

Article

Combined Effects of Physical Activity and Achievement of LDL-cholesterol Target on Coronary Plaque Volume Changes in Patients with Acute Coronary Syndrome

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Abstract: Background: We investigated the combined effects of physical activity (PA) and aggressive low-density lipoprotein cholesterol (LDL-C) reduction on the changes of coronary plaque volume (PV) in patients with acute coronary syndrome (ACS) assessed by volumetric intravascular ultrasound (IVUS) analysis. **Methods:** We retrospectively analyzed data from 2 different prospective clinical trials involving 101 ACS patients who underwent percutaneous coronary intervention (PCI) and assessed non-culprit sites of PCI lesions using IVUS at baseline and follow-up. After PCI, all patients participated in early phase II comprehensive cardiac rehabilitation. At follow-up, we examined the correlation between plaque change and both parameters (the value of LDL-C and PA). **Results:** Patients were divided into 4 groups according to whether the mean steps counts measured by pedometer was 7000 steps or more and the LDL-C levels at follow-up was less than 70 mg/dl. Baseline characteristics were identical among the 4 groups. At the follow-up, plaque regression in both achievement group (PA and LDL-C reduction) was higher than other 3 groups. In addition, plaque reduction was independently correlated with increased amount of PA and LDL-C reduction. **Conclusions:** Combined therapy of intensive PA and achievement of LDL-C target retarded coronary PV in patients with ACS.

Keywords: keyword 1; Acute coronary syndrome keyword 2; Cardiac rehabilitation 3; Coronary plaque regression 4; Physical activity 5; Achievement of LDL-C target 6; Integrated backscatter intravascular ultrasound

1. Introduction

The prognosis of ACS patients is poor, but managing LDL-C improves prognosis. The mechanism can be explained by the plaque regression with lipid-lowering treatment. Therefore, plaque regression due to lipid management has clinical significance. However, managing LDL-C alone is not enough and other risk management must be performed. One of the promising candidates is exercise therapy.

Comprehensive Cardiac rehabilitation (CR) including exercise therapy after ACS is associated with lower cardiovascular mortality, re-hospitalization, coronary revascularization. And the

mechanism of these events reduction is considered to be anti-atherosclerosis effect of CR [3]. In fact, we recently showed that coronary plaque volume (PV) regression in patients with ACS were significantly positive correlated with physical activity (PA) using serial integrated backscatter intravascular ultrasound (IVUS) [4]. In addition, we demonstrated that intensive PA retarded coronary PV progression and ameliorated lipid component in patients with ACS participating in late phase II CR [5]. Therefore, intensive PA appears to be an effective strategy against residual risk for plaque stabilization and clinical events. However, the combined effects of LDL-C reduction and PA on coronary PV have not been investigated especially in patients with ACS. The aim of this study was to investigate the combined effects of PA and achievement of LDL-C target on the changes of coronary PV in patients with ACS assessed by volumetric intravascular ultrasound (IVUS) analysis.

2. Methods

2.1. Study Subjects and protocol

Current research was a retrospective study that evaluated the efficacy of PA and LDL-C reduction in the database for two different clinical trials. One of these trials aimed to determine the effects of phase II CR on coronary PV in patients after ACS [4]. The other one examined the effects of CR involving intensive PA on coronary PV and components in patients with ACS [5]. The details of those two trials have been previously described [4, 5]. In brief, all patients were admitted with ACS and underwent emergency coronary stenting in a culprit lesion. At the beginning of the study and 6 or 8 months after PCI, the serial volumetric IVUS examination was performed to assess the changes of coronary plaque in non-culprit lesion. After the procedure, all patients participated in early-phase II CR. We recommended all patients to participate in late-phase II CR after discharge, and to perform walking in accordance with their exercise prescription. Follow up visits were scheduled every 4 weeks after PCI. We checked their exercise content and daily PA every visit. Baseline measurements included IVUS data and biochemical data on admission, and cardiopulmonary exercise test (CPX) on discharge. Follow up IVUS data, biochemical data, and CPX were repeated at follow-up. Upon the follow-up IVUS procedure, achievement of LDL-C targets for post-ACS management was defined as LDL-C < 70 mg/dL [6].

Based on the serial IVUS findings of the target segment relative to the baseline, plaque regression was defined as a decrease in the absolute change in the percent atheroma volume (PAV), whereas plaque progression was defined as an increase in the absolute change in the PAV.

This study was conducted according to the Declaration of Helsinki and all patients provided written informed consent and the Ethics Committee of each institution approved the study (the approval numbers from the Ethics Committees of Juntendo University Hospital and Showa University Hospital were ID 24-018, 17-171, and ID 1036, respectively). The study was registered in the UMIN Clinical Trials Registry System under trial ID UMIN000006038 and 000010031.

2.2. Early phase II CR protocol

The CR program consisting of warm-up stretching, aerobic exercise, and cool-down, was scheduled once a day in hospital, as described previously [4, 5]. Aerobic exercise was consisted of a cycle ergometer, treadmill, and walking on an in-cardiac rehabilitation room track. The total aerobic exercise time was approximately 20 min. The exercise intensity was prescribed individually at the anaerobic threshold (AT) level, as measured by an ergometer test using expiratory gas analysis rating of 11-13 on the standard Borg's perceived exertion scale. All subjects were instructed to follow the phase II diet of the American Heart Association at the beginning of CR. An educational program was also provided for each subject by physicians, nurses, and dietitians regarding CAD and its risk factors at the baseline.

2.3. Measurements

We assessed body composition and exercise tolerance at the beginning and follow up or 8 months. Anthropometric parameters were assessed using the body mass index (BMI), and waist size.

The percentages of body fat and lean body weight were measured by a TANITA MC-780A® Body Composition Analyzer (TANITA Co. Ltd, Tokyo, Japan), which measured in the state where it stood on the electrode based on bioelectrical impedance analysis. Derivation of body volume, together with measurement of body mass, permits calculation of body density and subsequent estimation of percent fat and fat-free mass. To measure peak oxygen consumption (peak VO_2) and oxygen uptake at the AT, patients underwent ergometer testing (Strength Ergo8, NIHON KOHDEN Co. Ltd, Tokyo, Japan) using an expiratory gas analysis machine (AE-310s, Minato Medical Science Co. Ltd, Osaka, Japan). After a period of resting, warm-up was performed for a few minutes at 0W, followed by ramp loading (10W/min) until subjective exhaustion, progressive angina, ST-segment depression ($\geq 2\text{mm}$), or sustained tachyarrhythmia. The point of AT was determined by the 'V-slope' method. Daily physical activity was evaluated using a pedometer (Lifecoder®, Suzuken Co, Ltd, Nagoya, Japan) which can record the mean step count and calculated mean energy of PA for up to 60 days.

2.4. Statistical analysis

The results were expressed as the mean value $\pm$ standard deviation and were compared using one-way analysis of variance or the Kruskal-Wallis test. Comparison of continuous variables among 4 groups were performed by analysis of variance (ANOVA). The absolute change between the baseline and follow-up data was compared by paired *t*-test or Wilcoxon signed rank test, according to their distributions. The correlation coefficients were determined by linear regression analysis. Stepwise multiple regression analysis was used to determine the independent predictors of the changes in the plaque volume. Statistical significance of the correlation coefficients was determined by the method of Fisher and Yates. A *P* value of less than 0.05 was considered significant. All data were analyzed using JMP software (Version 14 for Windows, SAS Institute Inc. Cary, NC, USA.).

3. Results

3.1. Study population and Clinical Characteristics

One of these trials enrolled 50 patients with ACS who were admitted to Juntendo University Hospital and Showa University Hospital between December 2009 and August 2012 [4]. The other one enrolled 51 patients with ACS who were admitted to Juntendo University Hospital between February 2013 and January 2016 [5]. We analyzed the data of a total of 101 patients. Overall, the patients had a mean age of 60.7 ± 0.2 years; 95% were men; and had the coronary risk factors of hypertension in 62%, diabetes mellitus in 43%, and dyslipidemia in 91%. The proportion of patients who had STEMI was 74%.

In the 101 patients, 2 patients could not continue by orthopedic disease, 2 patients drop out follow-up, or 35 patients were excluded due to the poor image quality of IVUS. In the present study, patients were divided into 4 groups according to whether the mean steps counts measured by pedometer was 7000 steps (median value) or more and the LDL-C levels at follow-up was less than 70 mg/dl. Finally, 102 patients (group 1; on-treatment LDL-C ≥ 70 mg/dl with daily mean steps $< 7,000$, $n=26$, group 2; on-treatment LDL-C < 70 mg/dl with daily mean steps $< 7,000$, $n=9$, group 3; on-treatment LDL-C ≥ 70 mg/dl with daily mean steps $\geq 7,000$, $n=17$, group 4; on-treatment LDL-C < 70 mg/dl with daily mean steps $\geq 7,000$, $n=10$) were assessed the clinical data, including IVUS measurements at baseline and follow-up (Figure 1).

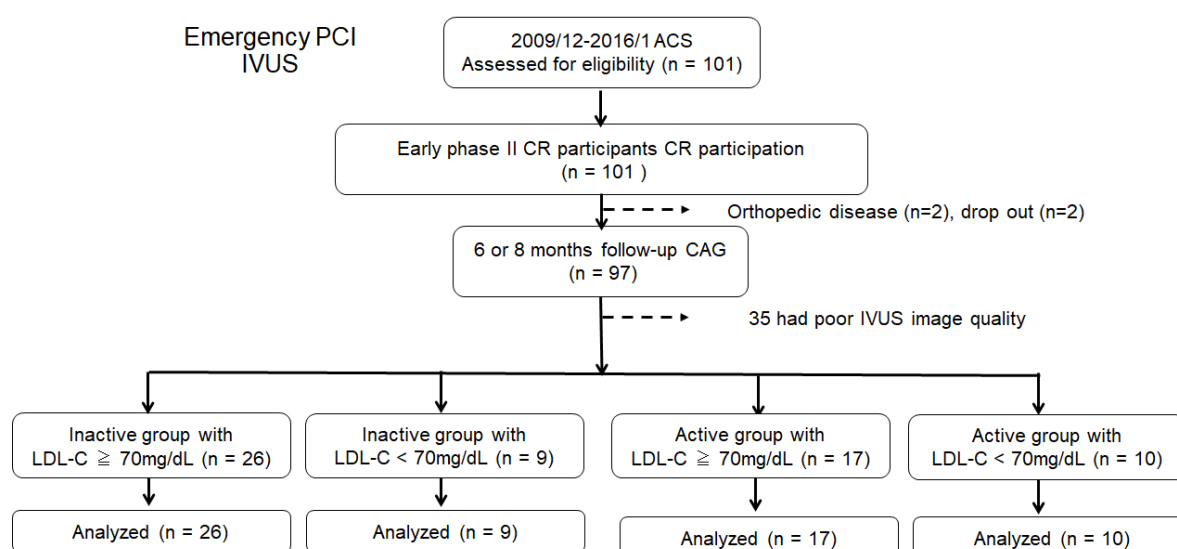


Figure 1. Study flow chart. Inactive group: Physical activity < 7000 steps / day. Active group: Physical activity $\geq$ 7000 steps / day.

The baseline clinical characteristics of the subjects and medication are presented in Table 1. There is a significant difference of age among the 4 groups. No significant differences of gender, coronary risk factors, classification of ACS, number of diseased vessels, the levels of the ejection fraction, or medication were observed among 4 groups.

Table 1. Baseline patient characteristics.

	Inactive group with LDL-C $\geq$ 70mg/dL (n = 26)	Inactive group with LDL-C < 70mg/dL (n = 9)	Active group with LDL-C $\geq$ 70mg/dL (n = 17)	Active group with LDL-C < 70mg/dL (n = 10)	P value
Age, y	62.5 $\pm$ 10.3	67.0 $\pm$ 12.0	56.6 $\pm$ 8.9	55.9 $\pm$ 6.8	0.02
Male (%)	23 (88)	9 (100)	17 (100)	9 (90)	NS
Hypertension (%)	16 (62)	6 (67)	10 (59)	7 (70)	NS
Diabetes mellitus (%)	9 (35)	3 (33)	10 (59)	5 (50)	NS
Dyslipidemia (%)	22 (85)	7 (78)	17 (100)	10 (100)	NS
Current smoking (%)	12 (46)	4 (44)	8 (47)	7 (70)	NS
Family history (%)	10 (38)	1 (11)	6 (35)	5 (50)	NS
Prior CAD (%)		3 (12)			
Classification of ACS (%)					
ST elevated MI (%)	20 (77)	6 (67)	8 (47)	5 (50)	NS
Non-ST elevated MI (%)	6 (23)	2 (22)	7 (41)	3 (30)	
Unstable angina (%)	0 (0)	1 (11)	2 (12)	2 (20)	
Diseased vessels (%)					
Single	16 (62)	7 (78)	13 (76)	5 (50)	NS
Double	10 (38)	2 (22)	4 (24)	4 (40)	
Triple	0 (0)	0 (0)	0 (0)	1 (10)	
Culprit vessel (%)					
RCA	12 (46)	3 (33)	5 (29)	2 (20)	NS
LAD	10 (39)	6 (67)	9 (53)	7 (70)	
LCX	4 (15)	0 (0)	3 (18)	1 (10)	
Maximum CK, IU/L	2008 $\pm$ 2153	1799 $\pm$ 2125	845 $\pm$ 1116	1960 $\pm$ 2105	NS
EF, %	55.6 $\pm$ 9.7	56.6 $\pm$ 12.0	55.0 $\pm$ 8.1	55.1 $\pm$ 10.7	NS
Medications, n (%)					
DAPT (%)	26 (100)	9 (100)	17 (100)	10 (100)	NS
ACE-I (%)	16 (62)	3 (33)	13 (76)	6 (60)	NS
ARB (%)	7 (27)	5 (56)	4 (24)	3 (30)	NS
β -blockers (%)	19 (73)	9 (100)	15 (88)	8 (80)	NS
CCB (%)	4 (15)	1 (11)	2 (12)	2 (20)	NS
Statin (%)	25 (96)	8 (89)	16 (94)	10 (100)	NS
Ezetimibe (%)	2 (10)	0 (0)	2 (12)	3 (33)	NS
α -GI (%)	4 (15)	0 (0)	2 (12)	0 (0)	NS
SU (%)	0 (0)	0 (0)	0	0 (0)	NS
Insulin (%)	0 (0)	1 (11)	1 (6)	1 (10)	NS

Data are presented as the mean value $\pm$ SD. NS: not significant

CAD: coronary artery disease, ACS: acute coronary syndrome, MI: myocardial infarction,

RCA: right coronary artery, LAD: left anterior descending artery, LCX: left circumflex artery, CK: creatine kinase, EF: ejection fraction,

DAPT: dual antiplatelet therapy, ACE-I: angiotensin converting enzyme inhibitors, ARB: angiotensin II receptor blocker, CCB: calcium-channel blockers,

α -GI: α -glucosidase inhibitors, SU: sulfonylurea

3.2. Physical activity in each patient during out-patients clinic

Figure 2 shows PA during 60 days after discharge in each patient. In the 101 patients, 2 patients who could not continue to keep physical activity by orthopedic disease and 2 patients were excluded due to drop out follow-up. Therefore, we presented the data of 97 patients that could be measured PA records by pedometers. In the overall population, the median PA was 6,933 steps/ day (IQR; 4500steps/ day to 8318 steps/ day). Therefore, in further analyses, we divided the study subjects into the following two groups by the median value of PA, 7000 steps.: active group (n = 27, daily PA $\geq$ 7,000 steps) and inactive group (n = 35, daily PA < 7,000 steps). At follow-up, inactive group had significant improvements in PA (both $P < 0.01$). The active group maintained their PA during this period. Among the 4 group, the levels of PA were significantly different at follow up ($P < 0.05$) (Figure 3).

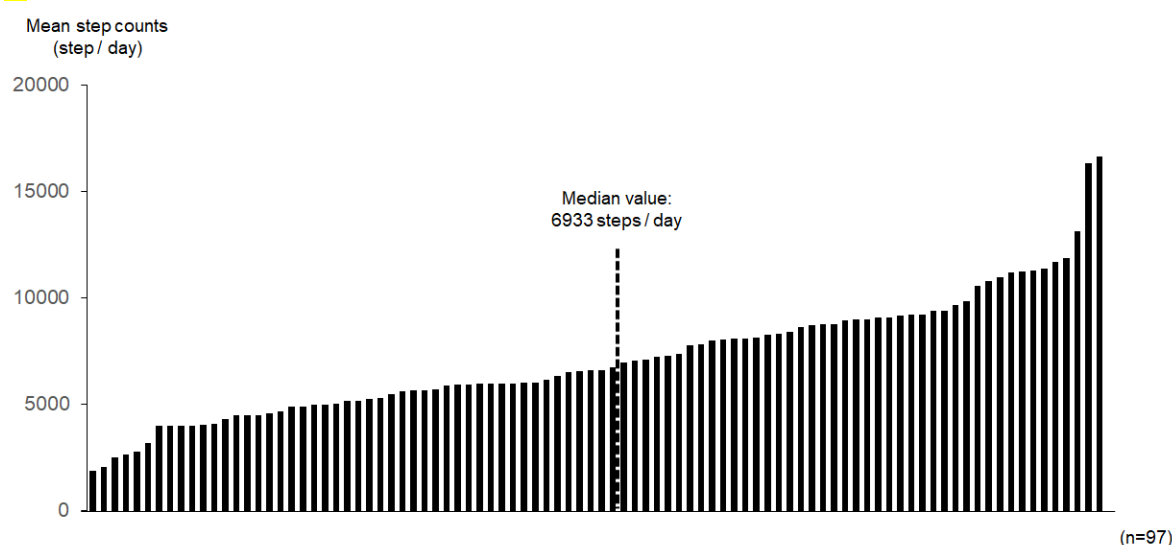


Figure 2. Physical activity in each patient during out-patients clinic

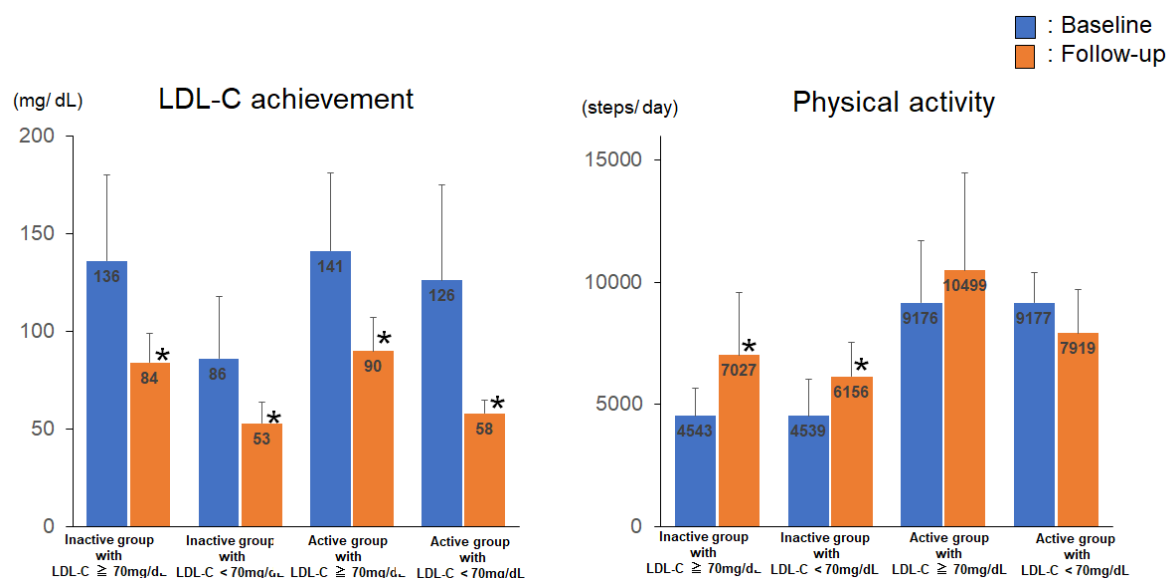


Figure 3. Comparison of LDL-C achievement and physical activity among the 4 groups at baseline and follow-up. * $p < 0.05$ compared with at baseline.

3.3. Serum Lipid Profiles, Glucose Parameters, Anthropometric parameters and exercise tolerance among the 4 groups at baseline and follow-up

Serum lipid profiles, glucose parameters, anthropometric parameters and exercise tolerance at baseline at follow-up are shown in Table 2. The mean baseline and follow-up LDL-C values were 128

± 45 mg/dL and 76 ± 20 mg/dL, respectively. In the overall population, the absolute change in the LDL-C was -50 ± 44 mg/dL and the percent change in LDL-C was -44 ± 24.2 %. At follow-up, 31 % of the patients achieved LDL-C levels less than 70 mg/dL. The levels of LDL-C and body mass index were significantly different among the 4 groups at baseline. The levels of high-density lipoprotein cholesterol (HDL-C), triglycerides, hemoglobin A1c and exercise tolerance at baseline were not significantly different among the 4 groups. At follow-up, the levels of LDL-C were significantly lower than those at baseline in each 4 groups (respectively, $P < 0.05$) (Figure 3). Whereas the levels of HDL-C, triglycerides, hemoglobin A1c and body mass index were not significantly different in the absolute changes at follow-up.

The fat weight and lean body weight at baseline and follow-up were not significantly different among the 4 groups. At baseline, the levels of peak VO_2 levels were no differences among the 4 groups. At follow-up, each group had significant improvements in exercise tolerance (respectively, $P < 0.05$).

Table 2. Comparison of anthropometric parameters, lipid profile and exercise tolerance among the 4 groups at baseline and follow-up.

	Inactive group with LDL-C $\geq$ 70mg/dL (n = 26)	Inactive group with LDL-C < 70mg/dL (n = 9)	Active group with LDL-C $\geq$ 70mg/dL (n = 17)	Active group with LDL-C < 70mg/dL (n = 10)	P value
Baseline					
Anthropometric parameters					
Body mass index (kg/m ²)	24.6 ± 3.4	22.1 ± 2.5	25.2 ± 2.8	26.9 ± 4.2	0.02
Fat weight (%)	27.8 ± 8.0	18.9 ± 10.0	23.8 ± 4.2	32.0 ± 12.3	NS
Lean body weight (kg)	49.0 ± 10.5	55.0 ± 14.7	55.5 ± 5.4	48.0 ± 3.4	NS
Exercise tolerance					
Peak VO_2 , ml·kg ⁻¹ ·min ⁻¹	15.4 ± 2.5	15.6 ± 3.4	16.4 ± 2.3	15.8 ± 3.5	NS
Lipid profile and glucose metabolism					
LDL-C, mg/dl	136 ± 44	86 ± 32	141 ± 40	126 ± 49	0.01
HDL-C, mg/dl	41 ± 11	46 ± 20	44 ± 11	42 ± 9	NS
TG, mg/dl	154 ± 96	98 ± 47	153 ± 51	179 ± 97	NS
FBS, mg/dl	115 ± 31	108 ± 22	108 ± 25	143 ± 60	NS
Hemoglobin A1c, %	5.8 ± 0.7	5.6 ± 0.4	5.7 ± 0.6	6.4 ± 1.3	0.09
Follow-up					
Anthropometric parameters					
Body mass index (kg/m ²)	23.7 ± 5.9	24.3 ± 4.6	24.9 ± 3.3	21.4 ± 9.7	NS
Fat weight (%)	25.7 ± 5.5	25.7 ± 4.8	22.2 ± 6.2	25.9 ± 10.9	NS
Lean body weight (kg)	51.2 ± 10.2	52.3 ± 7.3	53.5 ± 2.7	50.6 ± 9.2	NS
Exercise tolerance					
Peak VO_2 , ml·kg ⁻¹ ·min ⁻¹	18.9 ± 3.7*	19.1 ± 3.1*	21.8 ± 3.2*	20.0 ± 6.3*	NS
Lipid profile and glucose metabolism					
LDL-C, mg/dl	84 ± 15*	53 ± 11*	90 ± 18*	58 ± 7*	< .0001
HDL-C, mg/dl	40 ± 11	45 ± 15	45 ± 14	42 ± 8	NS
TG, mg/dl	158 ± 61	111 ± 55	127 ± 48	127 ± 55	0.09
FBS, mg/dl	98 ± 15	101 ± 12	98 ± 12	100 ± 16	NS
Hemoglobin A1c, %	5.6 ± 0.5	5.8 ± 0.7	5.6 ± 0.4	6.0 ± 0.9	NS

Data are presented as the mean value ± S.D. NS; not significant. * $P < 0.05$ compared with baseline
LDL-C; low-density lipoprotein cholesterol, HDL-C; high-density lipoprotein cholesterol, TG; triglyceride, FBS; fasting blood sugar

3.4. Volumetric analysis of the IVUS parameters

The volumetric analyses of the IVUS parameters are presented in Table 3. There were no significant differences in vessel volume, lumen volume, or PV at baseline among the 4 groups. The PV was reduced at the follow-up examination in active groups (both $P < 0.05$). However, The PV was not reduced at the follow-up examination in inactive groups (both $P < 0.05$). The percent change in PV significantly differ among the 4 groups (group 1; -2.1 ± 11.3 vs. group 2; 0.3 ± 13.3 vs. group 3; -9.6 ± 8.8 vs. group 4; -12.3 ± 11.0 %, $P = 0.01$). In particular, plaque regression in group 4 was higher than other 3 groups ($p = 0.03$ compared among 4 groups) (Figure 4).

Table 4. Comparison of IVUS data among the 4 groups.

	Inactive group with LDL-C $\geq$ 70mg/dL (n = 26)	Inactive group with LDL-C < 70mg/dL (n = 9)	Active group with LDL-C $\geq$ 70mg/dL (n = 17)	Active group with LDL-C < 70mg/dL (n = 10)	P value
IVUS profile at baseline					
Vessel volume, mm ³	212.1 $\pm$ 160.0	163.6 $\pm$ 109.7	197.1 $\pm$ 128.3	173.4 $\pm$ 78.5	NS
Lumen volume, mm ³	113.2 $\pm$ 91.3	91.3 $\pm$ 62.3	102.3 $\pm$ 67.4	88.6 $\pm$ 37.7	NS
Plaque volume, mm ³	98.8 $\pm$ 74.5	72.2 $\pm$ 49.8	94.8 $\pm$ 67.6	84.7 $\pm$ 45.0	NS
IVUS profile at follow-up					
Vessel volume, mm ³	208.1 $\pm$ 157.8	161.6 $\pm$ 112.8	186.8 $\pm$ 119.9*	150.0 $\pm$ 75.6*	NS
Lumen volume, mm ³	111.4 $\pm$ 86.4	92.4 $\pm$ 67.1	101.6 $\pm$ 67.3	84.6 $\pm$ 40.5	NS
Plaque volume, mm ³	96.6 $\pm$ 75.5	69.1 $\pm$ 47.6	85.2 $\pm$ 58.7*	74.4 $\pm$ 38.2*	NS
Percent change of VV, %	-2.4 $\pm$ 6.4	0.0 $\pm$ 19.7	-6.4 $\pm$ 8.9	-8.5 $\pm$ 10.0	NS
Percent change of LV, %	-1.5 $\pm$ 11.5	1.9 $\pm$ 30.0	-4.0 $\pm$ 17.3	-3.6 $\pm$ 12.2	NS
Percent change of PV, %	-2.1 $\pm$ 11.3	0.3 $\pm$ 13.3	-9.6 $\pm$ 8.8	-12.3 $\pm$ 11.0	0.01

Data are presented as the mean value $\pm$ S.D. *P < 0.05 compared with at baseline, NS; not significant
IVUS; intravascular ultrasound, VV; Vessel volume, LV; Lumen volume, PV; plaque volume

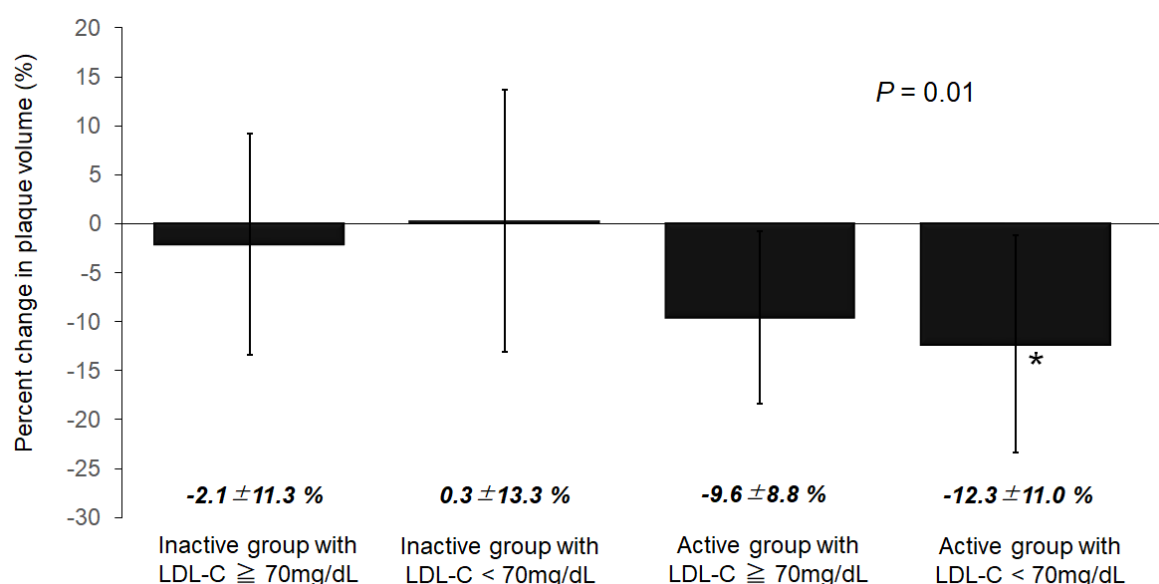


Figure 4. Percent change in plaque volume among the 4 groups. The percent change in PV significantly differ among the 4 groups (group 1; -2.1 $\pm$ 11.3 vs. group 2; 0.3 $\pm$ 13.3 vs. group 3; -9.6 $\pm$ 8.8 vs. group 4; -12.3 $\pm$ 11.0 %, P = 0.01). In particular, the percent change in PV in group 4 was significantly reduced. (*p = 0.03 compared among 4 groups by Dunnett test) PV; plaque volume.

3.5. Correlations between plaque changes and PA

The PA ($r = -0.45$, $P < 0.01$) and the changes of LDL-C ($r = -0.30$, $P = 0.01$) demonstrated significant negative correlations with the percent changes in PV, respectively. Therefore, we performed multivariable linear regression analyses as follows. In a multivariate analysis, including age, body mass index, diabetes absent or present, the levels of fasting glucose, the change of LDL-C, the change of HDL-C, PA, the change of oxygen consumption and plaque volume at baseline, PA ($\beta = -0.34$, $P = 0.02$) and the change of LDL-C ($\beta = -0.30$, $P = 0.03$) were significantly associated with the change in percent PV (Table 4).

Table 4. Multiple linear regression analysis of factors on the percent change of plaque volume.

	Univariate analysis		Multivariate analysis	
	β	P value	β	P value
Age	0.3	0.01		
Body mass index	-0.09	0.46		
Diabetes (absent-present)	-0.07	0.54		
Fasting glucose	0.04	0.76		
Delta LDL-C	0.3	0.01	0.3	0.03
Delta HDL-C	-0.21	0.1		
Physical activity	-0.45	0.0003	-0.34	0.02
Delta peak VO ₂	-0.09	0.44		
Plaque volume at baseline	0.09	0.50		

β : standardized partial regression coefficient

LDL-C; low-density lipoprotein cholesterol, HDL-C; high-density lipoprotein cholesterol,

VO₂: oxygen consumption,

4. Discussion

The major findings of this study were as follows: 1) The combination of higher PA and reduced LDL-C prevented the development of atherosclerosis 2) and the percent changes in PV was significantly and independently correlated with PA and LDL-C decrease. To the best of our knowledge, this is the first report, which investigated the combined effects of PA and achievement of LDL-cholesterol target on coronary PV in patients with ACS using IVUS.

Patients with ACS have multiple lesions with instability plaques. ACS are known to develop from mild atherosclerotic lesions with vulnerability plaque [7]. Further, LDL-C is a key modifiable risk factor in the development of plaque progression [8, 9]. In patients with coronary artery disease, cardiovascular events who achieve very low LDL-C levels are lower than those who achieve moderately low levels [10]. In 2017, the Japan Atherosclerosis Society issued guidelines recommended that target of LDL-C value for secondary prevention in ACS patients was less than 70 mg / dL [6]. We have reported that early aggressive lipid-lowering therapy by atorvastatin for 6 months significantly reduced the plaque volume in patients with ACS [11]. Furthermore, the JAPAN-ACS study which was based on a randomized, large-scale, multicenter study demonstrated that intensive statin therapy in patients with ACS resulted significant regression of coronary PV [12]. Therefore, it is essential to reduce LDL-C aggressively using statins.

There are many important coronary risk factors besides LDL-C, such as smoking, diabetes, dyslipidemia, hypertension, and physical inactivity. These factors are the residual treatment targets in patients with ACS. CR is a long-term, comprehensive secondary prevention program of medical assessment, exercise prescription, coronary risk factor control, education, and counseling for patients with cardiovascular disease. [13, 14]. The guideline of Japanese Circulation Society recommends moderate-to-vigorous-intensity aerobic exercise training 3 times a week and for 30min per session in patients with ACS [15]. We have already reported that intensive PA retarded and stabilized coronary PV in two different clinical trials [4, 5]. Previous study demonstrated that combination of statin therapy and lifestyle modification including PA inhibited angiographic minimal lumen stenosis [16]. However, there is no study regarding the combined effects of PA and LDL-C reduction on coronary PV changes using IVUS. This study is the first investigation for combined therapy of intensive PA and LDL-C reduction retarded coronary PV using IVUS in patients with ACS.

There are several mechanisms via which effects of intensive PA in addition to achievement of LDL-C target ameliorate coronary PV in patients with ACS. The inflammation markers like as C-reactive protein, interleukin-6 and a proinflammatory cytokine are a major factors in the development of ACS [17, 18]. Kurose *et al.* reported that the decrease in high sensitive C-reactive protein as an independent predictor of coronary plaque regression in patients with ACS who participated in CR [19]. We reported that CR for 6 months ameliorated not only metabolic parameters, but also the exercise capacity, muscle strength, and inflammatory state in metabolic syndrome patients after

CABG [20]. We demonstrated that IL-6 was low in the active group compared with the inactive group and was significantly and inversely correlated with exercise tolerance and PA at follow-up [5]. These results suggest that regular PA is associated with a reduction of inflammatory markers. Exercise training improves endothelium-dependent vasodilatation both in epicardial coronary vessels and in resistance vessels through enhance of endothelial nitric oxide synthase and reduction of reactive oxygen species in patients with CAD [21]. These pathways were partially explained the present results. Hambrecht *et al.* reported that regression of coronary atherosclerotic lesions was observed in patients with CAD expending an average of 2,200 kcal/week of regular physical exercise [22]. In this study, we prescribed the intensity of exercise for almost 3.3 metabolic equivalents (METs) to patients measured by CPX at discharge, and the calculated mean energy expenditure of PA in the active group was 2140 ± 202 kcal/week.

More than 30 years after the launch of statins, the strategy of "the lower, the better" for LDL-C is well established. Medical costs associated with cardiovascular disease are increasing considerably worldwide. Therefore, an efficacious, cost-effective therapy like CR which allows the effective use of medical resources is vital [23]. Therefore, CR program including life modification in addition to LDL-C reduction could be a suitable treatment strategy for "beyond LDL" for the residual cardiovascular risk in ACS patients.

There are several limitations in the present study. First, this is a small sample size. Studies with larger sample size are needed to confirm these findings. Secondly, a pedometer is unable to provide information regarding non-walking related activities. Therefore, the evaluation of the daily activity might be underestimated.

5. Conclusions

Combined effects of intensive PA and achievement of LDL-C target ameliorate coronary PV in patients with ACS. CR program including intensive PA in addition to LDL-C reduction could be a suitable treatment strategy for "beyond LDL" for the residual cardiovascular risk in ACS patients.

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