

# Relation Between Progression and Regression of Atherosclerotic Left Main Coronary Artery Disease and Serum Cholesterol Levels as Assessed With Serial Long-Term ( $\geq 12$ Months) Follow-Up Intravascular Ultrasound

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**Background**—The relation between serum lipids and risk of coronary events has been established, but there are no data demonstrating directly the relation between serum low-density lipoprotein (LDL) cholesterol and high-density lipoprotein (HDL) cholesterol versus serial changes in coronary plaque dimensions.

**Methods and Results**—We performed standard analyses of serial intravascular ultrasound (IVUS) studies of 60 left main coronary arteries obtained 18.3 $\pm$ 9.4 months apart to evaluate progression and regression of mild atherosclerotic plaques in relation to serum cholesterol levels. Overall, there was (1) a positive linear relation between LDL cholesterol and the annual changes in plaque plus media (P&M) cross-sectional area (CSA) ( $r=0.41$ ,  $P<0.0001$ ) with (2) an LDL value of 75 mg/dL as the cutoff when regression analysis predicted on average no annual P&M CSA increase; (3) an inverse relation between HDL cholesterol and annual changes in P&M CSA ( $r=-0.30$ ,  $P<0.02$ ); (4) an inverse relation between LDL cholesterol and annual changes in lumen CSA ( $r=-0.32$ ,  $P<0.01$ ); and (5) no relation between LDL and HDL cholesterol and the annual changes in total arterial CSA (remodeling). Despite similar baseline IVUS characteristics, patients with an LDL cholesterol level  $\geq 120$  mg/dL showed more annual P&M CSA progression and lumen reduction than patients with lower LDL cholesterol.

**Conclusions**—There is a positive linear relation between LDL cholesterol and annual changes in plaque size, with an LDL value of 75 mg/dL predicting, on average, no plaque progression. HDL cholesterol shows an inverse relation with annual changes in plaque size. (*Circulation*. 2003;108:2757-2762.)

**Key Words:** ultrasonics ■ coronary disease ■ cholesterol ■ lipids

The relation between serum lipids and coronary events has been established in patients with<sup>1,2</sup> and without<sup>3,4</sup> overt coronary artery disease. Clinical events occur as a result of atherosclerotic plaque formation and progression.<sup>5,6</sup> Serial examinations of plaques are particularly important, because they may allow insights into the mechanisms involved. Thus far, in coronary arteries, the relationship of risk factors, in particular serum lipids, to actual plaque progression (increase) or regression (decrease) has been inferred from indirect assessment of the coronary calcium score by cardiac computer tomography or angiography.<sup>7,8</sup> However, angiographic studies suggested only minimal lumen changes, often too small and occurring too slowly to account for the observed early clinical benefit of lipid-lowering strategies.<sup>8</sup>

Intravascular ultrasound (IVUS) allows transmural visualization of coronary arteries and direct measurements of lumen, plaque, and vessel dimensions.<sup>9-12</sup> As a consequence,

IVUS is an ideal tool for the assessment of the mechanisms that may be involved in the progression or regression of coronary artery disease. Nevertheless, the literature contains few serial IVUS studies of native coronary artery disease (mostly with 6 to 12 months of follow-up).<sup>13-15</sup> Only 1 serial IVUS pharmacological intervention study in 25 patients investigated the evolution of coronary artery disease in native (nontransplanted) coronary arteries with >1-year follow-up.<sup>13</sup> The left main (LM) coronary artery may be the most important target of atherosclerotic plaque accumulation,<sup>16</sup> and IVUS often reveals occult plaque.<sup>11,12</sup>

In the present study, we analyzed serial IVUS data of nonstenotic LM coronary arteries in patients with IVUS follow-up of  $\geq 12$  months. We compared changes in lumen, plaque, and arterial dimensions in relation to serum lipids, in particular, versus both LDL cholesterol and HDL cholesterol levels.

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## Methods

### Study Population

We analyzed serial IVUS studies of 60 LM coronary artery atherosclerotic plaques during  $\geq 12$  months of follow-up ( $18.3 \pm 9.4$  months). All patients were examined in the Essen University Cardiac Catheterization Laboratory. All plaques were de novo, were hemodynamically nonsignificant, and met the following criteria: (1) serial high-quality IVUS of the entire LM  $\geq 12$  months apart, (2) calcifications that did not limit quantitative assessment of vessel cross-sectional area (CSA), (3) nonostial plaque location, (4) angiographic lumen diameter stenosis  $< 30\%$  ("worst view" visual assessment), and (5) no intervention in the very proximal left anterior descending or circumflex coronary arteries, because these interventions could have affected the LM artery. This IVUS study was approved by the Local Council on Human Research. All patients signed a written informed consent form as approved by the Local Medical Ethics Committee.

### Cardiovascular Risk Factors, Clinical Data, and Medication

In our laboratory, we prospectively record demographics, cardiovascular risk factors, medications, and results of key laboratory tests of patients examined with IVUS. All laboratory tests were performed at baseline and follow-up as part of the clinical routine and were analyzed in the central laboratory of Essen University according to international standards. Cardiovascular risk factors that were recorded included diabetes mellitus and hypertension (both medication-dependent only), hypercholesterolemia (medication-dependent, total serum cholesterol  $> 200$  mg/dL, or LDL cholesterol  $> 160$  mg/dL), history of smoking, and family history of coronary artery disease. Data of laboratory tests were means of the baseline and follow-up values. Medications were recorded only if drugs were taken for  $> 50\%$  of the follow-up interval (eg, clopidogrel for 4 weeks was not tabulated). Plasma concentrations of total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides were measured by standard enzymatic methods, and the LDL/HDL ratio was calculated.

### IVUS Imaging Protocol

IVUS imaging was initially performed during percutaneous coronary interventions of mid or distal left anterior or left circumflex arteries. IVUS studies were performed after intracoronary injections of 200  $\mu$ g nitroglycerin with commercially available systems; a mechanical sector scanner (Boston Scientific Corp) incorporating a 30-MHz single-element beveled transducer or a solid-state device (Endosonics). Importantly, at Essen University, if a patient undergoes imaging with one IVUS system during an index procedure, the same IVUS system is used at follow-up. Slow, continuous pullbacks of the IVUS transducer were started as distal as possible in one of the left coronary arteries and were generally performed using a motorized pullback device (at 0.5 mm/s). IVUS images of the entire pullback were recorded on 0.5-in high-resolution s-VHS tape. In addition, a dedicated image-in-image system (Echo-Map, Siemens)<sup>17</sup> was used to record the "angiographic" position of the IVUS probe together with the corresponding IVUS image, especially at sites of characteristic landmarks (ie, calcifications or unusual plaque shapes) and/or the target site.

Follow-up IVUS studies were performed (using the same IVUS system as initially) during repeat coronary interventions ( $n=34$ , 57%) and during IVUS examinations of ambiguous coronary lesions or (clinically driven) follow-up catheterizations ( $n=26$ , 43%). IVUS was not performed as part of another study with long-term IVUS follow-up in any of these patients.

### Quantitative IVUS Analysis

The LM target site image slice was determined from the initial IVUS study; this was the site with the smallest lumen CSA within the LM plaque. If there were several slices with equal lumen size, the one with the largest external elastic membrane (EEM) and plaque-plus-media (P&M=EEM minus lumen) CSA was analyzed.<sup>9,12</sup> Exact

matching of the target site on initial and follow-up IVUS studies was ensured by use of side-by-side comparison of the serial IVUS video sequences along with information of the pullback speed; the operators' recorded comments (on videotape); and characteristic calcifications, vascular and perivascular landmarks, and plaque shapes. If required, x-ray sequences of the dedicated image-in-image system (Echo-Map) were revisited to optimize matching.<sup>17</sup>

The lumen CSA was measured by tracing the leading edge of the intima. The EEM CSA was measured by tracing the leading edge of the adventitia. In our laboratory, the intraclass correlation coefficient is 0.99 for repeated measurements of EEM, 0.96 for lumen, and 0.99 for P&M CSA. Plaque burden (%) was calculated as (P&M divided by EEM)  $\times 100\%$ . To compensate for variations in follow-up intervals and to obtain comparable data, we calculated absolute and relative changes ( $\Delta$ ) between initial and follow-up IVUS data; measurements were normalized for the length of the follow-up period (changes per year) and for baseline measurements. In analogy with 1 previous coronary progression-regression study,<sup>18</sup> we used an LDL cholesterol threshold of 120 mg/dL to compare patients with LDL cholesterol  $\geq 120$  mg/dL (group A) versus those with LDL cholesterol  $< 120$  mg/dL (group B).

### IVUS Assessment of Plaque Composition

IVUS images were read offline by 3 experienced IVUS analysts. Plaque composition was assessed visually as previously described.<sup>9</sup> The arc of target-lesion calcium ( $^\circ$ ) was measured with a protractor centered on the lumen; if necessary, the total arc of calcium was obtained by adding arcs of individual deposits. Plaques were classified as calcified if the total arc of lesion calcium was  $> 180^\circ$ . Extrapolation of the EEM boundary behind calcium was possible if each individual calcific deposit did not shadow  $> 75^\circ$  of the adventitial circumference.

### Statistical Analysis

Analyses were performed with SPSS 10.0.7 (Microsoft) for Windows. Dichotomous data are presented as frequencies and compared by use of  $\chi^2$  statistics or Fisher's exact test. Quantitative data are presented as mean  $\pm$  SD and compared by Student's *t* test and regression analysis. A probability value of  $P < 0.05$  was considered significant.

## Results

### Demographics, Medication, and Laboratory Testing of Patients

Twenty-six patients (43%) had a serum LDL cholesterol level  $\geq 120$  mg/dL (group A); 34 patients (57%) had LDL cholesterol values  $< 120$  mg/dL (group B). Demographics of both groups (all white) are presented in Table 1. Group A patients tended to have more systemic arterial hypertension. The medications of groups A and B were not different except for a higher incidence of statin use in group B (Table 2;  $P < 0.0005$ ).

In keeping with the definitions, group A patients had higher serum LDL cholesterol values (Table 1;  $P < 0.0001$ ). In addition, group A patients had greater total cholesterol ( $P < 0.0001$ ), lipoprotein(a) ( $P < 0.05$ ), apolipoprotein B ( $P < 0.0005$ ), and fibrinogen values ( $P < 0.05$ ). Group B patients showed a higher HDL cholesterol ( $P < 0.01$ ). Triglycerides values were similar in groups A and B.

### Baseline IVUS Data

The baseline IVUS characteristics were similar between the 2 groups (Table 2). The majority of plaques showed a soft or fibrous composition.

**TABLE 1. Patient Demographics, Medications, and Laboratory Tests**

	Group A (n=26)	Group B (n=34)	P
Time of follow-up, mo	16.4±6.2	19.6±11.1	0.2
Age, y	59±10	58±9	0.9
Men	21 (81)	29 (85)	0.7
Body mass index, kg/m <sup>2</sup>	27.4±3.5	26.2±3.0	0.2
Previous myocardial infarction	8 (31)	13 (38)	0.7
Hypercholesterolemia	20 (77)	8 (24)	<0.0001
Systemic arterial hypertension	23 (86)	20 (59)	0.05
Diabetes	4 (15)	4 (12)	0.7
Smoker	7 (27)	9 (27)	0.8
Family history of coronary artery disease	6 (23)	8 (24)	0.8
No. of vessels diseased			0.9
1	13 (50)	15 (44)	
2	6 (23)	10 (29)	
3	7 (27)	9 (27)	
Clinical syndrome			0.8
Stable angina CCS class			
I	8 (31)	9 (27)	
II	11 (42)	18 (53)	
III	5 (19)	4 (12)	
Unstable angina	2 (8)	3 (9)	
Medication			
Acetylsalicylic acid	26 (100)	34 (100)	1.0
ACE inhibitors	9 (35)	13 (38)	1.0
AT <sub>1</sub> antagonists	1 (4)	1 (3)	1.0
β-Blockers	16 (62)	20 (59)	1.0
Calcium channel blockers	9 (35)	8 (24)	0.5
Diuretics	9 (35)	9 (26)	0.7
Fibrates	2 (8)	1 (3)	0.6
Insulin	1 (4)	1 (3)	1.0
Nitrates	13 (50)	23 (68)	0.3
Oral antidiabetics	3 (12)	0 (0)	0.1
Statins	16 (62)	33 (97)	<0.0005
Laboratory tests*			
Total cholesterol, mg/dL	219±22	173±29	<0.0001
LDL cholesterol, mg/dL	158±25	89±20	<0.0001
HDL cholesterol, mg/dL	42±10	51±14	<0.01
Lipoprotein(a), mg/L	32±30	19±15	<0.05
Triglycerides, mg/dL	114±76	144±60	0.1
Apolipoprotein A <sub>1</sub> , mg/dL	149±20	150±21	0.8
Apolipoprotein B, mg/dL	116±16	97±20	<0.0005
Apolipoprotein B/A <sub>1</sub> , ratio	0.79±0.11	0.65±0.13	<0.0001
Fibrinogen, mg/dL	313±85	272±71	<0.05

Values are mean±SD or n (%). CCS indicates Canadian Cardiovascular Society.  
\*Mean values of measurements at time of initial and follow-up IVUS examinations.

**Serial IVUS Data**

Group A plaques (in patients with LDL cholesterol ≥120 mg/dL) showed more P&M progression than group B plaques (24/26 [92%] versus 17/34 [50%], *P*<0.001) and tended to

**TABLE 2. Baseline IVUS Data**

	Group A (n=26)	Group B (n=34)	P
EEM CSA, mm <sup>2</sup>	25.1±6.1	25.4±5.5	0.9
Lumen CSA, mm <sup>2</sup>	16.0±4.4	15.4±4.2	0.6
P&M CSA, mm <sup>2</sup>	9.1±3.1	10.0±4.2	0.4
Plaque burden, %	36.1±9.0	38.9±12.0	0.3
Total arc of calcium, degrees	79±111	66±105	0.7
Plaque composition, n (%)			0.9
Soft	6 (23)	10 (29)	
Fibrous	9 (35)	11 (32)	
Mixed	2 (8)	3 (9)	
Calcified	9 (35)	10 (29)	

have a greater frequency of lumen reduction (17/26 [65%] versus 15/34 [44%], *P*=0.17). There was no significant difference in the incidence of EEM increase: 20/26 (77%) versus 20/34 (59%), *P*=NS.

Absolute and relative annual changes of lumen, P&M, and EEM CSA are presented in Table 3. There was no difference in annual changes of EEM size, but group A plaques had a greater annual increase in P&M CSA (*P*<0.0001) and a greater annual decrease in lumen CSA (*P*<0.02, Figure 1). There was no change in IVUS plaque composition during follow-up or in total arc of calcium within the entire population or within groups A and B separately: 76±110°, 80±114°, and 67±107° (*P*>0.8 versus baseline).

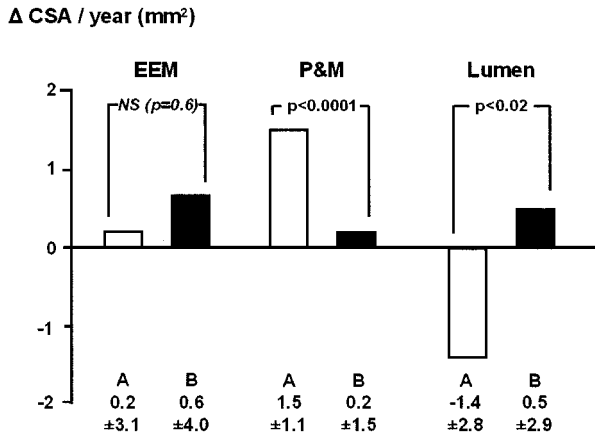
**Relation Between Cholesterol and Serial IVUS Data**

There was a positive linear relation between percent annual changes in P&M CSA versus LDL cholesterol (*r*=0.41, *P*<0.0001). There was a negative linear relation between percent annual changes in lumen size versus LDL cholesterol (*r*=−0.32, *P*<0.01) (Figure 2). There was a negative linear relation between annual changes in P&M CSA versus HDL cholesterol (*r*=0.30, *P*<0.02); this relation remained significant even after removal of the 2 outliers with HDL cholesterol >80 mg/dL (*r*=−0.36; *y*=−0.67*x*+42.0; *P*<0.01; *n*=58). However, there was no relation between either LDL or HDL cholesterol and annual changes in EEM CSA. The LDL/HDL ratio showed relations similar to LDL cholesterol alone (Figure 2).

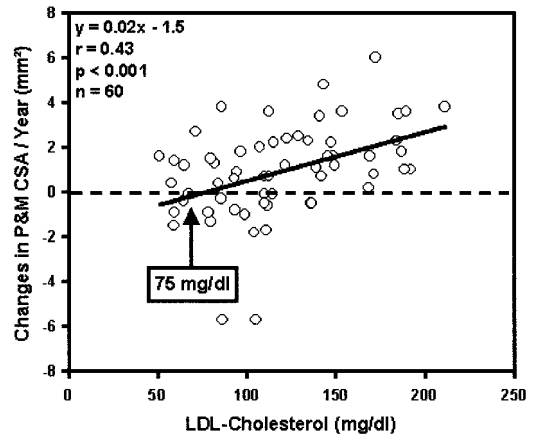
The relation between annual changes in P&M CSA and LDL cholesterol demonstrated that an LDL value of 75 mg/dL was the cutoff at which regression analysis predicted

**TABLE 3. Serial IVUS Data**

	Group A (n=26)	Group B (n=34)	P
ΔEEM CSA/y, mm <sup>2</sup>	0.2±3.1	0.6±4.0	0.6
ΔEEM CSA/y, %	2.3±11.0	3.3±14.0	0.8
ΔP&M CSA/y, mm <sup>2</sup>	1.5±1.1	0.2±1.5	<0.0001
ΔP&M CSA/y, %	21.2±18.1	4.0±15.2	<0.0005
ΔLumen CSA/y, mm <sup>2</sup>	−1.4±2.8	0.5±2.9	<0.02
ΔLumen CSA/y, %	−6.6±16.0	4.5±18.6	<0.01



**Figure 1.** Annual changes of IVUS parameters in group A (LDL cholesterol  $\geq 120$  mg/dL) vs group B (LDL cholesterol  $< 120$  mg/dL) plaques.

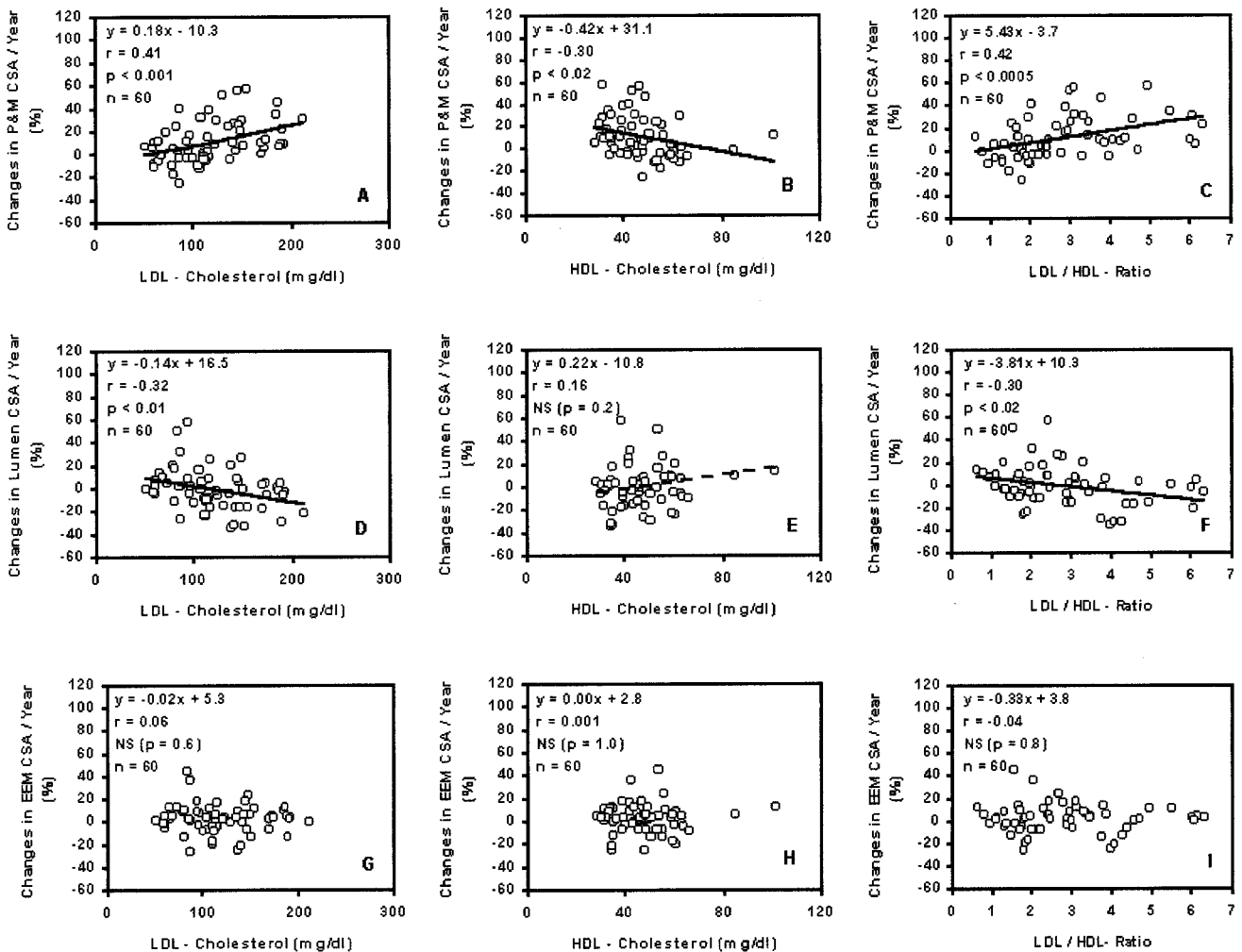


**Figure 3.** Relation between LDL cholesterol and annual changes in P&M CSA. An LDL value of 75 mg/dL was the cutoff at which regression analysis predicts no average annual P&M CSA increase.

no average annual plaque increase (Figure 3). However, individual patients exhibited plaque increase even at lower LDL cholesterol values. Similarly, a value of the LDL/HDL ratio of 1.3 was the cutoff at which regression analysis predicted no average annual plaque increase.

### Cholesterol and Serial IVUS Data in Patients Treated With Statins

When only those patients who were on statins were analyzed ( $n=49$ ), there was still a significant positive linear relation between percent annual changes in P&M CSA versus LDL



**Figure 2.** Relation between LDL cholesterol (left), HDL cholesterol (middle), and LDL/HDL ratio (right) vs serial IVUS data.

cholesterol ( $r=0.45$ ,  $P<0.001$ ) and a negative linear relation between annual changes in P&M CSA versus HDL cholesterol ( $r=-0.30$ ,  $P<0.05$ ). An LDL value of 72.5 mg/dL was the cutoff at which regression analysis predicted no average annual P&M CSA increase. Percent annual changes in lumen CSA tended to show a negative linear relation with LDL cholesterol ( $r=-0.25$ ,  $P=0.12$ ), but there was no relation with HDL cholesterol ( $r=0.14$ ,  $y=0.18x-6.6$ ;  $P=0.35$ ). Moreover, there was no relation between either LDL or HDL cholesterol and annual changes in EEM CSA ( $r=-0.02$  for both). The number of patients who were not on a statin ( $n=11$ ) was too small to permit similar meaningful analysis.

## Discussion

We found (1) a positive linear relation between LDL cholesterol and annual changes in P&M area with (2) an LDL value of 75 mg/dL as the cutoff at which regression analysis predicted, on average, no annual P&M area increase; (3) an inverse relation between HDL cholesterol and annual changes in P&M area; and (4) no relation between either LDL or HDL cholesterol and annual changes in total arterial area (ie, arterial remodeling). Because LDL and HDL cholesterol levels did not appear to affect arterial remodeling, there was an inverse relation between LDL cholesterol and annual changes in lumen area. Finally, although they had similar IVUS characteristics at baseline, patients with LDL cholesterol  $\geq 120$  mg/dL showed more annual plaque progression and lumen reduction than did patients with lower LDL cholesterol values.

### Serial Plaque and Lumen Changes and Cholesterol

There is ample accumulated evidence of the significance of cholesterol on the progression of atherosclerosis.<sup>19–21</sup> The present linear relations between LDL cholesterol and both P&M progression and lumen reduction agree with previous studies, and they emphasize the importance of lowering total cholesterol and LDL cholesterol for preventing disease progression.<sup>1–4,22–24</sup> The inverse relation between HDL cholesterol and IVUS P&M progression in the present study is also in good agreement with previous studies<sup>25,26</sup> that underlined the importance of increasing HDL cholesterol levels.

Previous large (nonserial) histopathological studies have demonstrated the relation between serum cholesterol and atherosclerotic disease severity<sup>27,28</sup> and plaque vulnerability.<sup>29</sup> Our study extends these previous observations by providing serial morphological evidence for the clinically established relation between disease progression and serum lipids.

Previous serial IVUS studies in native coronary arteries did not address the relation between cholesterol levels and plaque progression. These IVUS studies compared treatment with a particular statin versus dietary stabilization or usual care.<sup>13–15</sup>

Cholesterol lowering is an accepted principle in reducing the risk of coronary artery disease, and the extent to which cholesterol is lowered appears to be important. In addition, a greater reduction of LDL cholesterol is associated with a greater reduction in the risk of cardiovascular events, but clinical studies have not determined definitively whether there is a benefit in lowering cholesterol to very low levels.<sup>30</sup>

Our present study suggests that an LDL cholesterol value of 75 mg/dL is on average associated with no plaque progression. Importantly, because ethnic factors may influence the response to serum cholesterol levels,<sup>31</sup> the results of our study may apply only to white patients.

Our study did not address pharmacological intervention (lipid lowering) but rather was a clinical observational study in patients with coronary artery disease treated by conventional medical therapy, including statins in the vast majority of patients. The nature of our investigation implies that potential pleiotropic effects of statins could have contributed to our findings<sup>32</sup>; however, the data are not currently available to permit further subanalyses to exclude the effect of statins. Nevertheless, when we analyzed only those patients who were on a statin, the relations between LDL cholesterol and HDL cholesterol versus the percent annual changes in plaque size remained unchanged.

Baseline total arterial CSA was identical in patients with higher ( $\geq 120$  mg/dL) versus lower LDL cholesterol but was (for both groups) significantly larger than that of a historic population of nondiseased LM coronary arteries.<sup>11</sup> This suggests that, at baseline, plaques in both groups were already accompanied by positive (compensatory) arterial remodeling.<sup>11,12</sup> Moreover, both groups had a slight but similar further increase in total arterial area not related to LDL or HDL cholesterol levels. The variability of remodeling responses<sup>12</sup> may partially explain progressive lumen narrowing in some (but not all) individuals despite an effective modification of the lipid profile.<sup>24</sup> This is in contrast to one histopathological study showing a modest linear relationship between HDL cholesterol and positive remodeling assessed at a single time point.<sup>33</sup>

### Limitations

Although by most standards, this was a large serial IVUS study, all studies with long-term serial assessment of atherosclerosis are limited to a relatively small number of patients. The data of this study are unique and may well reflect clinical reality. However, because retrospective analyses of prospectively acquired data (demographics, medication, and laboratory tests) were performed, we cannot rule out a certain selection bias; we were able to include only patients with significant coronary artery disease who were admitted for repeat cardiac catheterization  $\geq 12$  months after baseline (this limitation applies to both groups). Therefore, the findings of the present study may not be applicable to the general population. We used 2 IVUS systems in the present study; however, when we compared the data from the 2 different IVUS systems, we found no differences, and separate linear regression analyses in data sets that were obtained by one or the other IVUS system provided almost identical results. Furthermore, individual patients were imaged with the same system at index and follow-up. 3D (ECG-gated) IVUS analysis<sup>34</sup> may be superior for the assessment of coronary dimensions and provides volumetric data. In addition, sophisticated computer-aided gray-scale IVUS analyses<sup>15</sup> or radio-frequency IVUS analyses<sup>35</sup> may be superior to visual IVUS analysis of plaque composition.

## Conclusions

Our data demonstrate a positive linear relation between LDL cholesterol and annual changes in plaque size, with an LDL value of 75 mg/dL as cutoff level that, on average, predicts no plaque progression. In addition, HDL cholesterol reveals an inverse relation with annual changes in plaque size.

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