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ORIGINAL ARTICLE
Ischemic Heart Disease

Effect of Reverse Vessel Remodeling on Regression of Coronary Atherosclerosis in Patients Treated With Aggressive Lipid- and Blood Pressure-Lowering Therapy

— Insight From MILLION Study —

Tadatsugu Gamou, MD; Kenji Sakata, MD, PhD; Hayato Tada, MD, PhD; Tetsuo Konno, MD, PhD; Kenshi Hayashi, MD, PhD; Hidekazu Ino, MD, PhD; Masakazu Yamagishi, MD, PhD; Masa-aki Kawashiri, MD, PhD on behalf of the MILLION Study Group

Background: The MILLION study, a prospective randomized multicenter study, revealed that lipid and blood pressure (BP)-lowering therapy resulted in regression of coronary plaque as determined by intravascular ultrasound (IVUS). In the present study we performed additional analysis to investigate the associated factors with regression of coronary plaque.

Methods and Results: We investigated serial 3D IVUS images from 68 patients in the MILLION study. Standard IVUS parameters were assessed at both baseline and follow-up (18–24 months). Volumetric data were standardized by length as normalized volume. In patients with plaque regression (n=52), plaque volume$_{normalized}$ significantly decreased from 64.8 to 55.8 mm^3 (P<0.0001) and vessel volume$_{normalized}$ significantly decreased from 135.0 to 127.5 mm^3 (P=0.0008). There was no difference in lumen volume$_{normalized}$ from 70.1 to 71.8 mm^3 (P=0.27). There were no correlations between % changes in vessel volume and cholesterol or BP. On the other hand, negative correlations between % change in vessel volume and vessel volume$_{normalized}$ at baseline (r=−0.352, P=0.009) or plaque volume$_{normalized}$ at baseline (r=−0.336, P=0.01) were observed.

Conclusions: The current data demonstrated that in patients with plaque regression treated by aggressive lipid and BP-lowering therapy, the plaque regression was derived from reverse vessel remodeling determined by vessel volume and plaque burden at baseline irrespective of decreases in lipids and BP.

Key Words: Amlodipine; Atorvastatin; Intravascular ultrasound; Reverse vessel remodeling

Compensatory enlargement of the human atherosclerotic coronary artery was originally observed in a necropsy study[1] and confirmed in clinical studies using intravascular ultrasound (IVUS),[2,3] which has high imaging resolution for measuring atheroma volume in the coronary artery. Such positive remodeling is associated with plaque vulnerability[4,5] and unstable clinical presentation.[6–8] Several previous studies using serial volumetric IVUS imaging have revealed that intensive lipid-lowering therapy with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins), blood pressure (BP)-lowering therapy with calcium-channel blockers, and angiotensin II receptor blockers (ARB) resulted in regression of coronary plaque volume.[9–15] Pioglitazone also resulted in regression of coronary plaque volume.[16,17] In addition, the studies showed that the plaque volume regression was associated with reverse remodeling of the arterial wall.[18,19] However, few data exist regarding the mechanism of regression of coronary plaque.

The MILLION study (Myocardial Ischemia Treated with PCI and Plaque Regression by Lipid Lowering & Blood Pressure Controlling assessed by Intravascular Ultrasonography), a prospective randomized multicenter study to evaluate the effects of aggressive treatment of low-density lipoprotein-cholesterol (LDL-C) with atorvastatin-based therapy and the control of BP by amlodipine-based therapy on the progression/regression of coronary plaque, demonstrated that both lipid- and BP-lowering therapy enhanced the reduction in coronary plaque.[20] In the present study we performed additional analysis using IVUS to investigate the associated factors with regression of coronary plaque.

Methods

Study Population

This subanalysis of the MILLION study was approved by

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Department of Cardiovascular and Internal Medicine, Kanazawa University Graduate School of Medicine, Kanazawa, Japan
Mailing address: Masa-aki Kawashiri, MD, PhD, Department of Cardiovascular and Internal Medicine, Kanazawa University Graduate School of Medicine, 13-1 Takara-machi, Kanazawa 920-8640, Japan. E-mail: mk@med.kanazawa-u.ac.jp

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Table 1. Baseline Characteristics of Patients in Subanalysis of MILLION Study	
Age (years)	62.9±11.8
Female	11 (21.2)
Body mass index (kg/m^2)	24.4±3.4
Hypertension	32 (61.5)
Diabetes	17 (32.7)
Current smoker	26 (50.0)
Acute coronary syndrome	32 (61.5)
Serum creatinine (mg/dL)	0.80±0.23
Prior lipid therapy	8 (15.4)

Data are mean±standard deviation, or number (%).

the institutional review boards at all participating institutions. Written informed consent was given by all patients enrolled at the start of the study. The study design has been previously reported.[21] In brief, 97 patients with coronary artery disease were randomized to 2 different groups after successful percutaneous coronary intervention under IVUS guidance: aggressive reduction of both LDL-C and BP, and standard reduction of both LDL-C and BP by atorvastatin- and amlodipine-based therapy. For the aggressive treatment group, the target serum level of LDL-C was 70 mg/dL and target BP was 120/70 mmHg. Target BP was determined in accordance with a previous study[22] with modification.[21] For the standard treatment group, the target serum level of LDL-C was 100 mg/dL and target BP was 140/90 mmHg. If the LDL-C or BP did not reach the target values after administration of maximal doses of atorvastatin or amlodipine, any lipid- or BP-lowering medicine could be added. Follow-up IVUS examinations were performed after 18–24 months of statin and calcium-channel-blocker therapy.

In the present study 68 patients with measurable IVUS data at both baseline and follow-up in the MILLION study were enrolled. We examined patients with plaque regression, which was defined as plaque volume at follow-up minus plaque volume at baseline <0 mm^3, and excluded patients with plaque progression, which was defined as plaque volume at follow-up minus plaque volume at baseline ≥0 mm^3, to elucidate the mechanism of regression of coronary plaque.

Serial Measurements of Lipids and BP

Serum cholesterol and triglycerides were measured every 2 months during the observation period for regulating the doses of atorvastatin or other lipid-lowering drugs. Apolipoproteins were analyzed at a central clinical laboratory (SRL, Inc., Tokyo, Japan) at baseline and follow-up. BP was measured using a manual cuff and stethoscope every month during the observation period for regulating the doses of amlodipine or other BP-lowering drugs.

IVUS Examination and Analysis

Details of the IVUS examination and analysis are documented elsewhere.[21] In brief, an Atlantis™ SR Pro 2 40-MHz imaging catheter (Boston Scientific, Natick, MA, USA) was used to analyze coronary plaque volume. IVUS data were derived >5 mm proximal or distal from the deployed stent, including a reproducible index such as side branches. Pullback of the IVUS catheter was performed automatically at 0.5 mm/s. Plaque volume was assessed by volumetric analysis with the echoPlaque2 system (Indec Systems Inc.). Standard 3D IVUS parameters such as ves-

Table 2. Lipid and BP Control Parameters in Subanalysis of MILLION Study			
	Baseline	Follow-up	P value
Total cholesterol (mg/dL)	208.9±34.1	138.6±21.1	<0.0001
% change		−31.8±13.2	
LDL-C (mg/dL)	118.3±20.0	68.0±13.6	<0.0001
% change		−40.8±17.5	
HDL-C (mg/dL)	46.3±9.4	46.7±9.2	0.77
% change		3.7±23.1	
Non-HDL-C (mg/dL)	162.6±56.5	91.9±22.3	<0.0001
% change		−41.4±13.6	
LDL-C/HDL-C ratio	2.7±0.9	1.5±0.5	<0.0001
% change		−39.9±27.0	
Triglycerides (mg/dL)	226.0±185.5	105.9±40.9	0.16
% change		−14.7±59.3	
Apolipoprotein A-I (mg/dL)	120.2±16.9	122.6±15.0	0.46
% change		5.2±22.2	
Apolipoprotein B (mg/dL)	105.6±18.5	63.9±12.6	<0.0001
% change		−38.9±12.3	
Apolipoprotein E (mg/dL)	4.5±0.9	3.2±0.8	<0.0001
% change		−25.4±25.6	
Systolic BP (mmHg)	138.6±17.4	118.5±11.2	<0.0001
% change		−12.6±16.2	
Diastolic BP (mmHg)	81.3±10.5	70.7±9.3	0.0001
% change		−10.6±21.5	

Data are mean±standard deviation. BP, blood pressure; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol.

Table 3. Intravascular Ultrasound Parameters in Subanalysis of MILLION Study

	Baseline	Follow-up	P value
Vessel volume$_{normalized}$ (mm^3)	135.0±52.9	127.5±47.4	0.0008
% change		−4.0±10.8	
Plaque volume$_{normalized}$ (mm^3)	64.8±26.9	55.8±23.7	<0.0001
% change		−13.4±9.9	
Lumen volume$_{normalized}$ (mm^3)	70.1±32.9	71.8±31.1	0.27
% change		6.1±22.2	
Average length (mm)	8.7±3.0		–

Data are mean±standard deviation.

Table 4. Correlations Between Vessel or Plaque Volume and Lipids or BP in Subanalysis of MILLION Study

	Correlation coefficient	P value
Vessel volume		
LDL-C	−0.100	0.47
HDL-C	−0.074	0.46
Non-HDL-C	0.049	0.73
LDL-C/HDL-C ratio	−0.084	0.55
Systolic BP	0.123	0.39
Diastolic BP	0.024	0.86
Plaque volume		
LDL-C	−0.129	0.36
HDL-C	0.193	0.09
Non-HDL-C	0.143	0.31
LDL-C/HDL-C ratio	−0.068	0.63
Systolic BP	0.062	0.66
Diastolic BP	−0.073	0.60

Each parameter uses % change. Abbreviations as in Table 2.

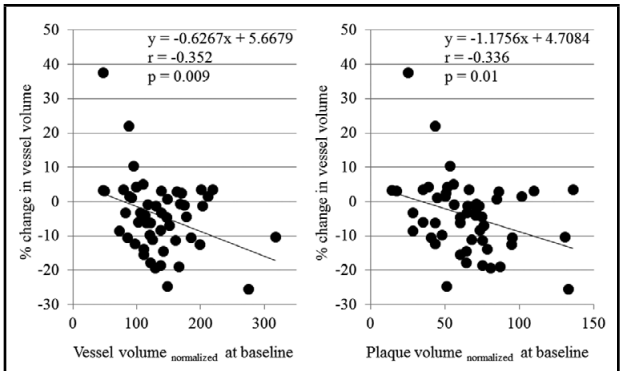

Figure 1. Correlation between % change in vessel volume and vessel or plaque volume at baseline. (**Left**) Negative correlation between % change in vessel volume and vessel volume$_{normalized}$ at baseline. (**Right**) Negative correlation between % change in vessel volume and plaque volume$_{normalized}$ at baseline.

sel, lumen and plaque volumes were assessed at both baseline and follow-up. Volumetric data were standardized by length as normalized volume, where the volume was multiplied by the median length analyzed in the entire cohort and divided by each observed length to compensate for differences in segment length between patients. The % change in plaque volume was defined as a change in plaque volume (follow-up minus baseline plaque volume) divided by baseline plaque volume.

The IVUS findings in this study were assessed by 2 investigators blinded to the clinical and angiographic data. To assess the reproducibility of IVUS measurements, images of 10 cases were randomly selected and reanalyzed at least 4 weeks after the initial reading. The intraobserver correlation coefficients for vessel volume and plaque volume were 0.999 and 0.999, and the percent error was 0.69±0.35% and 4.47±3.48%, respectively. The interobserver correlation coefficients for vessel volume and plaque volume were 0.999 and 0.993, and the percent error was 1.20±0.68% and 5.58±3.67%, respectively.

Statistical Analysis

Statistical analyses were performed with Stat View software version 5.0 (SAS Institute, Cary, NC, USA). Continuous variables are expressed as the mean±standard deviation. Qualitative variables are presented as numbers and percentages. Continuous variables were compared using Student's t-test or the Mann-Whitney U-test, and categorical data using the chi-square test or Fisher's exact test, as appropriate. Univariate linear regression analyses were performed to assess the relations between IVUS parameters and lipids or BP. A value of $P<0.05$ was considered statistically significant.

Results

Baseline Characteristics

Among the 68 patients, plaque regression was observed in 52 (76%). Mean age was 62.9 years, 21.2% of the patients were female, 61.5% of patients had hypertension, 32.7% of patients had diabetes, and 61.5% of patients had acute coronary syndrome (ACS). Prior lipid therapy was conducted in 15.4% (**Table 1**).

Lipid and BP Control

Total cholesterol significantly decreased from 208.9 to 138.6 mg/dL ($P<0.0001$) and LDL-C significantly decreased from 118.3 to 68.0 mg/dL ($P<0.0001$). Non-high-density lipoprotein-cholesterol (HDL-C) significantly decreased from 162.6 to 91.9 mg/dL ($P<0.0001$), and the LDL-C/HDL-C ratio significantly decreased from 2.7 to 1.5 ($P<0.0001$). Systolic BP significantly decreased from 138.6 to 118.5 mmHg ($P<0.0001$) and diastolic BP significantly decreased from 81.3 to 70.7 mmHg ($P=0.0001$) (**Table 2**).

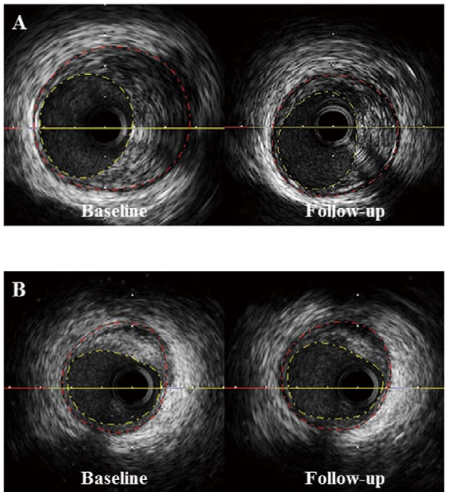

Figure 2. Representative of patients with plaque regression treated by aggressive lipid- and blood pressure-lowering therapy. (**A**) Larger vessel with large amount of plaque has the potential to show regression, whereas (**B**) a moderate-sized vessel with a small amount of plaque does not show regression as easily.

IVUS Parameters

In the patients with plaque regression, vessel volume$_{normalized}$ significantly decreased from 135.0 to 127.5 mm^3 (P=0.0008) and plaque volume$_{normalized}$ significantly decreased from 64.8 to 55.8 mm^3 (P<0.0001). There was no difference in lumen volume$_{normalized}$ from 70.1 to 71.8 mm^3 (P=0.27) (**Table 3**).

Correlations Between IVUS Parameters and Each Factor

There were no correlations between % change in vessel volume or plaque volume and lipids or BP (**Table 4**). On the other hand, negative correlations between % change in vessel volume and vessel volume$_{normalized}$ at baseline (r=−0.352, P=0.009) or plaque volume$_{normalized}$ at baseline (r=−0.336, P=0.01) were observed (**Figure 1**). This suggested that regression of plaque volume was dependent on the original plaque volume (**Figure 2**).

Influence of Other Factors on Plaque Regression

The potential influence of other factors, such as clinical presentation or therapy that included ARB and pioglitazone, on plaque regression was also evaluated. As for clinical presentation, % change in plaque volume was not significantly different between patients with ACS and patients with stable angina pectoris (−13.9±9.3% vs. −12.6±11.0%, P=0.64). As for medication, pioglitazone was not prescribed in the present cohort, although ARBs were prescribed to 22 of the 52 patients at follow-up. Under these conditions, % change in plaque volume was not significantly different between patients with and without ARBs (−13.5±11.6% vs. −13.3±8.6%, P=0.94).

Discussion

The main finding of this subanalysis of the MILLION study was that, in patients with plaque regression treated by aggressive lipid- and BP-lowering therapy, plaque regression derived from reverse vessel remodeling determined by the vessel volume and plaque burden at baseline irrespective of the decreases in lipids and BP.

Positive remodeling lesions have been found to contain more lipid-rich and less hard plaque components compared with negative remodeling lesions.[5] Such positive remodeling and large plaque areas are associated with unstable clinical presentation, whereas negative remodeling is more common in patients with stable clinical presentation.[6] Generally, the plaque regression rate may be high in ACS patients with positive remodeling receiving intensive lipid- and BP-lowering therapy. In practice, the COSMOS study for stable angina pectoris demonstrated 5.1% regression of plaque volume by rosuvastatin,[23] while the Japan-ACS study of ACS demonstrated 16.9% regression by pitavastatin and 18.1% regression by atorvastatin.[19] In the present study, regression of plaque volume was not significantly different between ACS and stable angina pectoris, which may be explained by the fact that the present analysis was performed in patients with plaque regression. Under those conditions plaque regression was associated with reverse vessel remodeling irrespective of clinical presentation. In addition, chronic statin treatment has been demonstrated to reduce positive remodeling in the culprit lesions of patients with acute myocardial infarction.[24] In the present study approximately 15% patients were already on lipid-lowering therapy before randomization, which might have influenced plaque characteristics and plaque progression/regression.

In the present study the % change in plaque volume was unrelated to the degree of decrease in lipids, including non-HDL-C and the LDL-C/HDL-C ratio, increase in HDL-C,[25] and decrease in BP. Also it should be true that lipid- and BP-lowering therapy separately reduce coronary plaque. Because all enrolled patients received both lipid- and BP-lowering therapy, it might be difficult to find differences in the ratio of plaque regression as compared with previous placebo-controlled studies.[9,26,27] In the present study it was difficult for ethical reasons to include a placebo arm of patients not receiving lipid-lowering therapy. Also, a recent report on a CETP inhibitor did not demonstrate an effect of elevated HDL-C on plaque regression.[28]

Some previous studies have shown that treatment with pioglitazone[16,17] and some ARBs[13–15] can reduce coronary plaque. None of the present patients were administered pioglitazone. ARBs were prescribed to approximately half of the patients at follow-up. Regression of plaque volume was not significantly different between patients with and without ARBs, which suggests that the % change in plaque volume was unrelated to changes in BP by ARB therapy,

although in the present study drugs had no limits of use except for statins and calcium-channel blockers.

Intensive statin treatment has been shown to reduce atheroma volume leading to a reduction in future cardiovascular events.[29] Moreover, in a previous study with all enrolled patients receiving lipid-lowering therapy, reverse vessel remodeling rather than coronary plaque regression could predict future cardiovascular events.[30] Therefore, when positive remodeling is observed by IVUS, more intensive lipid- and BP-lowering therapy should be administered to achieve reverse vessel remodeling.

Study Limitations

There remain several limitations to the present study. First, only 52 patients with coronary artery disease participated. However, even under these conditions we found that plaque regression by intensive therapy was dependent on original volume, although further studies with a larger number of patients are necessary to examine the mechanism of regression of coronary plaque in detail. Second, LDL-C at baseline was relative low. Approximately 15% patients were already on lipid-lowering therapy, which may have influenced plaque characteristics. However, under these conditions plaque regression was observed withy intensive treatment of LDL-C and BP. Recent data show that further plaque regression could be derived from extremely aggressive lipid lowering by PCSK9 inhibitor in addition to statins.[31] Finally, the definition of aggressive lipid- and BP-lowering therapy was the original object of the MILLION study. However, the achieved LDL-C levels were low even in the standard treatment group as well as in the aggressive treatment group, although the aggressive treatment group received significantly higher doses of atorvastatin than the standard treatment group. In this additional analysis, we examined patients with plaque regression among all participants regardless of the group. Therefore, no differences in the LDL-C level and BP in these groups might have had little influence on the present results.

Conclusions

The present data demonstrated that, in patients with plaque regression treated by aggressive lipid- and BP-lowering therapy, the plaque regression was derived from reverse vessel remodeling as determined by the vessel volume and plaque burden at baseline irrespective of the decrease in lipids and BP.

Conflict of Interest

Dr. Yamagishi received a research grant from Pfizer Ltd.

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