Circulation Journal
Official Journal of the Japanese Circulation Society
http://www.j-circ.or.jp

Reverse Vessel Remodeling But Not Coronary Plaque Regression Could Predict Future Cardiovascular Events in ACS Patients With Intensive Statin Therapy

– The Extended JAPAN-ACS Study –

Katsumi Miyauchi, MD; Hiroyuki Daida, MD; Takeshi Morimoto, MD; Takafumi Hiro, MD; Takeshi Kimura, MD; Yoshihisa Nakagawa, MD; Masakazu Yamagishi, MD; Yukio Ozaki, MD; Kazushige Kadota, MD; Kazuo Kimura, MD; Atsushi Hirayama, MD; Kazumi Kimura, MD; Yasuhiro Hasegawa, MD; Shinichiro Uchiyama, MD; Masunori Matsuzaki, MD for the JAPAN-ACS Investigators

Background: The JAPAN-ACS study demonstrated that statins significantly reduced coronary plaque volume in patients with acute coronary syndrome (ACS). The clinical implications of plaque regression for clinical outcomes in ACS patients has not been established. The Extended JAPAN-ACS study was conducted to evaluate the relationship between coronary plaque regression and long-term clinical outcome, and to explore the factors associated with cardiovascular events.

Methods and Results: Patients with intravascular ultrasound (IVUS) data at both enrollment and follow-up in the JAPAN-ACS study were enrolled and observed for at least 3 years. Patients were divided into lesser and greater coronary plaque regression groups. The primary endpoint was defined as a composite of the following events: cardiovascular death, nonfatal myocardial infarction, nonfatal cerebral infarction, and unstable angina. The median value of the percent change in plaque volume, –18.0%, was used as a cutoff point. There were 4 primary events (3.4%) in the lesser regression group, and 2 events (1.7%) in the greater regression group (P=0.4). Cumulative secondary cardiovascular events did not differ between the 2 groups. Multivariate analysis identified the high-density lipoprotein cholesterol (HDL-C) at baseline and the % change of the external elastic membrane volume as independent risk factors of cardiovascular events.

Conclusions: Coronary plaque regression induced by an intensive statin regimen did not predict future cardiovascular events in ACS patients. Rather, the baseline HDL-C level and reverse vessel remodeling might serve as predictors for cardiovascular events. (*Circ J* 2012; **76:** 825–832)

Key Words: Coronary plaque; High-density lipoprotein cholesterol; Intravascular ultrasound; Statins; Vessel remodeling

Intravascular ultrasound (IVUS) enables precise quantification of a patient's coronary plaque burden. Serial volumetric measurement of coronary plaque using IVUS can be used to evaluate the effect of pharmacological interventions. Indeed, several previous multicenter studies have revealed that statins attenuate the progression of atherosclerosis, even cause

Received February 3, 2012; revised manuscript received February 17, 2012; accepted February 21, 2012; released online March 16, 2012
Time for primary review: 10 days

Department of Cardiology, Juntendo University School of Medicine, Tokyo (K.M., H.D.); Center for General Internal Medicine and Emergency Care, Kinki University School of Medicine, Osakasayama (T.M.); Division of Cardiology, Department of Medicine, Nihon University School of Medicine, Tokyo (T.H., A.H.); Department of Cardiovascular Medicine, Kyoto University Graduate School of Medicine, Kyoto (T.K.); Department of Cardiology, Tenri Hospital, Tenri (Y.N.); Division of Cardiovascular Medicine, Kanazawa University Graduate School of Medicine, Kanazawa (M.Y.); Division of Cardiology, Fujita Health University, Toyoake (Y.O.); Department of Cardiology, Kurashiki Central Hospital, Kurashiki (K. Kadota); Division of Cardiology, Yokohama City University Medical Center, Yokohama (Kazuo Kimura); Department of Stroke Medicine, Kawasaki Medical School, Okayama (Kazumi Kimura); Department of Neurology, St. Marianna University School of Medicine, Kawasaki (Y.H.); Department of Neurology, Tokyo Women's Medical University, Tokyo (S.U.); and Division of Cardiology, Department of Medicine and Clinical Science, Yamaguchi University Graduate School of Medicine, Ube (M.M.), Japan

This paper was presented at the 76th Annual Scientific Meeting of the Japanese Circulation Society, Late Breaking Clinical Trials 3-4.
Trial registrations: ClinicalTrials.gov Identifier: NCT01223586 [http://clinicaltrials.gov/ct2/show/NCT01223586].
UMIN Unique trial Number: UMIN000003166 [https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr.cgi?function=brows&action=brows&type=summary&recptno=R000003375&language=E]

Mailing address: Katsumi Miyauchi, MD, Department of Cardiology, Juntendo University School of Medicine, 2-1-1 Hongo, Bunkyo-ku, Tokyo 113-8421, Japan. E-mail: ktmmy@juntendo.ac.jp

ISSN-1346-9843 doi:10.1253/circj.CJ-12-0135

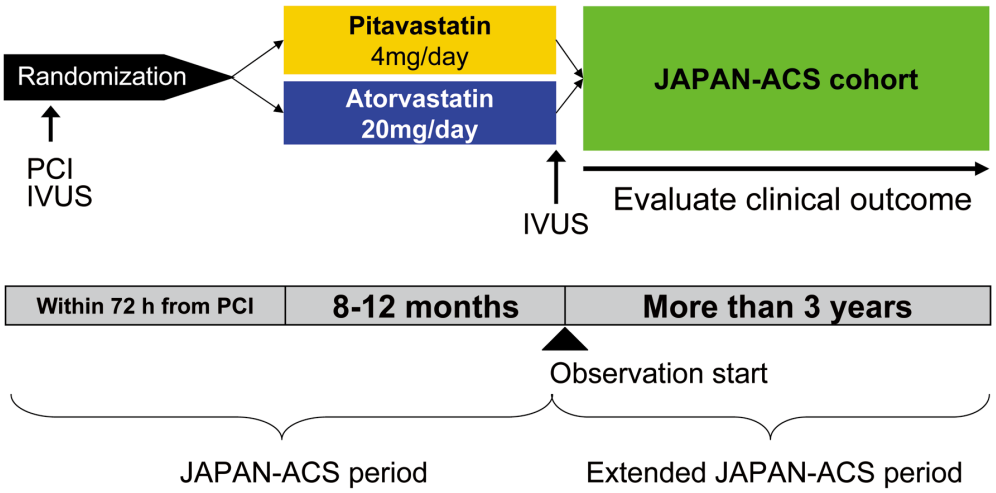

Figure 1. Scheme of the Extended JAPAN-ACS Study, which included all the JAPAN-ACS cohorts who had measurable Intravascular ultrasound (IVUS) data at both enrollment and follow-up. The observation period was set to at least 3 years.

regression of plaque volume.[1–4] IVUS studies of progression-regression of coronary atherosclerosis have been limited by the fact that plaque progression-regression on imaging is a surrogate endpoint. It is important to investigate whether the surrogate endpoint (ie, imaging) predicts future cardiovascular events. Previous IVUS studies have shown that the burden of coronary atherosclerosis and its progression is associated with an increased risk of adverse cardiovascular events in patients with stable coronary artery disease (CAD).[5] In the arena of acute coronary syndrome (ACS), the ESTABLISH study[6] and its extension study[7] revealed that intensive lipid-lowering therapy with statins resulted in coronary plaque regression, which was associated with a lower incidence of cardiovascular events. Therefore, it may be extrapolated that plaque regression measured by volumetric IVUS should be associated with a reduced cardiovascular event risk. However, these studies compared the change in plaque volume of a statin treatment group vs. a control group. There is a possibility that the statin itself contributed to the improved outcome because most cases of plaque reduction were associated with statin administration. Because of the absence of clear evidence from a randomized study, there needs to be an investigation of whether there is a direct relationship between a change in plaque and outcomes under statin administration during the examination period.

Editorial p 809

The JAPAN-ACS study[8,9] did not have a placebo arm; all patients were administered intensive statin treatment. To verify a direct relationship between coronary plaque volume and cardiovascular events of ACS patients in a multicenter setting, we conducted a long-term follow-up of the JAPAN-ACS study. In addition, we explored the factors that may influence cardiovascular events.

Methods

Study Design

The Extended JAPAN-ACS study was designed to evaluate the long-term clinical outcomes of patients in the JAPAN-ACS study,[8,9] which showed that administration of pitavastatin or atorvastatin in patients with ACS resulted in equivalent significant regression of coronary plaque volume. Patients who had measurable IVUS data at both enrollment and follow-up in the JAPAN-ACS study were enrolled in the extended study. The patients were observed for at least 3 years from the final visit of the JAPAN-ACS study (Figure 1). Data from blood analysis for lipid levels and inflammatory markers were obtained at the final observation in each participating center on a regular basis.

The Extended JAPAN-ACS study was conducted according to the "Declaration of Helsinki", and with the approval of the institutional review boards of all 32 participating institutions. Written informed consent to participate was given by all of the patients enrolled at the start of the JAPAN-ACS study, and participation in the Extended JAPAN-ACS study was endorsed by each patient. This study was registered at ClinicalTrials.gov (NCT01223586).

Endpoints

The primary endpoint was the time to first occurrence of a major cardiovascular event, defined as cardiovascular death, nonfatal myocardial infarction (MI), nonfatal cerebral infarction (CI) or unstable angina (UA) requiring emergency hospitalization.

Secondary endpoints were defined as follows: (1) cardiovascular composite events (cardiovascular death, nonfatal MI, nonfatal CI, UA requiring emergency hospitalization or ischemic-driven coronary revascularization); (2) coronary heart disease composite events (coronary heart disease death, nonfatal MI, UA requiring emergency hospitalization or ischemic-driven coronary revascularization); (3) cerebrovascular composite events (fatal and nonfatal stroke, transient ischemic attack (TIA) requiring hospitalization); (4) revascularization; (5) ischemic-driven revascularization; (6) hospitalization for heart failure; (7) operation for or rupture of aortic aneurysm; (8) revascularization for peripheral arterial disease (PAD); (9) carotid artery stenting (CAS) or carotid endarterectomy (CEA); (10) aortic dissection; (11) new occurrence of malignant tumor; and (11) all-cause mortality.

The independent Event Assessment Committee evaluated

Table 1. Baseline Characteristics of the Patients With Acute Coronary Syndrome

Characteristic	Lesser regression group (n=119)	Greater regression group (n=119)	P value
Age (years)*	64.4±11.4	62.7±10.8	0.2
Male, n (%)	103 (86.6)	93 (78.2)	0.09
Diabetes, n (%)	44 (37.0)	26 (21.9)	0.01
Hypertension, n (%)	80 (67.2)	73 (61.3)	0.3
Family history of CAD, n (%)	19 (16.0)	22 (18.5)	0.6
Smoking, n (%)	59 (49.6)	55 (46.2)	0.6
BMI (kg/m^2)*	24.1±3.4	24.0±3.1	0.7
Type of ACS, n (%)			0.5
STEACS	78 (65.6)	73 (61.3)	
NSTEACS	41 (34.5)	46 (38.7)	
Type of stents, n (%)			0.5
DES	35 (29.4)	43 (36.1)	
BMS	82 (68.9)	74 (62.2)	
POBA	2 (1.7)	2 (1.7)	
Concomitant drugs, n (%)			
Pitavastatin	59 (49.6)	58 (48.7)	0.9
ACE inhibitors or ARB	93 (78.2)	89 (74.8)	0.5
β-blockers	57 (47.9)	55 (46.2)	0.8
Calcium channel blockers	25 (21.0)	19 (16.0)	0.3
Aspirin	116 (97.5)	118 (99.2)	0.3
Thienopyridinic derivatives	109 (91.6)	107 (89.9)	0.7

*Recalculated at the beginning of Extended JAPAN-ACS study.
CAD, coronary artery disease; BMI, body mass index; ACS, acute coronary syndrome; STEACS, ST-elevation acute coronary syndrome; NSTEACS, non-STEACS; DES, drug-eluting stent; BMS, bare-metal stent; POBA, plain old balloon angioplasty; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.

Table 2. Laboratory Data and IVUS Parameters at the Beginning of the Extended JAPAN-ACS Study

	Lesser regression group	Greater regression group	P value
Laboratory data			
n	119	118	
LDL-C (mg/dl)	83.3±28.0	81.8±23.3	0.6
HDL-C (mg/dl)	47.7±11.6	48.0±12.9	0.8
Triglyceride (mg/dl)	129.2±80.2	120.4±61.4	0.3
hs-CRP (mg/L), median (IQR)	0.53 (0.29–1.1)	0.49 (0.30–1.1)	0.6
SBP (mmHg)	129.7±17.1	127.1±16.8	0.2
DBP (mmHg)	72.9±11.5	74.2±13.0	0.4
IVUS parameters			
n	119	119	
Plaque volume (mm^3)	57.0±31.5	38.9±23.5	<0.0001
% change in plaque volume*	–6.6±9.4	–28.3±8.9	<0.0001
% plaque volume	47.5±10.1	41.0±10.8	<0.0001
Nominal change in % plaque volume*	–2.4±4.8	–9.5±5.6	<0.0001
Normalized plaque volume (mm^3)	52.7±18.0	38.9±15.5	<0.0001
Nominal change in normalized plaque volume (mm^3)*	–3.6±5.6	–15.0±6.7	<0.0001
EEM volume (mm^3)	118.5±56.7	93.5±50.1	0.0004
% change in EEM volume*	–1.5±10.4	–11.0±10.5	<0.0001
Lumen volume (mm^3)	61.4±30.4	54.6±30.4	0.08
% change in lumen volume*	4.1±18.6	8.3±22.1	0.1

*% or nominal change in IVUS parameters were values at the end of the JAPAN-ACS study, namely at the start of the Extended JAPAN-ACS study.
IVUS, intravascular ultrasound; LDL-C, low-density lipoprotein-cholesterol; HDL-C, high-density lipoprotein-cholesterol; hs-CRP, high sensitivity C-reactive protein; IQR, intra quartile range; SBP, systolic blood pressure; DBP, diastolic blood pressure; EEM, external elastic membrane.
SI conversions: To convert LDL-C, HDL-C to mmol/L, multiply by 0.0259; triglyceride to mmol/L, multiply by 0.01129.
Continuous variables are represented as mean±SD or median (IQR).

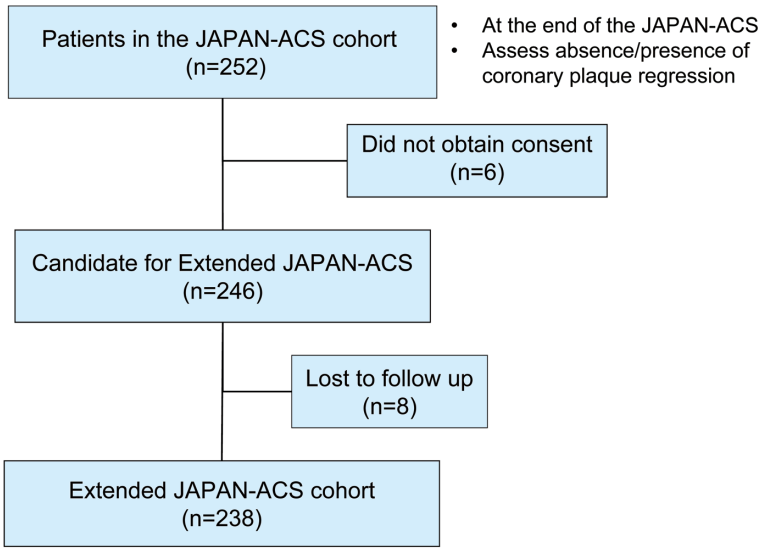

Figure 2. Disposition of patients.

major adverse cardiac events.

IVUS Parameters

Details of the IVUS procedure and examination are documented elsewhere.[9] The percent change in plaque volume (PV) was calculated as follows:

$$\frac{\text{PV (follow up)} - \text{(baseline)}}{\text{PV (baseline)}} \times 100$$

Coronary PV was calculated as the sum of the differences between the external elastic membrane (EEM) cross-sectional area and the lumen cross-sectional area across all evaluated frames as:

$$\text{PV} = \Sigma(\text{EEM}_{\text{CSA}} - \text{LUMEN}_{\text{CSA}}).$$

Percent PV (%PV) was calculated using the following formula:

$$\%\text{PV} = \frac{\Sigma(\text{EEM}_{\text{CSA}} - \text{LUMEN}_{\text{CSA}})}{\Sigma(\text{EEM}_{\text{CSA}})} \times 100$$

Normalized PV (NPV) was calculated as:

$$\text{NPV} = \text{PV} \times \frac{L_{\text{MED}}}{L_{\text{MEASURED}}}$$

where L_{MED} = median value of observed length in all subjects and L_{MEASURED} = observed length for each plaque.

Statistical Analysis

Following the descriptive statistics, comparisons of continuous variables between the 2 groups were performed using a 2-sample t-test or Wilcoxon's rank sum test, and those between the parameters at baseline and follow-up were performed by 1-sample t-tests or Wilcoxon's signed rank test according to their distributions. Comparisons of categorical variables between the 2 groups were performed by the chi-square and Fisher's exact tests where appropriate. Cumulative incidence for clinical outcome was estimated by the Kaplan-Meier method, and differences were assessed with the log-rank test.

A Cox proportional hazard model was used to identify independent risk factors. Baseline characteristics, laboratory data and IVUS parameters were examined as potential independent variables (Tables 1,2). Continuous variables were dichotomized by median value. Because diabetes was the strongest predictor of coronary plaque regression in the JAPAN-ACS study,[10] we predetermined to include diabetes in the multivariate Cox proportional hazard model.

The significance level was set at 5% for the 2-sided test (and 2.5% for the 1-sided test). All analyses were conducted by an independent statistician (T. Morimoto) with the use of JMP ver.9.0.1 and SAS software version 9.2 (SAS Institute Inc, Cary, NC, USA).

Results

Baseline Characteristics of the Patients

The disposition of the patients in the present study is shown in Figure 2. Among the 252 patients in the JAPAN-ACS cohort, we could not obtain consent from 6 patients, and 8 patients were lost to follow up, so a total of 238 patients comprised the Extended JAPAN-ACS cohort. Participants were divided into a lesser coronary plaque regression group or a greater regression group based on the percent change in PV in the JAPAN-ACS study. The median value of the percent change in PV, –18.03%, was used as a cutoff point. The median follow-up time to the primary endpoint (intraquartile range) was 3.7 (3.5–4.1) years in the lesser regression group and 3.8 (3.5–4.0) years in the greater regression group.

Baseline characteristics of the lesser and greater regression groups (each n=119) are presented in Table 1. Diabetic patients were included more frequently in the lesser regression group than in the greater regression group (P=0.010). There was no significant difference between groups for the other baseline characteristics. Mean age was 64 years, 82% of patients were men and 64% were hypertensive; 63% of patients had ST-elevation ACS, and drug-eluting stents were implanted in 33% and bare-metal stents in 66%.

Laboratory Data and IVUS Parameters

Mean serum level of low-density lipoprotein cholesterol (LDL-C) was 82.5±25.7 mg/dl and 47.8±12.2 mg/dl for high-density lipoprotein cholesterol (HDL-C). Systolic blood pressure was

Table 3. Clinical Outcomes

Endpoint	Lesser regression group (n=119)	Greater regression group (n=119)
Primary endpoint (composite of events), n (%)	4 (3.4)	2 (1.7)
Cardiovascular death, n (%)	0	0
Nonfatal myocardial infarction, n (%)	3 (2.5)	2 (1.7)
Nonfatal cerebral infarction, n (%)	1 (0.8)	0
Unstable angina requiring urgent hospitalization, n (%)	0	0
Secondary endpoints		
Cardiovascular composite events, n (%)*	9 (7.6)	5 (4.2)
Coronary composite events, n (%)†	8 (6.7)	5 (4.2)
Cerebrovascular composite events, n (%)‡	1 (0.8)	0
Revascularization, n (%)	10 (8.4)	7 (5.9)
Ischemic-driven revascularization, n (%)	5 (4.2)	3 (2.5)
Hospitalization for heart failure	3 (2.5)	1 (0.8)
Operation for or rupture of aortic aneurysm	0	1 (0.8)
Revascularization for PAD	3 (2.5)	2 (1.7)
CAS or CEA	1 (0.8)	0
Aortic dissection	1 (0.8)	0
New occurrence of malignant tumor	6 (5.0)	2 (1.7)
All-cause mortality	3 (2.5)	1 (0.8)

*Cardiovascular death, myocardial infarction, cerebral infarction, unstable angina, ischemic-driven revascularization excect target lesion revascularization (TLR).
†CHD death, myocardial infarction, unstable angina, ischemic-driven revascularization except TLR, n (%).
‡Fatal and non-fatal stroke, transient ischemic attack requiring hospitalization, n (%).
PAD, peripheral arterial disease; CAS, carotid artery stenting; CEA, carotid endarterectomy.

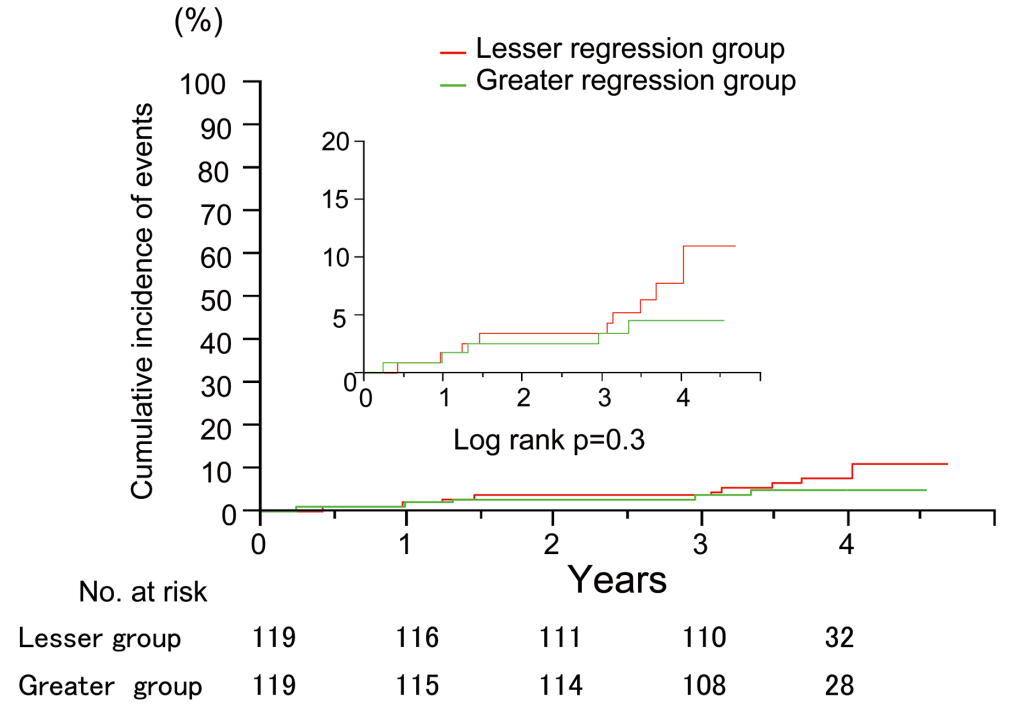

Figure 3. Comparison of cumulative cardiovascular event incidence between the lesser and greater plaque regression groups. Kaplan-Meier curves for cumulative cardiovascular events in the lesser (red line) and greater (green line) plaque regression groups. Secondary cardiovascular composite events (event number=14) were used.

Table 4. Factors Related to Clinical Outcome

Factors	HR (95%CI)
Univariate analysis	
HDL-C level at observation start (≥median value: 46 mg/dl)	0.24 (0.056–0.79)
% change in EEM volume at observation start (<median value: –6.56%)	0.25 (0.056–0.79)
Diabetes	1.3 (0.40–3.79)
Multivariate analysis	
HDL-C level at observation start (≥median value: 46 mg/dl)	0.26 (0.058–0.83)
% change in EEM volume at observation start (<median value: –6.56%)	0.28 (0.062–0.91)
Diabetes	1.19 (0.36–3.48)

HR, hazard ratio; CI, confidence interval; HDL-C, high-density lipoprotein-cholesterol; EEM, external elastic membrane.

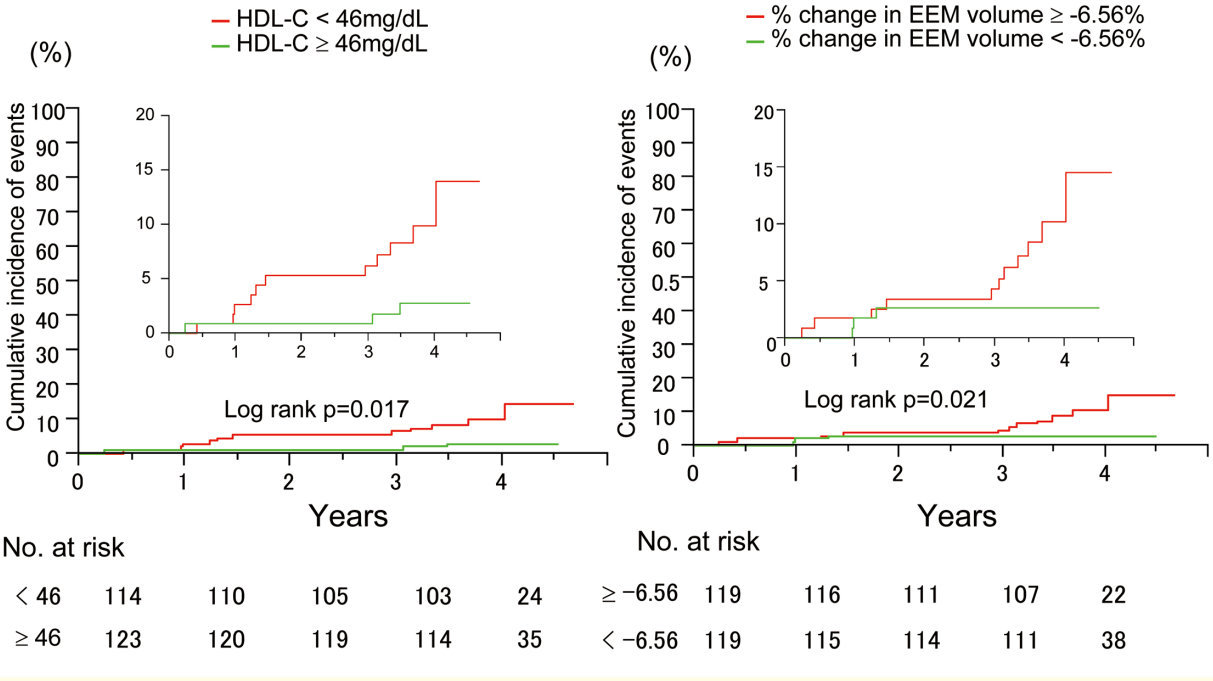

Figure 4. Effect of high-density lipoprotein cholesterol (HDL-C) and reverse vessel remodeling on cardiovascular events. (**A**) Kaplan-Meier curves for cumulative cardiovascular events in patients with lower (red line) and higher (green line) HDL-C level. (**B**) Kaplan-Meier curves for cumulative cardiovascular events in lesser (red line) and greater (green line) external elastic membrane volume regression.

128.4±17.9 mmHg and diastolic blood pressure was 73.5±12.3 mmHg at the start of the present study. There was no significant difference in the laboratory data between the lesser and greater regression groups (Table 2). Laboratory data at final follow-up are summarized in Table S1. The relationship between LDL-C or HDL-C and %PV was also examined. There is no significant correlation between LDL-C or HDL-C and PV.

Values for PV, %PV, NPV, EEM volume in the greater regression group were siginificantly smaller than those in the lesser regression group. The percent or nominal change of PV, %PV, NPV, EEM volume in the greater regression group were significantly larger than those in the lesser regression group. On the other hand, there was no significant difference between the 2 groups in lumen volume and its % change (Table 2).

Clinical Outcomes (Table 3)

There were 4 primary events (3.4%) in the lesser regression group, and 2 (1.7%) in the greater regression group (P=0.4). For the secondary endpoints, cardiovascular composite events occurred in 9 patients (7.6%) in the lesser regression group, and in 5 patients (4.2%) in the greater regression group. The %PV was similar in both groups who did or did not develop adverse events. The incidence of cumulative secondary cardiovascular composite events did not differ between the 2 groups (Figure 3). We also compared the incidence of cardiovascular

events between patients assigned to atorvastatin vs. pitavastatin at enrollment in the JAPAN-ACS study. There was no significant difference between the 2 statin groups in all patients and the high-adherence group (Figure S1). A total of 8 other adverse events were reported, including myalgia, edema and gastric ulcer; however, none of these adverse events was life-threatening.

Factors Associated With Cardiovascular Events

Factors associated with cardiovascular events were explored. Univariable analysis revealed that factors affected on cardiovascular events were HDL-C level and % change in EEM volume at the start of the Extended JAPAN-ACS study. The multivariable Cox hazard model also identified HDL-C level and % change in EEM volume as independent variables (Table 4). Patients were then divided into 2 groups according to the median value of HDL-C level and % change in EEM volume, respectively, and the incidence of cumulative secondary cardiovascular composite events was compared. Patients with a higher HDL-C level (≥46 mg/dl) and greater EEM volume regression (<−6.56%) had a significantly lower incidence of cumulative events than their counterparts (P=0.017, P=0.021, respectively; Figure 4).

Discussion

We found that coronary plaque regression induced by an intensive statin regimen could not predict future cardiovascular events in ACS patients. It was also concluded that baseline HDL-C level and the presence of reverse vessel remodeling might serve as predictors for cardiovascular events.

This insight was different from the result of the Extended-ESTABLISH study,[7] which reported a significant correlation between plaque regression and cardiovascular events. We consider that study designs are responsible for this discrepancy, because the Extended-ESTABLISH study had a placebo arm whereas all patients were under intensive statin therapy in the current study. The fact that PV regression was observed in almost 88% of patients in the present study might mask the relationship between plaque regression and cardiovascular events. This result was consistent with the lack of correlation between the reduction in LDL-C and the regression of PV in the JAPAN-ACS study,[9] in contrast to the ESTABLISH study.[6] Furthermore, these results are not unexpected given that the event rate observed in the extended JAPAN-ACS was exceedingly low, in fact almost 70% lower than the event rate of the Extended-ESTABLISH. This result may be a consequence of the method of statin use; in JAPAN-ACS during the trial period all patients were treated with a statin, whereas in the ESTABLISH study the control group participants received no statin therapy until 6 months into the study period. These findings suggest that intensive lipid-lowering therapy with statin achieves a favorable clinical outcome in high-risk patients.

Nicholls et al also documented a direct relationship between coronary plaque progression and future cardiovascular events in the setting of stable CAD.[5] One of the potential reasons for the inconsistency with our data might be the difference in clinical presentation (ACS vs. stable CAD). It was also possible there were genetic, racial or ethnic differences. In addition, a different IVUS procedure and examination may cause the inconsistency. We evaluated a single plaque in the culprit vessel whereas Nicholls et al observed the whole of a non-culprit coronary artery.

The present study also determined that the baseline HDL-C level and the presence of reverse vessel remodeling might serve as predictors for cardiovascular events. Under intensive statin therapy, so-called 'residual risk' might be exposed. Barter et al documented that HDL-C levels were predictive of major cardiovascular events in patients with LDL-C level <70 mg/dl.[11] Huxley et al reported from a meta-analysis that isolated low levels of HDL-C were associated with an increased risk of coronary heart disease.[12] The present data would support the strategy of increasing the HDL-C level of ACS patients in addition to intensive statin therapy.

Atherosclerosis influences vessel wall remodeling, with atherosclerotic plaque initially growing within an outwardly expanding vessel wall (positive remodeling). It is known that positive remodeling and larger vulnerable plaque areas are associated with ACS.[13,14] Using integrated backscatter-IVUS (IB-IVUS), Takeuchi et al reported that positive remodeling lesions contain more lipid-rich and less hard plaque components than non-positive remodeling lesions.[15] Ko et al also reported that vessel size was the most important independent predictor of lipid content by multivariate regression analysis.[16] In addition, Hattori et al recently documented that pitavastatin 4 mg/day induced favorable morphologic changes in plaque, with an increase in fibrous cap thickness, assessed by IB-IVUS and optical coherence tomography in patients with stable CAD.[17] These reports support that reverse vessel remodeling observed at 8–10 months after ACS onset might represent coronary plaque stabilization, and therefore could explain the better prognosis observed in the present study.

Study Limitations

Sample size might not be sufficient to validate the hypothesis. This was an inherent weakness of the design of the present study. In addition, the numbers of cardiovascular events were smaller than expected, especially stroke. We could not exclude the possibility that patients whose consent was not obtained or who were lost to follow-up might have experienced a cardiovascular event; however, the complete follow-up rate was relatively high (94.4%, 238/252). Patients' characteristics or conditions could provide alternative explanations. Relatively younger (average 64 years) patients who have been under concomitant medications such as statins, antiplatelet agents or antihypertensive drugs may have a lower incidence of cardiovascular events. It was reported that the rate of coronary death in Japan was almost one-quarter of that in northern Europe and in America.[18] This finding was supported by the REACH registry, which demonstrated that Japanese patients are at low risk for cardiovascular death, MI, or stroke compared with other regions and the relative risk reduction rate was 30% for Japanese during a 4-year follow-up.[19] In addition, recent clinical trials had fewer cardiovascular events than expected (annual rate of 2.5% in the placebo group), because statins were the standard treatment in Western countries.[20] Taken together, a further large-scale study based on precise sample size calculation is needed to clarify the results of the current study. In addition, it is possible that 3.5 years is too short to detect significant differences in cardiovascular events between plaque regression and progression, especially when all patients were treated by statins.

In conclusion, this study demonstrated that the baseline HDL-C level and the presence of reverse vessel remodeling, but not coronary plaque regression, may predict future cardiovascular events in ACS patients under intensive statin therapy. Strategies to increase HDL-C or to stabilize coronary plaque, in addition to intensive statin therapy, might provide a better prognosis for Japanese ACS patients.

Acknowledgments

We greatly acknowledge the contributions made by Yumika Fujino, Miya Hanazawa and Yumi Nozawa to data management.

Disclosures

Sources of Funding: The Japan Heart Foundation funded this study with an unrestricted grant from Kowa Company Ltd. Kowa participated in the preparation of the study design. However, the investigators made the final decisions on the study design, database maintenance, manuscript preparation, and submission of the article; an independent statistician (see Appendix) analyzed the data.

References

1. Nissen SE, Tuzcu EM, Schoenhagen P, Brown BG, Ganz P, Vogel RA, et al. Effect of intensive compared with moderate lipid lowering therapy on progression of coronary atherosclerosis. *JAMA* 2004; **291:** 1071–1080.
2. Nissen SE, Nicholls SJ, Sipahi I, Libby P, Raichlen JS, Ballantyne CM, et al. Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: The ASTEROID trial. *JAMA* 2006; **295:** 1556–1565.
3. Nicholls SJ, Ballantyne CM, Barter PJ, Chapman MJ, Erbel RM, Libby P, et al. Effect of two intensive statin regimens on progression of coronary disease. *N Engl J Med* 2011; **365:** 2078–2087.
4. Miyauchi K, Daida H. Clinical significance of intensive lipid-lowering therapy using statins in patients with coronary artery disease: LDL-cholesterol: The lower, the better; is it true for Asians? (Pro) *Circ J* 2010; **74:** 1718–1730.
5. Nicholls SJ, Hsu A, Wolski K, Hu B, Bayturan O, Lavoie A, et al. Intravascular ultrasound-derived measures of coronary atherosclerotic plaque burden and clinical outcome. *J Am Coll Cardiol* 2010; **55:** 2399–2407.
6. Okazaki S, Yokoyama T, Miyauchi K, Shimada K, Kurata T, Sato H, et al. Early statin treatment in patients with acute coronary syndrome: Demonstration of the beneficial effect on atherosclerotic lesions by serial volumetric intravascular ultrasound analysis during half a year after coronary event: The ESTABLISH Study. *Circulation* 2004; **110:** 1061–1068.
7. Dohi T, Miyauchi K, Okazaki S, Yokoyama T, Yanagisawa N, Tamura H, et al. Plaque regression determined by intravascular ultrasound predicts long-term outcomes of patients with acute coronary syndrome. *J Atheroscler Thromb* 2011; **18:** 231–239.
8. Miyauchi K, Kimura T, Morimoto T, Nakagawa Y, Yamagishi M, Ozaki Y, et al. Japan Assessment of Pitavastatin and Atorvastatin in Acute Coronary Syndrome (JAPAN-ACS): Rationale and design. *Circ J* 2006; **70:** 1624–1628.
9. Hiro T, Kimura T, Morimoto T, Miyauchi K, Nakagawa Y, Yamagishi M, et al. Effect of intensive statin therapy on regression of coronary atherosclerosis in patients with acute coronary syndrome: A multicenter randomized trial evaluated by volumetric intravascular ultrasound using pitavastatin versus atorvastatin (JAPAN-ACS study). *J Am Coll Cardiol* 2009; **293:** 293–302.
10. Hiro T, Kimura T, Morimoto T, Miyauchi K, Nakagawa Y, Yamagishi M, et al. Diabetes mellitus is a major negative determinant of coronary plaque regression during statin therapy in patients with acute coronary syndrome: Serial intravascular ultrasound observations from the Japan Assessment of Pitavastatin and Atorvastatin in Acute Coronary Syndrome Trial (the JAPAN-ACS Trial). *Circ J* 2010; **74:** 1165–1174.
11. Barter P, Gotto AM, Phil D, Maroni J, Szarek M, Grundy SM, et al. HDL cholesterol, very low levels of LDL cholesterol, and cardiovascular events. *N Engl J Med* 2007; **357:** 1301–1310.
12. Huxley RR, Barzi F, Lam TH, Czernichow S, Fang X, Welborn T, et al. Isolated low levels of high-density lipoprotein cholesterol are associated with an increased risk of coronary heart disease. *Circulation* 2011; **124:** 2056–2064.
13. Schoenhagen P, Ziada KM, Kapadia SR, Crowe TD, Nissen SE, Tuzcu EM. Extent and direction of arterial remodeling in stable versus unstable coronary syndromes: An intravascular ultrasound study. *Circulation* 2000; **101:** 598–603.
14. Asakura M, Ueda Y, Yamaguchi O, Crowe TD, Nissen SE, Tuzcu EM. Extensive development of vulnerable plaques as a pan-coronary process in patients with myocardial infarction: An angioscopic study. *J Am Coll Cardiol* 2001; **37:** 1284–1288.
15. Takeuchi H, Morino Y, Matsukage T, Masuda N, Kawamura Y, Kasai S, et al. Impact of vascular remodeling on the coronary plaque compositions: An investigation with in vivo tissue characterization using integrated backscatter-intravascular ultrasound. *Atherosclerosis* 2009; **202:** 476–482.
16. Ko YG, Son JW, Park SM, Kim JS, Choi D, Hong MK, et al. Effect of vessel size on lipid content of coronary plaques assessed by integrated backscatter intravascular ultrasound. *Circ J* 2010; **74:** 754–759.
17. Hattori K, Ozaki Y, Ismail TF, Okumura M, Naruse H, Kan S, et al. Impact of statin therapy on plaque characteristics as assessed by Serial OCT, grayscale and integrated backscatter-IVUS. *JACC Imag* 2012; **5:** 169–177.
18. Verschuren WM, Jacobs DR, Bloemberg BP, Kromhout D, Menotti A, Aravanis C, et al. Serum total cholesterol and long-term coronary heart disease mortality in different cultures: Twenty-five-year follow-up of the seven countries study. *JAMA* 1995; **274:** 131–136.
19. Bhatt DL, Eagle KA, Ohman EM, Hirsch AT, Goto S, Mahoney EM, et al. Comparative determinants of 4-year cardiovascular event rates in stable outpatients at risk of or with atherothrombosis. *JAMA* 2010; **304:** 1350–1357.
20. The AIM-HIGH Investigators. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. *N Engl J Med* 2011; **365:** 2255–2267.

Appendix

Steering Committee

Katsumi Miyauchi, MD; Takafumi Hiro, MD; Yoshihisa Nakagawa, MD; Masakazu Yamagishi, MD; Yukio Ozaki, MD (working members, respectively), Takeshi Kimura, MD; Hiroyuki Daida, MD (Co-principal investigators, respectively), Masunori Matsuzaki, MD (principal investigator).

Independent Event Assessment Committee

Kazushige Kadota, MD; Kazuo Kimura, MD; Atsushi Hirayama, MD; Kazumi Kimura, MD; Yasuhiro Hasegawa, MD; Shinichiro Uchiyama, MD.

Independent Statistician

Takeshi Morimoto, MD.

JAPAN-ACS Investigators

Aichi Medical University (Hiroaki Takashima, MD; Kenji Asai, MD; Yasushi Kuhara, MD); Akita Medical Center (Tadaya Sato, MD); Anjo Kosei Hospital (Masato Watarai, MD; Kenji Takamoto, MD); Ehime Prefectural Central Hospital (Hideki Okayama, MD); Fujita Health University (Yukio Ozaki, MD; Hiroyuki Naruse, MD); Fukuoka University (Keijiro Saku, MD; Shin-ichiro Miura, MD; Atsushi Iwata, MD); Gifu Prefectural General Medical Center (Toshiyuki Noda, MD; Shunichiro Warita); Hiroshima City Asa Hospital (Keigo Dote, MD; Masaya Kato, MD); Hiroshima City Hospital (Ichiro Inoue, MD; Takuji Kawagoe, MD); Japanese Red Cross Nagoya First Hospital (Haruo Kamiya, MD); Juntendo University (Hiroyuki Daida, MD; Katsumi Miyauchi, MD); Juntendo University Shizuoka Hospital (Satoru Suwa, MD); Juntendo University Urayasu Hospital (Yuji Nakazato, MD; Kosei Tanimoto, MD); Kansai Rosai Hospital (Masaaki Uematsu, MD; Fusako Sera, MD); Kokura Memorial Hospital (Masashi Iwabuchi, MD; Shinichi Shirai, MD); Kurashiki Central Hospital (Kazuaki Mitsudo, MD; Yasushi Fuku, MD); Kyoto University (Takeshi Kimura, MD; Y Tomoya Tada, MD); National Cardiovascular Center (Hiroshi Nonogi, MD); National Hospital Organization Hamada Medical Center (Hiroshi Iida, MD); National Hospital Organization Kagoshima Medical Center (Shinichi Minagoe, MD; Hitoshi Nakashima, MD, Masahiro Sonoda, MD; Hideki Tanaka, MD); NTT East Corporation Sapporo Hospital (Tetsuro Kouya, MD; Noriyuki Miyamoto, MD); Okayama Redcross General Hospital (Toru Ujihira, MD); Osaka City General Hospital (Akira Itoh, MD; Kazato Ito, MD); Saiseikai Kumamoto Hospital (Koichi Nakao, MD); The University of Tokyo (Yasunobu Hirata, MD, Jiro Ando, MD);Tokuyama Central Hospital (Hiroshi Ogawa, MD; Takahiro Iwami, MD); Toranomon Hospital (Sugao Ishiwata, MD; Yo Fujimoto, MD); Tsuchiya General Hospital (Yasuhiko Hayashi, MD; Nobuo Shiode, MD; Mamoru Toyofuku, MD); Wakayama Medical University (Takashi Akasaka, MD; Hironori Kitabata, MD); Yamaguchi University (Masunori Matsuzaki, MD; Takayuki Okamura, MD); Yokkaichi Municipal Hospital (Masaaki Kanashiro, MD; Toru Aoyama, MD); Yokohama City University Medical Center (Kiyoshi Hibi, MD; Mitsuaki Endo, MD).

Supplemental Files

Supplemental File 1

Table S1. Laboratory Data at Final Follow-up

Figure S1. Comparison of cardiovascular events incidence between atorvastatin- and pitavastatin-assigned patients.

Please find supplemental file(s);
http://dx.doi.org/10.1253/circj.CJ-12-0135