Use of Intravascular Ultrasound to Compare Effects of Different Strategies of Lipid-Lowering Therapy on Plaque Volume and Composition in Patients With Coronary Artery Disease

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Background—We studied whether lipid-lowering therapy with atorvastatin (target LDL cholesterol [LDL-C] <100 mg/dL) compared with a moderate treatment regimen that used other lipid-lowering drugs led to a lesser progression of atherosclerosis and to different changes in plaque echogenicity in patients with coronary artery disease.

Methods and Results—This study was a 12-month, open-label, randomized, multicenter trial, which used serial 3D intracoronary ultrasound to calculate plaque volume and plaque echogenicity. After transcatheter therapy, 131 patients were randomized (atorvastatin n = 65, usual care n = 66). The target plaque had to be a minor lesion (ie, a diameter stenosis of <50% on angiography). After 12 months, mean LDL-C was reduced from 155 to 86 mg/dL in the atorvastatin group and from 166 to 140 mg/dL in the usual care group. Mean absolute plaque volume showed a larger increase in the usual care group compared with the atorvastatin group (usual care 9.6 ± 28.1 mm³; atorvastatin 1.2 ± 30.4 mm³; P = 0.191). The hyperechogenicity index of the plaque increased to a larger extent for the atorvastatin group than for the usual care group, with a significant treatment effect for the percent change (atorvastatin 42.2%, usual care 10.1%; P = 0.021).

Conclusions—One year of lipid-lowering therapy to <100 mg/dL LDL-C most likely led to a slowdown of plaque growth of minor lesions. The significantly larger increase in plaque hyperechogenicity is most likely due to a change in plaque composition. (Circulation. 2001;104:387-392.)

Key Words: arteriosclerosis ■ coronary disease ■ lipids ■ plaque ■ ultrasonics

Coronary artery plaque disruption or erosion of the endothelial surface with subsequent thrombus formation leads to acute plaque growth and may result in sudden cardiac death, acute myocardial infarction, or unstable angina.¹⁻⁴ Large primary and secondary prevention studies with HMG-CoA reductase inhibitors have demonstrated that the effect of lipid-lowering therapy on cardiac events is much greater than the effect on the angiographically determined progression or regression of atherosclerosis.⁵⁻¹² This observation can be explained by the poor sensitivity of angiography to measure changes in plaque volume and by the assumption that mechanisms other than plaque size, such as enhanced endothelial function, a reduced thrombotic potential, or plaque composition, are responsible for the onset of a cardiac event.¹³,¹⁴ Intracoronary ultrasound (ICUS) is superior to angiography in the detection of early plaque formation and changes in plaque volume.¹⁵ Moreover, ICUS provides information on plaque echogenicity, which represents plaque composition.¹⁶,¹⁷

We postulated that compared with the usual treatment regimen with other lipid-lowering drugs, intensive lipid-lowering therapy with atorvastatin (target LDL cholesterol [LDL-C] <100 mg/dL) in patients with coronary artery disease and hypercholesterolemia would lead to a lesser progression of atherosclerosis and to different changes in plaque echogenicity. The primary efficacy parameters were...
coronary injection of 0.1 to 0.3 mg nitroglycerin, the ultrasound examinations were performed in the following manner: after intra-

Methods

Study Design
The present study was designed as an open-label, randomized, multicenter, parallel-group study in which 2 treatments, atorvastatin and usual care, were compared. Patients randomized for atorvastatin received an initial daily dose of 20 to 40 mg, which could be increased to 80 mg to reach the target level (LDL-C <100 mg/dL). Usual care consisted of a heterogeneous mix of lipid-lowering therapy, excluding atorvastatin. The treatment was determined by the patient’s primary physician, who was not encouraged by the investigators to treat the usual care patients in accordance with any specific guidelines. Before randomization and after 12 months, coronary angiography was performed, during which the ICUS measurements were performed. Clinical follow-up visits occurred after 1, 2, 3, 4, 6, 9, and 12 months. At each visit, a blood sample was taken, and data were collected on compliance and clinical events.

Patients
Patients aged 18 to 75 years were eligible for inclusion in the present study if they had been recommended for an intracoronary revascularization procedure and had successfully undergone intracoronary intervention. The target plaque qualified for the ICUS study if it had not been influenced by any previous therapeutic intervention, if the diameter of the stenosis was >50% on quantitative coronary angiography, and if the plaque was detected by ultrasound. The plaque had to be >10 mm proximal to the acute intervention site. Another coronary artery was imaged if there was no plaque visible in the intervened vessel. All patients had the following qualifying LDL-C level: >160 mg/dL, for patients off lipid-lowering therapy and >130 mg/dL, for patients on lipid-lowering therapy.

Major exclusion criteria were significant left main disease, unstable angina or myocardial infarction within the previous 4 weeks, an ejection fraction <40%, secondary causes of hypercholesterolemia, and severe hypertriglyceridemia (>400 mg/dL). Informed consent was obtained for the ICUS investigation as well as for the cholesterol-lowering phase of the trial. The protocol was approved by the appropriate institutional review boards in each of the study sites.

ICUS Imaging
Each center participating in the present study used the same system (2.9F, 30-MHz Microwas) at baseline and follow-up. All ICUS examinations were performed in the following manner: after intracoronary injection of 0.1 to 0.3 mg nitroglycerin, the ultrasound catheter was positioned distal to the lesion treated by coronary intervention or at least 3 cm distal to the ostium in a nontreated artery. The pullback was performed automatically at a speed of 0.5 mm/s. At the start of the pullback and at the site of the target plaque, the position of the catheter was recorded by angiography. The follow-up examination was performed before any subsequent intervention and in the same way as described above (if possible, with identical settings for the ultrasonic apparatus). ICUS measurements were recorded on SVHS video tapes and sent to the ICUS laboratory for central evaluation.

ICUS Analysis
An experienced ICUS investigator blinded to treatment assignment visualized the baseline and follow-up ICUS video images side by side and selected the target segment of the artery by using reproducible topographic landmarks to ensure a reliable comparison. The video images of the arterial segment were digitized by using a 3D image acquisition station (EchoScan, TomTec). Because the pullback speed and the frame-grabbing rate were constant, each image represents a 0.14-mm-thick segment of the artery. After 3D reconstruction, the start and end of the target lesion (plaque thickness >0.3 mm) was marked for further evaluation (Figure).

A second independent investigator, blinded to patient group and time of investigation, determined the lumen border and the total vessel border (defined as the area circumscribed by the external elastic membrane) for each ICUS image by the use of semiautomatic contour detection software. Standard measurements obtained included lesion length, vessel volume, and luminal volume. The plaque volume that represented the intima-media complex was calculated as vessel volume minus luminal volume.

Plaque echogenicity was determined with a computer-aided gray scale value analysis. The analysis required 3 steps: first, the determination of a threshold (mean intensity of the adventitia); second, the identification of calcium; and third, the classification of each pixel within the lesion (ratio of gray level intensity in the lesion to that of the adventitia). An intensity ratio of <1 was classified as hypoechoic, >1 was classified as hyperechoic, and >1 with shadowing was classified as calcified; a region behind a calcified plaque formed a fourth so-called unknown class. To quantify relative plaque echogenicity, indices for each class were calculated by the use of the following formula: hyperechogenicity index = (hyperechogenic volume/total plaque volume) × 100. The other indices were calculated in the same way.

The accuracy and reliability of ICUS image data have been investigated extensively in vivo and in vitro by correlation with histology. We could demonstrate in serial measurements of the identical coronary artery cross section within independent catheter pullback procedures a high correlation for area measurements: intraobserver agreement ranged from \( r = 0.98 \) to \( r = 0.99 \), and inter-
observer agreement ranged from $r=0.87$ to $r=0.98$. In addition, we found that different instrument settings did not provide a profound variable in the assessment of tissue echogenicity. 19

Lipid and Lipoprotein Levels
Plasma concentrations of total cholesterol, HDL cholesterol (HDL-C), and triglycerides were performed by a central laboratory by the use of the Friedewald formula [LDL-C = total cholesterol minus HDL-C minus (triglycerides/5)] to calculate LDL-C.

Statistical Analysis
Laboratory and ultrasound parameters were summarized by time point and treatment group with mean $\pm$ SD. Cardiac events were summarized with absolute and relative frequencies (percentages). The change from baseline to final visit was analyzed by means of ANOVA, with treatment as an effect. Both the difference of final visit minus baseline and the percent change from baseline to final visit were analyzed in the same way on an intention-to-treat basis, with a 2-sided $\alpha$ level of 0.05.

For the sample size determination, no information on the primary efficacy parameters were available at the time of protocol generation because 3D intravascular ultrasound was a new technique. A total of 100 patients seemed appropriate for obtaining quantitative information regarding the effect of lipid-lowering therapy on plaque morphology and for the planning of a follow-up study.

Results
Characteristics of the Patients
Of 131 patients, 65 were randomized to atorvastatin, and 66 were randomized to usual care. Both groups showed no significant difference with regard to baseline characteristics and lipid levels (Tables 1 and 2).

A total of 21 (12 atorvastatin and 9 usual care) patients were withdrawn prematurely. Withdrawals due to drug-related side effects occurred in 4 atorvastatin patients (rash, arthralgia, increase in creatinine level, and deep venous thrombosis [each $n=1$]). Other withdrawals relate to withdrawal of consent or medical reasons, such as coronary bypass grafting. Eleven patients completed the study but had no or a technically inadequate second ICUS investigation. Therefore, an ICUS measurement before and after treatment was available in 99 patients. There was no major cardiac complication resulting from the ICUS investigation. In 3 (1.4%) of 220 procedures, a coronary spasm occurred during ICUS imaging.

Lipid Protein Levels and Medication
The mean daily dose of atorvastatin was $32.5 \pm 12.7$ mg. In the usual care group, all patients were treated with $\geq 1$ lipid-lowering drug: various HMG-CoA reductase inhibitors except atorvastatin (48.5%), fibrates (43.9%), and cholestyramine (36.4%). After 12 months, the mean reduction in LDL-C was 42% in the atorvastatin group and 16% in the usual care group ($P<0.0001$) (Table 2). HDL-C increased, and triglycerides slightly decreased in both treatment groups.

The 2 groups were comparable with respect to concomitant medications: aspirin (98%), ticlopidine (50%), $\beta$-blocker (56%), and nitrates (27%).
TABLE 2. Changes in Lipid Parameters

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>Month 12</th>
<th>Percent Change From Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C, mg/dL</td>
<td>155±34</td>
<td>86±30</td>
<td>−42±26</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>166±47</td>
<td>140±48</td>
<td>−16±20</td>
</tr>
<tr>
<td>Usual care</td>
<td></td>
<td></td>
<td>P &lt; 0.0001</td>
</tr>
<tr>
<td>HDL-C, mg/dL</td>
<td>45±11</td>
<td>48±12</td>
<td>9±24</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>47±13</td>
<td>51±12</td>
<td>12±21</td>
</tr>
<tr>
<td>Usual care</td>
<td></td>
<td></td>
<td>P = 0.4235</td>
</tr>
<tr>
<td>Total-C, mg/dL</td>
<td>228±39</td>
<td>156±35</td>
<td>−29±19</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>242±48</td>
<td>215±54</td>
<td>−11±16</td>
</tr>
<tr>
<td>Usual care</td>
<td></td>
<td></td>
<td>P &lt; 0.0001</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>145±92</td>
<td>111±57</td>
<td>−9±94</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>147±90</td>
<td>123±61</td>
<td>−11±70</td>
</tr>
<tr>
<td>Usual care</td>
<td></td>
<td></td>
<td>P = 0.9551</td>
</tr>
</tbody>
</table>

Total-C indicates total cholesterol. Values are mean±SD.

ICUS Measurements
The total number of measured plaques was 135 (1 to 4 in a single patient; atorvastatin 1.35 per patient, and usual care 1.25 per patient). The intravascular ultrasound parameters for the different plaques per patient were derived from the mean of all values per patient and visit so that 1 value per patient and visit was included in the analysis.

The mean value for plaque volume increased with usual care (9.6±28.1 mm³), whereas for atorvastatin, a smaller mean increase was seen (1.2±30.4 mm³). However, this treatment group difference was not statistically significant for the absolute and percent changes (Table 3). Lesion length, vessel volume, and luminal volume also showed no significant treatment effects.

The hyperechogenicity index of the plaque increased to a larger extent for atorvastatin (1.9±8.3%) than for usual care (0.3±7.5%) (Table 4). This difference was statistically significant for the percent change (atorvastatin 42.2%, usual care 10.1%; P = 0.021). The other indices that describe plaque echogenicity showed no treatment group differences.

Ischemic Events
Ischemic events occurred in 14 atorvastatin patients and in 21 usual care patients (Table 5).

Discussion
The present study found that in patients with coronary artery disease and lipid-lowering therapy with atorvastatin to a mean level of 86 mg/dL, LDL-C compared with usual care (mean level 140 mg/dL) most likely led to less progression of plaque size and to significant different changes in plaque echogenicity in minor coronary lesions.

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Plaque echogenicity was determined by intravascular ultrasound with a computer-aided plaque characterization program on the basis of a gray level analysis. At baseline, ≈82% of the plaque volume was hypoechogenic and 12% was hyperechogenic, corresponding to lipid-rich plaques.¹⁶ For these plaques, we found a larger increase in the hyperechogenicity index in the atorvastatin group than in the usual care group, whereas the other indices that describe plaque echogenicity did not show any significant treatment differences. The mean percent change for the hyperechogenicity index was 42.2% in the atorvastatin group and 10.1% in the usual care group, with a significant treatment-group difference. However, one has to be aware that the actual difference was 1.9% versus 0.3%. Because the ultrasound appearance of the atherosclerotic plaque depends on its composition, the changes in hyperechogenicity are compatible with changes in plaque composition.

TABLE 4. Echogenicity Derived From ICUS Measurements

<table>
<thead>
<tr>
<th>Parameter Index</th>
<th>Atorvastatin (n=46)</th>
<th>Usual Case (n=50)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperechogenicity, % Baseline</td>
<td>11.4±5.9</td>
<td>12.2±6.6</td>
<td></td>
</tr>
<tr>
<td>Difference</td>
<td>1.9±8.3</td>
<td>0.3±7.5</td>
<td>0.178</td>
</tr>
<tr>
<td>Change</td>
<td>42.2±97.8</td>
<td>10.1±68.5</td>
<td>0.021</td>
</tr>
<tr>
<td>Hypoechogeticity, % Baseline</td>
<td>82.3±9.7</td>
<td>83.8±9.7</td>
<td></td>
</tr>
<tr>
<td>Difference</td>
<td>−2.3±9.6</td>
<td>−0.6±9.0</td>
<td>0.235</td>
</tr>
<tr>
<td>Change</td>
<td>−21.2±12.7</td>
<td>−0.3±12.1</td>
<td>0.308</td>
</tr>
<tr>
<td>Calcification, % Baseline</td>
<td>1.9±2.4</td>
<td>1.4±2.0</td>
<td></td>
</tr>
<tr>
<td>Difference</td>
<td>0.2±2.5</td>
<td>0±1.6</td>
<td>0.660</td>
</tr>
<tr>
<td>Unknown, % Baseline</td>
<td>4.4±6.3</td>
<td>2.6±3.4</td>
<td></td>
</tr>
<tr>
<td>Difference</td>
<td>0.2±3.8</td>
<td>0.3±2.5</td>
<td>0.865</td>
</tr>
</tbody>
</table>

Values are mean±SD.
The acoustic characterization of the composition of a coronary plaque has been validated by in vitro and in vivo studies and showed a good correlation with the morphological findings but does not provide precise histological findings. It is assumed that hyperechogenic plaque correlates with a larger fraction of dense fibrous or elastic tissue, that hypoechogenic plaque is associated with a greater fraction of loose fibrous, lipid, or necrotic tissue, and that acoustic shadowing indicates calcification. Because the precision with which small changes in structure can be detected by ultrasound is uncertain, the interpretation of our result that lipid-lowering therapy <100 mg/dL LDL-C changed the plaque composition to a more dense fibrous tissue is somewhat speculative, but this interpretation is supported by animal studies, which have demonstrated a reduction in the macrophage content and an increase of interstitial collagen of atherosclerotic lesions with lipid-lowering therapy. Consequently, there could be an increase in plaque stiffness and, presumably, a decrease in the passive phenomenon of plaque disruption. The hypothesis is supported by the lower cardiac event rate in our patients treated with atorvastatin but remains to be proved in larger clinical trials with randomization to specific target levels.

Vessel volume increased in the usual care and the atorvastatin groups. Although no statistically significant difference was observed, this increase was more pronounced in the usual care group. The increase may relate to a compensatory enlargement to the increased plaque burden in both groups. However, the changes in plaque composition induced by atorvastatin therapy (more fibrosis, smaller lipid pool) might be limiting this form of remodeling. Our observation emphasizes the complexity of the relationship between plaque size, plaque composition, and vessel volume.

### Study Limitations

Three-dimensional intravascular ultrasound does not permit the visualization of the entire coronary arterial tree, but the method has the advantage of quantifying reliably with high reproducibility that which is happening in the vessel wall at that particular site with a small or moderate atherosclerotic lesion. However, these lesions are much more numerous in patients with coronary artery disease than in those with severe lesions; they account for two thirds of the cases of unstable angina or acute myocardial infarction and appear to benefit more from lipid-lowering therapy than do severe lesions.

Moreover, it can be argued that the relationship between echogenicity and tissue composition is uncertain and that the use of radiofrequency signals is more reliable for plaque characterization. Nevertheless, computer-aided gray scale value analysis is, at present, the only existing approach to characterize plaque composition in a multicenter trial. It cannot be excluded that the changes in plaque volume and plaque echogenicity may have been influenced by coronary intervention, although the target lesion was 10 mm proximal to the intervention site.

Another limitation relates to the fact that 21 patients withdrew from the study. Because these patients were not available for follow-up investigations, no intention-to-treat analysis could be performed.

### Conclusions

Using serial 3D ICUS, we have demonstrated that a lipid-lowering therapy to <100 mg/dL LDL-C compared with usual care leads to a significantly larger increase in plaque hyperechogenicity and a smaller, but not significant, increase in plaque volume. These seminal findings warrant further conformation by larger multicenter trials.

### Appendix

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References
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