Atherosclerotic plaque stabilization is a promising clinical strategy to prevent cardiovascular events in patients with coronary artery disease (CAD). There is a correlation between coronary and carotid plaque instability, and echolucent plaques are recognized as vulnerable plaques.

**OBJECTIVES**

This study examined whether intensive cholesterol-lowering therapy with statins in nonhypercholesterolemic patients is effective in improving echolucency of vulnerable plaques assessed by ultrasound with integrated backscatter (IBS) analysis.

**BACKGROUND**

Atherosclerotic plaque stabilization is a promising clinical strategy to prevent cardiovascular events in patients with coronary artery disease (CAD). There is a correlation between coronary and carotid plaque instability, and echolucent plaques are recognized as vulnerable plaques.

**METHODS**

Consecutive nonhypercholesterolemic patients with CAD were randomly assigned Adult Treatment Panel-III diet therapy (diet group; n = 30) or pravastatin (statin group; n = 30). Echolucent carotid plaques were monitored by measuring intima-media thickness (IMT) and echogenicity by IBS for six months.

**RESULTS**

Total cholesterol, low-density lipoprotein cholesterol (LDL-C), and high-sensitivity C-reactive protein were significantly decreased in the statin group (from 197 ± 15 mg/dl to 170 ± 18 mg/dl [p < 0.001]; from 131 ± 14 mg/dl to 99 ± 14 mg/dl [p < 0.001]; and from 0.11 [0.04 to 0.22] mg/dl to 0.06 [0.04 to 0.11] mg/dl [p < 0.05], respectively), whereas only total cholesterol was moderately reduced (from 193 ± 24 mg/dl to 185 ± 22 mg/dl [p < 0.05]) and LDL-C and triglycerides insignificantly reduced in the diet group. Significant increases of echogenicity of carotid plaques were noted in the statin group but not in the diet group (from −18.5 ± 4.1 dB to −15.9 ± 3.7 dB [p < 0.001] and from −18.2 ± 4.0 dB to −18.9 ± 3.5 dB [p = 0.13], respectively) without significant regression of plaque-IMT values in both groups.

**CONCLUSIONS**

Statin therapy is rapidly effective in increasing echogenicity of vulnerable plaques without regression of plaque size in nonhypercholesterolemic patients with CAD. Quantitative assessment of carotid plaque quality by ultrasound with IBS is clinically useful for monitoring atherosclerotic lesions by evaluating vulnerability of atheroma. (J Am Coll Cardiol 2005;46: 22–30) © 2005 by the American College of Cardiology Foundation
Patients. This research was designed as an open-label prospective randomized study. Eligible for entry into this study were nonhypercholesterolemic patients (total cholesterol <220 mg/dl) who underwent elective and diagnostic coronary angiography at Kumamoto University Hospital between 2001 and 2003 because of an abnormality in the electrocardiogram or angina-like chest symptoms on effort. All patients underwent carotid ultrasound examination to determine the presence of echolucent carotid plaques. Sixty nonhypercholesterolemic patients with CAD who had echolucent carotid plaques were enrolled. All patients had angiographic documentation of organic stenosis (>50%) in ≥1 major coronary artery (single-vessel disease, n = 24; two-vessel disease, n = 21; three-vessel disease, n = 15). Patients were randomly divided into two treatment groups: diet group (n = 30) and statin group (n = 30). Diet group patients received dietary counseling and adopted the Adult Treatment Panel-III lipid-lowering diet. Statin group patients initially received pravastatin 10 mg/day, which was increased to a final dose of 20 mg/day as required to achieve target low-density lipoprotein cholesterol (LDL-C) levels of <100 mg/dl. Excluded were patients with severe valvular disease, trauma within the prior month, severe cardiomyopathy, malignant tumor, infectious disease, chronic inflammatory disease, end-stage renal failure, autoimmune disease, or acute coronary syndrome. Informed consent was obtained from all patients. The study protocol was constructed in 2000 and approved by the ethics committee at Kumamoto University Hospital.

Ultrasound evaluation. Using an 11.0-MHz linear array transducer (SONOS-5500, Philips, Andover, Massachusetts), carotid ultrasound examination was performed at baseline and follow-up. A single well-trained operator performed all carotid scans without having any information on the clinical characteristics of the patients. Each common, internal, and external carotid artery was carefully imaged in the anterior oblique, lateral, and posterior oblique planes to identify atherosclerotic lesions. On a longitudinal image of each carotid artery, intima-media thickness (IMT) was defined as the distance from the leading edge of the lumen-intima interface to that of the media-adventitia interface. Atherosclerotic plaques were defined as lesions with focal IMT ≥1.1 mm with localized protrusion of vessel wall into the lumen (14,20). Maximum IMT of plaques (plaque-IMT$_{max}$) was defined as the greatest axial thickness in the carotid arteries (Fig. 1).

Measurement of IBS. Integrated backscatter values of all carotid atherosclerotic plaques were measured as described previously (14,16,18). For each plaque, conventional high-resolution B-mode images were obtained. Atherosclerotic plaques on the acoustic density mode were analyzed using the manual outlined definition of region of interest (ROI), as shown in Figure 1. Instrument imaging adjustments such as transmit power, focus, time-gain compensation, and gain setting including the depth gain compensation curve were all set at fixed values, with the system control remaining unchanged for the measurement of all plaques during follow-up. The averaged power of the IBS signal within the ROI was measured and displayed in decibels (dB). The adventitia was adopted as the reference object in line with previous studies (16–18,21,22). Relative IBS value of the atherosclerotic plaque was expressed as the difference between the IBS value of the plaque and that of the adventitia (i.e., calibrated IBS value [cIBS] = [intima-media IBS value] − [adventitia IBS value]). Based on several previous reports of carotid echogenicity assessment with cIBS, we arbitrarily defined carotid plaques with cIBS values <−14.5 dB as “echolucent plaques” (14,16,18). In this study, intraobserver variability for repeated measurements was 0.5 ± 0.4 dB. No patient was found to have calcification severe enough to prevent measurement of IBS.

Magnetic resonance imaging evaluation of echolucent carotid plaques. Recently, it was proposed that magnetic resonance imaging (MRI) could evaluate carotid plaque component noninvasively (23). Echolucent carotid plaques (plaque-IMT$_{max}$ ≥4.0 mm) were imaged with a 1.5-T MR...
scanner (Magnetom Vision; Siemens, Erlangen, Germany) and phase-array surface coils. Fast spin-echo–based T1-weighted (T1W), proton density-weighted (PDW), and T2-weighted (T2W) images as well as time-of-flight (TOF) images of the echolucent plaques were obtained by standardized protocol. The scan was centered on the targeted carotid plaques with echolucent appearance, and the average scan time was 40 min. Carotid plaque component was assessed using previously established criteria (23).

Follow-up. Before and after treatment, the same operator, who was blinded to patient treatment and assignment, performed all carotid ultrasound examinations (measurement of plaque-IMTmax and cIBS). All ultrasound data at baseline and follow-up were recorded on S-VHS videotapes and digital magneto-optical drives. The best projection of the ultrasound probe was noted, and the distance from the bifurcation of the common carotid artery to the target plaques was measured so as to record plaque loci. Furthermore, where arterial calcification was evident this also was used as a landmark to identify the target plaque at follow-up. Peripheral blood samples were collected in the early morning before breakfast at the beginning of the study and follow-up period. Serum lipid parameters and high-sensitivity C-reactive protein (hsCRP) were measured in the hospital laboratory. During the follow-up period, all patients received the standardized medical therapy outlined in Table 1.

Statistical analysis. Results are expressed as mean ± SD. Triglycerides, hsCRP, body mass index (BMI), and plaque-IMTmax are expressed as median and interquartile range. Frequencies of gender, smoking, hypertension, and diabetes

Table 1. Baseline Clinical Characteristics of Patients

<table>
<thead>
<tr>
<th></th>
<th>Pravastatin (n = 30)</th>
<th>Diet (n = 30)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>69.9 ± 8.8</td>
<td>69.1 ± 9.6</td>
<td>0.74</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>21/9</td>
<td>21/9</td>
<td>—</td>
</tr>
<tr>
<td>Smoking</td>
<td>11 (37%)</td>
<td>12 (40%)</td>
<td>0.79</td>
</tr>
<tr>
<td>Hypertension</td>
<td>18 (60%)</td>
<td>21 (70%)</td>
<td>0.42</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>8 (27%)</td>
<td>6 (20%)</td>
<td>0.54</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.6 (21.8–25.0)</td>
<td>23.2 (22.0–24.8)</td>
<td>0.80</td>
</tr>
<tr>
<td>TC (mg/dl)</td>
<td>197 ± 15</td>
<td>193 ± 24</td>
<td>0.37</td>
</tr>
<tr>
<td>HDL-C (mg/dl)</td>
<td>49 ± 13</td>
<td>50 ± 12</td>
<td>0.81</td>
</tr>
<tr>
<td>LDL-C (mg/dl)</td>
<td>131 ± 14</td>
<td>126 ± 22</td>
<td>0.26</td>
</tr>
<tr>
<td>TG (mg/dl)</td>
<td>127 (96–150)</td>
<td>118 (92–144)</td>
<td>0.61</td>
</tr>
<tr>
<td>hsCRP (mg/dl)</td>
<td>0.11 (0.04–0.22)</td>
<td>0.14 (0.05–0.28)</td>
<td>0.41</td>
</tr>
<tr>
<td>IMTmax (mm)</td>
<td>2.19 (1.86–2.57)</td>
<td>2.07 (1.68–2.42)</td>
<td>0.18</td>
</tr>
<tr>
<td>cIBS (dB)</td>
<td>−18.5 ± 4.1</td>
<td>−18.2 ± 4.0</td>
<td>0.78</td>
</tr>
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</table>

Medication

<p>| | |</p>
<table>
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<tr>
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<tbody>
<tr>
<td>Beta-blocker</td>
<td>8 (27%)</td>
</tr>
<tr>
<td>Calcium antagonist</td>
<td>26 (87%)</td>
</tr>
<tr>
<td>ACE inhibitor or ARB</td>
<td>16 (53%)</td>
</tr>
<tr>
<td>Nitrate</td>
<td>9 (30%)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>29 (97%)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>2 (7%)</td>
</tr>
</tbody>
</table>

ACE = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; BMI = body mass index; cIBS = calibrated integrated backscatter; HDL-C = high-density lipoprotein cholesterol; hsCRP = high-sensitivity C-reactive protein; IMT = intima-media thickness; LDL-C = low-density lipoprotein cholesterol; TC = total cholesterol; TG = triglycerides.
mellitus were compared between the two groups using chi-square analysis. Comparisons between the two treatment groups were performed by unpaired t test (normally distributed variables: age, total cholesterol [TC], LDL-C, high-density lipoprotein cholesterol [HDL-C], and cIBS) and nonparametric Mann-Whitney U test (triglycerides [TG], hsCRP, BMI, and plaque-IMT max). Comparisons in each group from baseline to follow-up were assessed by paired Student t test (changes in TC, LDL-C, HDL-C, and cIBS) and Wilcoxon signed rank test (changes in TG, hsCRP, and plaque-IMT max). Associations between changes of continuous serum parameters (TC, LDL-C, HDL-C, TG, and hsCRP) and cIBS values were examined by calculating Pearson correlation coefficients and linear regression analysis. Multiple regression analysis was then performed with change of cIBS as the dependent variable and significant serum parameters as independent variables. Univariate logistic regression analysis with covariates listed in Table 1 was performed to determine effective factors for improving carotid echolucency. Statistical significance was defined as p < 0.05. All analyses were carried out by StatView-5.0 software (Tokyo, Japan).

**RESULTS**

**Baseline clinical characteristics.** Baseline clinical characteristics of the patients are shown in Table 1. All 60 patients completed the protocol. Medications were well tolerated during the follow-up period. Patients were followed for a period of 6.2 ± 0.8 months (statin group, 6.2 ± 1.0 months; diet group, 6.1 ± 0.6 months; p = 0.63) after starting treatment. The final dose of pravastatin was 10 mg/day in 26 patients and 20 mg/day in 4 patients. There was no significant difference in all baseline demographic parameters between the two groups (Table 1).

**Change in lipoprotein and hsCRP levels.** Table 2 shows changes of lipoprotein and hsCRP levels in the two study groups. In the statin group, TC, LDL-C, and hsCRP levels significantly decreased and HDL-C significantly increased from baseline to end of follow-up. In the diet group, only TC levels were moderately reduced (p < 0.05). At the end of follow-up, TC, LDL-C, and hsCRP levels were significantly lower in the statin group than in the diet group.

Dietary lipid-lowering therapy was significantly effective in reducing TC (from 193 ± 24 mg/dl to 185 ± 22 mg/dl; p < 0.05); however, statin therapy produced more intensive lipid-lowering effects than diet therapy (TC reduction: −28 ± 16 mg/dl and −8 ± 16 mg/dl, respectively; p < 0.001; LDL reduction: −33 ± 13 mg/dl and −5 ± 17 mg/dl, respectively; p < 0.001) (Fig. 2).

**Carotid plaque evaluation.** Figure 3 shows representative images of the echoluent carotid plaque examined by both high-resolution ultrasound (Figs. 3A to 3C) and multispectral MRI (Figs. 3D to 3G). The echoluent carotid plaques appeared hyperintense to isointense on T1W images, hypointense on T2W images, isointense to hypointense on PDW images, and isointense on TOF images, indicating that echoluent plaque exhibits a lipid-rich vulnerable condition by MRI criteria (23).

At baseline and follow-up, cIBS and plaque-IMT max values were obtained in all patients (Tables 1 and 2). Representative IBS images of targeted carotid plaque at baseline and follow-up are shown in Figure 4. At baseline, cIBS and plaque-IMT max values were not significantly different between the two groups. At follow-up, echogenicity assessed by cIBS values was significantly higher in the statin group than in the diet group (p < 0.01). Significant increases of echogenicity of the carotid plaques were observed in the statin group but not in the diet group (from −18.5 ± 4.1 dB to −15.9 ± 3.7 dB [p < 0.001] and from −18.2 ± 4.0 dB to −18.9 ± 3.5 dB [p = 0.13]; respectively) (Fig. 5A). The increase of cIBS values was significantly greater in the statin group than in the diet group (2.7 ± 2.3 dB vs. −0.7 ± 2.3 dB; p < 0.001) (Fig. 5B). A significant increase of cIBS values by pravastatin was also observed in CAD patients with “normal” cholesterol levels (TC < 200 mg/dl; n = 42) [cIBS change: statin group (n = 21), 2.4 ± 2.0; diet group (n = 21), −1.3 ± 2.1; p < 0.001]. Changes of cIBS values were significantly correlated with changes of TC (r = −0.50; p < 0.001; Fig. 6A) and LDL-C (r = −0.62; p < 0.001; Fig. 6B) levels but not with those of HDL (r = 0.23; p = 0.080), TG (r = −0.06; p = 0.65), and hsCRP (r = −0.24; p = 0.06) from baseline to follow-up. Multiple regression analysis revealed that only change of LDL-C levels was significantly and independently associated with increased cIBS (r = −0.59; p =

**Table 2. Follow-Up Data of Patients on Pravastatin Therapy and Diet Therapy**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>Follow-Up</th>
<th>Baseline</th>
<th>Follow-Up</th>
</tr>
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<tbody>
<tr>
<td>TC (mg/dl)</td>
<td>197 ± 15</td>
<td>170 ± 18‡</td>
<td>193 ± 24</td>
<td>185 ± 22‡</td>
</tr>
<tr>
<td>LDL-C (mg/dl)</td>
<td>131 ± 14</td>
<td>99 ± 14‡</td>
<td>126 ± 22</td>
<td>122 ± 16‡</td>
</tr>
<tr>
<td>HDL-C (mg/dl)</td>
<td>49 ± 13</td>
<td>54 ± 16†</td>
<td>50 ± 12</td>
<td>48 ± 10</td>
</tr>
<tr>
<td>TG (mg/dl)</td>
<td>127 (96–150)</td>
<td>120 (69–160)</td>
<td>118 (92–144)</td>
<td>114 (84–129)</td>
</tr>
<tr>
<td>hsCRP (mg/dl)</td>
<td>0.11 (0.04–0.22)</td>
<td>0.06 (0.04–0.11)‡</td>
<td>0.14 (0.05–0.28)</td>
<td>0.13 (0.05–0.34)‡</td>
</tr>
<tr>
<td>Plaque-IMT max (mm)</td>
<td>2.19 (1.86–2.57)</td>
<td>2.27 (2.00–2.69)</td>
<td>2.07 (1.69–2.42)</td>
<td>1.91 (1.64–2.31)</td>
</tr>
<tr>
<td>cIBS (dB)</td>
<td>−18.5 ± 4.1</td>
<td>−15.9 ± 3.7‡</td>
<td>−18.2 ± 4.0</td>
<td>−18.9 ± 3.5‡</td>
</tr>
</tbody>
</table>

* p < 0.01 vs. baseline; †p < 0.05 vs. baseline; ‡p < 0.01 at follow-up; §p < 0.05 at follow-up.

Abbreviations as in Table 1.
Logistic regression analysis with variables listed in Table 1 identified only statin therapy as an independent and significant predictive factor for improvement of cIBS values (p < 0.001; odds ratio 14.7; 95% CI 3.5 to 61.4). Plaque-IMT max was not significantly changed in both groups from baseline to follow-up (Fig. 5). Integrated backscatter values of the adventitia were not significantly different at baseline and follow-up in the two treatment groups and not significantly different from baseline to follow-up within each group (statin group: from 54.7 ± 3.7 dB to 54.6 ± 4.0 dB; p = NS; diet group: from 54.2 ± 4.3 dB to 54.0 ± 4.8 dB; p = NS). Eleven patients in the statin group (37%) and 10 patients in the diet group (33%) had calcification in carotid plaques at baseline (p = 0.79). We found no change of these calcified lesions between baseline and follow-up.

Clinical outcome during follow-up. No patient withdrew because of drug-related side effects, and no major adverse cardiovascular events (sudden cardiac death and acute coronary syndrome) were observed in either group during the follow-up period.

DISCUSSION

The present study demonstrates that intensive lipid-lowering therapy by pravastatin significantly improves echo-genicity of carotid plaques without significant regression of plaque size during short-term follow-up in nonhypercholesterolemic patients with CAD. This result suggests that intensive lipid-lowering therapy by pravastatin may contribute to plaque stabilization from an early stage of treatment even in nonhypercholesterolemic patients. This study also revealed that quantitative evaluation of vulnerability of atheroma by carotid ultrasound with IBS is possible. Furthermore, it suggests that this clinical strategy may be useful.
for evaluating the effects of treatment against atherosclerosis aimed at achieving plaque stabilization. This novel concept of quantitative evaluation and monitoring of atheroma quality by ultrasound follow-up can be introduced into current clinical management of patients with CAD.

Monitoring echolucent plaques and plaque stabilization. Previous studies have shown that statin therapy decreases the frequency of cardiovascular events without causing significant changes of vessel lumen diameter (24), raising the concept of plaque stabilization rather than regression. Recently, Takano et al. (7) demonstrated that one-year statin therapy improves coronary angioscopic findings in patients with CAD. However, it is difficult for physicians to verify plaque stabilization in patients in the clinical setting. Various promising new methods to assess plaque vulnerability have been reported (6–9), although practical examinations to determine whether current treatments are effective in plaque stabilization have not been established. Echolucent plaques have been characterized as lipid-rich (25) and macrophage-rich lesions (19), and increases of plaque echogenicity indicate improvement of plaque vulnerability (16). In the present study, we noninvasively measured plaque echogenicity by high-resolution carotid ultrasound with IBS and investigated the effects of plaque stabilization

**Figure 4.** Representative IBS images of carotid atheroma from baseline to follow-up. (A) Carotid atheroma at pretreatment. Values of cIBS and plaque-IMT<sub>max</sub> of this plaque are −17.8 dB and 2.05 mm, respectively. (B) The same carotid atheroma post-pravastatin therapy (6 months). Values of cIBS and plaque-IMT<sub>max</sub> of this plaque are −14.2 dB and 2.10 mm, respectively. Abbreviations as in Figure 1.

**Figure 5.** Changes of cIBS and plaque-IMT<sub>max</sub> values from baseline to follow-up in the two treatment groups. (A) Statin therapy significantly (p < 0.001) increased echogenicity from baseline to follow-up, whereas diet therapy did not. (B) The increase in cIBS values was significantly greater in the statin group than in the diet group (p < 0.001). (C) Plaque-IMT<sub>max</sub> values were not significantly changed from baseline to follow-up in either treatment group. (D) Regression values of plaque-IMT<sub>max</sub> were not significantly different between the statin group and diet group. Abbreviations as in Figure 1.
therapy by comparing and evaluating time-dependent changes of echogenicity in the target plaques. Monitoring echolucent plaques may provide meaningful information on changes of plaque vulnerability. Recently, we demonstrated that the presence of echolucent carotid plaques as assessed by carotid ultrasound with IBS is a useful predictor of cardiovascular events in patients with CAD (14), and there are reports that carotid plaques are significantly correlated with CAD (12,13). Because atherosclerosis is a systemic disease (26,27), it is thought that stabilization of carotid plaques may reflect stabilization of plaques elsewhere in the vasculature, including coronary atheroma.

**Effects of statins on plaque vulnerability assessed by echogenicity.** In this study, significant decreases of TC and LDL-C levels were observed by statin therapy in nonhypercholesterolemic patients. Furthermore, significant increases of carotid echogenicity assessed by cIBS values were noted in the statin group but not in the diet group, indicating successful improvement of plaque vulnerability by statins even in nonhypercholesterolemic patients. Previous clinical trials have demonstrated beneficial effects of statins within six-month treatment periods (1,28), suggesting early effects of this therapy on atherosclerotic plaques. The present study provides further evidence that intensive lipid-lowering therapy by statins may stabilize vulnerable human atheroma from an early stage of treatment.

“Pleiotropic effects” of statins against vascular diseases have been postulated (29). We found significant decrease of hsCRP by pravastatin therapy independent of LDL-C reduction (r = 0.19; p = 0.14), suggesting existence of pleiotropic effects of pravastatin on hsCRP levels. Meanwhile, there was significant correlation between changes of cIBS values (carotid echogenicity) and reduction of lipoprotein levels during the follow-up period. The interception value of change of cIBS at the point of no change of LDL-cholesterol level is below zero (−0.598 dB) in this study (Fig. 6B), suggesting that there were only slight pleiotropic effects of pravastatin on improvement of plaque echogenicity. The present results also indicate that intensive lipid-lowering therapy itself, but not cholesterol-independent effects, gives rise to plaque stabilization even in nonhypercholesterolemic patients with CAD.

**Plaque stabilization in nonhypercholesterolemic patients by statin.** Historic landmark clinical trials have clearly demonstrated beneficial effects of statin therapy in reducing cardiovascular events in hypercholesterolemic patients (1), but whether similar effects could be achieved in nonhypercholesterolemic patients was uncertain (30). The Heart Protection Study sensationally demonstrated that statins are effective in preventing cardiac complications even in nonhypercholesterolemic patients (31). Very recently, Cannon et al. (32) have shown that aggressive lipid lowering by statins provides good clinical prognosis in CAD patients after acute coronary syndrome. However, many physicians may still tend to hesitate giving statins to nonhypercholesterolemic patients with CAD even after large clinical trials have shown benefits of this drug class in similar populations (2,31). The present study monitored the direct effects of statins on plaque echogenicity, reflecting plaque vulnerability, and clearly showed improvement of atheromatous plaques in nonhypercholesterolemic patients with CAD. These results confirm statins’ effectiveness in achieving plaque stabilization. Surprisingly on the other hand, lipid-lowering effects by diet therapy alone were not very good in the present study even though diet therapy and lifestyle modification are known to prevent atherosclerosis and are a well-established strategy in the management of some CAD patients who may respond to the nonpharmacologic approach. We never deny beneficial effects and clinical significance of the diet therapy for prevention of cardiovascular complications.

**Study limitations.** The first limitation of this study was the small size of the patient groups. The second is that suppression of cardiovascular events could not be verified.
because of the short follow-up duration. A longitudinal prospective study of carotid ultrasound evaluation with IBS in a large number of patients is required. Recently Schmidt et al. (33) reported that beneficial effects of multiple risk intervention during six-year follow up were confined to those patients with echolucent plaques in the carotid artery. Our study strongly supports those results and demonstrated that the effects appear early during six months of treatment. The third limitation is that spreading inflammation and acoustic attenuation by plaque itself may have influenced adventitial echogenicity. On the other hand, we did not observe any change of IBS values in adventitia between baseline and follow-up; therefore we assume that the adventitia is a sufficiently reliable reference object when calculating IBS values, there is some possibility that adventitial inflammation and acoustic attenuation by plaque itself may have influenced adventitial echogenicity. The fourth caveat is that not only lipid-rich core but also mural thrombus on carotid plaques and intraplaque hemorrhage might be recognized as echolucent plaques. We are unable to confirm whether mural thrombus and intraplaque hemorrhage were mistaken as echolucent plaques in the present study. However, mural thrombus on carotid plaques and intraplaque hemorrhage are usually observed in symptomatic patients, e.g., with acute phase of stroke. It is less likely that the echolucent plaques targeted in the present study were such entities, because our cohort of patients all had stable CAD without acute symptom of brain ischemia. In future studies, MRI examination of carotid plaques may be helpful in clinical identification of lesions at baseline (23). Finally, although short-term statin therapy did not reduce carotid plaque-IMTmax in the present study, Okazaki et al. (36) recently demonstrated that statins reduce coronary plaque volume as examined by intravascular ultrasound at 6 months’ treatment in patients with acute coronary syndrome. Better technical development of carotid plaque volume measurement by ultrasound may provide more detailed information about regression of plaque volume by pharmacologic interventions, including statins.

CONCLUSIONS

Quantitative noninvasive short-term follow-up of echolucent plaques by carotid ultrasound with IBS to investigate quality changes of atheroma may be clinically useful for evaluating effects of lipid-lowering treatments aimed at plaque stabilization, even in nonhypercholesterolemic patients with CAD. Clinical strategies whereby quantitative analysis of plaque vulnerability by carotid ultrasound with IBS is employed may be valuable and important for the treatment of patients with established atherosclerosis.

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