onset of CE were excluded.

Figure 2 shows a representative case of definite CE. This patient met 3 major criteria (concomitant multiple coronary vessel embolization, evidence of fresh thrombus without atherosclerotic components, and concomitant systemic embolization) and 3 minor criteria (evidence of an embolic source detected by transesophageal echocardiography), no significant coronary stenosis except after thrombus aspiration, and chronic AF).

Analysis of Embolic Risk Using the $CHADS_2$ and CHA_2DS_2-VASc Scores

We assessed the embolic risk of CE patients with nonvalvular AF (NVAF) using the $CHADS_2$ and the CHA_2DS_2-VASc scores.[24] The $CHADS_2$ scoring system assigns 1 point for heart failure, hypertension (HT), age ≥ 75 years, and diabetes mellitus (DM), and 2 points for previous stroke or transient ischemic attack. The CHA_2DS_2-VASc score extends the $CHADS_2$ scoring system with more detailed

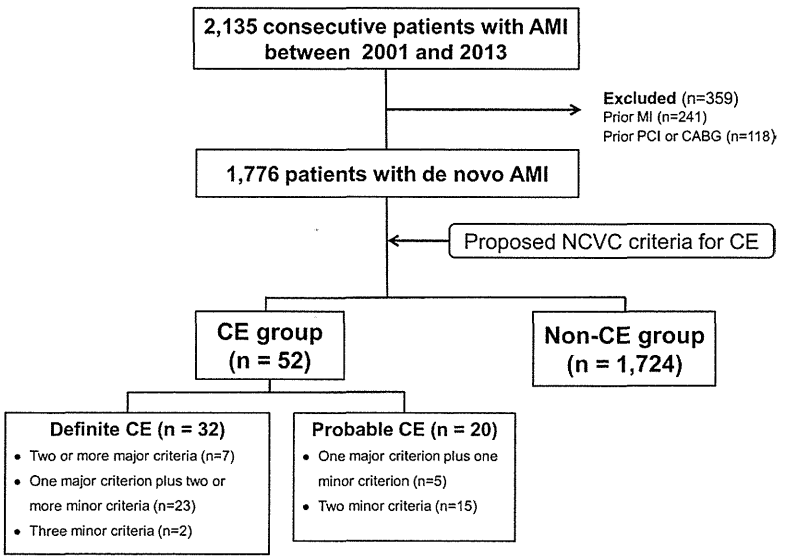

Figure 1. Flow chart of the study patients. We initially screened 2135 patients with AMI hospitalized between 2001 and 2013. We excluded 359 patients with previous MI, PCI, or CABG. A total of 1776 patients with AMI were ultimately analyzed in this study. According to the NCVC criteria for CE (see Table 1), 52 patients (2.9%) were diagnosed with CE; there were 32 patients diagnosed with definite CE and 20 patients diagnosed with probable CE. AMI indicates acute myocardial infarction; CABG, coronary artery bypass grafting; CE, coronary artery embolism; MI, myocardial infarction; NCVC, National Cerebral and Cardiovascular Center; and PCI, percutaneous coronary intervention.

Table 1. Proposed NCVC Criteria for the Clinical Diagnosis of Coronary Artery Embolism

Major criteria
▪ Angiographic evidence of coronary artery embolism and thrombosis without atherosclerotic components
▪ Concomitant coronary artery embolization at multiple sites*
▪ Concomitant systemic embolization without left ventricular thrombus attributable to acute myocardial infarction
Minor criteria
▪ <25% stenosis on coronary angiography, except for the culprit lesion
▪ Evidence of an embolic source based on transthoracic echocardiography, transesophageal echocardiography, computed tomography, or MRI
▪ Presence of embolic risk factors: atrial fibrillation, cardiomyopathy, rheumatic valve disease, prosthetic heart valve, patent foramen ovale, atrial septal defect, history of cardiac surgery, infective endocarditis, or hypercoagulable state
Definite CE
Two or more major criteria, or
One major criterion plus ≥2 minor criteria, or
Three minor criteria
Probable CE
One major criterion plus 1 minor criterion, or
Two minor criteria
A diagnosis of CE should not be made if there is
Pathological evidence of atherosclerotic thrombus
History of coronary revascularization
Coronary artery ectasia
Plaque disruption or erosion detected by intravascular ultrasound or optic coherence tomography in the proximal part of the culprit lesion

The present proposed diagnostic criteria for CE include 3 major and 3 minor criteria. Weighted scoring of the criteria is used to differentiate between definite and probable CE in patients with acute myocardial infarction. CE indicates coronary artery embolism; and NCVC, National Cerebral and Cardiovascular Center.

*Indicates multiple vessels within 1 coronary artery territory or multiple vessels in the coronary tree.

embolic risk assessment. This scoring system assigns 2 points for age ≥ 75 years and previous stroke or transient ischemic attack, and 1 point each for age 65 to 74 years, HT, DM, heart failure, vascular disease, and female sex. We also assessed the risk of bleeding using the HAS-BLED score.[25] The HAS-BLED scoring system assigns 1 point each for HT, renal dysfunction, liver dysfunction, stroke, bleeding history, labile international normalized ratio, age > 65 years, drug concomitantly, and alcohol abuse. A score of ≥3 indicates high bleeding risk.

End Points and Statistical Analysis

The major objective of this study was to estimate the prevalence of CE among patients with de novo AMI. We calculated the prevalence of CE among patients in our AMI database. We adopted the Bayesian-derived Jeffreys 95% confidence intervals (CIs) for proportions after comparing various CIs,[26] which were calculated by using the STATA CI command.[27]

End points included recurrent CE and major adverse cardiac and cerebrovascular events (MACCE), which consisted of cardiac death, myocardial infarction, ventricular tachycardia/ventricular fibrillation, stroke, or recurrent thromboembolism including CE >30 days after the onset of the initial CE event. Thromboembolic events include cardiogenic stroke, acute limb thromboembolism, and thromboembolic events in other organs. In-hospital and long-term outcomes were determined through medical record review, and, when necessary, through a questionnaire by mail and telephone follow-up. Because our AMI database (ie, non-CE group) had been followed only for cardiac and all-cause mortality but not MACCE, we presented the incidence of MACCE only in the CE group and compared the incidence of cardiac and all-cause mortality between the CE and non-CE groups.

Non-CE and CE subjects with AMI were matched based on a propensity score that included age; sex; history of DM, HT, and dyslipidemia; current smoking; and left ventricular ejection fraction. The propensity score was estimated using probit regression models,[28,29] with de novo AMI as the outcome and baseline clinical history and presentation characteristics as predictors (covariates are listed in Table 2, models 1 and 2). A propensity score–matched cohort was constructed with CE and non-CE patients on a 1:1 basis by using the nearest-neighbor matching method within a caliper of 0.01 of the propensity score with the psmatch2 procedure in the STATA program.[30] Details on how propensity score matching was performed are described in Materials in the online-only Data Supplement and Tables II through V in the online-only Data Supplement.

To compare the prognostic effects of CE between matched pairs, we used shared frailty models, which are used to model within-group correlations.[31,32] We used the matched pair as the random intercept in the Cox model with the STATA "shared" option for Cox regression.

Continuous variables are presented as means±standard deviation (SD) for normally distributed variables; they were compared using the *t* test. Nonnormally distributed variables are presented as medians (interquartile range). They were compared using the Mann-Whitney *U* test. Categorical baseline variables were compared using the Fisher exact test or the χ^2 test as appropriate. Kaplan–Meier methods were used to estimate survival curves for follow-up events. All *P* values <0.05 were considered statistically significant. All analyses were performed with SPSS (SPSS Japan, Tokyo, Japan) or STATA 13 (StataCorp, College Station, TX).

Results

Prevalence of CE in AMI and Comparison of Baseline Characteristics Between CE and Non-CE Patients

According to the proposed National Cerebral and Cardiovascular Center diagnostic criteria for CE, 52 (2.9%) of the 1776 patients with de novo AMI had CE (Figure 1), including 32 patients (62%) who fulfilled the criteria for definite CE and 20 patients (38%) categorized as having probable CE. The prevalence of CE was 2.9% (95% CI, 2.22–3.79). Table 2 compares the baseline clinical characteristics of the CE and non-CE groups. Of the 52 CE patients, 31 (60%) were male, with a mean age of 66±14 years. In comparison with the non-CE group, the CE group had a lower prevalence of HT (*P*=0.007), DM (*P*<0.001), dyslipidemia (*P*=0.001), and smoking (*P*=0.005). The CE group had a lower total number of coronary risk factors than the non-CE group (1.5±1.0 versus 2.6±1.2; *P*<0.001). The prevalence of AF was significantly higher in the CE group than in the non-CE group (73% versus 7%, *P*<0.001); there were 30 patients (58%) with NVAF in the CE group and 104 patients (6%) with NVAF in the non-CE group. The presenting diagnosis was STEMI in 65% of the CE group and 80% of the non-CE group (*P*=0.023). Peak creatine kinase was significantly higher in the non-CE group than in the CE group (3158±4013 versus 2210±2379 U/L, *P*=0.013), whereas no significant differences in left ventricular ejection fraction were seen between the two groups. Interestingly, although 30-day mortality in

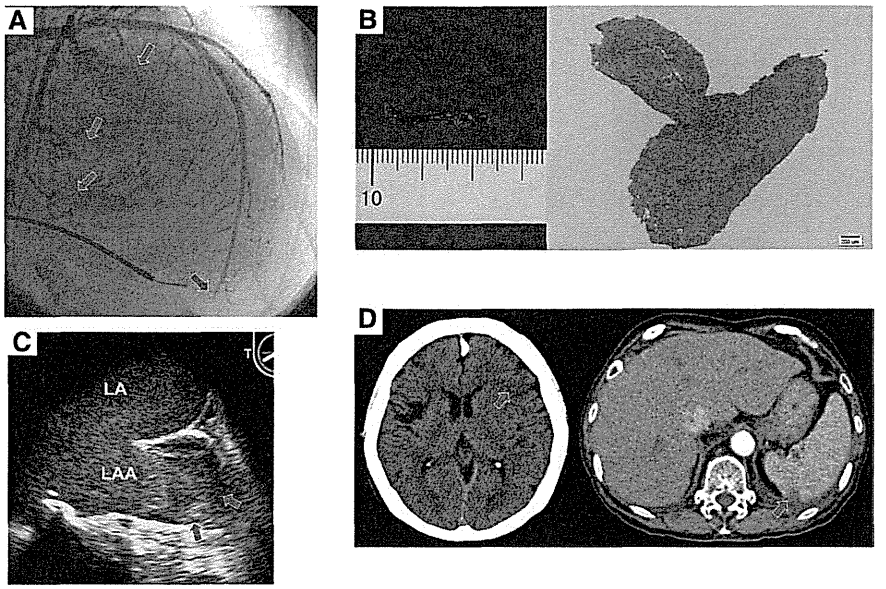

Figure 2. Representative case of definite CE. A 64-year-old woman presented with ST-segment–elevation myocardial infarction. **A**, Coronary angiography demonstrated total occlusion (red arrows) of the distal portion of the left anterior descending and circumflex arteries. **B**, Histological examination of the aspirated samples showed fresh red thrombus without evidence of an atherosclerotic component. **C**, Transesophageal echocardiography showed thrombus (red arrows) in the left atrial appendage (LAA). **D**, Computed tomography showed cerebral infarction (red arrow) and splenic infarction (red arrow). Based on these findings and a history of chronic atrial fibrillation, this patient was diagnosed with AMI attributable to definite CE (3 major criteria and 3 minor criteria for CE). AMI indicates acute myocardial infarction; CE, coronary artery embolism; and LA, left atrium.

the 2 groups was comparable (3 patients [6%] versus 55 patients [3%], P=0.240), all 3 CE patients died of noncardiac causes (lung cancer, n=2; stomach cancer, n=1). On the other hand, the 30-day cardiovascular death rate was significantly higher in the non-CE group than in the CE group (3% versus 0%, P<0.001).

Clinical Presentation, Causes, and Angiographic Findings of CE

Table 3 shows the clinical characteristics of CE. The most common underlying disease was AF (n=38; 73%). Cardiomyopathy was the next most common cause (n=13; 25%), followed by valvular heart disease (n=8, 15%). Of all 38 AF patients, 13

Table 2. Baseline Characteristics of Unmatched and Propensity Score–Matched Groups

	Unmatched Groups			Propensity Score-Matched Groups Model 1		Propensity Score-Matched Groups Model 2	
	CE (n=52)	non-CE (n=1724)	*P* Value	CE (n = 45)	non-CE (n=45)	CE (n=30)	non-CE (n=30)
Age, y	66±14	68±12	0.338	65±13	62±14	66±12	70±13
Male sex	31 (60)	1,229 (71)	0.087	27 (60)	31 (69)	19 (63)	15 (50)
Hypertension	25 (48)	1,155 (67)	0.007	22 (49)	21 (47)	15 (50)	19 (63)
Diabetes mellitus	4 (8)	692 (40)	<0.001	4 (9)	2 (4)	3 (10)	1 (3)
Dyslipidemia	16 (31)	936 (54)	0.001	14 (31)	19 (42)	10 (33)	12 (40)
Smoking	27 (52)	1226 (71)	0.005	24 (53)	23 (51)	18 (60)	11 (37)
Obesity (BMI ≥25 kg/m^2)	8 (15)	484 (28)	0.058				
Number of major coronary risk factors	1.5±1.0	2.6±1.2	<0.001				
Atrial fibrillation	38 (73)	116 (7)	<0.001				
Nonvalvular atrial fibrillation	30 (58)	104 (6)	<0.001				
STEMI	34 (65)	1371 (80)	0.023			21 (70)	19 (63)
Peak CK, units/L	2210±2379	3158±4013	0.013			1899±1502	2124±1569
Left ventricular EF, %	46±14	45±10	0.920	46±14	45±8	46±13	49±9
Chronic renal insufficiency							
30-day mortality	3 (6)	55 (3)	0.240				
Cardiovascular death	0 (0)	52 (3)	<0.001				
Noncardiovascular death	3 (6)	3 (0.2)	<0.001				

Categorical variables are expressed as n (%); continuous variables as mean±SD. Major coronary risk factors include hypertension, diabetes mellitus, dyslipidemia, smoking, and obesity. BMI indicates body mass index; CE, coronary artery embolism; CK, creatine kinase; EF, ejection fraction; SD, standard deviation; and STEMI, ST-segment–elevation myocardial infarction.

Table 3. Clinical Characteristics of CE

	CE (n=52)
Underlying cause of CE	
AF	38 (73)
Paroxysmal AF	13 (34)
Chronic AF	25 (66)
Nonvalvular AF	30 (58)
Cardiomyopathy	13 (25)
Idiopathic dilated cardiomyopathy	6 (46)
Hypertrophic cardiomyopathy	5 (38)
Hypertensive cardiomyopathy	1 (8)
Alcoholic cardiomyopathy	1 (8)
Valvular heart disease	8 (15)
Mitral valve stenosis	4 (50)
Aortic valve stenosis	4 (50)
Prosthetic valve	4 (50)
Malignancy	5 (10)
Lung	2 (40)
Stomach	1 (20)
Prostate	1 (20)
Breast (with tamoxifen therapy)	1 (20)
Septic emboli from IE	2 (4)
Embolism from a deep vein thrombus through a ASD	2 (4)
Involved vessel	
LMT	1 (2)
LAD	18 (35)
RCA	17 (33)
LCx	18 (35)
Multivessel embolization	8 (15)
Simultaneous systemic embolization	12 (23)
Cerebral infarction	8 (67)
Acute thromboembolic limb ischemia	3 (25)
Renal infarction	3 (25)
Splenic infarction	1 (4)
Intracardiac embolic source	16 (31)
Left atrium thrombus	12 (75)
Aortic valve vegetation attributable to IE	2 (13)
Mitral valve vegetation attributable to NBTE	1 (6)
Valsalva sinus thrombus	1 (6)

Categorical variables are expressed as n (%). ASD indicates atrial septal defect; AF, atrial fibrillation; CE, coronary artery embolism; IE, infectious endocarditis; LAD, left anterior descending artery; LCx, left circumflex artery; LMT, left main trunk; NBTE, nonbacterial thrombotic endocarditis; and RCA, right coronary artery.

(34%) had paroxysmal AF and 25 (66%) had chronic AF. There were 30 (58%) patients with NVAF. Of the 6 patients with dilated cardiomyopathy, 2 (33%) had chronic AF, and the remaining 4 (67%) had no history of either chronic or paroxysmal AF. On the other hand, all 5 patients with hypertrophic cardiomyopathy had chronic AF. Notable causes of CE were paradoxical embolism via an atrial septal defect attributable to deep vein thrombosis (n=2, 4%), malignancy (n=5, 10%), and septic emboli attributable to infective endocarditis (n=2, 4%).

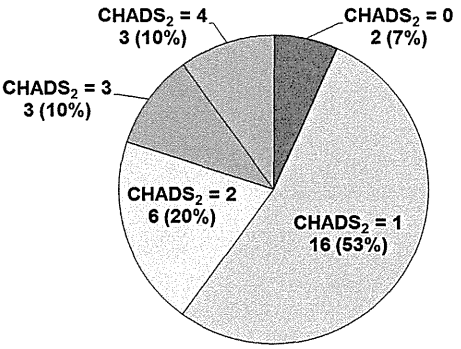

Figure 3. $CHADS_2$ scores in CE patients with nonvalvular atrial fibrillation (n=30). The $CHADS_2$ scoring system assigns 1 point each for heart failure, hypertension, age ≥75 years, and diabetes mellitus and 2 points each for previous stroke or transient ischemic attack. CE indicates coronary artery embolism.

There were no significant differences in the distribution of left anterior descending, left circumflex, and right coronary artery involvement. Coronary embolization at multiple sites was found in 8 patients (15%). Twelve (23%) patients presented with concomitant systemic embolization. Of these, 8 (67%) patients had stroke, 3 (25%) patients had acute lower limb ischemia, and 3 (25%) patients had renal infarction. An intracardiac embolic source was detected in 16 (31%) patients. Of these, 12 (75%) patients had left atrial thrombus and 2 (13%) patients had infected thrombi on the aortic valve. The diagnosis of intracardiac thrombi was made by transesophageal echocardiography in all patients, except 1 patient with end-stage lung cancer in whom a Valsalva sinus thrombus was detected by computed tomography angiography. All 12 patients with left atrial thrombus had AF (chronic AF, n=10; paroxysmal AF, n=2).

PCI Procedure for Patients With CE

A total of 29 (56%) patients underwent PCI; 28 of these 29 patients underwent initial thrombus aspiration and 1 patient was treated with balloon angioplasty alone. Of the 28 patients with initial thrombus aspiration, 5 (18%) patients underwent stent implantation and 4 (14%) patients underwent balloon angioplasty. Importantly, Thrombolysis in Acute Myocardial Infarction 3 flow was achieved in only 19 patients (66%). Reasons for failure in the remaining 10 patients included failure to cross into the distal lumen with the aspiration device owing to small vessel diameter (n=7) and residual distal thrombus after PCI (n=3).

Anticoagulation Status and $CHADS_2$/CHA_2DS_2-VAS Score in AF Patients

Of the 38 AF patients in the CE group, only 15 (39%) patients were treated with a vitamin K antagonist and their median international normalized ratio was 1.42 (range, 0.95–1.80) at the onset of CE. No patients were on non–vitamin K antagonist oral anticoagulants. Importantly, of the 30 patients with NVAF, 18 (60%) had a $CHADS_2$ score of 0 or 1 before the onset of CE (Figure 3). When those 18 patients with a low $CHADS_2$ score were reevaluated using the CHA_2DS_2-VASc score, 11 (61%) were categorized into a higher risk category (≥2) that would benefit from oral anticoagulation (Table 4).

Table 4. Reevaluation of Patients With a $CHADS_2$ Score of 0 or 1 Using the CHA_2DS_2-VASc Score

Age	Sex	Underlying Disease	$CHADS_2$ Score	CHA_2DS_2-VASc Score	HAS-BLED Score
77	F	–	1	4	1
88	F	–	1	3	1
74	F	Hypertensive cardiomyopathy	1	3	2
59	M	Alcoholic cardiomyopathy	1	2	2
73	M	–	1	2	1
71	M	–	1	2	1
70	M	–	1	2	1
81	M	–	1	2	1
64	M	HCM	1	2	0
66	M	–	1	2	1
58	F	HCM	1	2	2
43	M	DCM	1	1	0
64	M	–	1	1	0
45	M	DCM	1	1	1
64	M	HCM	1	1	0
43	M	–	1	1	0
55	F	–	0	1	0
50	M	–	0	0	0

DCM indicates dilated cardiomyopathy; F, female; HCM, hypertrophic cardiomyopathy; and M, male.

These patients did not have a high risk of bleeding based on the HAS-BLED score (<3).

Long-Term Outcomes of CE Patients

CE Recurrence and MACCE

Table 5 shows a summary of MACCE. During a median follow-up of 49 months (interquartile range, 19–93 months) with a 94.2% follow-up rate (n=49), 5 (10.4%) patients developed recurrent thromboembolic episodes: AMI attributable to CE in 2 patients (4.2%) and stroke in 3 patients (6.3%). All 5 patients with recurrent thromboembolism had AF (NVAF, n=3; valvular AF, n=2). The mean international normalized ratio at the time of the recurrent thromboembolism was 1.47±0.57. Figure 4A shows the Kaplan–Meier curves for survival free from the recurrence of CE or other thromboembolic events. After a primary CE event, the 5-year rate of recurrent CE or thromboembolism was 8.7%. The median time to a second episode of CE or thromboembolism was 35 months (interquartile range, 11–63 months).

Figure 4B shows the Kaplan–Meier curves for MACCE. Four patients experienced cardiac death (end-stage heart failure, n=3; sudden cardiac death, n=1), 2 had AMI, 3 developed stroke, and 2 experienced ventricular fibrillation (survived with bystander cardiopulmonary resuscitation and automated external defibrillation). The 5-year rate for MACCE was 27.1%.

Comparison of Long-Term Outcomes in Patients With CE Versus Non-CE AMI

We then compared the long-term outcomes between the CE and non-CE groups. Kaplan–Meier analysis showed a significantly higher incidence of all-cause death (hazard ratio [HR], 3.82; 95% CI, 2.06–6.48; $P<0.001$) and cardiac death (HR, 5.39; 95% CI, 2.38–10.6; $P<0.001$) in the CE group than in the non-CE group (Figure 5A and 5B). The 5-year rates of all-cause death and cardiac death in the CE group were significantly higher than those in the non-CE group (28% versus 7.6%, $P<0.001$; 17.5% versus 3.4%, $P<0.001$), respectively.

For further analysis, a propensity score–matched cohort consisting of 45 patients with CE and 45 patients without CE was selected (Table 2, model 1, and Tables II and III in the online-only Data Supplement). In this model that matched age; sex; history of DM, HT, and dyslipidemia; current smoking; and left ventricular ejection fraction, all-cause mortality (HR, 7.66; 95% CI, 1.65–35.45; $P<0.001$) and cardiac mortality (HR, 9.29; 95% CI, 1.13–76.5; $P<0.001$) were much

Table 5. Summary of MACCE During the Follow-up Period

MACCE	n (%)
Composite end point	11 (22.9)
Heart failure death	3 (6.3)
Sudden cardiac death	1 (2.1)
Ventricular fibrillation (successfully-resuscitated)	2 (4.2)
Recurrence of thromboembolism	5 (10.4)
CE resulting in AMI	2 (4.2)
Stroke	3 (6.3)
Other organs	0 (0)

Categorical variables are expressed as n (%). AMI indicates acute myocardial infarction; CE, coronary artery embolism; and MACCE, major adverse cardiac and cerebrovascular events (cardiovascular death, myocardial infarction, ventricular tachycardia/ventricular fibrillation, stroke, or recurrent thromboembolism including CE).

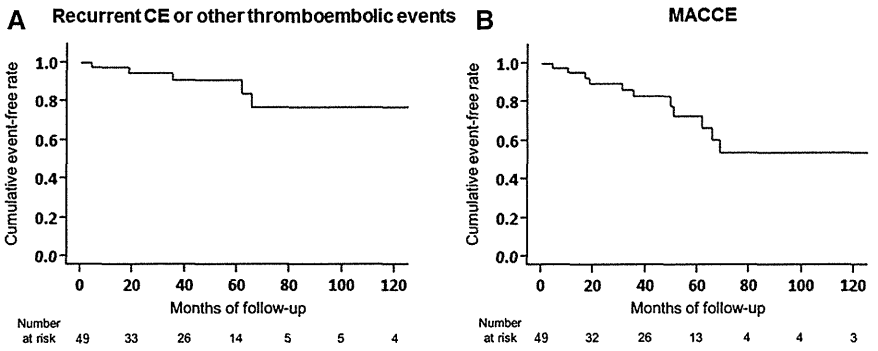

Figure 4. Kaplan–Meier curves for recurrent CE or other thromboembolic events and MACCE in patients with CE. Kaplan–Meier curves showing event-free survival with respect to recurrent CE or other thromboembolic events (**A**) and major adverse cardiac and cerebrovascular events (MACCE; **B**). MACCE include cardiac death, ventricular tachycardia/ventricular fibrillation, and recurrent thromboembolism >30 days after the onset of the initial CE event. The 5-year rate of recurrent CE or thromboembolism after a primary CE event was 8.7% (**A**). The 5-year rate for MACCE was 27.1% (**B**). CE indicates coronary artery embolism.

higher in the CE group than in the non-CE group. To further compare rates of cardiac and all-cause mortality between the 2 groups, an additional propensity score–matched cohort consisting of 30 patients with CE and 30 patients without CE was selected (Table 2, model 2, and Tables IV and V in the online-only Data Supplement). In this model that matched peak creatine kinase and history of STEMI in addition to all of the covariates in model 1, all-cause mortality (HR, 8.01; 95% CI, 1.42–45.13; P=0.018) and cardiac mortality (HR, 6.73; 95% CI, 1.07–42.28; P=0.042) were much higher in the CE group than in the non-CE group.

Discussion

The major findings of this study are as follows: (1) the prevalence of CE in patients with de novo AMI was 2.9%, (2) AF is the most frequent cause of CE; (3) 60% of NVAF patients in the CE group had low $CHADS_2$ scores; (4) the 5-year rate of thromboembolism, which includes CE recurrence, was 10.4% and the 5-year rate of MACCE was 27.1%. In addition, (5) although 30-day cardiovascular mortality in the CE group was significantly lower than that in the non-CE group, all-cause death and cardiac death during follow-up were significantly higher in the CE group than in the non-CE group. To the best of our knowledge, this is the first mechanistic study of the prevalence, clinical features, and prognosis of patients with AMI attributable to CE in the clinical setting.

Proposed Criteria for the Clinical Diagnosis of CE

In general, the diagnosis of CE has been made based on conventional angiographic features specific for coronary occlusion such as globular filling defects,[16] horse-riding thrombi,[8] or multiple filling defects[33] plus a couple of the following characteristics: (1) no atherosclerotic findings in the coronary trees, (2) presence of predisposing factors or comorbidities (ie, AF, intracardiac prosthesis, infective endocarditis, mural thrombus, or cardiac tumor), or (3) absence of significant stenosis at the culprit lesion after thrombus aspiration.[3] In this study, we have integrated these conventional findings as major and minor criteria (Table 1). Because recent advances in thrombectomy devices allow for the aspiration of histological samples that can provide additional information for diagnosing CE,[3] we have added pathological examination of aspirated thrombus as part of the major inclusion and exclusion criteria. Moreover, to represent the nature of thromboembolism, we have included concomitant systemic embolization as another major criterion in the present diagnostic criteria. To minimize including atherosclerotic causes of AMI, we have added the following as a minor criterion: < 25% stenosis on coronary angiography outside of the culprit lesion. We have also included plaque disruption and coronary erosion detected by optic coherence tomography and intravascular ultrasound as exclusion criteria. AMI secondary to coronary erosion is not associated with any significant atherosclerotic findings or plaque rupture.[34]

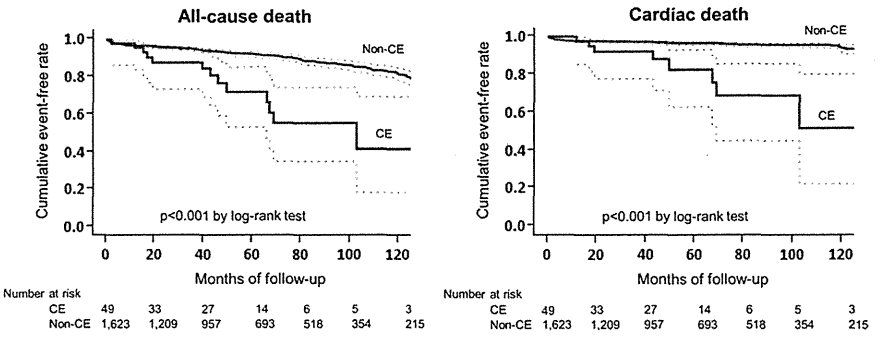

Figure 5. Comparison of long-term outcomes between AMI patients with and without CE. Kaplan–Meier curves showing the 5-year rate of survival free from all-cause death (**A**) and cardiac death (**B**). Kaplan–Meier analysis of all-cause and cardiac death demonstrated significantly poorer long-term outcomes in the CE group (solid red line) than in the non-CE group (solid blue line). The dotted lines indicate 95% confidence intervals. AMI indicates acute myocardial infarction; and CE, coronary artery embolism.

Prevalence of AF and Causes of CE

In the present study, we showed that the prevalence of de novo AMI attributable to CE according to our diagnostic criteria for CE was 2.9%. This is the first report on the prevalence of CE in AMI patients in a clinical setting. In comparison with a previous autopsy study that reported a CE prevalence of 13%,[2] the prevalence of CE in this study was relatively low. One possible explanation for this discrepancy may be attributable to the exclusion criteria used in this study. Because we intended to rigorously rule out atherosclerotic causes of AMI, we excluded patients with a history of coronary revascularization and ≥25% coronary stenosis under the new diagnostic criteria.

The cause of CE is multifactorial. In a 1978 autopsy-based study of 55 AMI patients, Prizel et al[2] reported that underlying diseases predisposing to CE included valvular heart disease (40%), cardiomyopathy (29%), coronary atherosclerosis (16%), and AF (24%). In another autopsy study, Charles et al[35] reported that the most common cause of CE was bacterial endocarditis; other causes included rheumatic heart disease, dilated cardiomyopathy, left atrial myxoma, arrhythmia, and myocardial infarction. In contrast to these previous autopsy reports, the present clinical study demonstrated that the most frequent underlying disease predisposing to CE was AF, and rheumatic or bacterial endocarditis constituted a small proportion of CE cases (Table 3). Decreases in the prevalence of rheumatic valvular heart disease and bacterial endocarditis with 3 decades of advances in medical therapy may have affected the prevalence of the underlying causes of CE. In addition, according to recent epidemiological studies in Europe and the United States, the prevalence of AF is ≈4% in individuals in their seventies, and ≈10% in those >80 years of age, indicating a significant increase with aging.[17]

Characteristics of CE

In this study, we found that CE patients have a lower prevalence of HT, DM, dyslipidemia, smoking, and total number of major coronary risk factors in comparison with non-CE AMI patients (Table 2). These findings may be related in part to the present exclusion criteria, even the minor criterion of <25% stenosis on coronary angiography outside the culprit lesion. Interestingly, in contrast to a previous autopsy study, there were no significant differences in the distribution of involved coronary vessels (Table 3). A previous autopsy study showed that CE occurs 3 to 4 times more often in the left coronary artery than in the right, and in the left anterior descending artery more often than in the left circumflex, because of their anatomic properties.[2] Such differences in the distribution of involved coronary vessels may be explained by bias related to the fact that arteries with larger territories are more likely to be involved in autopsy cases.

Clinical Implications of $CHADS_2$ and CHA_2DS_2-VASc Scores

In this study, 60% of NVAF patients had a $CHADS_2$ score of 0 or 1 (Figure 3) before CE onset. When those patients were reevaluated by using CHA_2DS_2-VASc, ≈61% were reassigned to a higher risk category (≥2) that would benefit from oral anticoagulation therapy (Table 4). This is clinically important, because many patients at low risk according to $CHADS_2$ are not truly low risk and treatment guidelines are not conclusive for patients at intermediate risk. Recent studies have demonstrated that CHA_2DS_2-VASc performs better than $CHADS_2$ in predicting patients at high risk for stroke and thromboembolism.[18,19] Consistent with these reports, our results suggest that the CHA_2DS_2-VASc score, not the $CHADS_2$ score, may yield useful clinical information regarding CE.

Thrombectomy During PCI for CE Patients and In-hospital Outcomes

In the present study, 58% of patients underwent PCI, of which 97% had thrombus aspiration as the initial PCI strategy. Thrombus aspiration devices have been used widely in recent years in STEMI patients with angiographic evidence of thrombus. They have been shown to be a feasible and effective strategy for the treatment of AMI, including CE-related infarction.[3] Importantly, histological examination of the aspirated thrombus provides additional information for diagnosing CE.[3] Although thrombus aspiration appears to be a reasonable option for CE patients, Stoel et al[14] reported that the smaller inner lumen diameter of aspiration catheters makes them less useful for aspirating large thrombi. In addition, crossing into the distal lumen with the aspiration device is challenging; indeed, 42% of the present patients were treated conservatively because of far distal occlusion or the small diameter of the vessel with the culprit lesion.

In this study, although the CE group had a Thrombolysis in Acute Myocardial Infarction 3 flow achievement rate of 66%, they had significantly lower peak creatine kinase and similar LVEF in comparison with the non-CE group. In addition, cardiovascular death within 30 days was significantly lower in the CE group than in the non-CE group (Table 2). These findings may be related in part to the distribution of occlusive thrombi in the coronary system after thrombus aspiration or PCI; that is, occlusive thrombi moved more distally from the culprit lesion after intervention, and this phenomenon may have affected infarct size and 30-day mortality.

Long-Term Prognosis of CE

The 5-year rate of thromboembolism including CE recurrence was 8.7% and the 5-year rate of MACCE was 27.1% in the present study population (Figure 4). It is notable that recurrent CE occurred exclusively in AF patients with inadequate international normalized ratio. This finding highlights the need for adequate vitamin K antagonist therapy for preventing CE recurrence. In addition, in comparison with the non-CE group, the 5-year rates of all-cause death and cardiac death in the CE group were unexpectedly high (Figure 5A and 5B). These unfavorable outcomes in the CE group were more pronounced in the propensity score–matched cohort analysis. The unexpectedly higher mortality rates in the CE group may be related to comorbidities (ie, cardiomyopathy or valvular heart disease). It should be noted that approximately one-third of those particular patients with underlying heart disease had AF, which may affect hemodynamics and lead to the development of heart failure. In the CE group, malignancy was a characteristic comorbidity. It was associated with noncardiovascular

death within 30 days but not long-term prognosis in the present study. These findings suggest that CE events may be related to an advanced stage of malignancy.

Limitations

The present study has several limitations. First, the retrospective and single-site nature of this study and the small number of cardiac events observed might have resulted in a certain extent of bias. Second, because the proposed diagnostic criteria exclude patients with ≥25% coronary artery stenosis or a history of revascularization, some patients with CE plus coronary artery disease may have been excluded; thus, the prevalence of CE may have been underestimated. Finally, the rates of all-cause and cardiac mortality in the non-CE group (ie, de novo AMI subjects without CE) in this study were much lower than those in Western countries.[36,37] However, a recent large prospective registry study in Japan demonstrated that all-cause mortality at 2 years of follow-up was 6.3% in patients with acute coronary syndrome.[38] Our observed mortality rate was consistent with that result.

Conclusion

This study found that the prevalence of CE in patients with AMI was 2.9%, and AF was the most frequent cause. Long-term outcomes indicate that CE patients represent a high-risk subpopulation of patients with AMI and therefore require close follow-up.

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Disclosures

None.

References

1. Waller BF. Atherosclerotic and nonatherosclerotic coronary artery factors in acute myocardial infarction. *Cardiovasc Clin.* 1989;20:29–104.
2. Prizel KR, Hutchins GM, Bulkley BH. Coronary artery embolism and myocardial infarction. *Ann Intern Med.* 1978;88:155–161.
3. Kotooka N, Otsuka Y, Yasuda S, Morii I, Kawamura A, Miyazaki S. Three cases of acute myocardial infarction due to coronary embolism: treatment using a thrombus aspiration device. *Jpn Heart J.* 2004;45:861–866.
4. Garg RK, Jolly N. Acute myocardial infarction secondary to thromboembolism in a patient with atrial fibrillation. *Int J Cardiol.* 2007;123:e18–e20. doi: 10.1016/j.ijcard.2006.11.095.
5. Van de Walle S, Dujardin K. A case of coronary embolism in a patient with paroxysmal atrial fibrillation receiving tamoxifen. *Int J Cardiol.* 2007;123:66–68.
6. Sakai K, Inoue K, Nobuyoshi M. Aspiration thrombectomy of a massive thrombotic embolus in acute myocardial infarction caused by coronary embolism. *Int Heart J.* 2007;48:387–392.
7. Taniike M, Nishino M, Egami Y, Kondo I, Shutta R, Tanaka K, Adachi T, Tanouchi J, Yamada Y, Kawano K. Acute myocardial infarction caused by a septic coronary embolism diagnosed and treated with a thrombectomy catheter. *Heart.* 2005;91:e34. doi: 10.1136/hrt.2004.055046.
8. Hernández F, Pombo M, Dalmau R, Andreu J, Alonso M, Albarrán A, Velázquez MT, Tascón JC. Acute coronary embolism: angiographic diagnosis and treatment with primary angioplasty. *Catheter Cardiovasc Interv.* 2002;55:491–494.
9. Iwama T, Asami K, Kubo I, Kitazume H. Hypertrophic cardiomyopathy complicated with acute myocardial infarction due to coronary embolism. *Intern Med.* 1997;36:613–617.
10. Takenaka T, Horimoto M, Igarashi K, Yoshie H, Tsujino I, Morihira M. Multiple coronary thromboemboli complicating valvular heart disease and atrial fibrillation. *Am Heart J.* 1996;131:194–196.
11. Acikel S, Dogan M, Aksoy MM, Akdemir R. Coronary embolism causing non-ST elevation myocardial infarction in a patient with paroxysmal atrial fibrillation: treatment with thrombus aspiration catheter. *Int J Cardiol.* 2011;149:e33–e35. doi: 10.1016/j.ijcard.2009.03.077.
12. Camaro C, Aengevaeren WR. Acute myocardial infarction due to coronary artery embolism in a patient with atrial fibrillation. *Neth Heart J.* 2009;17:297–299.
13. Dogan M, Acikel S, Aksoy MM, Cagirci G, Kilic H, Yesilay A, Akdemir R. Coronary saddle embolism causing myocardial infarction in a patient with mechanical mitral valve prosthesis: treatment with thrombolytic therapy. *Int J Cardiol.* 2009;135:e47–e48. doi: 10.1016/j.ijcard.2008.03.073.
14. Stoel MG, von Birgelen C, Zijlstra F. Aspiration of embolized thrombus during primary percutaneous coronary intervention. *Catheter Cardiovasc Interv.* 2009;73:781–786. doi: 10.1002/ccd.21894.
15. Tang L, Hu XQ, Zhou SH. Coronary artery embolism causing acute myocardial infarction in patients with mechanical heart valve prosthesis: which is the optimal treatment? *Heart Lung Circ.* 2014;23:422–427. doi: 10.1016/j.hlc.2013.10.086.
16. Ilia R, Weinstein JM, Wolak A, Cafri C. Coronary thrombus in ST elevation myocardial infarction and atrial fibrillation. *J Thromb Thrombolysis.* 2013;35:119–122. doi: 10.1007/s11239-012-0765-z.
17. Chugh SS, Blackshear JL, Shen WK, Hammill SC, Gersh BJ. Epidemiology and natural history of atrial fibrillation: clinical implications. *J Am Coll Cardiol.* 2001;37:371–378.
18. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Chest.* 2010;137:263–272. doi: 10.1378/chest.09-1584.
19. Olesen JB, Lip GY, Hansen ML, Hansen PR, Tolstrup JS, Lindhardsen J, Selmer C, Ahlehoff O, Olsen AM, Gislason GH, Torp-Pedersen C. Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: nationwide cohort study. *BMJ.* 2011;342:d124.
20. Senter S, Francis GS. A new, precise definition of acute myocardial infarction. *Cleve Clin J Med.* 2009;76:159–166. doi: 10.3949/ccjm.75a.08092.
21. Austen WG, Edwards JE, Frye RL, Gensini GG, Gott VL, Griffith LS, McGoon DC, Murphy ML, Roe BB. A reporting system on patients evaluated for coronary artery disease. Report of the Ad Hoc Committee for Grading of Coronary Artery Disease, Council on Cardiovascular Surgery, American Heart Association. *Circulation.* 1975;51(4 suppl):5–40.
22. Arakawa K, Yasuda S, Hao H, Kataoka Y, Morii I, Kasahara Y, Kawamura A, Ishibashi-Ueda H, Miyazaki S. Significant association between neutrophil aggregation in aspirated thrombus and myocardial damage in patients with ST-segment elevation acute myocardial infarction. *Circ J.* 2009;73:139–144.
23. Manginas A, Cokkinos DV. Coronary artery ectasias: imaging, functional assessment and clinical implications. *Eur Heart J.* 2006;27:1026–1031. doi: 10.1093/eurheartj/ehi725.
24. European Heart Rhythm Association, European Association for Cardio-Thoracic Surgery, Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S, Van Gelder IC, Al-Attar N, Hindricks G, Prendergast B, Heidbuchel H, Alfieri O, Angelini A, Atar D, Colonna P, De Caterina R, De Sutter J, Goette A, Gorenek B, Heldal M, Hohloser SH, Kolh P, Le Heuzey JY, Ponikowski P, Rutten FH. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Eur Heart J.* 2010;31:2369–2429.
25. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest.* 2010;138:1093–1100. doi: 10.1378/chest.10-0134.
26. Brown LD, Cai TT, DasGupta A. Interval estimation for a binomial proportion. *Stat Sci.* 2001;16:101–133.
27. Jeffreys H. An invariant form for the prior probability in estimation problems. *Proc R Soc Lond A Math Phys Sci.* 1946;186:453–461.
28. Rosenbaum PR, Rubin DB. Reducing bias in observational studies using subclassification on the propensity score. *J Am Statist Assoc.* 1984;79:516–524.
29. Imbens G. The role of the propensity score in estimating dose-response functions. *Biometrika.* 2000;87:706–710.
30. Guo S. *Propensity Score Analysis:* Statistical Methods and Applications. Thousand Oaks, CA: Sage publications; 2010.

31. Hougaard P. Life table methods for heterogeneous populations: Distributions describing the heterogeneity. *Biometrika.* 1984;71:75–83.
32. Gutierrez RG. Parametric frailty and shared frailty survival models. *Sata J.* 2002;2:22–44.
33. Wang LW, Omari A, Muller DW, Jacobs NH, Subbiah RN. Coronary artery embolization after successful surgical ablation of atrial fibrillation. *Circulation.* 2013;127:960–961. doi: 10.1161/CIRCULATIONAHA.112.150359.
34. Jia H, Abtahian F, Aguirre AD, Lee S, Chia S, Lowe H, Kato K, Yonetsu T, Vergallo R, Hu S, Tian J, Lee H, Park SJ, Jang YS, Raffel OC, Mizuno K, Uemura S, Itoh T, Kakuta T, Choi SY, Dauerman HL, Prasad A, Toma C, McNulty I, Zhang S, Yu B, Fuster V, Narula J, Virmani R, Jang IK. *In vivo* diagnosis of plaque erosion and calcified nodule in patients with acute coronary syndrome by intravascular optical coherence tomography. *J Am Coll Cardiol.* 2013;62:1748–1758. doi: 10.1016/j.jacc.2013.05.071.
35. Charles RG, Epstein EJ. Diagnosis of coronary embolism: a review. *J R Soc Med.* 1983;76:863–869.
36. Saito M, Fukami K, Hiramori K, Haze K, Sumiyoshi T, Kasagi H, Horibe H. Long-term prognosis of patients with acute myocardial infarction: is mortality and morbidity as low as the incidence of ischemic heart disease in Japan. *Am Heart J.* 1987;113:891–897.
37. Goldberg RJ, Currie K, White K, Brieger D, Steg PG, Goodman SG, Dabbous O, Fox KA, Gore JM. Six-month outcomes in a multinational registry of patients hospitalized with an acute coronary syndrome (the Global Registry of Acute Coronary Events [GRACE]). *Am J Cardiol.* 2004;93:288–293. doi: 10.1016/j.amjcard.2003.10.006.
38. Daida H, Miyauchi K, Ogawa H, Yokoi H, Matsumoto M, Kitakaze M, Kimura T, Matsubara T, Ikari Y, Kimura K, Tsukahara K, Origasa H, Morino Y, Tsutsui H, Kobayashi M, Isshiki T; PACIFIC investigators. Management and two-year long-term clinical outcome of acute coronary syndrome in Japan: prevention of atherothrombotic incidents following ischemic coronary attack (PACIFIC) registry. *Circ J.* 2013;77:934–943.

CLINICAL PERSPECTIVE

Coronary artery embolism is an infrequent but important cause of acute myocardial infarction. It is a nonatherosclerotic entity whose clinical characteristics have not been elucidated. This retrospective single-center study evaluated the prevalence, clinical features, initial management, and early and late outcomes of 52 patients with coronary artery embolism with the use of our proposed diagnostic criteria. We found that atrial fibrillation with a low burden of atherosclerotic risk factors was the most frequent cause of coronary artery embolism. Only 39% of patients with atrial fibrillation were treated with vitamin K antagonists, but their median international normalized ratios were inadequate. Thrombus aspiration as the initial management strategy was useful for achieving Thrombolysis in Acute Myocardial Infarction 3 grade flow in select patients. Although early clinical outcomes (30-day mortality) were comparable to those for acute myocardial infarction with atherosclerotic etiologies, both cardiac and all-cause mortality were unexpectedly high during long-term follow-up. Coronary artery embolization recurred in 3.8% of patients, all with atrial fibrillation. These findings underscore the need for close follow-up in this high-risk patient population.

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Effect of Intensive Statin Therapy on Coronary High-Intensity Plaques Detected by Noncontrast T1-Weighted Imaging

The AQUAMARINE Pilot Study

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ABSTRACT

BACKGROUND Coronary high-intensity plaques detected by noncontrast T1-weighted imaging may represent plaque instability. High-intensity plaques can be quantitatively assessed by a plaque-to-myocardium signal-intensity ratio (PMR).

OBJECTIVES This pilot, hypothesis-generating study sought to investigate whether intensive statin therapy would lower PMR.

METHODS Prospective serial noncontrast T1-weighted magnetic resonance imaging and computed tomography angiography were performed in 48 patients with coronary artery disease at baseline and after 12 months of intensive pitavastatin treatment with a target low-density lipoprotein cholesterol level <80 mg/dl. The control group consisted of coronary artery disease patients not treated with statins that were matched by propensity scoring (n = 48). The primary endpoint was the 12-month change in PMR. Changes in computed tomography angiography parameters and high-sensitivity C-reactive protein levels were analyzed.

RESULTS In the statin group, 12 months of statin therapy significantly improved low-density lipoprotein cholesterol levels (125 to 70 mg/dl; $p < 0.001$), PMR (1.38 to 1.11, an 18.9% reduction; $p < 0.001$), low-attenuation plaque volume, and the percentage of total atheroma volume on computed tomography. In the control group, the PMR increased significantly (from 1.22 to 1.49, a 19.2% increase; $p < 0.001$). Changes in PMR were correlated with changes in low-density lipoprotein cholesterol ($r = 0.533$; $p < 0.001$), high-sensitivity C-reactive protein ($r = 0.347$; $p < 0.001$), percentage of atheroma volume ($r = 0.477$; $p < 0.001$), and percentage of low-attenuation plaque volume ($r = 0.416$; $p < 0.001$).

CONCLUSIONS Statin treatment significantly reduced the PMR of high-intensity plaques. Noncontrast T1-weighted magnetic resonance imaging could become a useful technique for repeated quantitative assessment of plaque composition. (Attempts at Plaque Vulnerability Quantification with Magnetic Resonance Imaging Using Noncontrast T1-weighted Technique [AQUAMARINE]; UMIN000003567) (J Am Coll Cardiol 2015;66:245-56) © 2015 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome(s)

CAD = coronary artery disease

CMR = cardiac magnetic resonance

CTA = computed tomography angiography

HbA_{1c} = glycosylated hemoglobin

HDL-C = high-density lipoprotein cholesterol

HIP = high-intensity plaque

hs-CRP = high-sensitivity C-reactive protein

HU = Hounsfield unit

IPH = intraplaque hemorrhage

IVUS = intravascular ultrasound

LAP = low-attenuation plaque

LCL-C = low-density lipoprotein-cholesterol

PCI = percutaneous coronary intervention

PMR = plaque-to-myocardium signal-intensity ratio

RI = remodeling index

TAV = total atheroma volume

T1WI = T1-weighted magnetic resonance imaging

A coronary artery showing high-intensity plaque (HIP) on noncontrast T1-weighted magnetic resonance imaging (T1WI) has been reported to be high risk because of its strong correlation with positive remodeling and low attenuation observed on computed tomography angiography (CTA) or intravascular ultrasound (IVUS) (1). The T1WI technique highlights intraplaque components with short T1 as having a high signal intensity. A necrotic core with intraplaque hemorrhage (IPH) or thrombus gives rise to a short T1 signal (2,3). A plaque-to-myocardium signal-intensity ratio (PMR) ≥1.4 during T1WI may be a significant predictor of major adverse cardiac events in patients with coronary artery disease (CAD) (4). If coronary HIP with a high PMR represents a high-risk plaque and a greater likelihood of unfavorable outcomes, then it is reasonable to propose that a quantitative reduction in HIP may help plaque stabilization.

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Several randomized studies have demonstrated the benefits of statins in reducing both mortality and the incidence of acute coronary syndrome (ACS) (5-7). In addition to reducing levels of serum low-density lipoprotein-cholesterol (LDL-C), statins also may contribute to plaque stability by reducing inflammation (8), improving endothelial function, (9), and reinforcing the fibrous cap (10,11); these effects alter plaque volume and composition, both of which play crucial roles in the progression to ACS (12,13). Serial imaging studies suggest that statins favorably affect the magnitude of the lipid-rich necrotic core (10,14), but there are no prospective studies examining the effect of intensive statin therapy on coronary HIP or IPH. Hence, we undertook the prospectively designed, open-label AQUAMARINE (Attempts at Plaque Vulnerability Quantification with Magnetic Resonance Imaging Using Noncontrast T1-weighted Technique) pilot study to investigate whether intensive statin therapy could decrease the PMR of coronary HIPs through its plaque-stabilizing effects.

METHODS

The AQUAMARINE pilot study was a prospective, open-label, propensity score-matched study at 2 centers examining the effect of 12 months of pitavastatin therapy (with target LDL-C levels <80 mg/dl) on the PMR and CTA measures in patients with CAD. The primary endpoint was the change in the PMR of HIP after intensive pitavastatin treatment. The secondary endpoints were the change in CTA-measured indexes (described below) and high-sensitivity C-reactive protein (hs-CRP) levels as assayed by latex nephelometry from fasting serum samples (SRL, Tokyo, Japan).

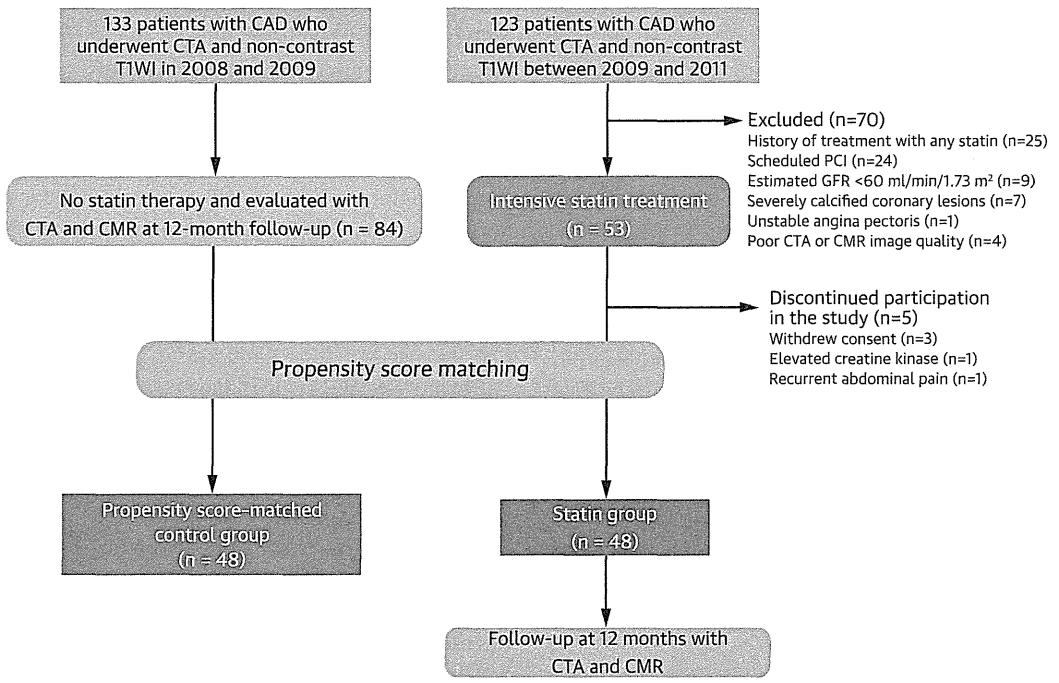
All imaging and laboratory data were analyzed by an independent attending physician and radiologist at the National Cerebral and Cardiovascular Center (Japan), including cardiac magnetic resonance (CMR) and CTA measurements. These evaluators were blinded to patient treatment status. This study was approved by the institutional review board of the National Cerebral and Cardiovascular Center and the ethics committee of Shin-Koga Hospital. Written informed consent was obtained from all enrolled patients.

Between June 2009 and December 2011, 123 consecutive patients with CAD were initially screened with CTA followed by CMR using noncontrast T1WI (**Figure 1**). Patients were excluded if they had 1) a history of treatment with any statin before enrollment (n = 25); 2) scheduled percutaneous coronary intervention (PCI) (n = 24); 3) an estimated glomerular filtration rate <60 ml/min/1.73 m^2 (n = 9); 4) severely calcified coronary lesions detected by CTA (n = 7); 5) unstable angina pectoris (n = 1); or 6) poor CMR or CTA image quality (n = 4). CAD was defined as a history of myocardial infarction or PCI, symptomatic angina pectoris or silent ischemia diagnosed with stress myocardial scintigraphy, or coronary arteriography-verified coronary artery stenosis >25%, as previously reported (4).

In the intensive therapy arm, 53 patients received pitavastatin 4 mg/day to achieve an LDL-C level <80 mg/dl (15). Of these patients, 5 needed to be excluded: 1 patient had elevated creatine kinase levels (although <5 times the upper limit of normal); 1 had recurrent abdominal pain; and 3 patients withdrew consent, leaving 48 patients in the treatment arm (**Figure 1**). CTA and CMR were performed at week 0 (baseline) and at 12 months (follow-up) after pitavastatin administration.

For ethical reasons, the institutional review board did not approve a study in which patients with CAD would be randomized to no lipid-lowering statin therapy. Therefore, the control group consisted of 133 CAD patients who underwent CTA and noncontrast T1WI at baseline and 12 months of follow-up between 2008 and 2009. Of these patients, 84 patients who did not receive statins or other LDL-lowering agents (e.g., ezetimibe) were matched according to a

FIGURE 1 Flow Chart of the Study Patients



This chart depicts the enrollment, exclusion, and matching of patients with coronary artery disease (CAD) who became part of the statin group or the propensity-matched control group. CMR = cardiac magnetic resonance; CTA = computed tomography angiography; GFR = glomerular filtration rate; PCI = percutaneous coronary intervention; T1WI = T1-weighted imaging.

propensity score on the basis of age, sex, body mass index, systolic blood pressure, history of diabetes mellitus, hypertension, dyslipidemia, and current smoking, as well as baseline LDL-C, total cholesterol, high-density lipoprotein cholesterol (HDL-C), triglycerides, glycosylated hemoglobin (HbA_{1c}) levels, hs-CRP, medications, and PMR. Subsequently, 48 propensity score-matched control subjects were included in the study. Control patients not on a statin declined any form of lipid-lowering pharmacotherapy and insisted on dietary intervention alone (n = 39), had a history of an adverse event associated with statin therapy (n = 6), or received ethyl icosapentate (n = 26) or bezafibrate or fenofibrate (n = 13).

CMR IMAGING AND ANALYSIS. CMR imaging consisted of magnetic resonance coronary angiography and plaque T1WI using a commercial 1.5-T magnetic resonance imager (Intera, Philips Medical Systems, Best, the Netherlands). The procedures used to acquire magnetic resonance images in this study have been previously described (4).

The methods that we used to evaluate plaque images also have been described previously (1,4). Briefly, 2 independent experienced investigators who were unaware of the patient data used the T1WI to calculate the PMR at the central core laboratory. The highest signal intensity detected in each plaque was considered the PMR value for that plaque in the segment-based analysis. On patient-based analysis, the highest PMR among the coronary plaques was considered the PMR for that patient. Examination of coronary segments was limited to 1 to 3, 5 to 7, and 11 to 13, on the basis of recommendations from the American Heart Association (16). To confirm that the location of an observed HIP corresponded to the presence of a coronary plaque, we used both cross-sectional and curved multiplanar reformation CTA images. Additionally, we used coregistration images to facilitate confirmation of the anatomic position of high-intensity lesions on T1WI and the coronary vessel on magnetic resonance coronary angiography using commercially available software (Virtual Place Raijin Workstation, AZE, Tokyo, Japan) (4). Regarding PMR quantification of coronary plaques without HIP, when CTA showed >20% coronary stenosis in segments 1 to 3, 5 to 7, or 11 to 13, the PMR of the target

lesion was measured using the coregistration method described previously. The intraobserver intraclass correlation coefficient was 0.94 (95% confidence interval [CI]: 0.80 to 0.98). The interobserver intraclass correlation was 0.88 (95% CI: 0.73 to 0.95). All correlation coefficients for the PMR were >0.8, with narrow CIs, indicating good intraobserver and interobserver agreement (4).

CTA SCANNING AND ANALYSIS. Coronary CTA was performed using a LightSpeed VCT scanner (GE Healthcare, Milwaukee, Wisconsin). The procedures used to acquire CTA images have been previously described (1). We used the same protocol and same dose of contrast medium at both baseline and follow-up CTA in each patient.

We examined coronary segments with >20% diameter stenosis in segments 1 to 3, 5 to 7, and 11 to 13. Quantitative lesion analysis was performed using software that facilitates plaque and lumen volume measurement (Ziostation2, Ziosoft, Tokyo, Japan). Parameters assessed included: 1) plaque volume; 2) remodeling index (RI) with plaques having an RI ≥1.10 considered to be within a positive remodeled artery (17); and 3) Hounsfield unit (HU), as coded by the software into low-attenuation plaques (LAPs) (<30 HU), intermediate attenuation plaques (30 to 150 HU), calcified plaques (351 to 1,000 HU), and lumen (151 to 350 HU) by color. The volume of each component was measured (17,18). Each lesion was analyzed for total atheroma volume (TAV), lumen volume, RI, LAP volume, percentage of total atheroma volume, and percentage of LAP volume.

DATA AND STATISTICAL ANALYSIS. We used propensity-score matching to adjust for the nonrandom absence of statin therapy after CMR and CTA. The propensity score was estimated by using probit regression models (19,20), with pre-evaluation statin administration as the outcome. It included baseline clinical history and presentation characteristics as predictors (covariates are listed in **Table 1**). A propensity score-matched cohort was constructed with statin receivers and nonreceivers matched on a 1:1 basis by a nearest-neighbor matching method within a caliper of 0.05 of the propensity score, using STATA's psmatch2 software (StataCorp LP, College Station, Texas) for propensity-score matching (21). Next, 48 patients were selected for the control group. because we previously identified a PMR of 1.4 as the optimal cutoff value for predicting coronary events (4), both the treatment and control groups were further classified according to the PMR cutoff value of either ≥1.4 or <1.4.

TABLE 1 Baseline Characteristics

	Unmatched Groups			Propensity Score-Matched Groups		
	Statin Group (n = 48)	Control Group (n = 84)	p Value	Statin Group (n = 48)	Control Group (n = 48)	p Value
Age, yrs	62.6	65.0	0.145	62.6	62.7	0.945
Male	44 (92)	71 (85)	0.290	44 (92)	45 (94)	0.782
Hypertension	34 (71)	61 (73)	0.843	34 (71)	35 (73)	0.897
Current smoker	18 (38)	44 (52)	0.107	18 (38)	19 (40)	0.896
Dyslipidemia	40 (83)	48 (57)	0.002	40 (83)	38 (79)	0.712
Diabetes mellitus	30 (63)	42 (50)	0.204	30 (63)	29 (60)	0.806
BMI, kg/m^2	24.8 ± 3.5	24.1 ± 3.0	0.192	24.8 ± 3.5	24.6 ± 2.8	0.815
SBP, mm Hg	143 ± 18	145 ± 22	0.458	143 ± 18	144 ± 20	0.784
TC, mg/dl	208 ± 34	195 ± 31	0.020	208 ± 34	211 ± 38	0.740
LDL, mg/dl	125 ± 25	114 ± 26	0.006	125 ± 25	126 ± 21	0.900
HDL, mg/dl	50 ± 13	51 ± 14	0.754	50 ± 13	51 ± 10	0.748
TG, mg/dl	179 ± 95	155 ± 107	0.190	179 ± 95	167 ± 81	0.592
HbA_{1c}, %	6.1 ± 1.2	6.3 ± 1.7	0.459	6.1 ± 1.2	6.1 ± 1.1	0.902
hs-CRP, mg/l	1.19 (0.65, 3.31)	1.04 (0.43, 2.60)	0.881	1.19 (0.65, 3.31)	1.12 (0.33, 3.42)	0.984
PMR	1.38 (1.20, 1.50)	1.20 (1.03, 1.44)	0.225	1.38 (1.20, 1.50)	1.22 (1.01, 1.56)	0.922
Medications						
Aspirin	43 (90)	74 (88)	1.000	43 (90)	44 (92)	1.000
Beta-blocker	28 (58)	42 (50)	0.372	28 (58)	21 (44)	0.220
ACEI or ARB	21 (44)	35 (42)	0.856	21 (44)	17 (35)	0.532

Values are mean ± SD, n (%), or median (first quartile, third quartile).

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; BMI = body mass index; HbA_{1c} = glycosylated hemoglobin; hs-CRP = high-sensitivity C-reactive protein; HDL = high-density lipoprotein; LDL = low-density lipoprotein; PMR = plaque-to-myocardium signal-intensity ratio; SBP = systolic blood pressure; TC = total cholesterol; TG = triglycerides.

Continuous variables are presented as mean ± SD for normally distributed variables; they were compared using the Student *t* test. Non-normally distributed variables are presented as median (interquartile range). They were compared using a Mann-Whitney *U* test. Categorical baseline variables were compared using the Fisher exact test or the chi-square test as appropriate. Given that plaque lumen volume, TAV, LAP volume, and RI were not normally distributed at baseline, the Wilcoxon signed rank test was used for comparisons involving CTA indexes and PMR between the statin and control groups. Because segments within patients were not independent, predicted PMRs were obtained from a linear mixed model with random intercepts in which each patient was considered as the hierarchy. Two-by-two repeated measures were included in the model with the group (statin vs. control) by time (baseline to follow-up) interaction term adjusted for correlations between individuals and segments. The xtmixed command in STATA was used for modeling.

We used linear regression analysis to assess the relationship between the percentage of change in the PMR during follow-up and the percentage of change in LDL-C, HDL-C, logarithmic hs-CRP, HbA_{1c}, percentage of TAV, and percentage of LAP volume. Statistical significance was defined as $p < 0.05$. All analyses were performed with SPSS for Windows, version 12.0 (SPSS Japan Inc., Tokyo, Japan) and STATA 13 (StataCorp).

RESULTS

Baseline clinical characteristics of the unmatched cohort (**Table 1**) showed significant differences in the prevalence of dyslipidemia as well as total cholesterol and LDL-C levels. There were 37 HIP-positive (PMR >1.0) patients (77%) in the intensive-statin group, consisting of 17 with a PMR ≥1.4 and 20 with a PMR between 1.0 and 1.4. Among the 48 control patients, 32 (67%) were HIP positive (PMR ≥1.4, n = 11; PMR 1.0 to 1.4, n = 21). As for the matched cohorts, the 2 groups were well matched at baseline, with no statistically significant differences in age, male sex, conventional coronary risk factors, systolic blood pressure, lipid profile, HbA_{1c}, hs-CRP levels, medications used, and PMR between the statin and control groups.

Table 2 shows the comparison of laboratory data at baseline and 12 months (mean: 13.2 ± 0.6; range: 12 to 15 months) in the 48 patients who completed intensive pitavastatin treatment and the 48 propensity score-matched control patients. In the statin group, mean LDL-C decreased from 125 ± 25 mg/dl to 70 ± 11 mg/dl (percentage of change from baseline: −42.1 ± 14.1%; $p < 0.001$), whereas there was no significant reduction in LDL-C in the control patients (from 126 ± 21 mg/dl to 121 ± 25 mg/dl; percentage change from baseline: −3.1 ± 18%; $p = 0.789$). In the statin group, total cholesterol and triglycerides also decreased significantly by the end of follow-up (percentage of change from baseline: −24.8 ± 14.4%; $p < 0.001$; and −22.7 ± 35.8%; $p < 0.001$, respectively). Also, hs-CRP levels were significantly reduced in the statin group (from 1.19 [0.65 to 3.31] mg/l to 0.62 [0.33 to 1.18] mg/l; −46.7 ± 32.2%; $p < 0.001$), but there was no significant change in the control group (from 1.12 [0.33 to 3.42] mg/l to 1.16 [0.48 to 3.58] mg/l; 2.0 ± 21.0%; $p = 0.773$). HbA_{1c} and HDL-C levels did not change significantly during follow-up in either group.

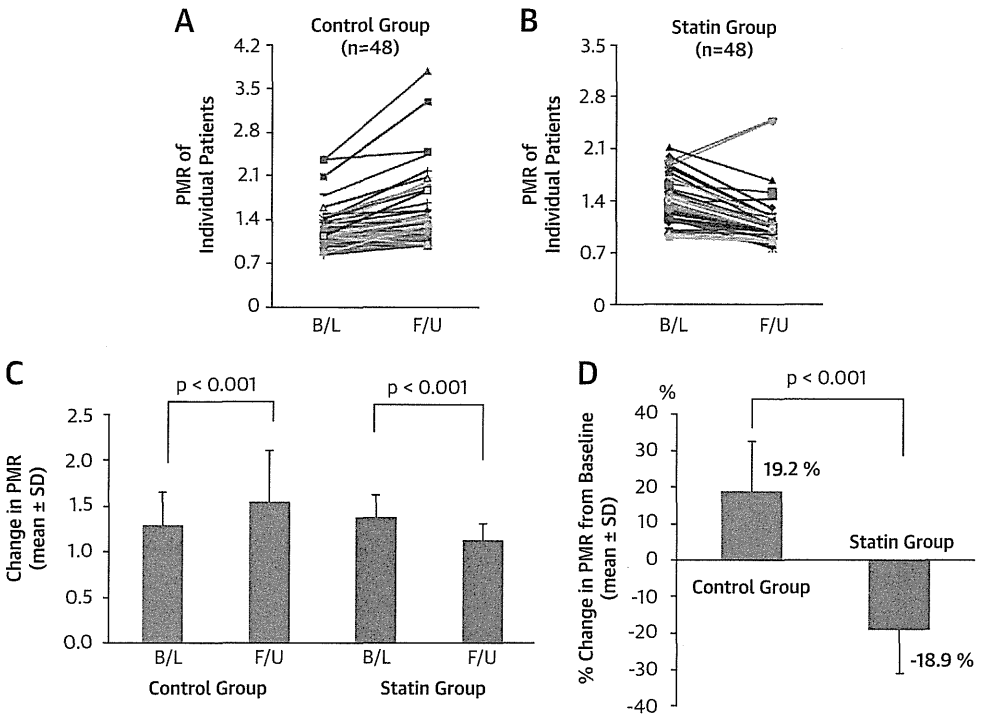
Figure 2 shows the changes in individual-level (**Figures 2A and 2B**) and group-level data on the PMR (**Figures 2C and 2D**), the primary efficacy endpoint. The baseline PMR was comparable (statin group: 1.38 [1.20 to 1.50] vs. control group: 1.22 [1.01 to 1.56]; $p = 0.922$). At 12 months, the PMR was significantly lower in the statin group (1.11 [1.02 to 1.25]; 18.9 ± 11.1% reduction from baseline; $p < 0.001$) compared with an increase in the control group (1.49 [1.18 to 1.96];

TABLE 2 Changes in Laboratory Data

	Statin Group			Propensity Score-Matched Control Group			Comparison*		
	Baseline	Follow-Up	p Value	Baseline	Follow-Up	p Value	Statin Group	Control Group	p Value
Lipid profiles									
TC, mg/dl	208 ± 34	152 ± 25	<0.001	211 ± 38	198 ± 34	0.041	−24.8 ± 14.4	−4.8 ± 23	<0.001
LDL, mg/dl	125 ± 25	70 ± 11	<0.001	126 ± 21	121 ± 25	0.789	−42.1 ± 14.1	−3.1 ± 18	<0.001
HDL, mg/dl	50 ± 13	52 ± 13	0.945	51 ± 10	48 ± 11	0.269	4.8 ± 14.0	−5.4 ± 19	0.085
TG, mg/dl	179 ± 95	138 ± 80	<0.001	167 ± 81	158 ± 66	0.244	−22.7 ± 35.8	−5.1 ± 28	0.021
HbA_{1c}, %	6.1 ± 1.2	6.2 ± 1.0	0.828	6.1 ± 1.1	6.2 ± 1.1	0.896	0.6 ± 8.5	1.1 ± 10	0.376
hs-CRP, mg/l	1.19 (0.65-3.31)	0.62 (0.33-1.18)	<0.001	1.12 (0.33-3.42)	1.16 (0.48-3.58)	0.773	−46.7 ± 32.2	2.0 ± 21.0	<0.001

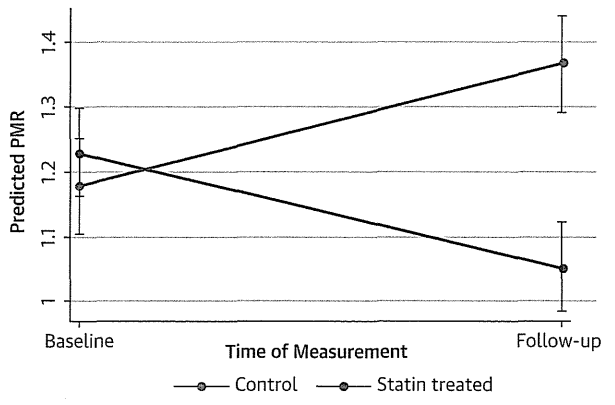
Values are mean ± SD or median (interquartile range). *Percentage of change from baseline over 1 year in the statin versus control group.
Abbreviations as in Table 1.

FIGURE 2 Comparisons of Change in PMR (Patient-Based Analysis)



Individual changes in the plaque-to-myocardium signal-intensity ratio (PMR) from baseline to 12 months in the control **(A)** and statin **(B)** groups. Each line represents 1 patient. **(C)** In the group comparison, there were no significant differences in PMR at baseline, but after 12 months, PMR had increased significantly in the control group and decreased significantly in the statin group. **(D)** A significant net difference was observed in the percentage of change in PMR from baseline between the 2 groups. B/L = baseline; F/U = follow-up.

FIGURE 3 Changes in Predicted PMR



Although baseline plaque-to-myocardium signal-intensity ratio (PMR) values were comparable between the 2 groups, during follow-up, PMR values significantly decreased in the statin group and increased in the control group (each $p < 0.001$).

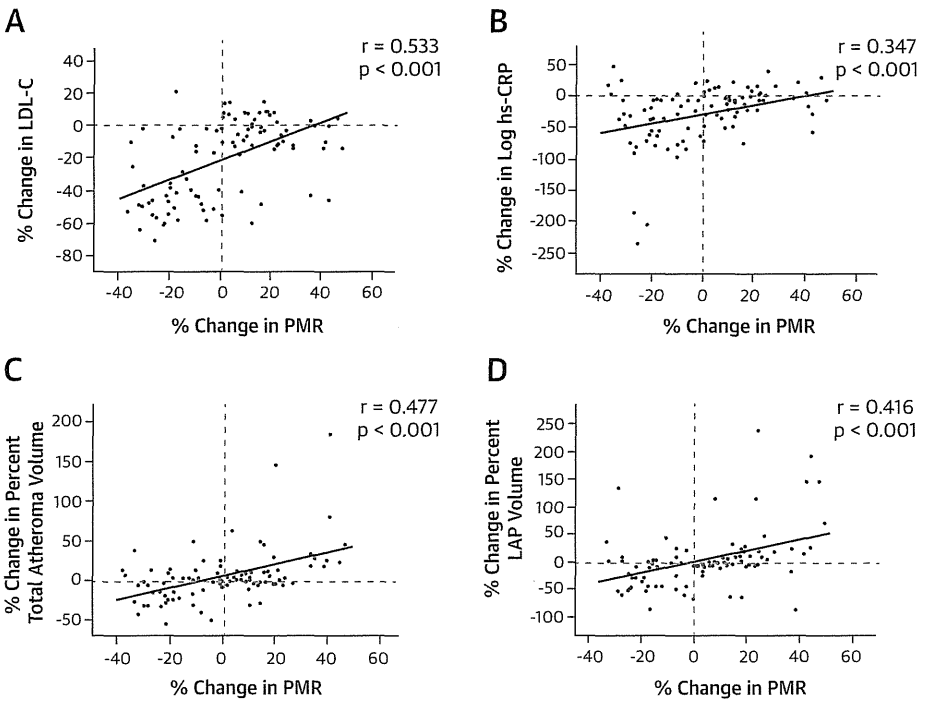
19.2 ± 13.2% elevation from baseline; $p < 0.001$) **(Figures 2C and 2D)**. A significant net difference was observed in the percentage of change in the PMR from baseline between the 2 groups ($p < 0.001$) **(Figure 2D)**. PMRs at baseline and follow-up stratified by statin treatment status and adjusted for individual-level correlations between segments estimated in a linear mixed model are summarized in **Figure 3** and Online Table 1. The effect of statin treatment status and the time-by-group interaction term were significant ($p = 0.008$ and $p < 0.001$, respectively). Baseline PMR values were similar in the statin and control groups ($p = 0.241$). During follow-up, PMR values were 0.313 lower in the statin group than in the control group (95% confidence interval: −0.401 to −0.225; $p < 0.001$). PMR values decreased in the statin group but increased in the control group during follow-up ($p < 0.001$). The percentage of change in the PMR was positively correlated with the percentage of change in LDL-C and logarithmic hs-CRP ($r = 0.533$; $p < 0.001$, and $r = 0.347$; $p < 0.001$,

respectively) (**Figures 4A and 4B**), but not with the percentage of change in HDL-C or HbA_{1c} (data not shown).

SEGMENT-BASED ANALYSIS. We analyzed 768 segments in 96 subjects. In the segment-based CMR analysis, 519 segments were excluded because they either contained lesions scheduled for PCI (18 segments), were previously treated with PCI and stenting (11 segments), had poor imaging quality near stents (48 segments), or had no significant coronary plaques with >20% stenosis identified by CTA (442 segments). The remaining 249 segments were studied and divided into 4 groups according to the cutoff PMR of 1.4 for predicting coronary events on the basis of our previous study (4): statin group/PMR ≥1.4 (25 segments), statin group/PMR <1.4 (111 segments), control group/PMR ≥1.4 (19 segments), and control group/PMR <1.4 (94 segments). **Figure 5** shows the changes in the PMR for each segment and summarizes the percentage of change in the PMR from baseline in these 4 groups. In the statin group, the percentage of reduction in the PMR from baseline was greater for PMR ≥1.4 plaques than PMR <1.4 plaques (19.0 ± 12.1% vs. 7.8 ± 11.3%; $p < 0.001$). In the control group, however, the percentage of increase in the PMR from baseline was higher for PMR ≥1.4 plaques (19.7 ± 15.1% vs. 12.0 ± 11.0%; $p = 0.037$).

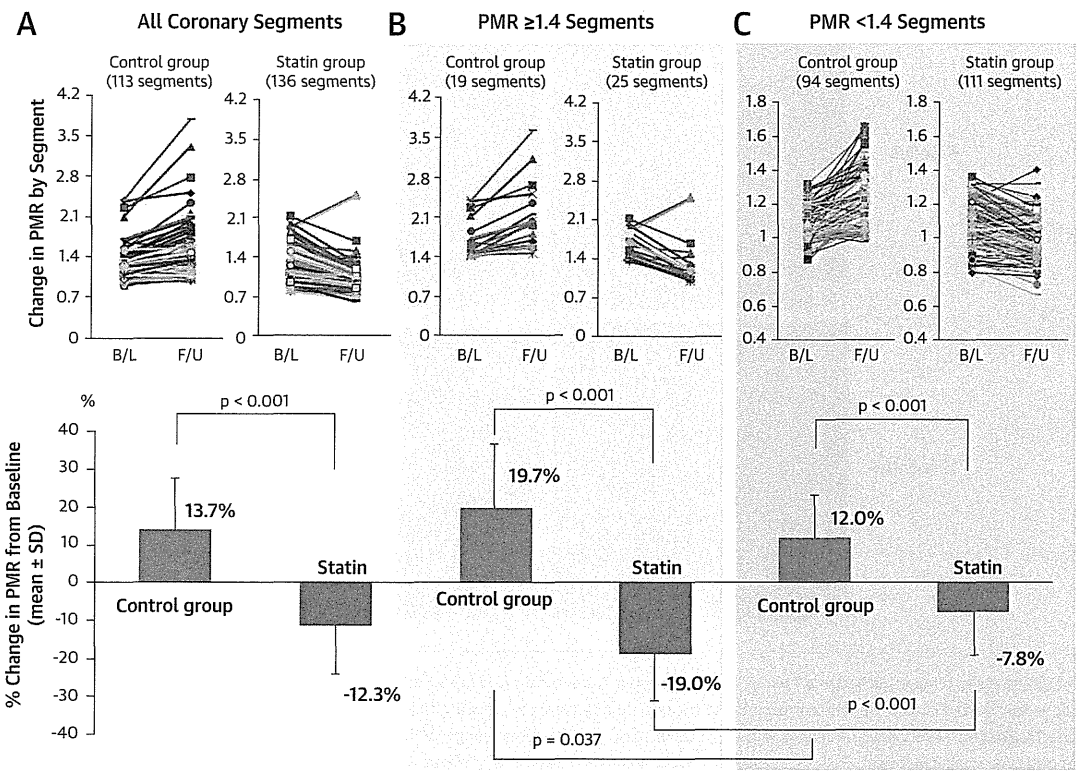
The 249 segments used in the segment-based analysis of change in the PMR were analyzed using CTA (**Table 3**). In the statin group, significant changes were observed in LAP volume, percentage of TAV, and percentage of LAP volume, whereas TAV, lumen volume, and RI did not significantly change after statin treatment. In the control group, TAV and LAP volume were higher at follow-up but not statistically significant ($p = 0.057$ and $p = 0.091$, respectively); lumen volume, percentage of TAV, percentage of LAP volume, and RI did not change significantly from baseline. Overall, there were significant positive correlations between the percentage of change in the PMR and TAV (**Figure 4C**) and LAP volume (**Figure 4D**). Representative CMR and CTA images in the statin and control groups are shown in **Figures 6 and 7**, respectively.

FIGURE 4 Correlations Between Change in the PMR and Plaque-Related Factors



Significant positive correlations were seen between the percentage of change in the plaque-to-myocardium signal-intensity ratio (PMR) and the percentage of change in low-density lipoprotein cholesterol (LDL-C) **(A)**; logarithmic high-sensitivity C-reactive protein (hs-CRP) **(B)**; percentage of total atheroma volume **(C)**; and percentage of low attenuation plaque (LAP) volume **(D)**.

FIGURE 5 Comparisons of Change in PMR (Segment-Based Analysis)



Individual **(top)** and group **(bottom)** changes in PMR are seen in all coronary segments **(A)**, PMR ≥1.4 segments **(B)**, and PMR <1.4 segments **(C)**. Abbreviations as in **Figure 2**.

DISCUSSION

The major findings of this pilot study include the following: 1) the PMR of coronary HIP was lowered by statin therapy, which was also associated with decreases in LDL-C and hs-CRP as well as a decrease in the percentage of TAV and percentage of LAP volume as evaluated by CTA; 2) the percentage of change in the PMR was greater in the statin group with PMR ≥1.4 segments; and 3) in the control group, which did not receive statins or other LDL-lowering agents, the PMR was higher at 12 months, especially in patients who had HIP with PMR ≥1.4. The present study suggests the feasibility of using serial CMR examinations using noncontrast T1WI in clinical trials designed to assess changes in coronary plaque characteristics **(Central Illustration)**.

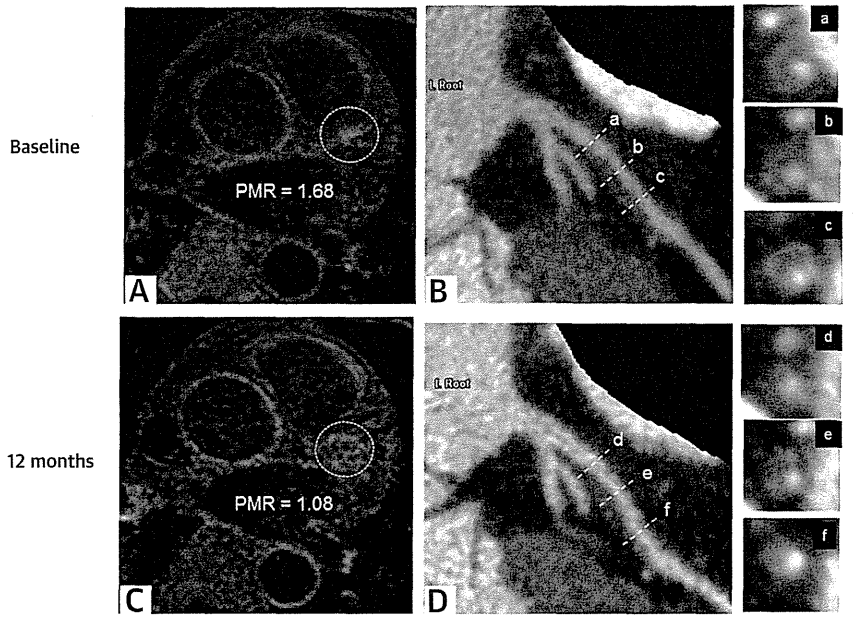
Observations from carotid plaque magnetic resonance imaging and histopathological validation

TABLE 3 CTA Measures

	Statin Group			Propensity Score-Matched Control Group			Comparison*		
	Baseline	Follow-Up	p Value	Baseline	Follow-Up	p Value	Statin Group	Control Group	p Value
TAV, mm^3	195.2 (126.1-255.2)	167.8 (118.2-230.3)	0.078	216.6 (153.9-285.3)	244.1 (144.3-340.6)	0.057	−5.0 ± 26.0	12.4 ± 25.0	0.028
Lumen volume, mm^3	203.9 (135.0-261.8)	201.7 (135.5-265.1)	0.460	197.2 (129.0-296.5)	189.5 (121.8-247.8)	0.095	3.5 ± 21.0	−3.9 ± 13	0.941
LAP volume (<30 HU), mm^3	31.2 (15.2-59.5)	23.3 (10.1-43.8)	0.007	23.7 (15.6-39.6)	25.8 (15.7-45.2)	0.091	−12.8 ± 18.0	8.3 ± 14.2	0.004
Percent TAV	53.6 (39.7-59.4)	46.9 (35.1-59.2)	0.047	55.3 (51.3-60.5)	56.9 (52.5-64.3)	0.381	−4.6 ± 13.6	3.1 ± 11.0	0.108
Percent LAP volume	19.3 (11.3-24.9)	17.0 (8.2-21.1)	<0.001	22.1 (19.3-26.5)	24.5 (19.7-26.1)	0.277	−11.0 ± 23.4	9.9 ± 10.1	<0.001
Remodeling index	1.24 (1.06-1.40)	1.21 (1.14-1.35)	0.145	1.21 (1.11-1.38)	1.23 (1.15-1.41)	0.151	−2.4 ± 9.4	1.7 ± 10.1	0.138

Values are median (interquartile range) or mean ± SD. *Percentage of change from baseline over 1 year in the statin versus control group.
CTA = computed tomography angiography; HU = Hounsfield unit; LAP = low-attenuation plaque; TAV = total atheroma volume.

FIGURE 6 PMR Regression With Statin Treatment



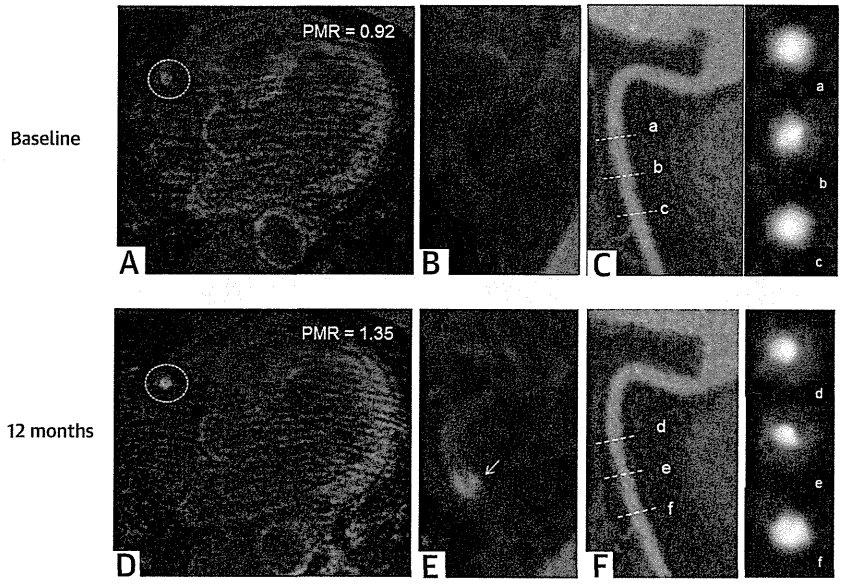
A high-intensity plaque (HIP) with a PMR of 1.68 is observed in the proximal segment of the left anterior descending artery (LAD) at baseline **(A, yellow dotted circle)**. This HIP corresponds to the low-density coronary plaque with positive remodeling in the proximal portion of the LAD on CTA **(B)**. Cross-sectional CTA images of this HIP lesion show positive remodeling with low attenuation plaque (LAP) **(a, b, c)**. After 12 months of intensive statin treatment, PMR decreased to 1.08 **(C, yellow dotted circle)**. CTA at follow-up shows a decrease in LAP volume **(D, d, e, f)**. Abbreviations as in **Figures 1 and 2**.

studies (2,3,22), as well as studies using optic coherence tomography (23) or specimens obtained through an aspiration catheter during PCI after ACS (24) suggest that a coronary HIP may represent IPH and thrombus formation. Kawasaki et al. (1) systematically evaluated the components of HIPs in patients undergoing CTA and IVUS. Coronary HIPs were closely correlated with IVUS attenuation, as well as with positive vascular remodeling and lower CT density on CTA. The estimation of HIP-PMR provides a useful quantitative measure that can be repeatedly analyzed without the need for radiation exposure, contrast agents, or invasive procedures (1,4). Therefore, it is reasonable to use HIP-PMR for the serial evaluation of plaque characterization, especially in response to plaque-modifying agents.

Numerous carotid magnetic resonance studies have demonstrated the critical role of IPH in plaque instability (25-27) and acute carotid vascular events (28). Statin therapy has been posited to prevent neovascularization (29) and limit the cholesterol content of red blood cell membranes (30) and the phospholipid ratio (31). Carotid IPH was less frequently observed in patients on statins before endarterectomy (32), and the use of statins before a transient ischemic attack or stroke was negatively associated with the presence of IPH (33). On the other hand, statin therapy has been associated with a decrease in the percentage of LAP volume as assessed by CTA (18). Komukai et al. (11) and Hattori et al. (10) demonstrated that stain-induced optical coherence tomography-verified increases in fibrous cap thickness were associated with decreases in serum atherogenic lipoproteins and inflammatory biomarkers. This suggests that statin therapy modifies plaque phenotype including its lipid-rich necrotic core, fibrous cap, and IPH, which in turn might have reduced PMR values in our study. Future studies should investigate whether the effect of statins on HIPs, as monitored by noninvasive CMR, is also associated with reductions in the risk of clinical events.

In our segment-based analysis, the degree of PMR attenuation after statin treatment was significantly greater in the high versus low PMR groups. Conversely, the magnitude of PMR increase was significantly greater in control patients with PMR $\geq$1.4 segments than control patients with PMR <1.4 segments (**Figure 5**). Taken together with our previous study demonstrating that coronary lesions with

FIGURE 7 PMR Progression in the Control Group



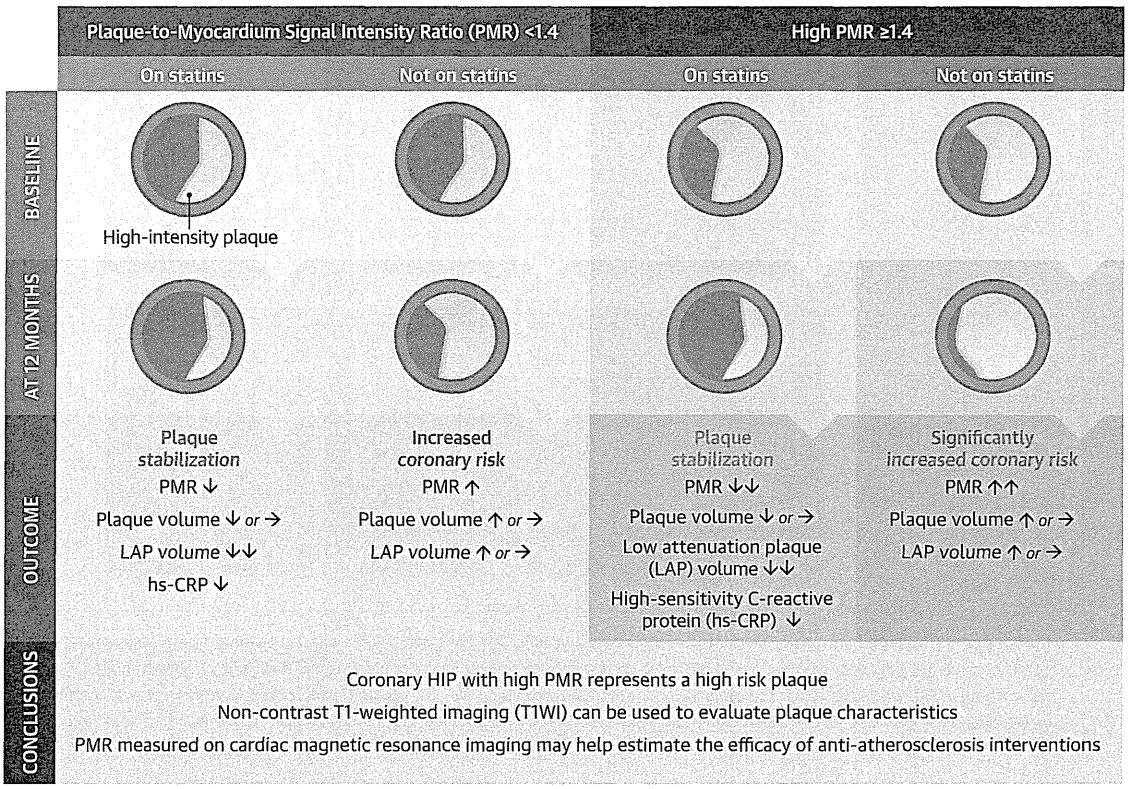
Noncontrast T1-weighted imaging at baseline does not show any HIPs. The PMR was 0.92 in a lesion in the proximal segment of the right coronary artery **(A, yellow dotted circle, and B)**, which corresponds to a minor coronary plaque on CTA **(C, a, b, c)**. However, after 12 months, a representative HIP was observed at the same lesion in the right coronary artery **(D, yellow dotted circle; E, yellow arrow)**, accompanied by an increase in the PMR to 1.35. CTA shows significant progression of coronary plaque morphology **(F, d, e, f)**. Abbreviations as in **Figures 2 and 6**.

PMR ≥1.4 are at significantly higher risk of subsequent ACS (4), the present findings indicate that coronary lesions with PMR ≥1.4 may be associated with accelerated plaque instability as well as increased signal intensity, which may reflect an increase in the volume of the necrotic core with IPH. This supports recent findings that fateful plaques are usually large with large necrotic cores (34).

However, increases in the PMR were observed even in PMR <1.4 segments (12.0% increase from baseline) (**Figure 5**), which are considered at lower risk of coronary events on the basis of our previous study (4). This suggests that even HIP with PMR <1.4 might evolve into a high-risk plaque during follow-up. Given that atherosclerosis is a dynamic process, our focus must remain on the entire disease process (35). Early identification of patients with HIP regardless of stenosis severity or plaque burden may prove valuable in the risk stratification of patients with CAD or multiple cardiovascular risk factors, including diabetes mellitus. Additionally, the present study proposes that noncontrast T1WI can potentially be used for comparing plaque characteristics at different time points and may assist in assessing the efficacy of antiatherosclerotic pharmacological interventions.

STUDY LIMITATIONS. As an observational study with a small number of patients examined, there may be inherent flaws related to selection bias, spurious observations, unmeasured covariates, and nonrandom allocation to treatment. However, we sought to minimize these issues by using a propensity model for multivariate analysis and added a summary of coronary events in the 2 groups during follow-up on the basis of an exact logistic regression analysis (Online Table 2). These data suggest that patients with HIPs seem to be at a higher risk of future coronary events. Second, because plaque measurements using CTA were performed semiautomatically, there is a possibility of measurement error. Third, intensive statin therapy did not change TAV and vessel RI as detected by CTA in this study. This was inconsistent with previous IVUS studies demonstrating that intensive statin treatment induces reductions in TAV as well as an absolute decrease in vessel RI (15,36). CTA has lower spatial resolution than IVUS for the measurement of plaque volume, which may in part be related to these inconsistencies. Finally, Noyes et al. (37) reported that plaque regression occurred after an average of 19.7 months of statin treatment. Because target LDL-C levels in this study were comparable with other intensive statin IVUS studies (15,36), mean

CENTRAL ILLUSTRATION **Statin and HIP on CMR**



Noguchi, T. et al. J Am Coll Cardiol. 2015; 66(3):245-56.

Statin therapy reduces the plaque-to-myocardium signal intensity ratio (PMR) of coronary high-intensity plaque (HIP) through its plaque-stabilizing effects in association with decreases in low-density lipoprotein cholesterol, high-sensitivity C-reactive protein (hs-CRP), and low attenuation plaque (LAP) volume. In contrast, the PMR in the control group increased without significant morphological changes detected by computed tomography angiography measures. CMR = cardiac magnetic resonance; IPH = intraplaque hemorrhage; T1WI = T1-weighted imaging.

changes in plaque volume and PMR at 1 year of follow-up were acceptable. However, studies of serial changes in the PMR of HIP beyond 1 year might provide additional insights.

Most importantly, HIP assessment may be more conveniently possible in Japanese subjects by virtue of the body habitus and its applicability elsewhere has yet to be determined. Therefore, the findings and proposals from the study are considered hypothesis generating.

CONCLUSIONS

The present study demonstrates that intensive statin therapy reduces HIP-PMR identified by noncontrast T1WI, which may represent a useful method for quantitatively monitoring changes in plaque vulnerability.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: HIPs detected by noncontrast T1WI are associated with ischemic coronary events.

TRANSLATIONAL OUTLOOK: Further studies are needed to verify the clinical utility of adjusting the intensity of statin therapy based on plaque intensity values assessed by CMR to reduce the risk of coronary events.