Original Article

More Intensive Lipid Lowering is Associated with Regression of Coronary Atherosclerosis in Diabetic Patients with Acute Coronary Syndrome - Sub-Analysis of JAPAN-ACS Study

Hidenori Arai[1], Takafumi Hiro[2], Takeshi Kimura[3], Takeshi Morimoto[4], Katsumi Miyauchi[5], Yoshihisa Nakagawa[6], Masakazu Yamagishi[7], Yukio Ozaki[8], Kazuo Kimura[9], Satoshi Saito[10], Tetsu Yamaguchi[11], Hiroyuki Daida[5], and Masunori Matsuzaki[12], for the JAPAN-ACS Investigators

[1]Department of Human Health Sciences, Kyoto University Graduate School of Medicine, Kyoto, Japan
[2]Division of Cardiology, Department of Medicine, Nihon University School of Medicine, Tokyo, Japan
[3]Department of Cardiovascular Medicine, Kyoto University Graduate School of Medicine, Kyoto, Japan
[4]Center for Medical Education, Kyoto University Graduate School of Medicine, Kyoto, Japan
[5]Department of Cardiology, Juntendo University School of Medicine, Tokyo, Japan
[6]Department of Cardiology, Tenri Hospital, Nara, Japan
[7]Division of Cardiovascular Medicine, Kanazawa University Graduate School of Medicine, Kanazawa, Japan
[8]Department of Cardiology, Fujita Health University, Toyoake, Japan
[9]Division of Cardiology, Yokohama City University Medical Center, Yokohama, Japan
[10]Keiai Hospital, Tokyo, Japan
[11]Toranomon Hospital, Tokyo, Japan
[12]Division of Cardiology, Department of Medicine and Clinical Science, Yamaguchi University Graduate School of Medicine, Ube, Japan

***Aim*: We have shown that aggressive lipid lowering by pitavastatin and atorvastatin results in marked regression of atherosclerotic coronary lesions after acute coronary syndrome (ACS). The purpose of this study was to address the association of lipid levels after statin therapy with regression of atherosclerotic coronary lesions and major cardiovascular events in patients after ACS.**
***Methods*: JAPAN-ACS is a prospective, randomized open-label study performed at 33 centers in Japan. Patients with ACS undergoing intravascular ultrasound (IVUS)-guided percutaneous coronary intervention (PCI) were randomly assigned to receive either 4 mg/day pitavastatin or 20 mg/day atorvastatin within 72 hours after PCI. IVUS image was obtained in 251 patients, including 73 diabetic patients. Lipid profiles at the end of the study were divided into quartiles and the association with the percent change in non-culprit coronary plaque volume (PV) was assessed in total and diabetic patients. We also studied whether baseline and follow-up levels of HDL-cholesterol are associated with restenosis after PCI.**
***Results*: Decreasing LDL-cholesterol, non-HDL-cholesterol, LDL-C/HDL-C ratio, apolipoprotein B quartiles were associated with a progressively smaller plaque burden in total and diabetic patients. In diabetic patients, further reduction of these parameters was associated with a significantly greater reduction in PV. We also found that patients with lower HDL-cholesterol had a significantly higher incidence of target lesion revascularization.**
Conclusions: Early intensive statin therapy in patients after ACS results in remarkable regression of coronary PV. Diabetic patients can have a benefit with more intensive therapy to achieve a lower target level in Japanese.

J Atheroscler Thromb, 2010; 17:1096-1107.

Key words; Acute coronary syndrome, Plaque, Statin, Intravascular ultrasound, Diabetes mellitus

Address for correspondence: Hidenori Arai, Department of Human Health Sciences, Kyoto University Graduate School of Medicine, Kyoto, Japan
E-mail: harai@kuhp.kyoto-u.ac.jp
Received: April 13, 2010
Accepted for publication: June 1, 2010

Introduction

Accumulating evidence indicates that statins can reduce both cardiovascular morbidity and mortality in primary and secondary prevention, including patients

with acute coronary syndrome (ACS)[1-3]. Lowering LDL-cholesterol to even lower levels is associated with a further reduction in cardiovascular risk, as shown in the Treatment to New Target (TNT) Study[4] and in the Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL) Study of secondary prevention[5]. These studies support the hypothesis that a lower LDL-cholesterol level can induce a greater risk reduction, at least in secondary prevention.

Moreover, many studies with surrogate endpoints show improvement of atherosclerosis by aggressively lowering LDL-cholesterol. Studies using intravascular ultrasound (IVUS) imaging demonstrate that statins attenuate the progression of atherosclerosis or even enable regression of atheromatous plaque[6, 7]. An IVUS study of patients with ACS also demonstrated that atorvastatin can reduce non-culprit coronary plaque in Japanese[8]; however, this was a relatively small trial conducted at a single center. Therefore, a larger multicenter study is expected to address the further roles of statins in patients with ACS.

We previously reported the results of the JAPAN-ACS (Japan Assessment of Pitavastatin and Atorvastatin in Acute Coronary Syndrome) study to address the role of statins in patients with ACS[9]. The JAPAN-ACS was performed as a prospective, randomized open-label parallel-group study with a blind endpoint evaluation at 33 centers, to comparatively examine the effect of 8- to 12-month treatment with pitavastatin and atorvastatin on the degree of coronary plaque regression in non-culprit lesions of the culprit vessel treated by PCI in patients with ACS. This study demonstrated the non-inferiority of pitavastatin 4 mg/day to atorvastatin 20 mg/day, with approximately 17% regression of the plaque volume (PV), suggesting that the effect of inducing plaque regression can be generalized to other statins with similar LDL-lowering effects with atorvastatin. However, in this study, diabetic patients showed less regression of coronary atheroma than non-diabetic patients in spite of similar LDL-cholesterol reduction by statins. In the sub-analysis of JAPAN-ACS we showed significant correlations between the percent change in PV and percent change of the LDL-cholesterol level or follow-up LDL-cholesterol level in diabetic patients[10]; however, a question remains whether there is an appropriate target lipid level to obtain the maximum effect on plaque regression. Therefore, in this sub-analysis of JAPAN-ACS we examined the association of lipid levels after statin therapy with the regression of atherosclerotic coronary lesions in diabetic and total patients after ACS. This analysis was performed in the entire patient population, using the full analysis set of the JAPAN-ACS study, as the regressive effect of the two statins was shown to be equivalent.

In this study we also asked whether baseline and follow-up levels of HDL-cholesterol are associated with restenosis or other cardiovascular events after PCI to show the effect of low HDL-cholesterolemia on coronary events, because previous studies have shown that low levels of HDL-cholesterol can predict major cardiovascular events[11-13].

Methods

Study Design

The present study is a post-hoc sub-analysis of the JAPAN-ACS (Japan Assessment of Pitavastatin and Atorvastatin in Acute Coronary Syndrome) study. JAPAN-ACS is a prospective, randomized open-label parallel group study with blind endpoint evaluation at 33 centers to examine the effect of 8−12 months treatment with pitavastatin versus atorvastatin in coronary plaque regression in non-percutaneous coronary intervention (PCI) sites of the culprit vessel in patients with ACS. The details of the study design have been reported previously[9, 14]. In brief, ACS patients selected in this study were over 20 years of age with hypercholesterolemia and had undergone successful PCI under IVUS guidance. They were found to have coronary plaques (more than 500 μm in thickness, or percent plaque area ≥20%) in the culprit vessel at least 5 mm from the PCI- treated lesions. ACS was defined as unstable angina pectoris, non-ST-elevation myocardial infarction (MI) or ST-elevation MI. The diagnosis of ACS was made based on the fulfillment of at least two of the following three criteria: 1) evidence of coronary ischemia on ECG, 2) increase (≥2 times) in the serum creatinine phosphokinase (CK) or CK-MB levels, and/or troponin-T positivity, 3) presence of symptoms suggestive of ACS. Diabetes mellitus and other complications were diagnosed by the attending physicians. This study was conducted according to the 'Declaration of Helsinki', and with the approval of the institutional review boards of all 33 participating institutions. Written informed consent to participate was obtained from all of the patients enrolled.

Intravascular Ultrasound Procedure and Examination

Details of the intravascular ultrasound (IVUS) procedure and examination are documented elsewhere[9]. In brief, following IVUS-guided PCI for the culprit lesion in the patients with ACS, a final IVUS examination for analysis was performed in the culprit vessel. The IVUS catheter Atlantis SR Pro2 (Boston

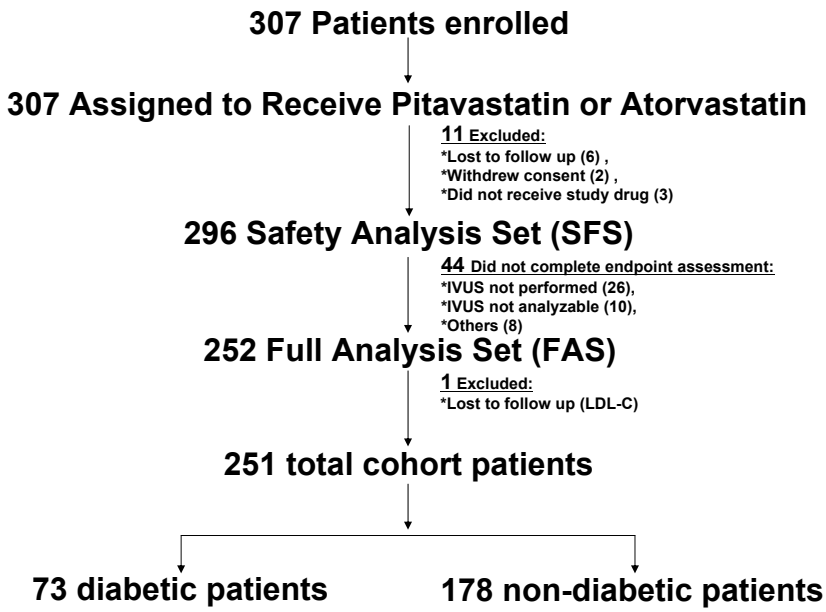

Fig. 1. Characteristics of Patients in JAPAN-ACS.

Scientific, Natik, USA) was used, and a motorized pullback device withdrew the transducer at 0.5 mm/sec. The consoles used were the ClearView or Galaxy 2 system (Boston Scientific, Natik, USA). The same imaging system with the same type of IVUS catheter was used for both the baseline and follow-up examinations

Two independent experienced investigators performed the quantitative IVUS analysis at the central laboratory. The target segment for analysis was identified as a non-PCI site of the culprit vessel (>5 mm proximal or distal to the PCI site) based on reproducible indices. Manual tracing was performed in every 0.1 mm cross-section and the software (echoPlaque2; INDEC systems Inc., Santa Clara, USA) automatically interpolated the tracings of 5 cross-sections between two manually traced images; therefore, the volume was calculated from each of the 0.017 mm-interval segments.

Blood Examination

Blood examinations for lipid levels were performed at baseline and 8−12 months follow-up. Lipid profiles were measured at SRL Co, Ltd. (Tokyo, Japan).

Statistical Analysis

We used the full analysis set (FAS) of data for primary analyses. Patient data were included in FAS if patients had ACS and measurable IVUS both at enrollment and follow-up. Because non-inferiority was shown between pitavastatin and atorvastatin, we combined the data of both groups and performed this subanalysis. LDL-cholesterol, non-HDL-cholesterol, LDL-C/HDL-C ratio, and apolipoprotein B (apo B) at the end of the study were divided into quartiles and the percentage change in PV in each quartile was compared in total and diabetic patients by ANOVA or *t* test when appropriate. The chi-square test was used for categorical variables. We also analyzed the association of baseline and follow-up HDL-cholesterol (over or equal to 40 mg/dL or less than 40 mg/dL) with the rate of restenosis in this cohort. The significance level was 5% two-sided (2.5% one-sided) and all statistical analyses were performed using the SAS System Release 9.1 (SAS institute, Cary, USA).

Results

Patient Population

The characterstics of patients in the present study are shown in **Fig. 1**. Between November 1, 2005 and October 31, 2006, 307 patients were enrolled at 33 centers in Japan, and 153 patients were randomly assigned to receive pitavastatin and 154 to atorvastatin. IVUS images qualifying for evaluation both at baseline and follow-up were obtained in 125 patients (82%) in the pitavastatin group and in 127 patients (82%) in the atorvastatin group. The median follow-up time with intraquartile range in the pitavastatin group was 9.3 (8.5−10.3) months and 9.6 (8.6−10.5) months in the atorvastatin group, respectively.

The details of baseline demographics and characteristics in this study have been reported elsewhere[9]. Among 251 total cohorts, 73 patients were diabetic.

There were no differences in the percent change of PV and LDL-cholesterol reduction between pitavastatin and atorvastatin groups in patients with or without diabetes. In diabetic patients, the percent change of PV was −13.7±15.1% ($p<0.001$, from baseline) in the pitavastatin group ($n=36$) and −12.0±13.9% ($p<0.001$, from baseline) in the atorvastatin group ($n=38$) ($p=0.7$, pitavastatin vs. atorvastatin). The percent change of PV was −18.1±13.2% ($p<0.001$, from baseline) in the pitavastatin group ($n=89$) and −20.7±13.6% ($p<0.001$, from baseline) in the atorvastatin group ($n=89$) in non-diabetic patients ($p=0.2$, pitavastatin vs. atorvastatin), while in diabetic patients, the percent change of LDL-cholesterol was −35.7±21.1% ($p<0.001$, from baseline) in the pitavastatin group ($n=35$) and −37.6±22.6% ($p<0.001$, from baseline) in the atorvastatin group ($n=38$) ($p=0.7$, pitavastatin vs. atorvastatin). The percent change of LDL-cholesterol was −36.4±19.0% ($p<0.001$, from baseline) in the pitavastatin ($n=89$) group and −34.9±23.1% ($p<0.001$, from baseline) in the atorvastatin group ($n=87$) in non-diabetic patients ($p=0.7$, pitavastatin vs. atorvastatin).

Table 1. Median and interquartiles of lipid profiles in total and diabetic patients

total cohort ($n=251$)			
Quartile	25%	50%	75%
LDL-C (mg/dL)	66	79	98
non HDL-C (mg/dL)	84	99	124
Apo B (mg/dL)	60	72	86
LDL-C/HDL-C	1.32	1.77	2.23
diabetic patients ($n=73$)			
Quartile	25%	50%	75%
LDL-C (mg/dL)	56.5	75	101.5
non HDL-C (mg/dL)	82	95	125.5
Apo B (mg/dL)	57	70	88
LDL-C/HDL-C	1.14	1.75	2.37

Association of Percent Change in Plaque Volume with Quartiles of Lipid Parameters

Table 1 shows 25th and 75th percentiles and medians in each lipid parameter in total and diabetic populations. According to these numbers we divided the total and diabetic patients into quartiles and compared the percent change of PV in each group (**Table 2**). Decreasing LDL-cholesterol, non-HDL-cholesterol, apo B, and LDL-C/HDL-C ratio quartiles were associated with a progressively larger percent change of PV

Table 2. Association of % change in plaque volume with quartile of lipid parameters

		quartile at follow up	1st	2nd	3rd	4th	*p* value
LDL-C	total	mean (range) [mg/dL]	53.2 (<66)	71.4 (66–79)	87.7 (79–98)	117.2 (98<)	
		% change in plaque volume (SD) [%]	−15.4 (12.7)	−20.3 (14.4)	−20 (13.0)	−14.2 (15.2)	0.03
	DM	mean (range) [mg/dL]	48.7 (<56.5)	69.1 (56.5–75)	88.6 (75–101.5)	119.4 (101.5<)	
		% change in plaque volume (SD) [%]	−16.5 (13.6)	−16.9 (14.5)	−10.6 (13.0)	−6.7 (15.2)	0.1
nonHDL-C	total	mean (range) [mg/dL]	70.0 (<84)	90.1 (84–99)	109.6 (99–124)	143.9 (124<)	
		% change in plaque volume (SD) [%]	−15.6 (12.8)	−18.5 (12.7)	−21.4 (14.0)	−14.0 (15.6)	0.01
	DM	mean (range) [mg/dL]	63.9 (<82)	87.4 (82–95)	111.6 (95–125.5)	149.9 (125.5<)	
		% change in plaque volume (SD) [%]	−16.2 (14.0)	−15.3 (14.6)	−12.4 (13.3)	−6.9 (15.4)	0.2
apoB	total	mean (range) [mg/dL]	50.5 (<60)	65.6 (60–72)	78.5 (72–86)	99.2 (86<)	
		% change in plaque volume (SD) [%]	−16.1 (12.4)	−19.2 (15.2)	−21.3 (11.7)	−13.2 (15.6)	0.006
	DM	mean (range) [mg/dL]	47.4 (<57)	62.6 (57–70)	78.8 (70–88)	99.6 (88<)	
		% change in plaque volume (SD) [%]	−16.3 (13.2)	−15.9 (14.3)	−14.6 (11.4)	−5.3 (15.9)	0.049
LDL-C/HDL-C	total	mean (range) [mg/dL]	1.02 (<1.32)	1.54 (1.32–1.77)	1.95 (1.77–2.23)	2.75 (2.23<)	
		% change in plaque volume (SD) [%]	−16.7 (14.5)	−19.5 (14.1)	−20.1 (13.1)	−13.6 (13.8)	0.03
	DM	mean (range) [mg/dL]	0.86 (<1.14)	1.48 (1.14–1.75)	1.95 (1.75–2.37)	2.86 (2.37<)	
		% change in plaque volume (SD) [%]	−18.6 (14.8)	−13.7 (14.6)	−14.2 (12.6)	−4.1 (13.0)	0.02

Table 3. Baseline characteristics of total cohort with quartiles of follow up LDL-cholesterol

Characteristic	1st ($n=62$)	2nd ($n=62$)	3rd ($n=64$)	4th ($n=63$)	p value
Age (years)	66.4 ± 9.9	61.4 ± 11.0	61.6 ± 10.6	60.4 ± 12.1	0.01
Male (%)	81	92	81	73	0.042
BMI (kg/m^2)	24.3 ± 3.5	24.7 ± 3.3	23.9 ± 3.6	24.5 ± 3.7	0.6
Waist circumference (cm)	86.7 ± 8.6	88.1 ± 7.7	86.3 ± 9.0	87.2 ± 10.6	0.7
Diabetes (%)	35	27	20	33	0.2
Hypertension (%)	65	69	59	57	0.5
Family history of CAD (%)	23	19	16	14	0.6
Smoking (%)	34	50	58	46	0.054
Alcohol drinker (%)	68	52	38	35	0.001
Culprit vessel (%)					
RCA	31	21	42	33	0.1
LAD	53	68	48	48	
LCx	16	11	8	19	
LMT	0	0	2	0	
BMS (%)	63	69	67	63	0.6
DES (%)	37	27	30	33	
Other than stent (POBA) (%)	0	3	3	3	
TC (mg/dL)	184.3 ± 30.1	184.8 ± 27.7	203.7 ± 30.4	216.7 ± 43.5	< 0.0001
LDL-C (mg/dL)	117.2 ± 27.7	122.2 ± 23.9	138.3 ± 27.3	152.2 ± 37.3	< 0.0001
TG (mg/dL)	106.0 (72.5, 139.8)	111.5 (67.0, 141.3)	120.0 (76.8,157.8)	106.0 (80.5, 154.5)	0.4$^{\#}$
HDL-C (mg/dL)	46.1 ± 9.1	43.0 ± 9.7	44.4 ± 9.9	44.2 ± 10.3	0.3
non-HDL-C (mg/dL)	137.3 ± 27.9	142.0 ± 26.0	159.3 ± 29.2	171.4 ± 38.4	< 0.0001
LDL-C/HDL-C	2.6 ± 0.8	3.0 ± 0.8	3.3 ± 0.9	3.5 ± 0.8	< 0.0001
Apo A-I (mg/dL)	116.3 ± 20.0	106.8 ± 17.3	111.2 ± 18.9	109.3 ± 20.6	0.047
Apo B (mg/dL)	92.6 ± 20.4	97.6 ± 18.3	110.6 ± 20.1	116.0 ± 26.2	< 0.0001
Apo E (mg/dL)	4.3 ± 1.4	4.0 ± 1.1	4.1 ± 1.0	4.3 ± 1.1	0.4
Apo B/Apo A-I	0.82 ± 0.22	0.93 ± 0.22	1.02 ± 0.23	1.08 ± 0.25	< 0.0001

TG is expressed as median and interquartile range, $^{\#}$: Wilcoxon/Kruskal-Wallis test

in total and diabetic patients. The difference was significant in all parameters of the total cohort, while the difference was significant only in apo B and LDL-C/HDL-C in diabetic patients. We also analyzed baseline demographics of each quartile according to follow-up LDL-cholesterol (**Table 3**). The mean age and the prevalence of alcohol drinkers were higher in the first quartile than the other quartiles, which might affect less PV change in the first quartile. Total cholesterol, LDL-cholesterol, non-HDL-cholesterol, apo B, and apo B/apo AI were higher in the third and fourth quartiles than the others.

Because we noticed a smaller percent change of PV in the fourth quartile than the others, we compared the percent change of PV between the combined data from the first to third quartiles and the fourth quartile in each lipid parameter (**Fig. 2**). There was a significant difference between the two groups by t test in all the lipid parameters, indicating that the fourth quartile had less plaque regression than the others.

Next, we compared the percent change of PV in diabetic patients. The baseline characteristics of diabetic patients according to the quartiles of follow-up LDL are shown in **Table 4**. There was no significant difference in age, sex, BMI, waist circumference, or the prevalence of hypertension, family history of coronary artery disease, smoking, and alcohol drinking in this cohort, while total cholesterol, LDL-cholesterol, non-HDL-cholesterol, LDL-C/HDL-C ratio, apo B, apo B/apo AI ratio were higher in the third and fourth quartiles than the others. When we performed the same analysis with the total cohort, a significant difference was found between the combined data from the first to third quartiles and the fourth quartile, except non-HDL-cholesterol (**Fig. 3**). Because further

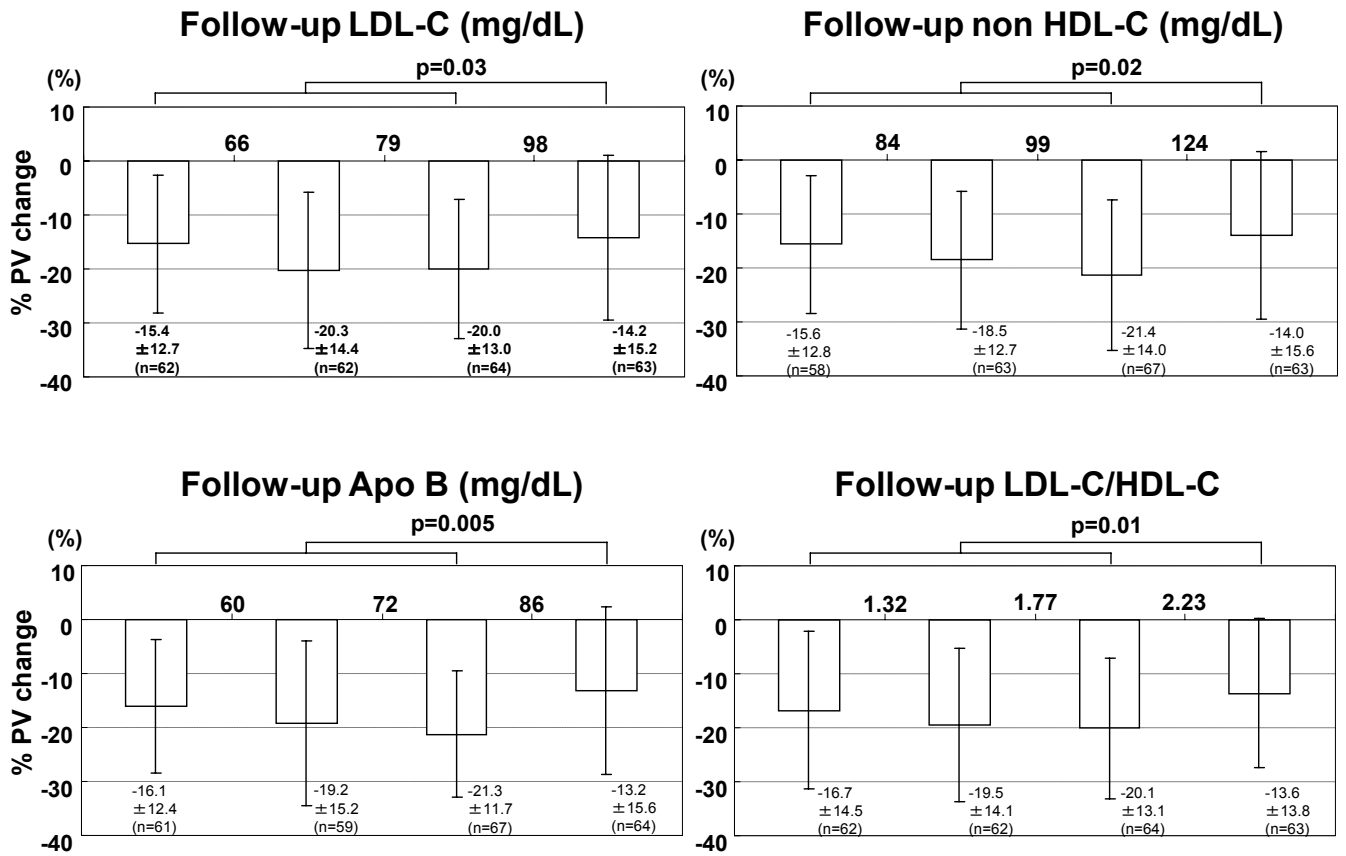

Fig. 2. Percent change of PVin each quartile of follow-up lipid parameters in the total cohort.

reduction of lipid profiles seemed to result in further reduction of PV in diabetic patients, we also compared the percent PV change after dividing them into 2 groups according to the median. As shown in **Fig. 4**, a significant difference was found between the two groups, except in non-HDL-cholesterol. However, the *p* value was smaller in LDL-cholesterol when we used the median as a cutoff value, while it was larger in apo B. Although we did not find significant differences in non-HDL-cholesterol, a *p* value of 0.028 was obtained when we used a cutoff of 100 mg/dL for non HDL-cholesterol.

Effect of HDL-Cholesterol Levels on Major Adverse Cardiovascular Events

To examine the effect of HDL-cholesterol levels on major adverse cardiovascular events (MACE), such as target lesion revascularization (TLR) and target vessel revascularization (TVR), we compared their incidence in the total cohort according to baseline and follow-up HDL-cholesterol levels (≥40 mg/dL or <40 mg/dL). As shown in **Table 5**, patients with lower HDL-cholesterol at baseline or follow-up showed a significantly higher incidence of TLR, but not of TVR or other vessel revascularization. The baseline characteristics of the two groups according to the levels of follow-up HDL-cholesterol levels are shown in **Table 6**. There was no significant difference in demographic characteristics between the two groups. As expected, HDL-cholesterol and apo AI were higher and the LDL-C/HDL-C ratio and apo B/AI were lower in patients with higher HDL-cholesterol. A similar finding was observed when we divided the patients according to baseline HDL-cholesterol levels (data not shown).

Discussion

In this post-hoc analysis of the JAPAN-ACS study we have shown that diabetic patients had more regression by targeting lower levels of LDL, non-HDL cholesterol, and LDL-C/HDL-C with intensive lipid-lowering therapy in Japanese; however, our data may indicate that the same target can be used for apo B in diabetic or non-diabetic ACS patients. We also found that patients with lower HDL-cholesterol had a higher

Table 4. Baseline characteristics of diabetic patients with quartiles of follow-up LDL-C

Characteristic	1st ($n=18$)	2nd ($n=18$)	3rd ($n=19$)	4th ($n=18$)	p value
Age (years)	64.2 ± 10.8	62.0 ± 9.7	60.6 ± 10.8	64.2 ± 11.3	0.7
Male (%)	83	94	84	67	0.2
BMI (kg/m^2)	24.4 ± 3.6	25.9 ± 3.1	24.8 ± 3.8	24.4 ± 4.4	0.6
Waist circumference (cm)	87.1 ± 7.4	89.1 ± 6.0	89.4 ± 8.0	88.4 ± 10.7	0.9
Hypertension (%)	67	78	74	67	0.8
Family history of CAD (%)	28	11	16	17	0.6
Smoking (%)	39	39	63	50	0.4
Alcohol drinker (%)	67	61	47	39	0.3
Culprit vessel (%)					
RCA	28	22	47	44	0.5
LAD	44	61	32	39	
LCx	28	17	21	17	
LMT	0	0	0	0	
BMS (%)	44	72	74	72	0.2
DES (%)	56	22	21	28	
Other than stent (POBA) (%)	0	6	5	0	
TC (mg/dL)	186.4 ± 33.8	187.1 ± 25.0	201.5 ± 23.0	217.3 ± 48.7	0.03
LDL-C (mg/dL)	115.9 ± 30.0	123.5 ± 21.3	138.7 ± 17.0	149.1 ± 44.3	0.006
TG (mg/dL)	112.0 (76.0, 153.0)	117.0 (77.0, 140.5)	127.0 (107.0, 173.0)	134.0 (76.3, 191.3)	0.6[#]
HDL-C (mg/dL)	48.6 ± 9.7	42.7 ± 6.3	41.3 ± 13.3	45.9 ± 12.1	0.2
non-HDL-C (mg/dL)	134.5 ± 28.6	144.4 ± 24.1	160.2 ± 19.4	170.6 ± 43.4	0.004
LDL-C/HDL-C	2.4 ± 0.8	3.0 ± 0.7	3.6 ± 0.9	3.3 ± 0.9	0.0004
Apo A-I (mg/dL)	123.6 ± 21.3	107.4 ± 16.3	106.4 ± 26.5	109.1 ± 23.6	0.09
Apo B (mg/dL)	92.4 ± 20.9	96.9 ± 18.5	111.8 ± 14.9	115.7 ± 27.3	0.003
Apo E (mg/dL)	4.3 ± 1.2	4.3 ± 1.0	4.2 ± 1.0	4.4 ± 1.0	0.95
Apo B/Apo A-I	0.76 ± 0.20	0.92 ± 0.23	1.10 ± 0.26	1.09 ± 0.26	0.0001

TG is expressed as median and interquartile range, [#]: Wilcoxon/Kruskal-Wallis test

risk for target lesion revascularization, and should be considered for additional therapy to prevent restenosis.

IVUS provides a precise evaluation of the vascular wall and has been shown to be the most sensitive and reliable technique for measuring coronary atherosclerosis progression and regression[15]. Several IVUS trials have shown that intensive lipid-lowering therapy is associated with a decrease of atherosclerosis progression or regression of plaque burden[6]. In the JAPAN-ACS we found much more regression of coronary atheroma after statin therapy than these studies in US[6, 7]. Consistent with our findings, Okazaki *et al.* also showed similar regression with 20 mg atorvastatin after ACS[8]. These data may indicate that Japanese patients are more susceptible to statin therapy in terms of atheroma regression; however, Takayama *et al.* have recently shown that rosuvastatin can induce significant regression of coronary PV (−5.1%) in Japanese patients with stable CAD[16], consistent with the findings by Nissen *et al.*[6, 7]. Taken together, the differences in regression rates between ours and those of Nissen *et al.* might be derived from the patient population; stable CAD and ACS patients. It is still difficult to investigate non-culprit coronary arteries by IVUS in Japan, which might also explain the difference between Japanese and US studies.

The National Cholesterol Education Program currently recommends an optional target LDL-cholesterol of < 70 mg/dL for patients at high risk of cardiovascular events, including those with an ACS event[17], while the Japanese guideline recommends an LDL-cholesterol target < 100 mg/dL for secondary prevention[18]. However, this study might provide a rationale for more aggressive lipid lowering, targeting LDL-cholesterol of < 75 or 70 mg/dL in diabetic patients after ACS, while non-diabetic patients can be treated to reach LDL-cholesterol of < 100 mg/dL. Our data also support non-HDL-cholesterol as an additional target

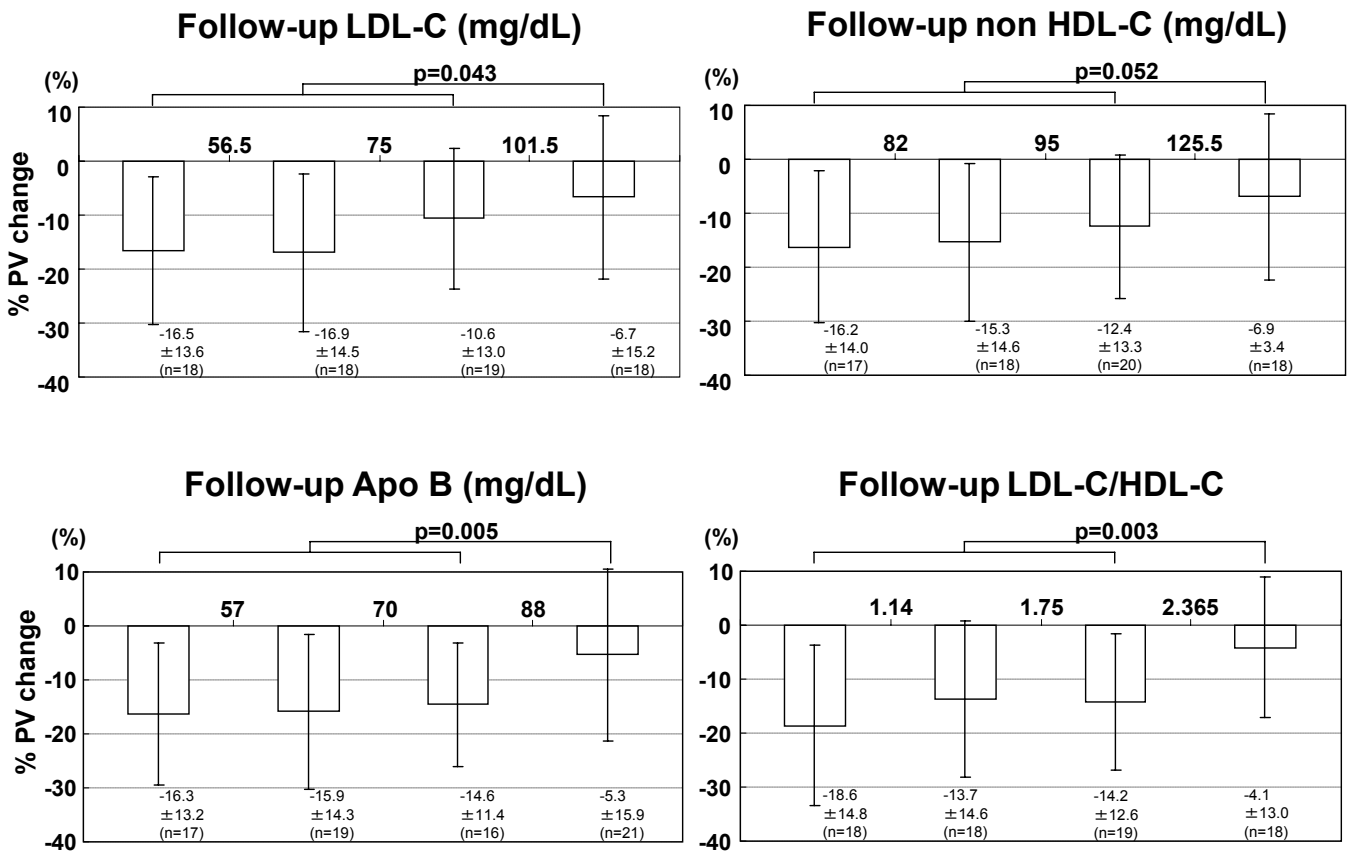

Fig. 3. Percent change of PV in each quartile of follow-up lipid parameters in diabetic patients.

for the management of ACS patients. Although the median cutoff did not result in a significant difference, a significant difference was observed when we used 100 mg/dL for the cutoff, which is consistent with the guidelines of the National Cholesterol Education Program for very high-risk patients. In terms of apo B, we obtained a smaller *p* value when we used a cutoff of 88 mg/dL than 70 mg/L in diabetic patients, which was almost the same in the total cohort. We showed less regression of coronary atheroma in diabetic patients after intensive statin treatment even though the mean LDL-cholesterol levels were almost the same in diabetic and non-diabetic patients. Considering that diabetic patients tend to have small dense LDL, the data on apo B might indicate that LDL particle number should be reduced to a certain level to obtain the maximum effects for plaque regression in diabetic patients. Further study is required to develop a rationale for aggressive lipid-lowering therapy in Japanese.

In this sub-analysis, we showed that low HDL-cholesterolemia <40 mg/dL was associated with increased TLR after ACS. As shown in **Table 6**, there was no demographic difference between the two groups except apo A1 and the ratio of LDL to HDL-cholesterol and the apo B to apo A1 ratio, indicating that low levels of HDL-cholesterol are a powerful predictor of major cardiovascular events even in patients treated with the maximum dose of statins. Previous studies have also shown that HDL-cholesterol levels during statin treatment are independently predictive of major cardiovascular events even in patients with LDL-cholesterol levels less than 70 mg/dL[11, 12]. Recently, Taylor *et al.* have shown that the use of extended-release niacin causes significant regression of carotid intima-media thickness when combined with a statin[19]; therefore, additional treatment might be required to raise HDL-cholesterol to prevent major cardiovascular events in patients with low HDL-cholesterolemia.

The current study has some limitations. The first is that LDL-cholesterol was determined by a direct method, not by a Friedwald equation because the equation could not be applied for blood samples from some patients. Recently, Nakamura *et al.* have shown that the direct measurement of LDL-cholesterol is still poor in terms of accuracy and stability[20]; however, even when we used the equation, we found similar

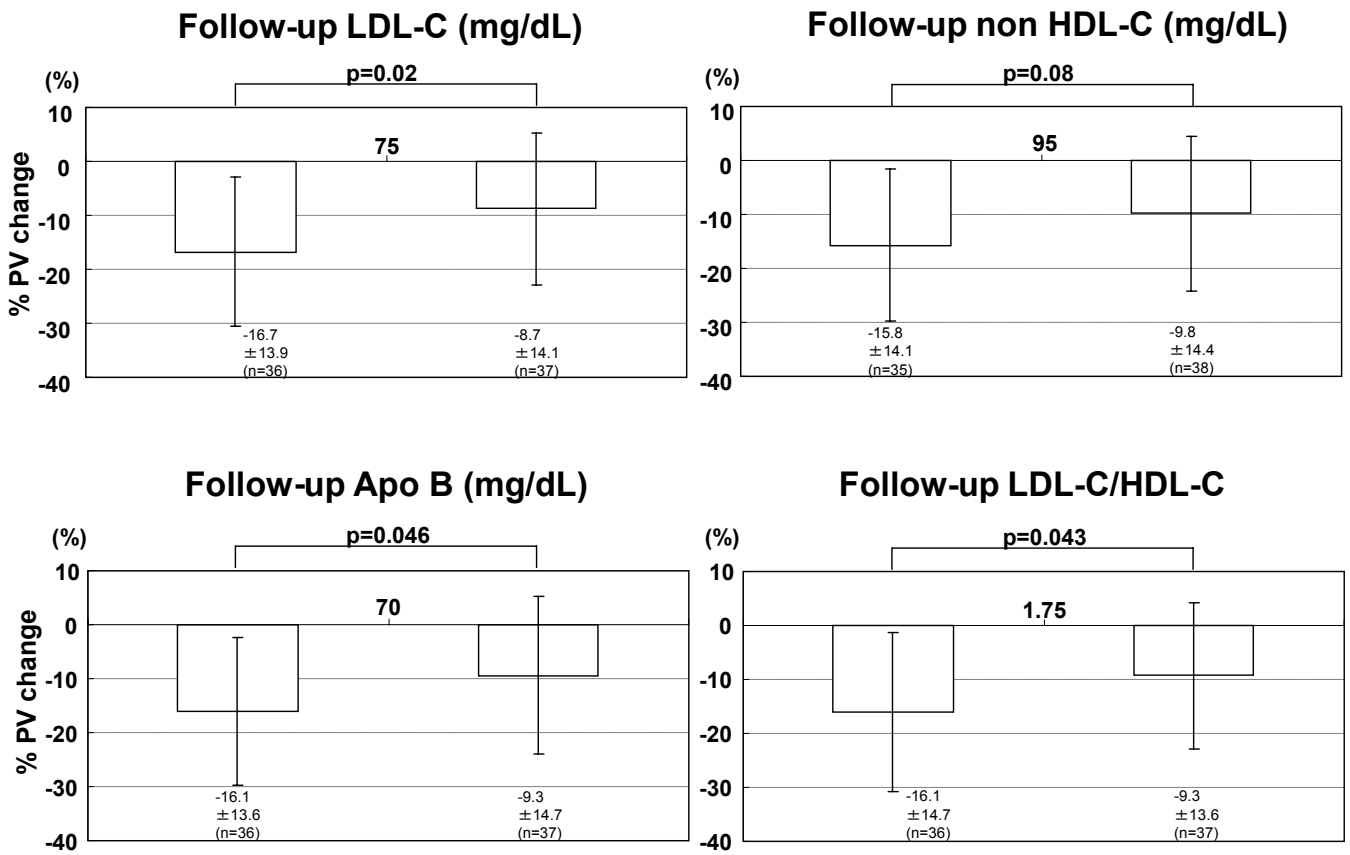

Fig. 4. Percent change of PV according to the median of follow-up lipid parameters in diabetic patients.

Table 5. Relationship between baseline and follow-up HDL-C levels with major adverse cardiovascular events (MACE)

baseline HDL-C	HDL-C < 40 mg/dL (*n* = 85)	HDL-C ≧ 40 mg/dL (*n* = 164)	*p* value
MACE	21 (24.7)	32 (19.5)	0.9
TLR	16 (18.8)	13 (7.9)	0.01
TVR (non-TLR)	3 (3.5)	11 (6.7)	0.3
Other vessel revascularization	6 (7.1)	10 (6.1)	0.09
follow-up HDL-C	HDL-C < 40 mg/dL (*n* = 64)	HDL-C ≧ 40 mg/dL (*n* = 187)	*p* value
MACE	15 (23.4)	38 (20.3)	0.6
TLR	12 (18.8)	17 (9.1)	0.046
TVR (non-TLR)	3 (4.7)	11 (5.9)	0.7
Other vessel revascularization	5 (7.8)	11 (5.9)	0.6

MACE: Major Adverse Cardiac Events
TLR: Target Lesion Revascularization
TVR: Target Vessel Revascularization

n (%)

results with this analysis (data not shown). The second is that this study lacked a control group receiving a placebo or less-intensive lipid-lowering therapy because the JAPAN-ACS study was designed to prove the non-inferiority of pitavastatin against atorvastatin. In this sub-analysis we combined the data on both statins; however, we deemed it ethically unacceptable to give a placebo to patients with ACS. The third is that the diagnosis of diabetes mellitus was made by the attending physicians, and no oral glucose tolerance

Table 6. Baseline characteristics of total cohort with HDL-C

Characteristic	follow-up HDL-C < 40 mg/dL (n = 64)	follow-up HDL-C ≧ 40 mg/dL (n = 187)	p value
Age (years)	62.8 ± 10.6	62.2 ± 11.3	0.7
Male (%)	89	79	0.064
BMI (kg/m^2)	24.4 ± 3.4	24.4 ± 3.6	0.99
Waist circumference (cm)	88.4 ± 8.9	86.6 ± 9.1	0.2
Diabetes (%)	25	30	0.4
Hypertension (%)	61	63	0.8
Family history of CAD (%)	22	17	0.3
Smoking (%)	52	45	0.4
Alcohol drinker (%)	45	49	0.6
Culprit vessel (%)			
RCA	25	34	0.4
LAD	61	52	
LCx	14	13	
LMT	0	0	
BMS (%)	70	64	0.6
DES (%)	28	33	
Other than stent (POBA) (%)	2	3	
TC (mg/dL)	189.9 ± 28.6	200.0 ± 37.8	0.052
LDL-C (mg/dL)	130.9 ± 27.3	133.0 ± 33.9	0.6
TG (mg/dL)	119.0 (85.3, 155.5)	105.0 (74.0, 143.0)	0.09$^{\#}$
HDL-C (mg/dL)	37.5 ± 6.5	46.8 ± 9.6	< 0.0001
non-HDL-C (mg/dL)	152.3 ± 27.7	152.5 ± 35.2	0.98
LDL-C/HDL-C	3.6 ± 0.9	2.9 ± 0.8	< 0.0001
Apo A-I (mg/dL)	98.0 ± 14.8	115.4 ± 18.9	< 0.001
Apo B (mg/dL)	105.2 ± 20.1	103.9 ± 24.3	0.7
Apo E (mg/dL)	3.9 ± 1.1	4.2 ± 1.2	0.057
Apo B/Apo A-I	1.09 ± 0.22	0.92 ± 0.24	< 0.0001

TG is expressed as median and interquartile range, $^{\#}$: Wilcoxon/Kruskal-Wallis test

test was performed to confirm diabetes, which is why we did not analyze non-diabetic patients.

In conclusion, early intensive statin therapy in Japanese patients after ACS resulted in the marked regression of coronary PV in total and diabetic patients. Diabetic patients can obtain more benefit from intensive lipid-lowering therapy with lower target levels of LDL, non-HDL-cholesterol, and LDL-C/HDL-C in Japanese. These lipid profiles may be related to the coronary plaque burden in statin-treated patients. On the other hand, low HDL-cholesterol levels are related to major cardiovascular events; therefore, patients with lower HDL-C are recommended for more intensive and comprehensive management to prevent the recurrence of coronary events.

Acknowledgements

We greatly acknowlege the contributions made by Izumi Miki, Saeko Minematsu, Yumika Fujino, and Miya Hanazawa for data management, Hiroko Kanou, Tatsuhiro Fujimura, and Genta Hashimoto for IVUS core laboratory management and IVUS planimetry, and Natsuko Yamamoto for QCA core laboratory managements.

Appendices

Steering Committee

Takafumi Hiro, MD, Katsumi Miyauchi, 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

Kazuo Kimura, MD, Satoshi Saito, MD, Tetsu Yamaguchi, MD

Independent Statistician

Takeshi Morimoto, MD

JAPAN-ACS Investigators

Aichi Medical University (Takayuki Ito, MD, Hiroaki Takashima, MD); Akita Medical Center (Tadaya Sato, MD); Anjo Kosei Hospital (Masato Watarai, MD); Ehime Prefectural Central Hospital (Yukio Kazatani, MD, Shinichi Hiramatsu, MD); Fujita Health University (Hitoshi Hishida, MD, Yukio Ozaki, MD, Hiroyuki Naruse, MD); Fukuoka University (Keijiro Saku, MD, Shin-ichiro Miura, MD, Atsushi Iwata, MD); Gifu Prefectural General Medical Center (Sachiro Watanabe, MD, Toshiyuki Noda, MD, Ryuhei Tanaka, MD, Koji Ono, MD); Hiroshima City Asa Hospital (Keigo Dote, MD, Masaya Kato, MD, Shota Sasaki, MD, Kentaro Ueda, MD); Hiroshima City Hospital (Ichiro Inoue, MD, Takuji Kawagoe, MD); Japanese Redcross 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 (Shinsuke Nanto, MD, Fusako Sera ,MD); Kokura Memorial Hospital (Masakiyo Nobuyoshi, MD, Hitoshi Yasumoto, MD); Kurashiki Central Hospital (Kazuaki Mitsudo, MD, Yasushi Fuku, MD); Kyoto University (Takeshi Kimura, MD, Yoshihisa Nakagawa, MD); National Cardiovascular Center (Hiroshi Nonogi, MD, Yoritaka Otsuka, MD, Nobuaki Kokubu, MD); National Hospital Organization Hamada Medical Center (Hiroshi Iida, MD, Mutsuo Nakayama, MD); National Hospital Organization Kagoshima Medical Center (Shinichi Minagoe, MD, Hitoshi Nakajima, MD, Masahiro Sonoda, MD); NTT East Corporation Sapporo Hospital (Tetsuro Kouya, MD, Noriyuki Miyamoto, MD, Yoshiyuki Suzuki, MD, Sachie Taguchi, MD); Okayama Redcross General Hospital (Toru Ujihira, MD, Hironori Saitou, MD, Tetsuya Sato, MD); Osaka City General Hospital (Akira Itoh, MD, Kei Yunoki, MD); Saiseikai Kumamoto Hospital (Takashi Honda, MD, Koichi Nakao, MD, Norihiro Yamada, MD); Sendai Kosei Hospital (Taiichiro Meguro, MD, Kaname Takizawa, MD); Tokuyama Central Hospital (Hiroshi Ogawa, MD, Takahiro Iwami, MD); Toranomon Hospital (Sugao Ishiwata, MD, Yo Fujimoto, MD); Tsuchiya Genaral Hospital (Yasuhiko Hayashi, MD, Mamoru Toyofuku, MD, Masaya Otsuka, MD); University of Tokyo (Yasunobu Hirata, MD, Jiro Ando, MD); Wakayama Medical University (Takashi Akasaka, MD, Takashi Kubo, MD, Hironori Kitabata, MD); Yamaguchi University (Masunori Matsuzaki, MD, Takafumi Hiro, MD, Takashi Fujii, MD, Takayuki Okamura, MD, Jutaro Yamada, MD, Genta Hashimoto, MD, Tatsuhiro Fujimura, MD); Yokkaichi Municipal Hospital (Satoshi Ichimiya, MD, Masaaki Kanashiro, MD, Junji Watanabe, MD, Seiji Fukui, MD, Taiki Ohashi, MD, Nobutake Kurebayashi, MD); Yokohama City University Medical Center (Kiyoshi Hibi, MD).

References

1) Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, Kirby A, Sourjina T, Peto R, Collins R, Simes R: Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet, 2005; 366: 1267-1278
2) Schwartz GG, Olsson AG, Ezekowitz MD, Ganz P, Oliver MF, Waters D, Zeiher A, Chaitman BR, Leslie S, Stern T: Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial. JAMA, 2001; 285: 1711-1718
3) Cannon CP, Braunwald E, McCabe CH, Rader DJ, Rouleau JL, Belder R, Joyal SV, Hill KA, Pfeffer MA, Skene AM: Intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med, 2004; 350: 1495-1504
4) LaRosa JC, Grundy SM, Waters DD, Shear C, Barter P, Fruchart JC, Gotto AM, Greten H, Kastelein JJ, Shepherd J, Wenger NK: Intensive lipid lowering with atorvastatin in patients with stable coronary disease. N Engl J Med, 2005; 352: 1425-1435
5) Pedersen TR, Faergeman O, Kastelein JJ, Olsson AG, Tikkanen MJ, Holme I, Larsen ML, Bendiksen FS, Lindahl C, Szarek M, Tsai J: High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial. JAMA, 2005; 294: 2437-2445
6) Nissen SE, Nicholls SJ, Sipahi I, Libby P, Raichlen JS, Ballantyne CM, Davignon J, Erbel R, Fruchart JC, Tardif JC, Schoenhagen P, Crowe T, Cain V, Wolski K, Goormastic M, Tuzcu EM: Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: the ASTEROID trial. JAMA, 2006; 295: 1556-1565
7) Nissen SE, Tuzcu EM, Schoenhagen P, Brown BG, Ganz P, Vogel RA, Crowe T, Howard G, Cooper CJ, Brodie B, Grines CL, DeMaria AN: Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomized controlled trial. JAMA, 2004; 291: 1071-1080
8) Okazaki S, Yokoyama T, Miyauchi K, Shimada K, Kurata

T, Sato H, Daida H: 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
9) Hiro T, Kimura T, Morimoto T, Miyauchi K, Nakagawa Y, Yamagishi M, Ozaki Y, Kimura K, Saito S, Yamaguchi T, Daida H, Matsuzaki M: 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 [Japan assessment of pitavastatin and atorvastatin in acute coronary syndrome] study). J Am Coll Cardiol, 2009; 54: 293-302
10) Hiro T, Kimura T, Morimoto T, Miyauchi K, Nakagawa Y, Yamagishi M, Ozaki Y, Kimura K, Saito S, Yamaguchi T, Daida H, Matsuzaki M; JAPAN-ACS Investigators: 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) Olsson AG, Schwartz GG, Szarek M, Sasiela WJ, Ezekowitz MD, Ganz P, Oliver MF, Waters D, Zeiher A: High-density lipoprotein, but not low-density lipoprotein cholesterol levels influence short-term prognosis after acute coronary syndrome: results from the MIRACL trial. Eur Heart J, 2005; 26: 890-896
12) Barter P, Gotto AM, LaRosa JC, Maroni J, Szarek M, Grundy SM, Kastelein JJ, Bittner V, Fruchart JC: HDL cholesterol, very low levels of LDL cholesterol, and cardiovascular events. N Engl J Med, 2007; 357: 1301-1310
13) Ghazzal ZB, Dhawan SS, Sheikh A, Douglas JS, Veledar E, Mavromatis K, Pohlel FK, Vaccarino V: Usefulness of serum high-density lipoprotein cholesterol level as an independent predictor of one-year mortality after percutaneous coronary interventions. Am J Cardiol, 2009; 103: 902-906
14) Miyauchi K, Kimura T, Morimoto T, Nakagawa Y, Yamagishi M, Ozaki Y, Hiro T, Daida H, Matsuzaki M: Japan assessment of pitavastatin and atorvastatin in acute coronary syndrome (JAPAN-ACS): rationale and design. Circ J, 2006; 70: 1624-1628
15) Nicholls SJ, Sipahi I, Schoenhagen P, Crowe T, Tuzcu EM, Nissen SE: Application of intravascular ultrasound in anti-atherosclerotic drug development. Nat Rev Drug Discov, 2006; 5: 485-492
16) Takayama T, Hiro T, Yamagishi M, Daida H, Hirayama A, Saito S, Yamaguchi T, Matsuzaki M: Effect of rosuvastatin on coronary atheroma in stable coronary artery disease: multicenter coronary atherosclerosis study measuring effects of rosuvastatin using intravascular ultrasound in Japanese subjects (COSMOS). Circ J, 2009; 73: 2110-2117
17) Grundy SM, Cleeman JI, Merz CN, Brewer HB Jr, Clark LT, Hunninghake DB, Pasternak RC, Smith SC Jr, Stone NJ: Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel Ⅲ Guidelines. J Am Coll Cardiol, 2004; 44: 720-732
18) Teramoto T, Sasaki J, Ueshima H, Egusa G, Kinoshita M, Shimamoto K, Daida H, Biro S, Hirobe K, Funahashi T, Yokote K, Yokode M, Committee for E, Clinical Management of A. Goals of dyslipidemia management. J Atheroscler Thromb, 2007; 14: 209-212
19) Taylor AJ, Villines TC, Stanek EJ, Devine PJ, Griffen L, Miller M, Weissman NJ, Turco M: Extended-release niacin or ezetimibe and carotid intima-media thickness. N Engl J Med, 2009; 361: 2113-2122
20) Nakamura M, Koyama I, Iso H, Sato S, Okazaki M, Kiyama M, Shimamoto T, Konishi M: Measurement performance of reagent manufacturers by Centers for Disease Control and Prevention/Cholesterol Reference Method Laboratory Network lipid standardization specified for metabolic syndrome-focused health checkups program in Japan. J Atheroscler Thromb, 2009; 16: 756-763