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ORIGINAL ARTICLE
Metabolic Disorder

Clustering of Metabolic Syndrome Components Attenuates Coronary Plaque Regression During Intensive Statin Therapy in Patients With Acute Coronary Syndrome

– The JAPAN-ACS Subanalysis Study –

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Background: The JAPAN-ACS (Japan Assessment of Pitavastatin and Atorvastatin in Acute Coronary Syndrome) trial showed that intensive statin therapy could induce significant coronary plaque regression in acute coronary syndrome (ACS). We evaluated the impact of metabolic syndrome (MetS) and its components on coronary plaque regression in the JAPAN-ACS patients.

Methods and Results: Serial intravascular ultrasound measurements over 8–12 months were performed in 242 ACS patients receiving pitavastatin or atorvastatin. Patients were divided into groups according to the presence of MetS or the number of MetS components. Although the percent change in plaque volume (%PV) was not significantly different between the MetS (n=119) and non-MetS (n=123) groups (P=0.50), it was significantly associated with an increasing number of MetS components (component 0: −24.0%, n=7; components 1: −20.8%, n=31; components 2: −16.1%, n=69; components 3: −18.7%, n=83; components 4: −13.5%, n=52; P=0.037 for trend). The percent change in body mass index (%BMI) significantly correlated with %PV (r=0.15, P=0.021), especially in the MetS components 4 group (r=0.35, P=0.017). In addition, %BMI was an independent predictor of plaque regression after adjustment for the changes of low- and high-density lipoprotein cholesterol, triglycerides and HbA_{1c}.

Conclusions: The clustering of MetS components, but not the presence of MetS itself, could attenuate coronary plaque regression during intensive statin therapy in ACS patients. Therefore, to achieve a greater degree of plaque regression, it is necessary to treat to each MetS component and use lifestyle modification. (*Circ J* 2012; **76:** 2840−2847)

Key Words: Acute coronary syndrome; Intravascular ultrasound; Metabolic syndrome components; Plaque; Statins

Metabolic syndrome (MetS) is characterized by the clustering of several components, such as abdominal obesity, hyperglycemia, low level of high-density lipoprotein cholesterol (HDL-C), impaired glucose tolerance, and hypertension. It has been reported that MetS is a critical cardiovascular risk and is associated with increased incidence of atherosclerotic cardiovascular events and mortality.[1–3] Recurrent cardiovascular events are more likely after acute coronary syndrome (ACS) than in the setting of stable angina, and MetS is highly prevalent in ACS patients.[4]

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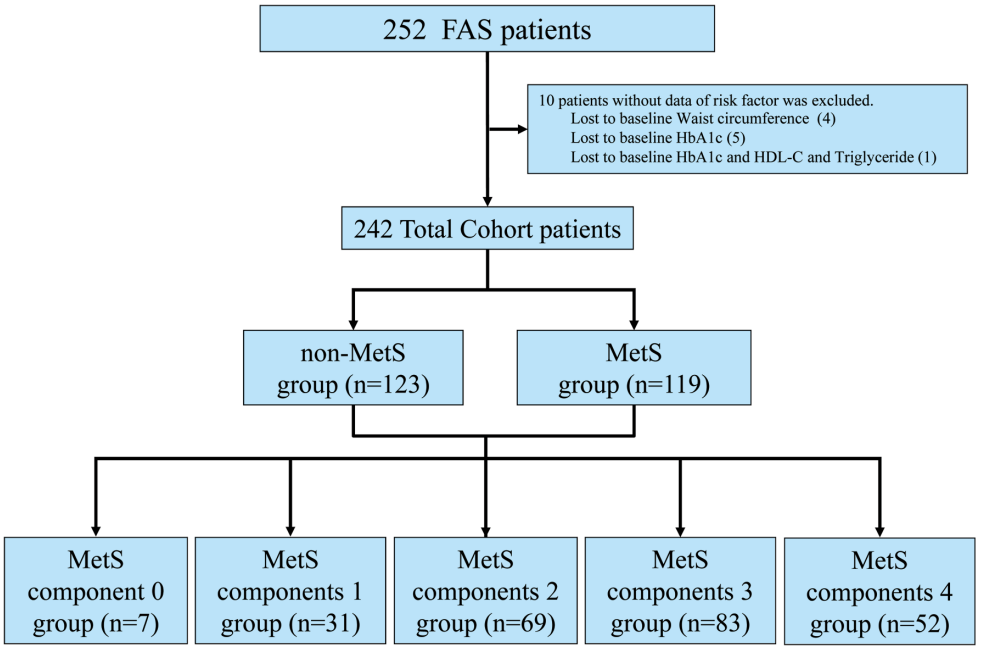

Figure 1. Disposition of the study patients.

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Furthermore, there is a higher incidence of adverse cardiovascular events in ACS patients with MetS than in those without MetS.[5,6] Clinical trials have reported that HMG-CoA reductase inhibitors (statins) reduce the incidence of secondary cardiovascular events in patients with ACS.[7,8] Moreover, an intravascular ultrasound (IVUS) study demonstrated that intensive statin therapy showed significant coronary plaque regression in patients with ACS.[9] Accordingly, the JAPAN-ACS (Japan Assessment of Pitavastatin and Atorvastatin in Acute Coronary Syndrome), a prospective, randomized, open-label, parallel group study, was undertaken and demonstrated that intensive statin therapy with 4 mg/day of pitavastatin or 20 mg/day of atorvastatin in ACS patients resulted in significant regression of atheroma burden with negative vessel remodeling in a multicenter trial using a central IVUS core-laboratory. In addition, non-inferiority of pitavastatin to atorvastatin was demonstrated.[10]

A previous IVUS study showed that the degree of plaque regression was attenuated with individual component risk factors of MetS, rather than with the presence of MetS itself.[11] However, it has not yet been clarified whether the prevalence of MetS and clustering of its components affects the degree of coronary plaque regression during intensive statin therapy in ACS patients. Therefore, the aim of the present study was to evaluate the impact of MetS and clustering of its components on the degree of coronary plaque regression during intensive statin therapy in Japanese ACS patients assessed by serial volumetric IVUS measurements.

Methods

Study Design and Ethical Considerations

We performed a subanalysis of the JAPAN-ACS study because the plaque regression effect of the 2 statins was shown to be equivalent in that study.[10] The research protocol of JAPAN-ACS has been previously outlined in detail.[12] Briefly, ACS patients were randomized within 72 h of successful PCI under IVUS guidance to receive either pitavastatin (4 mg) or atorvastatin (20 mg) daily. IVUS examination and blood sampling were performed at baseline and repeated after 8–12 months of the baseline PCI. The study was conducted in accordance with the principles of the Helsinki Declaration and approved by the institutional review boards of all 33 participating institutions. Written informed consent was given by each patient.

Definitions of MetS and MetS Components

MetS was defined according to the criteria of the Japanese Examination Committee.[13] Waist circumference ≥85 cm in men or ≥90 cm in women, and 2 or more of the following criteria were considered to indicate MetS: (1) HDL-C <40 mg/dl and/or triglycerides ≥150 mg/dl, (2) known hypertension or blood pressure ≥130/85 mmHg, (3) known diabetes mellitus or hemoglobin A_{1c} (HbA_{1c}) ≥5.8% (instead of fasting glucose level ≥110 mg/dl).[14] HbA_{1c} was represented as the National Glycohemoglobin Standardization Program (NGSP) value. Participants were divided into 5 groups according to the number of MetS components.

IVUS Procedure and Examination

Details of the IVUS procedure and examination are documented elsewhere.[10] In brief, following IVUS-guided PCI for the culprit lesion in patients with ACS, a final IVUS examination for analysis was performed in the culprit vessel. An IVUS catheter Atlantis SR Pro2 (Boston Scientific, Natick, MA, USA)

Table 1. Baseline Clinical Characteristics and Concomitant Medications of 242 ACS Patients

No. of MetS components	0 (n=7)	1 (n=31)	2 (n=69)	3 (n=83)	4 (n=52)	P value
Age (years)	60.1±11.3	66.5±10.7	63.3±11.9	62.6±10.3	59.7±11.3	0.097
Male, n (%)	4 (57)	22 (71)	52 (75)	71 (86)	49 (94)	0.009
BMI (kg/m^2)	21.8±1.2	22.1±2.9	22.9±3.1	25.4±3.4	25.8±3.1	<0.0001
Waist circumference (cm)	77.1±5.3	78.9±7.4	83.4±8.5	90.6±7.5	92.2±6.2	<0.0001
History of MI, n (%)	0 (0)	0 (0)	4 (6)	5 (6)	5 (10)	0.442
History of angina, n (%)	0 (0)	3 (10)	6 (9)	5 (6)	6 (12)	0.733
Previous PCI, n (%)	0 (0)	0 (0)	4 (6)	8 (10)	5 (10)	0.351
Previous CABG, n (%)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0.642
Hypertension, n (%)	0 (0)	11 (35)	41 (59)	57 (69)	40 (77)	<0.0001
Diabetes mellitus, n (%)	0 (0)	3 (10)	13 (19)	28 (34)	26 (50)	<0.0001
Smoking, n (%)	0 (0)	15 (48)	26 (38)	43 (52)	31 (60)	0.013
Type of ACS						
AMI, n (%)	6 (86)	21 (68)	59 (86)	67 (81)	37 (71)	0.181
UAP, n (%)	1 (14)	10 (32)	10 (14)	16 (19)	15 (29)	0.181
Abnormal Q-wave, n (%)	1 (14)	10 (32)	21 (30)	32 (39)	17 (33)	0.655
Max CK median (IQR) (IU/L)	1,764 (652–1,887)	438 (126–1,983)	1,798 (327–3,205)	1,382 (393–2,406)	518 (194–1,890)	0.374
Culprit vessel						0.200
RCA, n (%)	4 (57)	7 (23)	18 (26)	34 (41)	15 (29)	
LAD, n (%)	2 (29)	23 (74)	40 (58)	37 (45)	29 (56)	
LCX, n (%)	1 (14)	1 (3)	11 (16)	11 (13)	8 (15)	
LMT, n (%)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	
IVUS analysis segment						
Proximal to the culprit, n (%)	0 (0)	9 (29)	24 (35)	26 (31)	15 (29)	0.435
Distal to the culprit, n (%)	7 (100)	22 (71)	45 (65)	57 (69)	37 (71)	0.435
Concomitant drugs						
Statins						
Pitavastatin, n (%)	4 (57)	15 (48)	41 (59)	37 (45)	24 (46)	0.419
Atorvastatin, n (%)	3 (43)	16 (52)	28 (41)	46 (55)	28 (54)	0.419
Aspirin, n (%)	7 (100)	31 (100)	68 (99)	81 (98)	51 (98)	0.914
Ticlopidine, n (%)	6 (86)	24 (77)	58 (84)	67 (81)	46 (88)	0.702
Clopidogrel, n (%)	0 (0)	2 (6)	5 (7)	6 (7)	3 (6)	0.957
ARB, n (%)	2 (29)	16 (52)	28 (41)	44 (53)	29 (56)	0.320
ACEI, n (%)	3 (43)	5 (16)	26 (38)	27 (33)	11 (21)	0.110
CCB, n (%)	0 (0)	7 (23)	10 (14)	17 (20)	14 (27)	0.310
Nitrate, n (%)	1 (14)	5 (16)	15 (22)	13 (16)	4 (8)	0.350
β-blocker, n (%)	2 (29)	15 (48)	30 (43)	37 (45)	25 (48)	0.882

Data are expressed as n (%) unless otherwise specified. Continuous variables were represented by mean±SD or median (IQR).
ACE, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; AMI, acute coronary infarction; ARB, angiotensin receptor blocker; BMI, body mass index; CABG, coronary artery bypass grafting; CCB, calcium-channel blocker; IQR, intraquartile range; LAD, left anterior descending; LCX, left circumflex branch; LMT, left main trunk; MI, myocardial infarction; PCI, percutaneous coronary intervention; RCA, right coronary artery; UAP, unstable angina pectoris.

was used, and a motorized pullback device withdrew the transducer at the speed of 0.5 mm/s. The consoles used were the ClearView or Galaxy 2 system (Boston Scientific). 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 a central core-laboratory. The target segment for analysis was identified at a non-PCI site of the culprit vessel (>5 mm proximal or distal to the PCI site) based on some reproducible indices. Manual tracing was performed in every 0.1-mm cross-section and the software (echoPlaque2, INDEC systems, Santa Clara, CA, USA) automatically interpolated the tracings of 5 cross-sections between 2 manually traced images. Therefore, the volume was calculated from each of the 0.017-mm separated segments.

IVUS Measurements

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

$$PV=\sum (EEM_{CSA}-LUMEN_{CSA}),$$

where CSA is the cross-sectional area. The percent change in PV after 8–12 months of pitavastatin or atorvastatin therapy was calculated as:

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

Statistical Analysis

We evaluated a complete full analysis set (FAS) of the JAPAN-

Table 2. Laboratory Data at Baseline and Follow-up of 242 ACS Patients

No. of MetS components	0 (n=7)	1 (n=31)	2 (n=69)	3 (n=83)	4 (n=52)	P value
Systolic BP (mmHg)						
Baseline	114.4±12.8	127.6±24.4	137.5±21.9	138.8±26.7	147.6±25.8	0.001
Follow-up	124.9±15.5	125.5±15.6	127.3±18.8	130.4±16.3	128.5±17.2	0.620
Diastolic BP (mmHg)						
Baseline	69.6±10.4	74.5±15.7	79.4±14.4	77.9±14.9	82.3±16.9	0.091
Follow-up	66.7±21.2	72.1±9.9	70.3±12.0	75.3±12.1	74.3±13.3	0.073
Total cholesterol (mg/dl)						
Baseline	210.1±48.7	200.4±37.4	192.6±32.9	198.3±35.6	195.0±37.8	0.649
Follow-up	165.6±41.4	152.8±25.4	155.5±29.2	148.2±32.8	150.6±28.4	0.443
Percent change	–19.1±20.1	–22.3±14.9	–18.0±16.3	–24.5±15.7	–20.6±19.3	0.196
LDL-C (mg/dl)						
Baseline	132.4±40.6	138.1±38.1	128.3±29.2	132.6±31.0	131.9±32.6	0.723
Follow-up	89.0±34.5	82.4±20.9	85.2±25.8	78.5±24.9	85.1±24.0	0.408
Percent change	–28.8±28.7	–38.4±15.3	–32.0±21.2	–39.6±20.0	–32.5±24.2	0.123
Triglycerides (mg/dl)						
Baseline	83.1±34.9	83.5±28.1	102.9±42.4	128.2±59.0	147.4±61.1	<0.0001
Follow-up	65.3±18.6	99.9±43.9	120.6±80.6	133.8±77.2	138.5±58.5	0.016
Percent change	–12.2±33.2	28.9±59.7	33.4±89.5	16.0±61.1	2.8±48.2	0.083
HDL-C (mg/dl)						
Baseline	61.0±14.3	48.4±7.5	45.7±8.6	43.8±9.3	37.9±7.5	<0.0001
Follow-up	62.9±12.1	52.9±11.0	48.5±9.8	46.7±13.8	42.5±10.3	<0.0001
Percent change	5.8±23.6	10.5±22.5	7.4±19.2	7.2±24.8	13.4±23.3	0.552
LDL-C/HDL-C						
Baseline	2.3±0.8	2.9±1.0	2.9±0.7	3.1±0.9	3.6±0.9	<0.0001
Follow-up	1.4±0.5	1.6±0.5	1.8±0.7	1.8±0.7	2.1±0.7	0.007
Percent change	–30.3±31.1	–43.1±13.6	–35.3±21.9	–41.7±21.5	–39.1±21.8	0.223
RLP-C (mg/dl)						
Baseline	4.0±1.6	3.6±0.9	4.0±2.0	4.4±3.0	5.2±3.1	0.038
Follow-up	2.3±1.1	2.9±1.7	4.1±4.1	4.3±3.2	4.1±2.3	0.157
Percent change	–36.5±28.8	–19.1±45.1	18.3±100.3	20.2±97.2	–12.5±51.1	0.029
MDA-LDL (U/L)						
Baseline	102.4±35.9	111.9±29.6	128.1±43.7	133.5±44.2	140.0±58.7	0.037
Follow-up	89.1±26.4	81.8±22.1	93.0±29.3	91.8±33.0	95.0±35.5	0.425
Percent change	–6.1±35.5	–23.1±26.1	–22.4±28.5	–28.1±24.7	–26.2±27.1	0.251
hs-CRP median (IQR) (mg/L)						
Baseline	7.9 (5.3–19.9)	16.0 (4.1–65.2)	24.2 (4.8–67.8)	14.9 (4.7–50.1)	25.2 (6.1–74.7)	0.135
Follow-up	0.4 (0.1–0.5)	0.4 (0.2–0.5)	0.5 (0.3–0.8)	0.5 (0.3–1.2)	0.8 (0.5–1.7)	0.546
Percent change	–98.3 (–98.9 to –93.0)	–97.1 (–99.4 to –93.9)	–97.5 (–99.3 to –87.9)	–95.3 (–98.4 to –89.2)	–97.2 (–98.8 to –88.1)	0.513
HbA_{1c} (%)						
Baseline	5.5±0.1	5.7±0.7	6.1±1.2	6.4±1.1	6.9±1.3	<0.0001
Follow-up	5.7±0.2	5.8±0.3	6.2±1.0	6.4±0.9	6.8±1.3	<0.0001
Percent change	0.2±0.2	0.1±0.6	0.1±0.6	0.0±0.8	–0.1±1.1	0.588

Values are mean±SD or median (IQR).
ACS, acute coronary syndrome; HbA_{1c}, hemoglobin A_{1c}; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; MDA-LDL, malondialdehyde-modified low-density lipoprotein; RLP-C, remnant-like particle-cholesterol.
HbA_{1c} levels are represented as National Glycohemoglobin Standardization Program (NGSP) values.

ACS study for this subanalysis. Patients were included in the FAS if they had ACS and measurable IVUS lesions at both enrollment and follow-up. Descriptive statistics are presented as mean±SD or n (%). Differences between groups were assessed with the chi-square test for categorical variables, and assessed with ANOVA or Wilcoxon rank-sum test for continuous variables. Differences between baseline and follow-up were assessed with paired t-test or Wilcoxon signed rank test. We conducted a trend test for the relationship between the number of MetS components and the percent change in PV. The correlation between the percent change in PV and the percent change in body mass index (BMI) were analyzed by linear regression analysis and correlation coefficient. All statistical analyses were performed with JMP8 (SAS Institute,

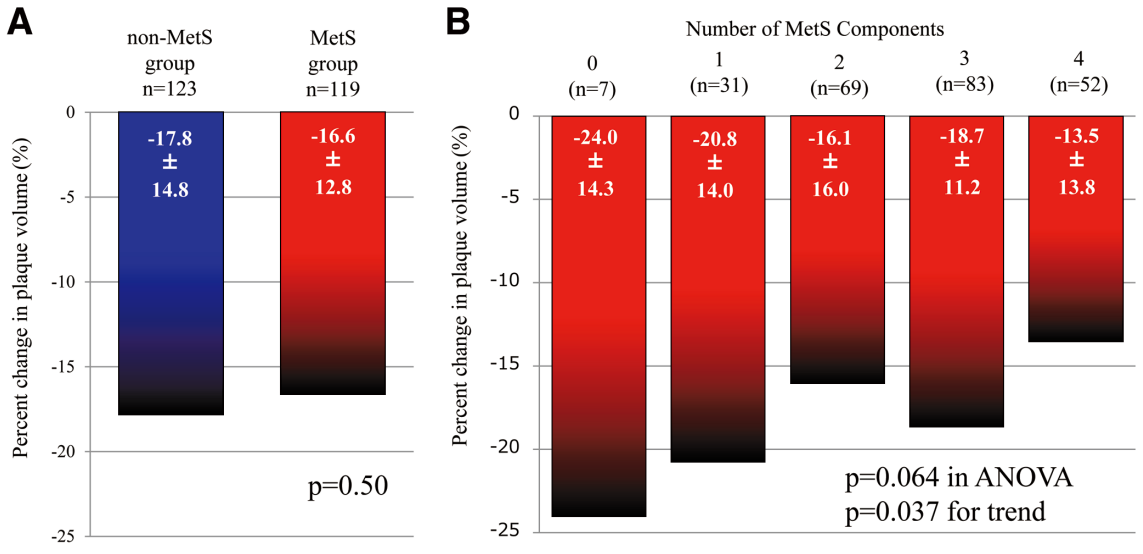

Figure 2. Components of the metabolic syndrome (MetS) and the degree of plaque regression. (**A**) Percent change in plaque volume in the non-MetS and MetS groups. (**B**) Percent change in plaque volume in the 5 groups according to MetS components. Variables are represented by mean±SD.

Cary, NC, USA). A value of P<0.05 was considered statistically significant.

Results

Baseline Characteristics

The disposition of the patients in the present study is shown in Figure 1; 10 patients lacking data on their risk factors were excluded from the analyses of the total of 252 FAS patients. The remaining 242 patients were divided into MetS (n=119) and non-MetS (n=123) groups, and further divided into 5 groups according to the number of components: MetS components 0 (n=7), MetS components 1 (n=31), MetS components 2 (n=69), MetS components 3 (n=83), and MetS components 4 (n=52). Most of the baseline clinical characteristics were comparable among the 5 groups (Table 1). Some parameters such as sex (P=0.009), BMI (P<0.0001), waist circumference (P<0.0001), hypertension (P<0.0001), diabetes mellitus (P<0.0001), and smoking habit (P=0.013) were significantly different among the 5 groups.

Baseline and Follow-up Laboratory Data

The laboratory data at baseline and follow-up are shown in Table 2. At baseline, there was no significant difference in low-density lipoprotein cholesterol (LDL-C) level among the 5 groups (P=0.723), whereas systolic blood pressure (SBP) (P=0.001), triglycerides (P<0.0001), HDL-C level (P<0.0001), LDL-C/HDL-C ratio (P<0.0001), remnant-like particle-cholesterol (RLP-C) level (P=0.038), malondialdehyde-modified (MDA)-LDL level (P=0.037) and HbA_{1c} (P<0.0001) were significantly different among the 5 groups.

During the treatment period, the LDL-C level was similar among the 5 groups (P=0.408).

Plaque Regression in the MetS and Non-MetS Groups

Although there was a significant reduction of PV in both the MetS and non-MetS groups (P<0.0001 and P<0.0001, respectively), the degree of the percent change in PV was not different between the groups at follow-up (−16.6±12.8% vs. −17.8±14.8%, P=0.50) (Figure 2A).

IVUS Parameters and the Number of MetS Components

The IVUS parameters among the 5 MetS component groups were assessed and although there was no significant difference in IVUS parameters among the 5 groups, the degree of plaque regression was significantly attenuated with an increasing number of MetS components (MetS components 0: −24.0±14.3%; MetS components 1: −20.8±14.0%; MetS components 2: −16.1±16.0%; MetS components 3: −18.7±11.2%; MetS components 4: −13.5±13.8%, P=0.037 for trend) (Table 3, Figure 2B).

Correlation Between BMI and PV

The correlation between BMI and PV was assessed (Figure 3). The percent change in BMI significantly correlated with the percent change in PV (r=0.15, P=0.021), especially in the MetS components 4 group (r=0.35, P=0.017). In addition, the percent change in BMI was an independent predictor of PV change (β=0.289, 95% confidence interval (CI) 0.05–0.53 per increment of 1%) after adjusted for change of LDL-C, triglycerides, HDL-C, and HbA_{1c} (Table 4).

Major Adverse Cardiovascular Events (MACE)

In the 1-year clinical follow-up, there was a significant difference in the prevalence of MACE (the incidence of coronary revascularization, and myocardial infarction) among the 5 MetS components groups (0% vs. 9.7% vs. 15.9% vs. 30.1% vs. 25.0%, P=0.044).

Discussion

In the JAPAN-ACS study, marked plaque regression in ACS patients was associated with intensive lipid-lowering therapy by statins.[10] However, little is known about whether the pres-

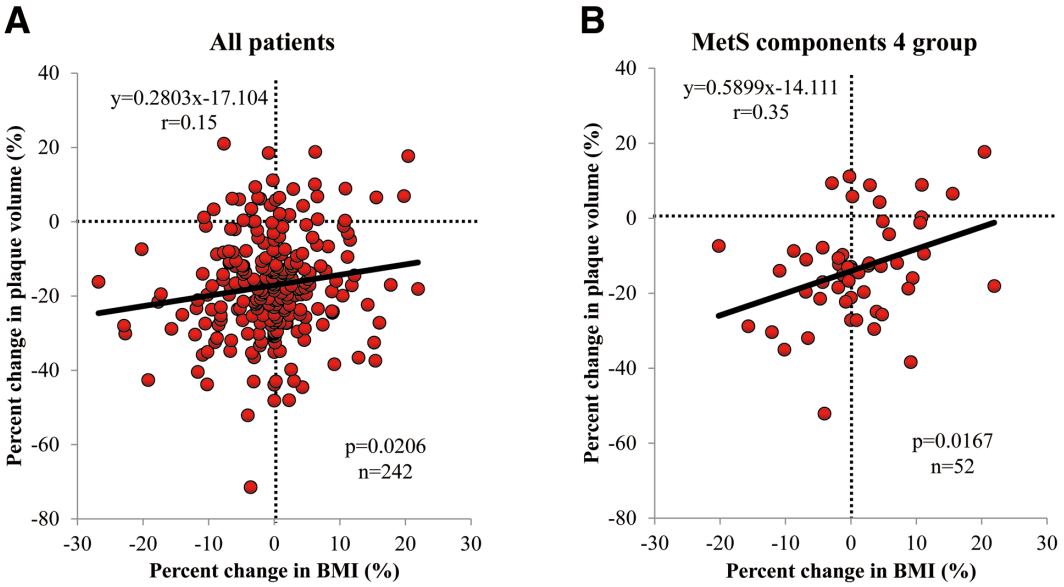

Figure 3. Correlation between percent change in body mass index (BMI) and percent change in plaque volume. Relationship between percent change in BMI and percent change in plaque volume in all patients (**A**) and the metabolic syndrome (MetS) components 4 group (**B**).

Table 3. Volumetric IVUS Measurements in 242 ACS Patients

No. of MetS components	0 (n=7)	1 (n=31)	2 (n=69)	3 (n=83)	4 (n=52)	P value
Analyzed length at baseline (mm)	7.4±1.5	6.6±3.0	6.4±3.4	6.9±2.9	6.8±2.9	0.782
Plaque volume (mm³)						
Baseline	60.0±22.4	58.7±32.1	52.1±34.3	58.2±31.4	58.7±32.8	0.741
Follow-up	46.5±20.9	46.1±26.7	45.7±35.2	47.5±26.4	50.9±28.3	0.904
Percent change	–24.0±14.3	–20.8±14.0	–16.1±16.0	–18.7±11.2	–13.5±13.8	0.064
Vessel volume (mm³)						
Baseline	116.0±28.7	115.4±57.4	105.6±64.0	114.4±56.1	117.2±63.9	0.842
Follow-up	104.7±24.6	103.8±49.8	100.9±63.4	106.3±50.2	111.1±58.0	0.904
Percent change	–9.0±8.2	–8.3±11.3	–4.8±12.7	–5.9±10.8	–4.7±10.5	0.549
Lumen volume (mm³)						
Baseline	56.0±9.6	56.7±30.7	53.6±33.2	56.2±29.5	58.5±35.7	0.947
Follow-up	58.2±7.6	57.7±29.3	55.2±32.8	58.8±27.8	60.1±34.3	0.927
Percent change	4.9±8.4	5.7±19.9	7.1±21.8	8.3±20.8	5.5±20.4	0.935
Plaque volume (%)						
Baseline	50.2±8.9	50.1±10.2	48.7±11.2	50.2±10.6	50.8±9.4	0.855
Follow-up	42.3±11.5	43.2±10.6	43.1±11.9	43.6±10.6	46.2±10.3	0.555
Nominal change	–7.9±4.5	–7.0±6.7	–5.6±6.6	–6.7±5.6	–4.6±6.5	0.268
Normalized plaque volume (mm³)						
Baseline	50.5±12.4	55.3±15.9	52.8±19.8	54.5±19.9	56.0±19.0	0.875
Follow-up	38.8±13.3	43.8±14.2	45.0±20.5	44.4±17.5	48.5±18.1	0.566
Nominal change	–11.6±6.7	–11.5±9.2	–7.8±8.7	–10.1±7.4	–7.5±7.8	0.080

Values are mean±SD. ACS, acute coronary syndrome; IVUS, intravascular ultrasound.

ence of MetS or the number of MetS components affects coronary plaque progression/regression in patients with ACS.

In our subanalysis of the multicenter JAPAN-ACS study, we evaluated the degree of plaque regression between MetS and non-MetS subgroups and subgroups according to the number of MetS components in patients with ACS undergoing intensive lipid-lowering therapy.

There was no difference in the degree of plaque regression between the MetS and non-MetS groups, but the degree of plaque regression was significantly attenuated according to the number of MetS components (components 0–4), although the baseline and follow-up LDL-C levels were similar between

Table 4. Factors Affecting the Degree of Plaque Regression (Multivariate Analysis) in of 242 ACS Patients

Factor	All patients (n=242)			MetS components 4 group (n=52)		
	β	95% CI	P value	β	95% CI	P value
Percent change in BMI (%)	0.289	0.05 to 0.53	0.020	0.594	0.13 to 1.06	0.013
Percent change in LDL-C (%)	0.076	−0.01 to 0.16	0.084	−0.062	−0.23 to 0.11	0.470
Percent change in triglycerides (%)	−0.006	−0.03 to 0.02	0.626	0.081	0.00 to 0.16	0.053
Percent change in HDL-C (%)	−0.028	−0.11 to 0.05	0.497	0.01	−0.16 to 0.18	0.902
Percent change in HbA_{1c} (%)	−2.007	−4.28 to 0.27	0.083	0.056	−3.48 to 3.59	0.975

Abbreviations as in Tables 1,2.

groups. We previously reported that MetS was significantly associated with either large lipid volume or small fibrous volume among 122 PCI-treated patients with mild to moderate stable coronary lesions identified by integrated backscatter IVUS. In that study, there was a significant difference in the ratio of lipid-rich plaque among 3 of the MetS components groups: MetS components 0–2, MetS components 3, and MetS components 4–5.[15] It was concluded that MetS was an independent predictor of lipid-rich plaque, contributing to an increased risk of cardiovascular disease. However, an observational study can not evaluate the impact of MetS and its components on coronary PV change in ACS patients under statin intervention. Considering both previous study[15] and present study, the number of MetS components could be associated with coronary plaque quantity and quality.

To our knowledge, our analysis is the first investigation of whether the number of MetS components affects coronary plaque progression/regression in ACS patients.

The MetS consists of metabolic abnormalities, among which visceral obesity plays a central role.[16] HDL-C has anti-atherosclerotic properties because it not only scavenges excess cholesterol from peripheral vessels but also has antiinflammatory and antioxidative effects.[17,18] Previous reports documented that changes in coronary PV correlated inversely with the changes in plasma levels of HDL-C.[19,20] These findings suggest that HDL-C plays an important role in coronary plaque progression/regression.

It has not been adequately investigated whether the triglyceride level correlates with coronary plaque progression/regression, although that level is known to correlate inversely with the HDL-C level.[21]

With regard to diabetes mellitus, Hiro et al reported that the regression of coronary plaque induced by statin therapy was weaker in diabetic patients (−12.8%) than in non-diabetics patients (−19.4%), even though the reduction in LDL-C levels was similar.[22] These results suggest the abnormal glucose tolerance, which is a MetS component, might attenuate the effect of statins on coronary plaque regression.

Sipahi et al demonstrated a continuous relationship between SBP and the rate of progression of coronary atherosclerosis over a broad range of blood pressure from 100 mmHg to the hypertensive range.[23] A previous IVUS study[9] evaluated coronary plaque progression/regression in ACS patients with lipid-lowering therapy by statins, and it is now generally recognized that the degree of plaque regression correlates well with LDL-C reduction.[9,24,25] However, the concept of MetS does not include the component of LDL-C level, so we should recognize MetS components as a residual risk of coronary atherosclerosis even if the LDL-C level is well-controlled to guideline-recommended levels.

The pathology of MetS mainly derives from obesity or visceral fat. Previous reports have assessed BMI as well as waist circumference as a MetS component and BMI is recognized as a risk factor for cardiovascular events.[5,26–28] Tani et al demonstrated that baseline BMI correlated with coronary PV change, and an increase in BMI attenuated pravastatin-induced coronary plaque regression in their IVUS study.[29] In the present study, baseline BMI showed a positive correlation with baseline waist circumference (r=0.75, P<0.0001, unpublished data), and the change in BMI during the study period significantly correlated with coronary PV change. In addition, the change in BMI was an independent predictor of coronary plaque progression even after adjustment for change in LDL-C, triglycerides, HDL-C and HbA_{1c}. From the perspective of prevention, a management of obesity, in addition to the effect of the clustering of MetS components at baseline, could induce more coronary plaque regression in ACS patients under intensive lipid-lowering therapy.

Study Limitations

First, this study was a relatively small IVUS study of 242 participants. However, the JAPAN-ACS study was one of the largest serial IVUS studies conducted in the setting of ACS.[10] Second, it remains to be determined whether coronary plaque regression translates into improved clinical outcomes. However, there are several studies that have shown that coronary plaque progression or regression observed by IVUS serves as a predictor of future cardiovascular events.[30–32]

Conclusions

Coronary plaque regression induced under intensive statin therapy after PCI for ACS was attenuated according to the clustering of MetS components. In addition, an improvement in obesity is an independent predictor of coronary plaque regression in these patients. Therefore, to achieve a greater degree of plaque regression in ACS patients, it is necessary to treat to each MetS component and the obesity, which are located upstream of the MetS pathogenesis, in addition to intensive statin therapy.

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Disclosures

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