Determinants of Arterial Wall Remodeling During Lipid-Lowering Therapy

Serial Intravascular Ultrasound Observations From the Reversal of Atherosclerosis With Aggressive Lipid Lowering Therapy (REVERSAL) Trial

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Background—Coronary plaque progression and instability are associated with expansive remodeling of the arterial wall. However, the remodeling response during plaque-stabilizing therapy and its relationship to markers of lipid metabolism and inflammation are incompletely understood.

Methods and Results—Serial intravascular ultrasound (IVUS) data from the Reversal of Atherosclerosis with Aggressive Lipid Lowering Therapy (REVERSAL) trial were obtained during 18 months of intensive versus moderate lipid-lowering therapy. In a subgroup of 210 patients, focal coronary lesions with mild luminal narrowing were identified. Lumen area, external elastic membrane (EEM) area, and plaque area were determined at the lesion and proximal reference sites at baseline and during follow-up. The remodeling ratio (RR) was calculated by dividing the lesion EEM area by the reference EEM area. The relationship between the change in remodeling, change in plaque area, lipid profile, and inflammatory markers was examined. At the lesion site, a progression in plaque area (8.9±25.7%) and a decrease in the RR (−3.0±11.2%) occurred during follow-up. In multivariable analyses, the percentage change in plaque area ($P<0.0001$), baseline lesion area ($P<0.0001$), baseline lesion lumen area (0.019), logarithmic value of the change in high-sensitivity C-reactive protein ($P=0.027$), and hypertension at baseline ($P=0.014$) showed a significant, direct relation with the RR at follow-up. Lesion location in the right coronary artery ($P=0.006$), percentage change in triglyceride levels ($P=0.049$), and age ($P=0.037$) demonstrated a significant, inverse relation with the RR at follow-up. Changes in LDL cholesterol, HDL cholesterol, and treatment group demonstrated no significant associations.

Conclusions—Constrictive remodeling of the arterial wall was observed during plaque-stabilizing therapy with statin medications and appears related to their antiinflammatory effects. (Circulation. 2006;113:2826-2834.)

Key Words: arteriosclerosis ▪ imaging ▪ inflammation ▪ intravascular ultrasonography ▪ plaque ▪ remodeling ▪ statins

Recent serial clinical and intravascular ultrasound (IVUS) trials have demonstrated discordant beneficial effects of lipid-lowering treatment, including a reduction in adverse cardiovascular events and atherosclerotic plaque stabilization.1,2 This disease-stabilizing effect of statin treatment is related to independent contributions from reductions in LDL and C-reactive protein (CRP).3,4 However, the focal changes in the arterial wall associated with disease progression and stabilization are incompletely understood. In previous historical studies, plaque progression and instability were associated with focal inflammation and expansion of the vessel diameter at the lesion site.5-7 This expansive remodeling of the arterial wall can be assessed with IVUS by comparing the outer vessel area (ie, the external elastic membrane; EEM area) at the lesion and reference sites. In previous IVUS studies, expansive wall remodeling has consistently been associated with unstable clinical presentation.8,9

Serial IVUS data from recent multicenter trials provide the opportunity to examine the changes in vessel wall remodeling during plaque-stabilizing, lipid-lowering treatment. We hypothesized that plaque regression would be associated with constrictive wall remodeling and intended to examine the relationship to serum markers of lipid metabolism and inflammation. Consequently, in a prospectively designed substudy of the Reversal of Atherosclerosis with Aggressive

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Lipid Lowering Therapy (REVERSAL) population, we identified focal, mildly stenotic atherosclerotic lesions and observed the serial remodeling response during lipid-lowering therapy. In multivariable analyses, we examined the influence of changes in plaque burden, lipid profile, CRP, and other cardiovascular risk factors on the remodeling response.

**Methods**

**Patient Population**

We report results from a prospectively designed substudy of the REVERSAL trial. The REVERSAL trial enrolled patients 30 to 75 years of age who underwent coronary angiography for a clinical indication and demonstrated at least 1 obstructive lesion with an angiographic luminal diameter narrowing of 20% or more. A “target vessel” segment with a minimum length of 30 mm, without luminal narrowing of 50% or greater and no previous angioplasty, was identified for IVUS interrogation. Lipid criteria required an LDL cholesterol (LDL-C) value between 125 and 210 mg/dL at baseline. After a 2-week placebo run-in period, patients were randomized to either 80 mg atorvastatin (intensive treatment group) or 40 mg pravastatin (moderate treatment group) daily in a blinded fashion. During routine clinic visits the patients were examined, and laboratory studies were performed every 3 months for 18 months. After the 18-month treatment period, patients underwent a repeat cardiac catheterization and IVUS examination of the matched segments under identical conditions.

In the REVERSAL trial, 654 patients were randomized at 34 centers between June 1999 and September 2001. From these, a total of 502 patients completed the protocol, 249 in the pravastatin arm and 253 in the atorvastatin arm. We identified focal atherosclerotic lesions with mild luminal narrowing in 53% (266) of the patients. Of these, a total of 210 (42% of the REVERSAL population) had complete data for a focal lesion and a reference site matched at baseline and at follow-up. This subanalysis was approved by the institutional review board at our institution.

**IVUS Analysis**

**Lesion Identification and Matching**

Tapes were reanalyzed by an experienced investigator, and focal atherosclerotic lesions were identified. Lesion sites were defined as a focal site with <50% angiographic narrowing and visible plaque accumulation (plaque thickness >0.5 mm). A normal or near-normal proximal reference segment (plaque thickness <0.3 mm) was identified within a distance of 10 mm from the lesion site, without intervening side branches. One lesion was included per patient. In the follow-up IVUS analysis, the same lesion was identified. Matching of sites between baseline and follow-up analyses was guided by side branches and characteristic lesion morphology. In the final data analysis, only lesions with an identifiable lesion and a proximal reference, matched at baseline and follow-up, were included. In all patients, baseline and follow-up IVUS was performed with the same IVUS catheter type and IVUS system. Therefore, correction with previously described equations was not performed.

**IVUS Analysis and Standard Measurements**

For each lesion and reference site, planimetry of the lumen and external elastic membrane (EEM) areas was performed by an investigator blinded to the treatment group. With the use of National Institutes of Health (NIH) Image 1.62 software (NIH public domain software; NIH, Bethesda, Md), calibration was performed by measuring 1-mm grid marks encoded in the image. Manual planimetry was then used to trace the leading edges of the luminal and EEM borders. At both the lesion and proximal reference site, EEM area, lumen area, plaque area, and percentage plaque burden were determined in accordance with international standards.

**Remodeling Measurements**

Arterial wall remodeling was assessed by comparing the outer vessel border at the lesion and reference sites (Figures 1 and 2). The outer vessel border is defined by the EEM area. The remodeling ratio (RR) at baseline and follow-up was defined as the ratio of the EEM area at the lesion to that at the proximal reference site. Remodeling was analyzed as a continuous variable. In addition, 3 remodeling categories were defined: (1) Expansive remodeling, describing expansion of the EEM at the lesion site, was defined as an RR >1.05; (2) the absence of remodeling was defined as an RR between 0.95 and 1.05; and (3) constrictive remodeling, describing the constriction of the EEM at the lesion site, was defined as an RR <0.95.

**Serial IVUS Measurements**

**Percentage Change in RR**

The percentage change in RR was calculated as the difference in RR between baseline and follow-up divided by the baseline RR.
Percentage Change in Plaque Area

The percentage change in plaque area was computed as the difference in plaque area between baseline and follow-up divided by the baseline plaque area.

Serial Measurements of Markers of Lipid Metabolism and Inflammation

The biochemical analysis was performed at a central laboratory (Medical Research Laboratory, Highland Heights, Ky). Total cholesterol, LDL-C, HDL-C, and triglycerides were analyzed with an enzymatic colorimetric assay (Hitachi 747, Tokyo, Japan). High-sensitivity (hs)-CRP was analyzed by an immunonephelometric assay (Behring nephelometer 100, Westwood, Marburg, Germany).

For normally distributed variables, including total cholesterol, LDL-C, HDL-C, and triglycerides, the percentage change during follow-up was calculated as the difference between baseline and follow-up values divided by the baseline value. Because hs-CRP values were not normally distributed, logarithmic transformation was performed. The change in hs-CRP between baseline and follow-up was described by the logarithm of the ratio of follow-up hs-CRP divided by baseline hs-CRP [change in hs-CRP = \log(hs-CRP_{follow-up}/hs-CRP_{baseline})].

Statistical Methods

Simple descriptive statistics were used to summarize the data. For categorical variables, this included frequencies and percentages. For continuous variables, this included the mean and standard deviation and, in the case of nonnormally distributed variables, median and interquartile range. In addition, cross-tabs and plots were generated.

Because the patients in this subgroup analysis were not randomized, baseline variables were tested for differences in treatment groups. Univariate tests of treatment group differences at follow-up were conducted after adjusting for baseline values.

The primary outcomes studied were the RR at follow-up and the categorization of that RR as <0.95, 0.95 to 1.05, and >1.05. Potential predictors included baseline IVUS characteristics, demographic information, traditional cardiovascular risk factors, and serum markers of lipid metabolism and inflammation. For serum markers of lipid metabolism, the percentage change from baseline to follow-up was used. Because CRP values were not normally distributed, the change in hs-CRP was analyzed as the natural logarithm of the ratio between follow-up and baseline values. Missing values were imputed from the mean value (no more than 3 values for each of 12 possible predictor variables).

For identification of the factors predicting remodeling, bootstrap analysis was performed with all baseline clinical, biochemical, and IVUS variables as well as the change in biochemical variables as possible predictors (see online-only Data Supplement). Based on this bootstrap analysis, variables were chosen for the initial multivariable analysis. The best final multivariable model included only those variables that significantly added to the model in the presence of the other factors. An ordinal logistic regression was used to determine whether the categorized follow-up RR was affected by the variables. Unless otherwise stated, statistical testing was conducted with 2-sided alternatives, with a type I error level of 0.05. SAS, version 8.2, was used to conduct all analyses (SAS Institute, Cary, NC).

The authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

Lesion Characteristics

A focal lesion was identified in 210 patients. The lesion was located in the left main coronary artery in 16 patients (7.6%), left anterior descending coronary artery in 68 patients (32.4%), left circumflex artery in 68 patients (32.4%), and right coronary artery in 58 patients (27.6%). The baseline characteristics of this subgroup (Table 1) were not different from those of the entire REVERSAL population.

Laboratory Results

Table 2 summarizes laboratory values at baseline and follow-up and the changes at follow-up for the entire population and the treatment groups. As expected, significant changes in lipid levels and hs-CRP were found, with a more pronounced effect in the intensive treatment group.

IVUS Measurements at Baseline and Follow-Up

Table 3 summarizes IVUS measurements at baseline and follow-up for the overall group of patients and the treatment groups. In the overall group, there was a small but significant increase in both EEM and lumen area between baseline and
follow-up. The baseline mean percentage plaque burden at the lesion and the reference site was 49.9±9.9% and 29.5±7.8%, respectively. It was unchanged at follow-up, measuring 49.8±10.1% and 29.8±7.8% (P=0.46 and 0.47), respectively. Plaque area at the lesion site increased from 7.6±2.8 mm² to 8.1±3.2 mm², which represents a significant increase in percentage change in plaque area (8.9%±25.7, P<0.0001 for comparison of baseline to follow-up).

Remodeling at Baseline and Follow-Up
Table 3 also summarizes the RR at baseline and follow-up for the overall group and the treatment groups. In the overall

| TABLE 2. Baseline Demographic Characteristics: Total and Treatment Groups |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Characteristic   | Total (n=210)   | Intensive Treatment, Atorvastatin (n=106) | Moderate Treatment, Pravastatin (n=104) | P     |
| Age, y, mean±SD  | 55.5±9.9        | 55.3±10.6        | 55.8±9.1        | 0.74  |
| BMI, kg/m², mean±SD | 30.1±5.4        | 29.9±5.4         | 30.2±5.4        | 0.69  |
| Sex, men, n (%)  | 149 (71.0)      | 77 (72.6)        | 72 (69.2)       | 0.59  |
| Race, white, n (%) | 186 (88.6)      | 96 (90.6)        | 90 (86.5)       | 0.36  |
| Current smoker, n (%) | 58 (27.6)      | 31 (29.3)        | 27 (26.0)       | 0.59  |
| Prior statin use, n (%) | 67 (32.0)      | 32 (30.2)        | 35 (33.7)       | 0.59  |
| Hypertension, n (%) | 135 (64.3)     | 67 (63.2)        | 68 (65.4)       | 0.74  |
| Diabetes mellitus, n (%) | 34 (16.2)      | 21 (19.8)        | 13 (12.5)       | 0.15  |
| Metabolic syndrome, n (%) | 82 (39.0)     | 45 (42.5)        | 37 (35.6)       | 0.31  |
| Angina pectoris, n (%) | 192 (91.4)    | 97 (91.5)        | 95 (91.4)       | 0.97  |
| Myocardial infarction, n (%) | 75 (35.7)     | 38 (35.9)        | 37 (35.6)       | 0.97  |
| Peripheral vascular disease, n (%) | 20 (9.5)      | 11 (10.4)        | 9 (8.7)         | 0.67  |
| Heart failure, n (%) | 8 (3.8)         | 6 (5.7)          | 2 (1.9)         | 0.16  |

BMI indicates body mass index.

Plus/minus values are mean±SD.

*†Test for treatment group differences.
†Test for treatment group differences, controlling for baseline value.
group, the RR decreased from 1.07±0.15 to 1.03±0.14, which represents a significant decrease in the percentage change of the RR (−3.0±11.2%, *P*<0.0001 for comparison of baseline to follow-up). Table 4 shows the frequency of remodeling categories at baseline and follow-up. There was a shift to constrictive remodeling categories during follow-up.

**Influence of Treatment Group**

There were no significant differences in IVUS measurements between the intensive and moderate treatment groups. In both groups, there was a small increase in plaque area between baseline and follow-up (7.9±25.8% and 9.9±25.7%, respectively, *P*=0.57). The change in RR was not significantly

**TABLE 3. Baseline, Follow-Up, and Change From Baseline in IVUS End Points: Total and Treatment Groups**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Baseline</th>
<th>Follow-Up</th>
<th>% Change From Baseline</th>
<th><em>P</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (n=210)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EEM area lesion, mm²</td>
<td>15.3±5.2</td>
<td>16.4±6.0</td>
<td>7.8±18.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Lumen area lesion, mm²</td>
<td>7.7±3.4</td>
<td>8.3±3.7</td>
<td>8.4±22.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Plaque area lesion, mm²</td>
<td>7.6±2.8</td>
<td>8.1±3.2</td>
<td>8.9±25.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Percent plaque burden lesion</td>
<td>49.9±9.9</td>
<td>49.8±10.1</td>
<td>0.7±13.8</td>
<td>0.46</td>
</tr>
<tr>
<td>RR</td>
<td>1.07±0.15</td>
<td>1.03±0.14</td>
<td>−3.0±11.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Atorvastatin (n=106)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EEM area lesion, mm²</td>
<td>15.2±5.0</td>
<td>16.1±5.3</td>
<td>6.6±17.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Lumen area lesion, mm²</td>
<td>7.7±3.3</td>
<td>8.2±3.4</td>
<td>7.3±20.3</td>
<td>0.0002</td>
</tr>
<tr>
<td>Plaque area lesion, mm²</td>
<td>7.5±2.7</td>
<td>7.9±2.7</td>
<td>7.9±25.8</td>
<td>0.0002</td>
</tr>
<tr>
<td>Percent plaque burden lesion</td>
<td>49.7±9.9</td>
<td>49.6±9.8</td>
<td>0.8±13.9</td>
<td>0.64</td>
</tr>
<tr>
<td>RR</td>
<td>1.06±0.14</td>
<td>1.02±0.12</td>
<td>−3.3±10.4</td>
<td>0.024</td>
</tr>
<tr>
<td>Pravastatin (n=104)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EEM area lesion, mm²</td>
<td>15.4±5.4</td>
<td>16.8±6.6</td>
<td>9.0±19.7</td>
<td>0.0002</td>
</tr>
<tr>
<td>Lumen area lesion, mm²</td>
<td>7.8±3.5</td>
<td>8.5±4.0</td>
<td>9.5±24.7</td>
<td>0.0003</td>
</tr>
<tr>
<td>Plaque area lesion, mm²</td>
<td>7.7±2.8</td>
<td>8.4±3.5</td>
<td>9.9±25.7</td>
<td>0.0022</td>
</tr>
<tr>
<td>Percent plaque burden lesion</td>
<td>50.2±10.0</td>
<td>50.1±10.5</td>
<td>0.6±13.8</td>
<td>0.57</td>
</tr>
<tr>
<td>RR</td>
<td>1.07±0.16</td>
<td>1.03±0.15</td>
<td>−2.7±12.0</td>
<td>0.0013</td>
</tr>
</tbody>
</table>

*Test for differences at follow-up, controlling for baseline value or of variable within treatment group.

**TABLE 4. Remodeling Categories at Baseline and Follow-Up: Total and Treatment Groups**

<table>
<thead>
<tr>
<th>Remodeling Category</th>
<th>Follow-Up: Constrictive</th>
<th>Follow-Up: No Remodeling</th>
<th>Follow-Up: Expansive</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline: constrictive</td>
<td>29 (13.3)*</td>
<td>10 (4.8)‡</td>
<td>5 (2.4)‡</td>
<td>44 (21)</td>
</tr>
<tr>
<td>Baseline: no remodeling</td>
<td>10 (4.8)†</td>
<td>21 (10.0)*</td>
<td>20 (9.5)‡</td>
<td>51 (24.3)</td>
</tr>
<tr>
<td>Baseline: expansive</td>
<td>13 (6.2)†</td>
<td>37 (17.6)†</td>
<td>65 (31.0)*</td>
<td>115 (54.8)</td>
</tr>
<tr>
<td>Total</td>
<td>52 (24.8)</td>
<td>68 (32.4)</td>
<td>90 (42.9)</td>
<td>210 (100)</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline: constrictive</td>
<td>14 (13.2)*</td>
<td>5 (4.7)‡</td>
<td>4 (3.7)‡</td>
<td>23 (21.7)</td>
</tr>
<tr>
<td>Baseline: no remodeling</td>
<td>6 (5.7)†</td>
<td>10 (9.4)*</td>
<td>11 (10.4)‡</td>
<td>27 (25.5)</td>
</tr>
<tr>
<td>Baseline: expansive</td>
<td>6 (5.7)†</td>
<td>19 (17.9)†</td>
<td>31 (29.3)*</td>
<td>56 (52.8)</td>
</tr>
<tr>
<td>Total</td>
<td>26 (24.5)</td>
<td>34 (32.1)</td>
<td>46 (43.4)</td>
<td>106 (100)</td>
</tr>
<tr>
<td>Pravastatin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline: constrictive</td>
<td>15 (14.4)*</td>
<td>5 (4.8)‡</td>
<td>1 (1.0)‡</td>
<td>21 (20.2)</td>
</tr>
<tr>
<td>Baseline: no remodeling</td>
<td>4 (3.9)†</td>
<td>11 (10.6)*</td>
<td>9 (8.7)‡</td>
<td>24 (23.1)</td>
</tr>
<tr>
<td>Baseline: expansive</td>
<td>7 (6.7)†</td>
<td>18 (17.3)†</td>
<td>34 (32.7)*</td>
<td>59 (56.7)</td>
</tr>
<tr>
<td>Total</td>
<td>26 (25.0)</td>
<td>34 (32.7)</td>
<td>44 (42.3)</td>
<td>104 (100)</td>
</tr>
</tbody>
</table>

Values are given as number (percentage).

*Lesions without a change between baseline and follow-up (n=115; 55%).
†Lesions with a shift to constrictive remodeling (n=60; 29%).
‡Lesions with a shift to expansive remodeling (n=35; 17%).
Analyzing serial IVUS data from the REVERSAL trial, we
analyzed the relation between changes in remodeling, plaque
progression/regression during statin therapy demonstrated
the process of vessel wall expansion during plaque pro-
gression as described by Glagov et al,5 vessel constriction
has consistently been associated with restenosis.16,17
Experimental studies have suggested that disease regression
might in fact be associated with constrictive remodeling.26–28
In analogy to published Comparison of Amlodipine vs
Enalapril to Limit Occurrences of Thrombosis (CAMELOT) study that
examined temporal changes of arterial wall remodeling dur-
ing lipid-lowering therapy. Our results demonstrate that
plaque-stabilizing effect of statin therapy is associated
with structural changes in the vessel wall that are not
reflected in the reduction of plaque burden. These results
suggest that arterial remodeling is an independent factor in
disease progression and stabilization with a close relation-
ship to inflammation. It is an attractive hypothesis that the
systemic marker CRP reflects focal inflammatory pro-
cesses, including the effect of matrix metalloproteinases,
affecting both remodeling and plaque stability.29–31
The relation between baseline hypertension and expan-
sive remodeling is intriguing in the context of the recently
published Comparison of AMLodipine vs Enalapril to
Limit Occurrences of Thrombosis (CAMELOT) study that

### TABLE 5. Multivariable Analysis for RR at Follow-Up

<table>
<thead>
<tr>
<th></th>
<th>Parameter Estimate</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent change in plaque area</td>
<td>&lt;0.0001</td>
<td>0.122±0.027</td>
</tr>
<tr>
<td>RR at baseline</td>
<td>&lt;0.0001</td>
<td>0.567±0.047</td>
</tr>
<tr>
<td>Lumen area lesion</td>
<td>0.019</td>
<td>0.005±0.002</td>
</tr>
<tr>
<td>Lesion location in right coronary artery</td>
<td>0.006</td>
<td>−0.042±0.015</td>
</tr>
<tr>
<td>Log change in hs-CRP</td>
<td>0.027</td>
<td>0.013±0.006</td>
</tr>
<tr>
<td>Hypertension at baseline</td>
<td>0.014</td>
<td>0.037±0.015</td>
</tr>
<tr>
<td>Percent change in triglyceride level</td>
<td>0.049</td>
<td>−0.031±0.016</td>
</tr>
<tr>
<td>Age</td>
<td>0.037</td>
<td>−0.002±0.001</td>
</tr>
<tr>
<td>Treatment</td>
<td>0.64</td>
<td>−0.007±0.014</td>
</tr>
</tbody>
</table>

*The parameter estimate describes the magnitude and direction of the relationship between a change in the variable and the RR. Positive and negative values correspond to direct and inverse relations, respectively.

The relation between baseline hypertension and expansive remodeling is intriguing in the context of the recently published Comparison of AMLodipine vs Enalapril to Limit Occurrences of Thrombosis (CAMELOT) study that

in vessel size or expansive remodeling has been associated
with an increase in inflammatory cells and proteolytic
enzymes at the lesion site.6,7 In clinical IVUS studies, expan-
sive wall remodeling has consistently been associated
with plaque instability and unstable clinical presenta-
tion.8,9 In the present study, the shift to constrictive wall
remodeling during lipid-lowering treatment is intriguing
but consistent with previous IVUS reports. In studies
describing changes in advanced lesions after percutaneous
coronary intervention, constrictive wall remodeling has
been associated with restenosis.10,11 Experimental studies
with histological analysis after percutaneous intervention
have further demonstrated that constrictive remodeling is
associated with plaque compositional changes character-
ized by increased fibrosis.12 In native coronary lesions of
nonhuman primates, histological studies have demonstra-
ted lipid depletion and fibrosis during lipid-lowering
therapy.13–15

Based on these results, lipid depletion and fibrosis are
considered to be related to the concept of plaque regression
and stabilization.8,22,23 In clinical IVUS studies, the stabil-
zizing effect of lipid-lowering therapy is primarily re-
lected in changes of plaque burden.2 However, standard
gray-scale analysis in serial clinical IVUS studies has
demonstrated a shift to a more fibrotic lesion morphology
during lipid-lowering therapy,24 and quantitative analysis
of vessel wall composition is emerging.25 Other studies
have suggested that disease regression might in fact be
associated with constrictive remodeling.26–28 In analogy to
the process of vessel wall expansion during plaque pro-
gression as described by Glagov et al,5 vessel constriction
during regression has been termed “reverse remodeling.”

However, the determinants of the remodeling response
during lipid-lowering therapy are incompletely under-
stood. Recent IVUS studies analyzing the determinants of
plaque progression/regression during statin therapy dem-
onstrated an independent effect of LDL and CRP reduction
on plaque burden.3,4 Our results suggest that the determi-
nants of remodeling are different. Particularly interesting
is the lack of an independent relation to LDL-C and the
positive relation to CRP. The lack of a relation with
LDL-C may indicate that the beneficial effect of LDL
lowering is primarily mediated through the reduction of
plaque burden. In contrast, the independent, direct relation
with CRP may demonstrate that the antiinflammatory,
plaque-stabilizing effect of statin therapy is associated
with structural changes in the vessel wall that are not
reflected in the reduction of plaque burden. These results
suggest that arterial remodeling is an independent factor in
disease progression and stabilization with a close relation-
ship to inflammation. It is an attractive hypothesis that the
systemic marker CRP reflects focal inflammatory pro-
cesses, including the effect of matrix metalloproteinases,
affecting both remodeling and plaque stability.29–31

The relation between baseline hypertension and expan-
sive remodeling is intriguing in the context of the recently
published Comparison of AMLodipine vs Enalapril to
Limit Occurrences of Thrombosis (CAMELOT) study that

### Discussion

Analyzing serial IVUS data from the REVERSAL trial,2 we
examined temporal changes of arterial wall remodeling
during lipid-lowering therapy. Our results demonstrate that
plaque-stabilizing therapy with statin medications is associ-
ated with constrictive wall remodeling. In multivariable
analyses, the percentage change in plaque area, baseline RR,
baseline lesion lumen area, logarithmic change in hs-CRP,
and hypertension at baseline (P=0.014) showed a significant,
direct relation with the RR at follow-up. Lesion location in the right coronary artery (P=0.006), percentage change in triglyceride levels (P=0.049), and age (P=0.037) demonstrated a significant, inverse relation with the RR at follow-up (Table 5). In the presence of the aforementioned variables, the change in HDL-C, the change in LDL-C, and treatment assignment did not add to the final model.

Our results provide important new insights into the pathophysiology of focal vessel wall changes during plaque stabilization. A relationship of arterial wall remodeling with plaque stability/vulnerability has been observed in previous studies. In histological studies, the expansion

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described a relationship between blood pressure lowering and attenuated changes in plaque burden in normotensive patients. The relations between an increase in triglycerides, older age, and lesion location in the right coronary artery with constrictive remodeling are similar to those found in previous studies. The relation between larger baseline lumen area and expansive remodeling is interesting in the context of the original observations of Glagov et al that expansive remodeling is limited by increasing plaque area at the lesion site, leading to increasing luminal stenosis beyond a 40% cross-sectional plaque area. Table 4 shows complex changes in the remodeling categories. These subgroups are too small to determine the association with clinical variables, and further studies are necessary to understand these relationships. Lastly, we found no difference between the intensive and moderate statin treatment groups. However, even though the result is not significant, the shift toward constrictive remodeling was greater in the intensive group than in the moderate group. Larger studies may be necessary to show a significant difference. On the other hand, our results could suggest that the achieved extent of the statin effect (on-treatment LDL-C and HDL-C, lowering of CRP, reduction of plaque growth) is more important than the treatment assignment itself.

Limitations

To attain the low variability in plaque burden measurements required for serial pharmacological studies, the REVERSAL trial and other similar studies have used a volumetric analysis approach of entire coronary segments, thus avoiding matching of individual lesions. In contrast, the conventional methodology used for assessment of remodeling, which was also applied in this analysis, relies on matching of focal lesion sites. Matching of the lesion and the reference site and subsequent calculation of the RR are expected to be associated with increased measurement variability. We calculated the reproducibility for the remodeling calculation in a separate variability analysis. Both the interobserver and intraobserver variability was relatively poor, with the probability values for a paired t test of the difference in the change in RR approaching statistical significance (P=0.162 and 0.073, respectively).

Assessment of focal remodeling may also be confounded by disease and remodeling at the reference site. To minimize that possibility, we chose the reference site as one with no significant disease, defined as a maximal intimal thickness <0.3 mm. Despite its limitations, remodeling analysis of individual lesions may allow the identification of focal, pathophysiological processes that determine remodeling. In contrast, definitions of remodeling in entire vessel segments, describing the volumetric response of the EEM during lesion progression/regression, may allow us to understand the systemic response of the vessel wall during disease progression. The differences between these approaches are incompletely understood and will need to be addressed in future studies.

Other limitations are related to the patient population. The data were obtained for a subgroup of the REVERSAL population (210 of 654 patients) in whom focal lesions could be identified. The definition of focal lesion as described in the literature is to some degree arbitrary. Although baseline characteristics were not different from those of the overall REVERSAL population, the smaller population raises questions about the generalizability of our findings. In particular, the results may differ in lesions with more diffuse plaque distribution, which would require a volumetric analysis. The influence of CRP is expected to be more pronounced in patients with acute coronary syndromes, and such a population would therefore be best suited to evaluate the relationship between positive remodeling and inflammation. However, the CRP level in the REVERSAL subjects, who were initially referred for percutaneous intervention, identified a high-risk population according to current guidelines. Because the lipid inclusion criteria in the REVERSAL trial specified an LDL range that included only patients with hypercholesterolemia (125 to 210 mg/dL), our findings may not apply to vessel segments of normcholesterolemic subjects. In addition, narrowing the range of LDL may have affected the correlation with remodeling. Therefore, the lack of a relationship between the change in LDL and remodeling will need confirmation in unselected patient populations.

Conclusion

Analyzing serial IVUS data from the REVERSAL trial, we have demonstrated that constrictive arterial wall remodeling was the predominant response during plaque-stabilizing treatment with statin medications. In multivariable analyses, the percentage change in plaque area, baseline RR, baseline lesion lumen area, logarithmic change in hs-CRP, and hypertension at baseline showed a significant, direct relation with the RR at follow-up. Lesion location in the right coronary artery, percentage change in triglyceride levels, and age demonstrated a significant, inverse relation with the RR at follow-up. In the presence of these variables, changes in LDL-C and HDL-C were not found to have an independent relation.

These findings have important implications for the understanding of plaque stability and remodeling. Together with previous findings describing the association of expansive wall remodeling with lesion inflammation and unstable clinical presentation, our results are consistent with the hypothesis that constrictive remodeling is associated with plaque stabilization. Arterial wall remodeling is an independent factor in disease progression and stabilization and appears to be related to the inflammatory activity of atherosclerotic lesions.

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References


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**CLINICAL PERSPECTIVE**

Previous research has shown that culprit lesions in arteries causing acute cardiovascular syndromes, including heart attack and stroke, are characterized by inflammation and expansive remodeling of the vessel wall. The present article demonstrates that plaque-stabilizing therapy with statin medications is associated with constrictive remodeling of the arterial wall. This beneficial effect is related to a reduction in the inflammatory marker C-reactive protein. The concept that plaque regression and stabilization are accompanied by a reduction in vessel size is in direct contrast to the “bigger-is-better” paradigm derived from treatment of focal culprit lesions in the catheterization laboratory. It becomes increasingly obvious that the systemic, pharmacological treatment of coronary atherosclerosis is more complex and requires an understanding of changes in the vessel wall. The development of improved pharmacological strategies to control these vessel wall alterations will be critical for the successful reduction of cardiovascular disease, including heart attack and stroke.
Determinants of Arterial Wall Remodeling During Lipid-Lowering Therapy: Serial Intravascular Ultrasound Observations From the Reversal of Atherosclerosis With Aggressive Lipid Lowering Therapy (REVERSAL) Trial

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