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Impact of Olmesartan on Progression of Coronary Atherosclerosis

A Serial Volumetric Intravascular Ultrasound Analysis From the OLIVUS (Impact of OLmesarten on progression of coronary atherosclerosis: evaluation by IntraVascular UltraSound) Trial

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Objectives The aim of this study was to evaluate the impact of olmesartan on progression of coronary atherosclerosis.

Background Prior intravascular ultrasound (IVUS) trial results suggest slowing of coronary atheroma progression with some medicines but have not shown convincing evidence of regression with angiotension-II receptor blocking agents.

Methods A prospective, randomized, multicenter trial—OLIVUS (Impact of OLmesartan on progression of coronary atherosclerosis: evaluation by IntraVascular UltraSound)—was performed in 247 stable angina pectoris patients with native coronary artery disease. When these patients underwent percutaneous coronary intervention for culprit lesions, IVUS was performed in their nonculprit vessels (without angiographically documented coronary stenosis [<50%]). Patients were randomly assigned to receive 10 to 40 mg of olmesartan or control and treated with a combination of beta-blockers, calcium channel blockers, diuretics, nitrates, glycemic control agents, and/or statins per physician's guidance. Serial IVUS examinations (baseline and 14-month follow-up) were performed to assess coronary atheroma volume. Volumetric IVUS analyses included lumen, plaque, vessel volume, percent atheroma volume (PAV), percent change in total atheroma volume (TAV) and PAV.

Results Patient characteristics and blood pressure control were identical between the 2 groups. However, follow-up IVUS showed significantly decreased TAV and percent change in PAV in the olmesartan group (5.4% vs. 0.6 % for TAV and 3.1% vs. −0.7% for percent change in PAV, control vs. olmesartan, $p < 0.05$ for all).

Conclusions These observations suggest a positive role in a potentially lower rate of coronary atheroma progression through the administration of olmesartan, an angiotension-II receptor blocking agent, for patients with stable angina pectoris. (J Am Coll Cardiol 2010;55:976–82) © 2010 by the American College of Cardiology Foundation

Extensive cardiovascular disease is the major cause of morbidity and mortality in patients with angina pectoris. Therefore, optimal atheroma management is a key strategy for preventing subsequent cardiovascular events. Prior intravascular ultrasound (IVUS) trials have reported a slowing of coronary atheroma progression or regression with some medicines, such as statins or pioglitazone, suggesting the possibility for pharmacological interventions (1–13). By contrast, chronic activation of the renin-angiotensin system is a well-established contributor to the development and progression of atherosclerosis (14). Although angiotension-II receptor blocking agents (ARBs) are widely used for the treatment of hypertension, their anti-inflammatory or antioxidized efficacy through directly blocking the action of angiotensin-II have also been reported (4,15–19). In addition, according to the results of

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recent trials, the similarities of effects on preventing myocardial infarction (MI) between ARB and angiotensin-converting enzyme (ACE) inhibitors have also been reported (20). However, the potential advantage beyond antihypertensive efficacy for plaque modification has not been well-clarified in atherosclerotic human coronary arteries. Thus, we investigated the impact of administration of olmesartan, an ARB, on the progression of coronary atherosclerosis as assessed by serial IVUS interrogation.

Abbreviations and Acronyms

ACE = angiotensin-converting enzyme
ARB = angiotension-II receptor blocking agent
IVUS = intravascular ultrasound
MI = myocardial infarction
PAV = percent atheroma volume
PCI = percutaneous coronary intervention
TAV = total atheroma volume

Methods

Patients and study design. The OLIVUS (Impact of OLmesartan on the progression of coronary atherosclerosis: evaluation by IntraVascular UltraSound) trial is a prospective, randomized, multicenter trial. The study protocol was approved by all participating institutional review boards, and all patients provided written informed consent. Patients with clinically stable angina pectoris and hypertension scheduled for percutaneous coronary intervention (PCI) were enrolled. After PCI for their culprit lesions, IVUS was performed over 40 mm in their nonculprit vessels—defined as without angiographically documented coronary stenosis <50%—to determine atheroma volume at baseline.

Patients with complicated lesions, such as excessive tortuosity or calcified lesions, unable to cross with IVUS, chronic renal failure (serum creatinine >1.5), unstable patients, recent MI within 4 weeks, poor ejection fraction <25%, and patients already taking ACE inhibitors or ARBs were excluded from the trial. Patients were randomized to control or olmesartan 10 to 40 mg titrated to maximally tolerated dose by 8 weeks. In addition, patients were treated with a combination of beta-blockers, calcium channel blockers, diuretics, nitrates, glycemic control agents, and/or statins per physician's guidance. After 12 to 16 months, IVUS of the originally examined coronary artery was performed during the routine follow-up angiogram. Our primary end point of interest was the impact of administration of olmesartan on coronary atherosclerotic changes evaluated by volumetric IVUS. Other outcomes included adverse events, such as cardiovascular death, nonfatal MI, nonfatal stroke, noncardiovascular death, hospital stay for unstable angina, hospital stay for chronic heart failure, or deterioration of chronic renal failure.

IVUS. The IVUS studies were performed with a commercially available imaging system with a 40-MHz mechanical transducer ultrasound catheter (Boston Scientific Corporation, Natick, Massachusetts). After intracoronary nitroglycerin administration, the imaging catheter was advanced over the coronary wire to the mid-to-distal vessel under fluoroscopic guidance. Cine runs, before and during contrast injection, were performed to define the position of the catheter distal to an identifiable side branch. With automated pullback (0.5 mm/s), digital ultrasound images were obtained and recorded on DVDs for subsequent off-line IVUS analysis. The DVDs containing the IVUS pullbacks were analyzed in a blinded fashion by the IVUS core laboratory in the Sakakibara Heart Institute of Okayama. After image acquisition, 3-dimensional volumetric analysis was performed with Simpson's method by dedicated software (EchoPlaque, Indec Systems, Mountain View, California). The operator selected a distal fiduciary site, usually a branch site, as the beginning point for analysis. Subsequently, every 30th frame image was analyzed, generating a series of cross-sections spaced exactly 0.5 mm apart. The final cross-section analyzed was obtained at a proximal fiduciary site. Corresponding coronary segments over the 40 mm in the non–PCI-culprit vessels were selected, and IVUS measurements included vessel, lumen, and total atheroma volume (TAV). To standardize for vessel size, percent atheroma volume (PAV)—defined as atheroma volume divided by vessel volume—was also calculated. The serial progression rate of atherosclerosis was compared with change in TAV and change in PAV, measured by (follow-up TAV − baseline TAV)/baseline TAV × 100 and (follow-up PAV − baseline PAV)/baseline PAV × 100, respectively. A representative case is presented in Figure 1. Intraobserver variability has been previously reported (21).

Statistical methods. Analyses were performed with SPSS version 11 software (SPSS, Inc., Chicago, Illinois). Laboratory and ultrasound parameters are described with frequencies, whereas continuous variables are reported as mean, median (with 95% confidence intervals [CIs]), and SDs. Whether data were normally distributed was examined by the Kolmogrov-Smirnov test. If data were not normally distributed, testing for significant differences of each parameter between baseline and follow-up was performed with the Mann-Whitney *U* test. Serial atheroma and PAV changes were compared with a 2-tailed, paired Student *t* test. Linear regression was applied to determine correlations between blood pressure reduction and atheroma progression rate. Multiple linear regression and logistic regression analysis were applied to determine the independent predictors of coronary atheroma changes.

A p value of 0.05 was considered to be statistically significant. In the protocol, the assumptions used for power calculations required a sample size of 98 patients/treatment group to provide 80% power (assuming an SD of 12.5%) to detect a 5.0% difference in the primary efficacy parameter, change in PAV, with a 5% type I error rate for a 2-sided test. With an anticipated dropout rate of approximately 20%, enrollment of 123 patients/treatment group (total 246 randomized patients) was specified to provide an adequate number of evaluable IVUS patients.

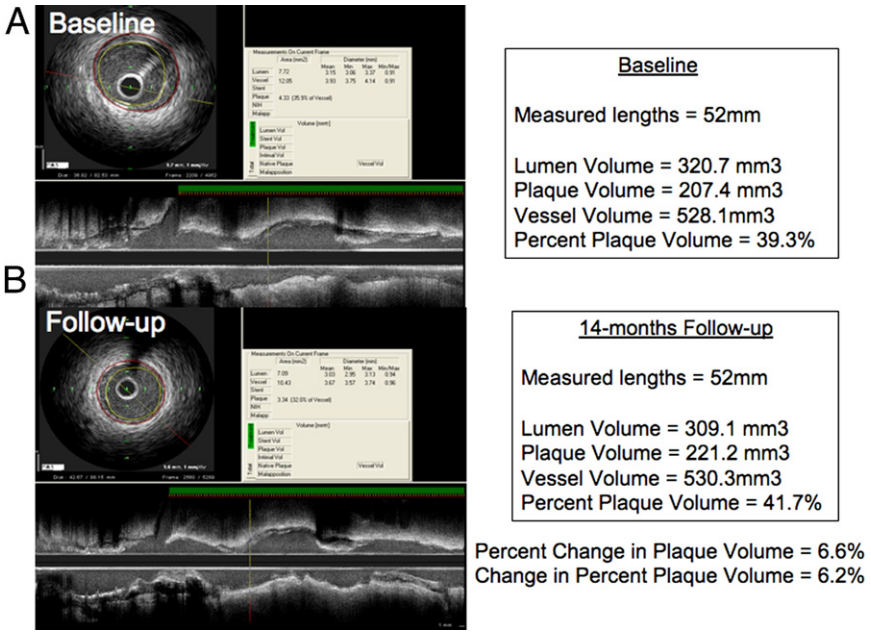

Figure 1 **Representative Serial Volumetric IVUS Analysis in the Control Group**

(A) Baseline intravascular ultrasound (IVUS); **(B)** 14-month follow-up. Serial changes of IVUS parameters are summarized on the **right**.

Results

Between February 2006 and August 2007, 247 patients with stable angina pectoris undergoing PCI were enrolled in this trial. During follow-up, 15 patients in the control group and 17 patients in the olmesartan group dropped out from the trial because of adverse events, laboratory abnormality, or withdrawal of consent. Therefore, follow-up IVUS (average 388 ± 54 days) was performed in 215 participants; however, 4 cases in the control group and 6 cases in the olmesartan group were excluded from analysis due to poor IVUS image quality, such as nonuniform rotational distortion, inconsistent pullback, or large axial movement of the IVUS catheter. As a result, a total of 205 patients completed the serial IVUS analysis, and average analyzed lengths were 42.6 mm. The numbers of patients screened and randomized and reasons for dropping out are reported in Figure 2. Vital status was ascertained in 230 patients (93.1%) at the end of the study. Of the 109 (86.5%) patients taking olmesartan at the end of the study, 105 (83.3%) were receiving the full dose (20 to 40 mg), with only 4 (3.2%) receiving a reduced dose.

Patient characteristics and blood pressure changes. Patient characteristics and medications at baseline are summarized in Tables 1 and 2. All data are identical between the control and olmesartan groups. At the time of enrollment, approximately 30% to 40% of patients were already being treated with antihypertensive agents, except ACE inhibitor or ARB and/or statins. Serial changes in blood pressure are presented in Table 3. In this trial, control of blood pressure was at the physician's discretion except for administration of

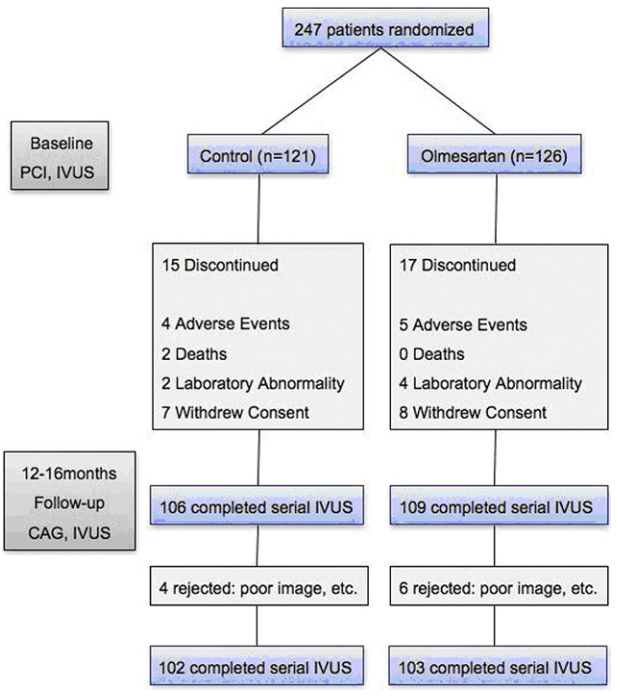

Figure 2 **Number of Patients Screened and Randomized and Reasons for Drop-Out in the OLIVUS Trial**

CAG = coronary angiography; IVUS = intravascular ultrasound; OLIVUS = Impact of OLmesartan on progression of coronary atherosclerosis: evaluation by IntraVascular UltraSound; PCI = percutaneous coronary intervention.

Table 1 Baseline Patient Characteristics and Laboratory Values

	Control (n = 121)	Olmesartan (n = 126)	p Value
Male	68	76	NS
Age (yrs)	68.4 ± 8.8	67.8 ± 8.7	NS
Smoking	31	34	NS
Diabetes	35	31	NS
Previous MI	13	15	NS
Analyzed vessel (LAD/LCX/RCA)	33/33/34	29/31/40	NS
Body mass index (kg/m^2)	23.9 ± 3.5	24.7 ± 3.2	NS
Creatinine (mg/dl)	1.0 ± 0.41	0.99 ± 0.25	NS
eGFR (ml/min/1.73 m^2)	57.9 ± 19.2	59.6 ± 17.5	NS
HbA1c (%)	5.9 ± 1.2	6.1 ± 1.1	NS
LDL cholesterol (mg/dl)	107.0 ± 30.2	103.8 ± 24.8	NS
HDL cholesterol (mg/dl)	50.4 ± 12.6	47.1 ± 12.7	NS
Triglycerides (mg/dl)	142 ± 64	164 ± 126	NS
Patients already on antihypertensive agents	38.8	39.7	NS
Patients already on statins	33.0	30.9	NS

Values are %, n, or mean ± SD.
eGFR = estimated glomerular filtration rate; HbA1c = hemoglobin A1c; HDL = high-density lipoprotein; LAD = left anterior descending coronary artery; LCX = left circumflex artery; LDL = low-density lipoprotein; MI = myocardial infarction; RCA = right coronary artery.

olmesartan. Although significant improvement of blood pressure was observed in both groups, there was no significant difference between the control and olmesartan groups.

Major cardiovascular events. Adjudicated major cardiovascular events are summarized in Table 4. There was no difference in terms of cardiovascular death, nonfatal MI or nonfatal stroke, coronary revascularization, hospital stay for congestive heart failure, or deterioration for chronic renal failure between the 2 groups.

Volumetric IVUS analysis. Table 5 summarizes the volumetric IVUS results changes in IVUS parameters from baseline to follow-up. Significant development of atheroma volume and PAV were found in the control group between baseline and follow-up ($p < 0.05$). Except for PAV at baseline, there were no differences in any other IVUS parameter measured between the control and olmesartan groups. Table 6 illustrates the results for the nominal and percentage change in atheroma volume, which is the primary efficacy parameter. In a comparison of the 2 regimens, the progression rate was significantly lower in the olmesartan group ($p = 0.016$ for nominal change in TAV, and $p = 0.038$ for PAV change). The nominal changes in atheroma volume and PAV were positive in the control group (7.1 mm^3 and 1.1%, respectively), indicating net progression ($p = 0.009$ and $p = 0.039$ compared with baseline, respectively). In the olmesartan group, the nominal change in atheroma volume and PAV were negative (−2.6 mm^3 and −0.1%, respectively), showing no disease progression ($p = 0.34$ and $p = 0.89$ compared with baseline, respectively). However, in this trial, there was no statistically significant correlation between blood pressure reduction and atheroma progression rate. Results of a multiple linear regression test—which is defined as percentage change of atheroma volume as a dependent variable—are summarized in Table 7, and results of logistic regression test for increased atheroma volume during follow-up periods are in Figure 3. Both results identified olmesartan administration as 1 of the factors that decreased atheroma volume. In the diabetic subanalysis, there was significant difference in PAV changes when compared with baseline hemoglobin A1c <6.5% and ≥6.5% groups (−0.40% vs. 5.1%, $p = 0.01$). However, in the statin subanalysis, there was no difference between the 2 groups. By contrast, there was a difference in PAV change when compared with baseline low-density lipoprotein cholesterol <120 and ≥120 mg/dl groups (0.2% vs. 4.1%, $p = 0.06$).

Table 2 Baseline Medication

	Control (n = 121)	Olmesartan (n = 126)	p Value
Aspirin (%)	100.0	100.0	NS
Beta-blocker (%)	13.2	12.7	NS
Calcium-channel blockers (%)	49.6	41.3	NS
Statins (%)	57.0	52.3	NS
Oral glycemic agents (%)	17.3	19.8	NS
Insulin (%)	7.1	5.6	NS

Table 3 Serial Changes in Blood Pressure

	Control (n = 121)	Olmesartan (n = 126)	p Value
Baseline			
Systolic BP (mm Hg)	144.4 ± 23.6*	142.4 ± 24.3	NS
Diastolic BP (mm Hg)	79.2 ± 10.8*	81.1 ± 12.9*	NS
14-month follow-up			
Systolic BP (mm Hg)	137.9 ± 25.3*	138.4 ± 21.4	NS
Diastolic BP (mm Hg)	74.7 ± 14.6*	77.4 ± 11.3*	NS

*$p < 0.05$ from baseline.
BP = blood pressure.

Table 4 Outcome for Adjudicated Major Cardiovascular Events

	Control (n = 121)	Olmesartan (n = 126)	p Value
Composite of CV death, nonfatal MI, or nonfatal stroke (%)	2.5	1.6	NS
Cardiovascular death (%)	1.7	0.0	0.31
Nonfatal MI (%)	0.0	1.6	0.17
Nonfatal stroke (%)	0.8	0.0	NS
Noncardiovascular death (%)	0.0	0.0	NS
Hospital stay for unstable angina (%)	0.8	0.0	NS
Coronary revascularization (%)	10.0	7.9	0.61
Hospital stay for CHF (%)	0.8	1.6	NS
Deterioration of CRF (%)	0.8	0.8	NS

CHF = congestive heart failure; CRF = chronic renal failure; CV = cardiovascular; MI = myocardial infarction.

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Table 5 Results of Serial Volumetric IVUS

	Control (n = 121)	Olmesartan (n = 126)	p Value
IVUS measured lengths (mm)	42.7	42.5	NS
Baseline			
Atheroma volume (mm^3)	208.8 ± 151.5*	230.2 ± 151.7	NS
Vessel volume (mm^3)	494.8 ± 301.2	512.0 ± 307.6	NS
PAV (%)	40.6 ± 10.8†	43.8 ± 10.2	0.03
14-month follow-up			
Atheroma volume (mm^3)	215.9 ± 156.8*	227.6 ± 145.8	NS
Vessel volume (mm^3)	502.5 ± 306.4	509.9 ± 302.7	NS
PAV (%)	41.7 ± 11.5†	43.7 ± 10.4	NS

*p < 0.01; †p < 0.05 between baseline to follow-up.
IVUS = intravascular ultrasound; PAV = percent atheroma volume.

Discussion

In the present study, significant effect for lower rate of coronary atheroma progression was observed in patients receiving olmesartan, an ARB, compared with the control group during the 14-month follow-up period. Currently, ARBs are widely used for the treatment of hypertension. They also have beneficial effects on hypertension-related cardiovascular end organ damage, possibly due to reduction of oxidative stress and inflammation (14,16–18,22,23). Among the several ARBs available in the clinical setting, olmesartan is thought to have a significantly stronger blood pressure-lowering effect than other ARBs with their respective starting doses (19). In addition, previous clinical studies reported the potential decrease of atheromatous plaque burden in the human artery after administration of olmesartan or ARB compared with the control group (24,25). Thus, it might be not surprising that olmesartan showed coronary plaque regression in this trial. However, the underlying mechanisms as well as the clinical impact of ARB remain a matter of ongoing debate. According to the results of a recent trial, the similarity of effects on reducing MI between ARB and ACE inhibitors should help to dispel concerns that ARB might not reduce MI (20). Our study data might show the corroborating efficacy for these medicines in terms of preventing the progression of atherosclerosis.

Table 6 Changes in IVUS Parameters From Baseline to Follow-Up

	Control (n = 121)	Olmesartan (n = 126)	p Value
Nominal change			
Atheroma volume (mm^3)	7.1 (1.8–12.4)*	−2.6 (−7.9–2.8)	0.011
Lumen volume (mm^3)	0.3 (−8.7–9.3)	0.4 (−7.6–8.3)	0.989
Vessel volume (mm^3)	7.8 (2.5–10.5)	−2.1 (−8.5–2.5)	0.178
PAV (%)	1.1 (0.1–2.1)†	−0.1 (−0.9–0.8)	0.085
Change in total atheroma volume and PAV			
Total atheroma volume (%)	5.4 (2.4–8.5)	0.6 (−1.9–3.1)	0.016
PAV (%)	3.1 (0.7–5.6)	−0.7 (−3.4–2.0)	0.038

Value within parentheses indicates 95% confidence interval. *p = 0.009; †p = 0.039 between baseline and follow-up.
Abbreviations as in Table 5.

Table 7 Results of a Multiple Linear Regression Test

Parameters	Regression Coefficient	SEM	p Value
Age	0.09	0.13	0.51
Male	0.61	2.40	0.80
Olmesartan	−4.51	2.07	0.03
Statin	−1.47	2.07	0.48
Smoking	−4.53	2.28	0.048
Baseline HbA1c	1.18	0.93	0.21

Dependent variable = atheroma volume change.
HbA1c = hemoglobin A1c.

In the present trial, there was no significant effect on the adjudicated major cardiovascular events during the 14-month follow-up period. The primary end point of this trial was change in coronary atheroma volume, assessed by serial IVUS; therefore, we enrolled only a small number of patients with stable angina. Furthermore, it has been reported that there is a delay of 6 to 12 months before the benefits of an ARB emerge and that it might take several years of treatment for the full benefits to manifest (20). Longer-term follow-up and a larger study might be required to confirm the long-term results.

There was no significant difference in terms of changes of blood pressure (26–29). In this trial, control of blood pressure was left to the physician's discretion except for administration of ARBs and ACE inhibitors; therefore, an incremental dose of other antihypertensive agents, such as beta-blockers, calcium channel blockers, and/or diuretics, might have contributed to the similarities in blood pressure control between the 2 groups.

Previous studies with arbitrary short segment analyses have described progression or regression with respect to atheroma volume changes over time in coronary arteries.

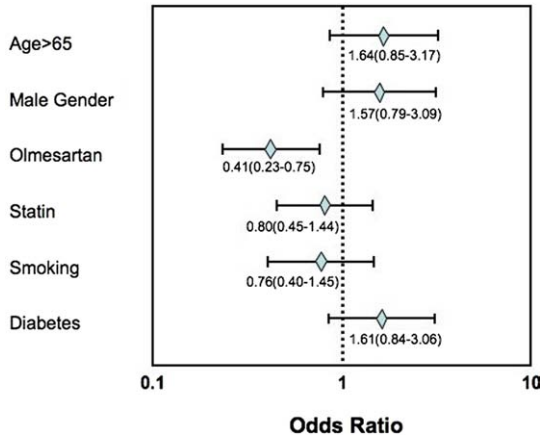

Figure 3 Odds Ratio (95% Confidence Interval) for Increased Atheroma Volume During Follow-Up Periods

However, plaque deposition is a continuous variable; thus, arbitrary short segment analyses might not necessarily indicate the degree or extent of atherosclerosis in the entire coronary tree. In the present study, volumetric IVUS analyses were completed exclusively in entire vessels; therefore, these IVUS parameters represent atheroma progression of measured coronary arteries. According to our serial IVUS observations, progression/regression atheroma burden through administration of olmesartan seems to be associated with vessel remodeling. These findings are concurrent with previous studies using statins and might suggest a possible similar atheroma reductive process for ARB (30–32). In the present study, multivariate analysis identified olmesartan administration as 1 of the factors that decreased atheroma volume. However, a high proportion of patients in our study were already being treated with lipid-lowering agents, antiplatelet agents, and/or other blood-pressure–lowering drugs, except ARBs or ACE inhibitors, which might have minimized the differences in plaque changes seen between the 2 randomized groups, compared with those seen in previous trials.

There were several studies assessing temporal changes in percent plaque volume with IVUS (1–9,33,34). Compared with previous studies, results of the present study seem to show convincing serial changes of coronary atheroma volume. In the present study, the differences in IVUS parameters were relatively small—perhaps associated with this study population having received optimized lipid-lowering therapy, beta-blockers, and antiplatelet drugs—compared with subjects in previous clinical trials. Nevertheless, the olmesartan group had a substantially lower progression rate than would have been predicted for the low-density lipoprotein cholesterol level achieved. In addition, in the present trial, there was no statistically significant correlation between blood pressure reduction and atheroma progression rate (27,28). This might suggest the potential manifold action of olmesartan, apart from the antihypertensive effect, that might be beneficial, such as activity leading to atheroma stabilization and reduction. We believe this is the first clinical trial that shows potential reduced progression of coronary atherosclerosis with an ARB. Our study data might add another striking benefit to the ever-growing list of positive outcomes associated with olmesartan administration.

Study limitations. First, a small number of patients with stable angina pectoris were enrolled; therefore, some selection bias might exist. Second, the IVUS results showed relatively larger SDs; however, these are not unusual for this kind of study. In addition, development of coronary atheroma might not be directly associated with the incidence of a cardiovascular event; therefore, qualitative plaque assessment, such as virtual histology-IVUS or optical coherence tomography, and longer-term follow-up might also be required. In addition, a high proportion of patients in our study were already being treated with optimal lipid-lowering therapy; therefore, it might be difficult to show an effect in addition to that treatment.

Conclusions

These observations suggest a positive role in a potentially lower rate of coronary atheroma progression through the administration of olmesartan, an ARB, for patients with stable angina pectoris.

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