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ORIGINAL ARTICLE
Ischemic Heart Disease

Effects of Ezetimibe-Statin Combination Therapy on Coronary Atherosclerosis in Acute Coronary Syndrome

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Background: The results of previous clinical trials on the effects of ezetimibe-statin combination therapy on atherosclerosis are inconsistent, and the anti-atherosclerotic effect of ezetimibe remains controversial.

Methods and Results: We conducted a prospective, randomized open-label study at 10 centers. One hundred and twenty-eight statin-naïve patients with acute coronary syndrome (ACS) undergoing intravascular ultrasound (IVUS)-guided percutaneous coronary intervention were randomized to receive either 2 mg/day pitavastatin plus 10 mg/day ezetimibe, or 2 mg/day pitavastatin. One hundred and 3 patients had evaluable IVUS of non-culprit coronary lesions at baseline and at follow-up. The primary endpoint was the percentage change in non-culprit coronary plaque volume (PV) and lipid PV on integrated backscatter IVUS. Mean low-density lipoprotein cholesterol was reduced from 123 mg/dL to 64 mg/dL in the combination therapy group (n=50) and 126 mg/dL to 87 mg/dL in the statin alone group (n=53; between-group difference, 16.9%, P<0.0001). The percent change in PV was –5.1% in the combination therapy group and –6.2% in the statin alone group (P=0.66), although both groups had reduction of PV compared with baseline (both P<0.01). The percent change in lipid PV did not differ between the groups (4.3 vs. –3.0%, P=0.37).

Conclusions: In statin-naïve patients with ACS, combined therapy with ezetimibe and statin did not result in a significant change in coronary plaque regression or tissue component compared with statin alone. [Clinical Trial Registration: www.clinicaltrials.gov (NCT00549926)]

Key Words: Acute coronary syndrome; Intravascular ultrasound; Lipid-lowering therapy; Low-density lipoprotein cholesterol

Several randomized clinical trials have shown that lowering low-density lipoprotein cholesterol (LDL-C) with high-dose statin reduces LDL-C and improves clinical outcome compared with standard dose statin therapy or placebo.[1–3] A meta-analysis of 27 such randomized trials concluded that 1.0 mmol/L (38.66 mg/dL) reduction in LDL-C by statin resulted in proportional reduction of cardiovascular events by 16% in women and by 22% in men.[4] Double-dose statin, however, offers only limited additional lowering of LDL-C,[5,6] and high-dose statin therapy is associated with increased incidence of side-effects.[7]

In contrast, several studies have demonstrated that ezetimibe, which reduces cholesterol absorption from the small intestine through inhibition of the Nieman-Pick C1-like1 protein, can produce significant reduction in serum LCL-C and has cardiovascular protective effects. When added to statin, ezetimibe provides an incremental reduction in LDL-C of 16–26%.[5,6] The clinical trial Improved Reduction of Outcomes: Vytorin Efficacy International Trial

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(IMPROVE-IT) reported the clinical benefits of the combination of ezetimibe and statin during a median follow-up of 6 years.[8] In a recent randomized study, Tsujita et al demonstrated the superiority of the combination of ezetimibe and statin on coronary atherosclerosis, compared with statin alone, in patients with coronary artery disease.[9] Similarly, the SANDS clinical trial concluded that the beneficial effects of the combination of ezetimibe plus statin on carotid atherosclerosis was similar to that of statin alone in patients with similar reduction in LDL-C.[10] Other clinical trials on the combination of ezetimibe and statin on carotid atherosclerosis, however, noted variable results: both beneficial[10] and non-favorable outcomes.[11,12] Thus, the anti-atherosclerotic effects of ezetimibe remain controversial. The present prospective, randomized open-label study conducted at 10 centers in Japan, compared the effects of 2 mg/day pitavastatin with those of the combination of 2 mg/day pitavastatin plus 10 mg/day ezetimibe on percent change in coronary plaque volume (PV) and lipid PV, as determined on intravascular ultrasonography (IVUS).

Methods

Subjects

This prospective, randomized open-label parallel group study with blind endpoint evaluation was conducted at 10 health centers to compare the effects of pitavastatin plus ezetimibe vs. pitavastatin alone on coronary atherosclerosis in statin-naïve patients with acute coronary syndrome (ACS). All subjects were diagnosed with ACS and underwent successful percutaneous coronary intervention (PCI) for the culprit lesion under IVUS guidance. ACS was defined as unstable angina pectoris, non-ST-segment elevation myocardial infarction (NSTEMI) or ST-segment elevation myocardial infarction (STEMI).[13] We excluded patients with severely calcified lesions, coronary bypass graft lesion, restenotic lesion, treatment with lipid-lowering agents (statin, niacin, probucol, fibrate, and anion exchange resin), homozygous familial hypercholesterolemia, hemodynamic instability, cardiogenic shock, planned revascularization of the target plaque, history of revascularization of the target plaque, active liver disease (alanine aminotransferase ≥100 IU/L), or severe renal insufficiency (serum creatinine ≥2.0 mg/dL). Culprit lesions were classified according to the electrocardiographic change and angiographic appearance during PCI.

A total of 128 patients with ACS who underwent IVUS-guided PCI were centrally randomized into the pitavastatin (2 mg/day) plus ezetimibe (10 mg/day) group and pitavastatin monotherapy (2 mg/day) group using an internet-based program, and stratified according to hyperlipidemia and diabetes using the minimization method. We used the minimization method to minimize imbalances between important factors in both groups. Changes in lipid profile, C-reactive protein (CRP), and pentraxin 3 were calculated at follow-up and expressed relative to baseline.

The study was registered at www.clinicaltrials.gov (NCT00549926) and conducted according to the Declaration of Helsinki. The study protocol was approved by the institutional human ethics review board of each center and written informed consent was obtained from each patient.

IVUS

The PCI strategy, such as the decision to stent without balloon pre-dilatation or post-dilatation after stent implantation was left to the discretion of the individual operator. After PCI, IVUS was conducted to evaluate non-culprit coronary lesions and this was performed at baseline and at 8–12-month follow-up in 103 patients. After another 200 μg nitroglycerin i.c., a 40-MHz IVUS catheter (ViewIT, Terumo, Tokyo, Japan) was advanced over a 0.014-in guidewire and positioned as far distally as could be safely reached, and imaging was performed in a retrograde fashion to the aorto-ostial junction at an automatic pullback speed of 0.5 mm/s, facilitating the observation of the lesion. IVUS in the non-culprit vessel was strongly recommended, but non-culprit lesion in the culprit vessel was allowed according to the clinical situation in the setting of ACS. IVUS was also performed at 8–12-month follow-up, and the same IVUS imaging system was used in all examinations.

Two independent experienced investigators blinded to the clinical data analyzed the IVUS quantitatively in the independent core laboratory (Cardiocore, Yokohama, Japan). IVUS analysis was performed using a validated planimetry system (Visiatlas ver. 2.0, Terumo). The target segment for analysis was a mild-moderate stenosis in the non-culprit vessel. In the case of non-culprit vessel IVUS deemed impossible by the operators, the non-PCI site of the culprit vessel (>5 mm proximal or distal to the PCI site) was selected. Spotty calcification, side branch, and stent edge were used as reproducible landmarks to synchronize the target plaque at baseline and at follow-up. For each patient, the cross-sectional area (CSA) of the external elastic membrane (EEM) and of the intravascular lumen was measured according to the standards of the American College of Cardiology.[14] The luminal/intimal borders were contoured manually to determine the lumen CSA. The EEM CSA, representing the area encompassed by the medial-adventitial border, was measured by tracing the leading edge of the adventitia to determine the CSA of the vessel. Conventional IVUS and integrated backscatter (IB)-IVUS measurements at 1-mm intervals were performed. The IB-IVUS technology has been described in detail in several previous reports.[15–17] Data were captured on Visiwave console software and the tissue composition of coronary plaque was digitally labelled as lipid, fibrosis (fibrosis plus dense fibrosis), and calcification, according to the radiofrequency ultrasound backscatter signals. We previously reported good intraobserver and interobserver agreement regarding measurement of coronary plaque components.[18] Changes in lipid profile, CRP, and grayscale and various IB-IVUS variables were calculated (follow-up value minus baseline value). Furthermore, EEM volume and lumen volume were calculated using Simpson's rule. PV represented EEM volume minus lumen volume. The volume of each plaque component was also calculated using Simpson's rule.

Calculation of Endpoints

The primary endpoint was the percent change in coronary PV and in lipid PV during the follow-up period. %Change in PV was calculated as $[(PV_{follow\text{-}up}-PV_{baseline})/PV_{baseline}]\times 100$, where PV=$\Sigma$(EEM CSA−lumen CSA). Lipid PV was calculated as Σlipid plaque CSA. The secondary endpoints were absolute change in %PV and in normalized PV (NPV). %PV was calculated using the following formula: %PV=[PV/Σ(EEM CSA)]×100. NPV was calculated as $PV\times[L_{MED}/L_{MEASURED}]$, where L_{MED}=the median observed length in all subjects and $L_{MEASURED}$=the observed length for each plaque. The intra- and inter-observer intra-class

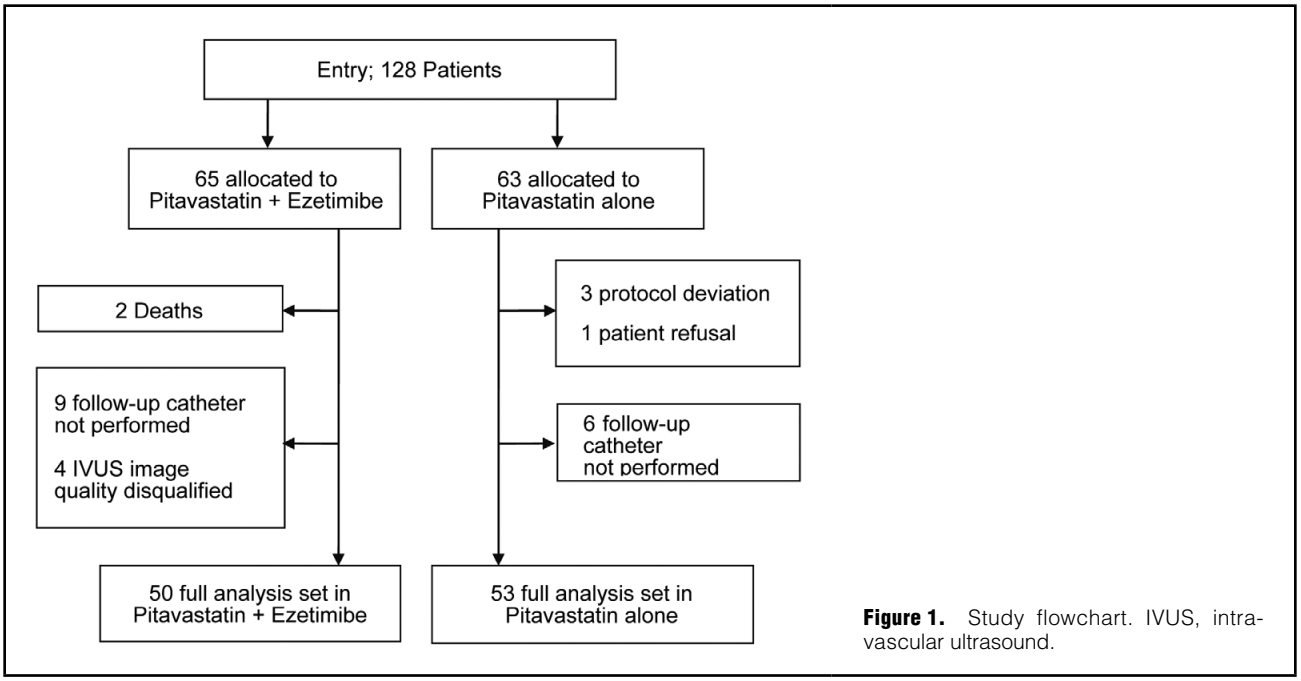

Figure 1. Study flowchart. IVUS, intravascular ultrasound.

correlation coefficients (ICC) for the vessel, lumen, and plaque areas were 0.999 and 0.999, 0.996 and 0.993, and 0.993 and 0.991, respectively, as reported previously.[18]

Definition of Major Adverse Cardiac Events (MACE)

MACE were defined as a composite of cardiac death, myocardial infarction, or any repeat revascularization during the study period.

Statistical Analysis

Quantitative data are expressed as mean±SD for continuous variables and frequencies for categorical variables. The Kolmogorov-Smirnov test was used to determine the pattern of data distribution (normal or skewed). For normally distributed data, differences between patient groups were tested using Student's t-test. Given that Student's t-test assumes homogeneity of variance, Levene's test was applied to assess the equality of variances in each group. For Leven test $P<0.05$, Welch's t-test was used. For skewed data distribution, between-group differences were tested using Mann-Whitney U-test. Categorical data were compared using the chi-squared test or Fisher's exact test as appropriate.

For difference in percent change in PV, a sample size ≥43 patients in each treatment group was required to provide 80% power at a 2-sided α of 0.05 to demonstrate a relative 5.7% difference,[19] assuming a 9.3% standard deviation.[20] To allow for 20% dropout rate, we recruited 120 patients.

All tests were 2-tailed, and $P<5\%$ was considered to reflect statistical significance. Statistical analysis was performed using the Statistical Package for Social Sciences (IBM SPSS statistics 22.0 for Windows, SPSS, Chicago, IL, USA).

Results

Patient Characteristics

Figure 1 shows the number of patients at each step of the selection and randomization process and the reasons for discontinuation. Between October 2010 and September 2012, 128 patients at 10 centers were randomized and received the study drug, and 103 (80.5%) had evaluable IVUS data at both baseline and follow-up. Thus, the full analysis set (FAS) consisted of 50 patients in the ezetimibe plus statin (combination) group and 53 patients in the statin monotherapy group (**Table 1**). The mean time interval between baseline and follow-up was 10.0±1.9 months The 2 treatment groups were well balanced with regard to baseline demographics and clinical characteristics. Mean age was 63.2±10.8 years, 79% of patients were men, 30% had diabetes, 72% had STEMI, and drug-eluting stents were used in 28% and bare-metal stents in 69%. According to the study protocol, all patients received statin treatment. There were no significant differences between the groups with regard to medication at discharge.

Effects of Lipid-Lowering Therapy

Table 2 summarizes the laboratory results for the FAS group conducted at baseline and 10-month follow-up. Mean LDL-C decreased significantly from 123 to 64 mg/dL in the combination group (n=50) and from 126 to 87 mg/dL in the statin alone group (n=53; between-group difference, 16.9%, $P<0.0001$). Thus, the combination therapy produced greater reduction in LDL-C compared with statin alone (−45.7% vs. −28.8%, $P<0.0001$). Furthermore, high-sensitivity CRP (hs-CRP) decreased significantly from 1.75±2.16 mg/dL at baseline to 0.12±0.19 mg/dL after 10-month therapy in the combination group ($P<0.0001$), and from 2.92±3.57 mg/dL to 0.14±0.22 mg/dL in the statin monotherapy ($P<0.0001$). Similarly, pentraxin 3 decreased significantly from baseline to 10-month follow-up in both groups. The reductions in hs-CRP and pentraxin 3, however, were similar between the 2 groups.

Effects of Lipid-Lowering Therapy on IVUS Endpoints

Changes in grayscale and IB-IVUS parameters are summarized in **Table 3**. The primary endpoint, percent change in

Table 1. Baseline Clinical Characteristics

	Pitavastatin plus ezetimibe	Pitavastatin monotherapy	P-value
n	50	53	
Age (years)	63±10	63±12	0.941
Male sex	41 (82)	41 (77)	0.559
Hypertension	23 (46)	34 (64)	0.064
Diabetes mellitus	10 (20)	11 (21)	0.924
Current smoking	22 (44)	20 (38)	0.653
STEMI	38 (76)	36 (68)	0.362
Family history of CAD	9 (18)	14 (26)	0.305
No. diseased vessels			0.977
1	32 (64)	35 (66)	
2	12 (24)	12 (23)	
3	6 (12)	6 (11)	
Medication			
Nitrates	2 (4)	1 (2)	0.610
Calcium channel blockers	13 (26)	7 (13)	0.101
β-blockers	30 (60)	31 (51)	0.876
AIIRA	14 (28)	13 (25)	0.689
ACEI	29 (58)	30 (57)	0.886

Data given as mean±SD or n (%). AIIRA, angiotensin II receptor antagonist; ACEI, angiotensin-converting enzyme inhibitor; CAD, coronary artery disease; STEMI, ST-segment elevation myocardial infarction.

Table 2. Laboratory Results: Baseline vs. 10-Month Follow-up

	Pitavastatin plus ezetimibe	Pitavastatin monotherapy	P-value
n	50	53	
Lipid profile			
Baseline			
TC (mg/dL)	191±34	196±37	0.441
LDL-C (mg/dL)	123±32	126±33	0.598
HDL-C (mg/dL)	45±14	46±11	0.597
TG (mg/dL)	109±64	112±52	0.800
10-month follow-up			
TC (mg/dL)	132±20***	156±29***	<0.0001
LDL-C (mg/dL)	64±18***	87±21***	<0.0001
HDL-C (mg/dL)	49±12*	49±15	0.853
TG (mg/dL)	108±53	129±77	0.107
Change in lipid profiles			
ΔTC (mg/dL)	−59±33	−41±34	0.017
ΔLDL-C (mg/dL)	−58±27	−40±31	0.005
ΔHDL-C (mg/dL)	4±10	2±12	0.358
ΔTG (mg/dL)	−3±71	18±65	0.152
Hs-CRP (mg/dL)			
Baseline	1.8±2.2	2.9±3.6	0.181
10-month follow-up	0.1±0.2***	0.1±0.2***	0.715
Change	−1.7±2.2	−2.8±3.6	0.298
Pentraxin 3 (ng/mL)			
Baseline	5.8±5.0	6.1±4.3	0.737
10-month follow-up	2.4±2.1***	2.4±3.1***	0.992
Change	−3.4±4.9	−3.7±4.3	0.795
Peak CK (IU/L)	1,940±1,973	1,916±2,318	0.955

Data given as n, mean±SD, or n (%). *P<0.05, ***P<0.001 (baseline vs. follow-up). CK, creatine kinase; HDL-C, high-density lipoprotein cholesterol; hs-CrP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides.

Table 3. IVUS: Baseline vs. Follow-up

	Pitavastatin plus ezetimibe	Pitavastatin monotherapy	P-value
n	50	53	
Non-culprit vessels analysis	37 (74)	43 (81)	0.385
Baseline			
Length of analyzed lesion (mm)	38±19	41±18	0.396
EEM volume (mm^3)	534±375	585±335	0.465
Lumen volume (mm^3)	301±211	334±210	0.425
PV (mm^3)	233±175	251±155	0.580
Percent atheroma volume (%)	44.3±9.4	43.9±10.6	0.816
8–12-month follow-up			
Length of analyzed lesion (mm)	38±19	41±19	0.374
EEM volume (mm^3)	523±382*	574±335*	0.472
Lumen volume (mm^3)	301±219	334±211	0.438
PV (mm^3)	222±175**	240±153**	0.577
Percent PV (%)	42.9±9.6***	42.0±10.0**	0.650
Change			
ΔEEM volume (mm^3)	−11±39	−12±35	0.973
ΔLumen volume (mm^3)	0±29	0±26	0.966
ΔPV (mm^3)	−11±22	−11±23	0.997
Percent change in PV (%)	−5.1±12.2	−6.2±13.8	0.664
Absolute change			
Normalized PV (mm^3)	−6.9±25.6	−8.3±30.8	0.798
Percent PV (%)	−1.5±4.3	−1.9±4.7	0.639

Data given as n, mean±SD, or n (%). *P<0.05, **P<0.01, ***P<0.001 (baseline vs. follow-up). EEM, external elastic membrane; IVUS, intravascular ultrasound; PV, plaque volume.

Table 4. IB-IVUS: Baseline vs. 10-Month Follow-up

	Pitavastatin plus ezetimibe	Pitavastatin monotherapy	P-value
n	50	53	
Baseline			
Lipid PV (mm^3)	133±132	140±106	0.750
Fibrous PV (mm^3)	98±61	108±65	0.415
Calcium volume (mm^3)	2.4±1.7	2.8±2.7	0.368
Follow-up at 10 months			
Lipid PV (mm^3)	125±113	127±101	0.927
Fibrous PV (mm^3)	94±77	110±69	0.279
Calcium volume (mm^3)	2.4±2.0	2.9±2.6	0.237
Percent change			
Lipid PV (%)	4.3±39.1	−3.0±43.3	0.374
Fibrous PV (%)	−1.0±44.8	9.1±50.2	0.286
Calcification volume (%)	66.9±259.9	148.3±351.7	0.187

Data given as mean±SD. IB-IVUS, integrated backscatter intravascular ultrasound; PV, plaque volume.

PV, was significantly lower in both groups (combination group, −5.1%; statin group, −6.2%, P<0.01, each), but the between-group difference was not significant (P=0.66; **Table 3**). Similarly, the percent change in lipid PV was not significantly different between the 2 groups (4.3 vs. −3.0%, P=0.37, **Table 4**). The secondary endpoint, absolute change in percent atheroma volume, was not different between the 2 groups (−1.5 vs. −1.9%, P=0.64).

Subgroup Analysis

We observed no significant difference in the primary endpoint with regard to age, sex, coronary risk factors, or angiographic or IVUS variables (**Table 5**).

Lipid Profile and Percent Change in Plaque Volume There were no significant correlations between percent change in LDL-C during the study period and percent change in PV in the combination group or the statin monotherapy group (**Figure 2A**). Similarly, no significant correlations were observed between percent change in LDL-C and percent change in lipid PV in either group (**Figure 2B**).

Markers of Cholesterol Synthesis and Absorption: IVUS Endpoints In a subgroup of patients (n=77), serum concentration of the markers of cholesterol synthesis (lathosterol) and absorption (campesterol and sitosterol) was measured.

Table 5. Primary Endpoint: Subanalysis

	%change in coronary PV		P-value
	Pitavastatin plus ezetimibe	Pitavastatin monotherapy	
All (n=103)	−5.1±12.2	−6.2±13.8	0.664
Lesion length			
≥10 mm (n=91)	−6.2±10.1	−4.3±9.2	0.385
≥30 mm (n=72)	−4.3±10.3	−4.9±9.1	0.809
Age			
<70 years (n=72)	−5.5±13.0	−6.7±16.0	0.717
≥70 years (n=32)	−4.3±9.4	−5.3±9.1	0.764
Sex			
Male (n=82)	−3.8±12.6	−6.0±15.5	0.472
Female (n=21)	−11.0±7.9	−6.7±6.1	0.182
Diagnosis			
STEMI (n=74)	−5.9±11.0	−6.0±15.9	0.974
Non-STEACS (n=29)	−2.5±15.7	−6.7±8.4	0.368
Current smoker			
Yes (n=43)	−3.1±8.1	−7.1±19.4	0.387
No (n=60)	−6.6±14.6	−5.6±8.79	0.752
Hypertension			
Yes (n=57)	−2.9±9.7	−5.5±16.4	0.497
No (n=46)	−6.9±13.9	−7.4±7.4	0.889
DM			
Yes (n=21)	−6.4±8.0	−13.0±24.7	0.428
No (n=82)	−4.7±13.0	−4.4±8.9	0.892
Family history of CAD			
Yes (n=23)	0.8±14.8	−1.5±10.4	0.669
No (n=80)	−6.3±11.3	−7.9±14.6	0.603
Analyzed vessel			
Culprit vessel (n=23)	−2.3±5.2	−0.6±4.1	0.616
Non-culprit vessel (n=80)	−5.0±10.5	−7.1±14.4	0.458
Analyzed location			
LAD (n=56)	−3.0±13.7	−6.0±8.4	0.347
LCX/RCA (n=47)	−8.0±8.9	−6.3±17.8	0.700
No. diseased vessels			
1 vessel (n=67)	−5.5±12.7	−6.4±8.7	0.734
≥2 vessels (n=36)	−4.2±11.6	−5.7±20.9	0.794
Analyzed plaque vulnerability			
With lipid pool (n=37)	5.8±11.0	−3.0±8.3	0.399
Without lipid pool (n=65)	−3.4±11.5	−7.7±15.7	0.223

Data given as mean±SD. CAD, coronary artery disease; DM, diabetes mellitus; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; non-STEACS, non-ST-elevation acute coronary syndrome; PV, plaque volume; RCA, right coronary artery; STEMI, ST-segment elevation acute myocardial infarction.

Patients were stratified according to the medians of lathosterol, campesterol, and sitosterol (**Table 6**). In any subgroup, the primary and secondary endpoints were not significantly different between the combination group and the statin alone group on quantitative grayscale IVUS.

MACE The treated group consisted of all patients who received any dose of study medication (128 randomized patients) and was considered for analysis of safety and adverse events. As expected, given the relatively small number of patients, the number of patients who developed MACE during the 10-month follow-up was not different between the 2 groups (9 patients in the combination group and 6 in the statin monotherapy group, P=0.63). There were 2 deaths (cardiac death in 1 and non-cardiac in another) in the combination group vs. none in the monotherapy group (P=0.50). Repeat revascularization was performed in 10.7% (7/65) of the combination group and in 9.5% (6/63) of the statin alone group (P=0.82).

Discussion

The main findings of this study are as follows: (1) the combination of ezetimibe and statin reduced the level of LCL-C by 17%; (2) coronary plaque regression was observed after 10-month treatment with either type of therapy (i.e., combination therapy or statin monotherapy); (3) the larger reduction in LDL-C with the combination therapy did not translate into greater regression of the

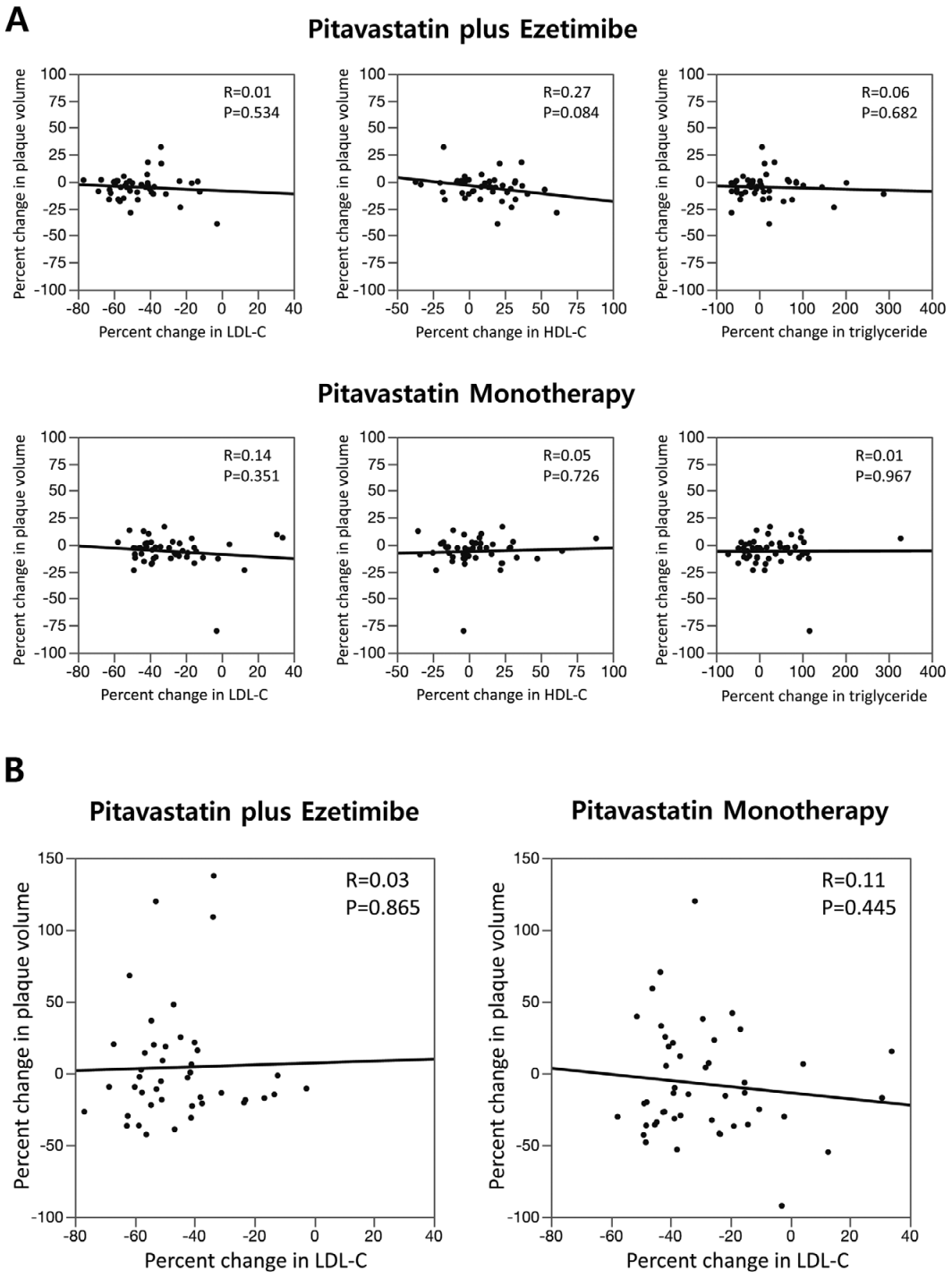

Figure 2. (**A**) Percent change in plaque volume vs. percent change in lipid profile and (**B**) percent change in low-density lipoprotein cholesterol (LDL-C) vs. percent change in plaque volume for the pitavastatin plus ezetimibe and pitavastatin monotherapy groups. HDL-C, high-density lipoprotein cholesterol.

non-culprit atherosclerotic plaque or change in plaque tissue characteristics in statin-naïve patients with ACS; and (4) the results were consistent across subgroups stratified according to the markers of cholesterol synthesis and absorption.

Theoretically, specific strategies targeting LDL-C in ACS may be beneficial with regard to the regression of atherosclerosis.[21] Ezetimibe has been shown to reduce the levels of inflammatory markers,[12,22] improve endothelial function,[23] and lower LCL-C by approximately 15% beyond

Table 6. IVUS Endpoints: Subgroup Analysis

	Pitavastatin plus ezetimibe	Pitavastatin monotherapy	P-value
Sitosterol <2.0 μg/mL (n=32)†			
Percent change in PV (%)	−9.3±11.0	−5.4±9.6	0.296
Absolute change in normalized PV (mm^3)	−15.5±32.3	−0.3±24.7	0.139
Absolute change in percent PV (%)	−2.6±4.5	−1.6±2.8	0.468
Sitosterol ≥2.0 μg/mL (n=45)			
Percent change in PV (%)	−5.1±12.0	−8.6±17.9	0.457
Absolute change in normalized PV (mm^3)	−5.3±21.3	−15.8±38.1	0.278
Absolute change in percent PV (%)	−1.5±4.3	−1.9±4.7	0.639
Campesterol <4.3 μg/mL (n=35)†			
Percent change in PV (%)	−8.4±11.1	−5.9±7.9	0.510
Absolute change in normalized PV (mm^3)	−13.5±30.5	−3.9±14.7	0.309
Absolute change in percent PV (%)	−2.5±4.6	−1.5±3.0	0.529
Campesterol ≥4.3 μg/mL (n=42)			
Percent change in PV (%)	−5.1±12.3	−8.1±17.8	0.572
Absolute change in normalized PV (mm^3)	−5.0±21.2	−12.8±40.3	0.492
Absolute change in percent PV (%)	−0.53±4.3	−2.8±5.8	0.196
Lathosterol <2.3 μg/mL (n=38)†			
Percent change in PV (%)	−5.4±11.5	−6.6±9.6	0.727
Absolute change in normalized PV (mm^3)	−6.6±22.2	−9.2±24.4	0.729
Absolute change in percent PV (%)	−1.6±2.9	−2.2±2.9	0.473
Lathosterol ≥2.3 μg/mL (n=39)			
Percent change in PV (%)	−8.7±11.7	−8.2±19.6	0.918
Absolute change in normalized PV (mm^3)	−13.7±31.6	−10.8±42.6	0.809
Absolute change in percent PV (%)	−1.9±5.8	−2.5±6.6	0.738

Data given as mean±SD or †median±SD. IVUS, intravascular ultrasound; PV, plaque volume.

the effects of concomitant statin therapy.[12,24,25] The combination therapy, however, has also been reported to have no impact on the progression of carotid atherosclerosis in several other studies. For example, the Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) clinical trial showed that the addition of ezetimibe to simvastatin did not reduce the intima-media thickness (IMT) of the carotid artery wall in patients with familial hypercholesterolemia, although a between-group difference in LDL-C >15% was observed throughout the 24-month treatment period.[12] Furthermore, the Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 6–HDL and LDL Treatment Strategies (ARBITER 6–HALTS) trial compared the effect of 14-month treatment with niacin or ezetimibe on the carotid IMT in patients with coronary artery disease (CAD) or high risk for CAD.[26] While niacin had greater efficacy with regard to the change in IMT compared with ezetimibe, ezetimibe led to paradoxical progression of IMT although it resulted in greater reduction in LDL-C with cumulative drug exposure,[11] suggesting that ezetimibe may worsen arterial atherosclerosis. Although the effect of ezetimibe on coronary atherosclerosis may differ from that on carotid atherosclerosis, the present lack of anti-regression effect on coronary atherosclerosis by ezetimibe suggests that this cholesterol-lowering agent has different mechanisms of action compared with statins.

Lipid-lowering treatment is a first-line therapy for ACS, based on the findings of previous large-scale randomized trials of reductions in high LDL-C after high-dose statin therapy and reduced rate of atherosclerotic cardiovascular disease (ASCVD). The 2013 American Heart Association and American College of Cardiology (AHA/ACC) guidelines recommended high-intensity statin therapy as a secondary prevention strategy in patients with ASCVD, regardless of the LDL-C level.[27] In the present study, no correlation was observed between LDL-C reduction and plaque regression. In IMPROVE-IT, the addition of ezetimibe to high-dose statin therapy resulted in a significantly lower risk of cardiovascular events,[8] suggesting that lipid-lowering therapy other than statin may have anti-atherosclerotic effect. The PRECISE-IVUS trial was the first to show reduction of coronary atherosclerosis with dual lipid-lowering therapy of ezetimibe and statin compared with statin alone.[9] In contrast, the present results do not support the anti-atherosclerotic effect of ezetimibe when added to statin in statin-naïve patients with ACS. There are 3 main differences between the PRECISE-IVUS trial and the present study: first, they increased atorvastatin by titration with a treatment goal of LDL-C <70 mg/dL, while we selected a fixed dose of pitavastatin 2 mg/day. As a result, the present achieved LDL-C level in the ezetimibe–statin combination group (64±18 vs. 63±16 mg/dL) was similar to that in the PRECISE-IVUS trial, while that in the statin monotherapy group was higher (87±21 vs. 73±20 mg/dL). Second, the PRECISE-IVUS trial enrolled a 2-fold larger number of patients and assessed non-culprit plaque in the culprit vessel for PCI, while we measured a 4-fold longer lesion length by examining non-culprit plaque in mainly "non-culprit vessels". And third, the PRECISE-IVUS trial enrolled both ACS and stable angina pectoris cohorts irrespective of previous statin use, whereas we enrolled

patients with ACS and excluded those who had previously received statin treatment. It is therefore reasonable to conclude that the effects of the ezetimibe-statin combination therapy can vary according to the patient sample,[28] method of treatment, and time of assessment of outcome. In a substudy of the PRECISE-IVUS trial, the IVUS endpoints were compared according to the presence or absence of statin pretreatment.[29] In patients who received statin pretreatment, atorvastatin/ezetimibe combination had greater effect in reducing %PV compared with atorvastatin alone (−1.8% vs. −0.1%, P=0.002), whereas a non-significant effect was observed in patients who did not receive statin pretreatment (−1.3 vs. −0.9, P=0.12). In addition, West et al found that statin-naïve patients randomized to statin plus ezetimibe or statin alone had similar changes in peripheral PV despite a significant reduction in LDL-C.[30] Furthermore, in the placebo arm of the Global Assessment of Plaque Regression With a PCSK9 Antibody as Measured by Intravascular Ultrasound (GLAGOV) trial, 98.3% of patients had statin pre-treatment, and baseline mean LDL-C was 92.4 mg/dL.[31] Neither %PV nor total PV changed from baseline to 78-week follow-up, indicating that the effect of statin on PV is not long-lasting. Thus, it is plausible that ezetimibe may exert a regressive effect when statin has lost its effect on PV. Alternatively, given that statin is known to increase LCL-C absorption,[32] ezetimibe may exhibit its favorable effect on coronary atherosclerosis after a certain period of statin pretreatment. Given that we excluded patients with statin pretreatment, the true effect of ezetimibe on coronary atherosclerosis may have been altered or delayed in the present analysis. The present results question the value of simultaneous use of statin and ezetimibe in patients with ACS who did not receive statin at presentation.

Study Limitations

Several limitations must be given consideration. First, both baseline and follow-up IVUS data were available for only 103 of the 128 randomized patients (80.5%). Patients who did not complete the trial may have different plaque behavior, although the acquisition rate in the present study is similar to that reported in previous trials.[9,33,34] Second, the sample size of 103 patients was relatively small. Given the negative overall result, we cannot definitively rule out type II error. The percent reduction in PV was numerically smaller in the combination therapy group and it seems unlikely to be clinically meaningful, even with a larger number of patients. The present sample size, however, obviously lacks statistical power to prove non-inferiority and should be considered as hypothesis generating. Third, the period of 10 months may not have been long enough to detect differences in plaque behavior between the 2 groups. Nevertheless, the sample size was sufficient to detect significant plaque regression from baseline to 10-month follow-up in both groups. Fourth, we strongly encouraged the use of IVUS in the non-culprit vessel because it enables longer segment analysis, thereby increasing the reliability of the data. Given the safety issues, however, non-culprit plaques in culprit vessels were analyzed in 23 patients (22%).

Conclusions

In statin-naïve patients with ACS, the combination of ezetimibe–statin therapy had no add-on effect on regression of coronary atherosclerosis compared with statin alone. A larger number of patients including a heterogeneous population with and without statin pretreatment and long-term follow-up is needed to establish the true effects of such therapy on coronary atherosclerosis.

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