

ORIGINAL ARTICLE

Statin Therapy, LDL Cholesterol, C-Reactive Protein, and Coronary Artery Disease

Steven E. Nissen, M.D., E. Murat Tuzcu, M.D., Paul Schoenhagen, M.D., Tim Crowe, B.S., William J. Sasiela, Ph.D., John Tsai, M.D., John Orazem, Ph.D., Raymond D. Magorien, M.D., Charles O'Shaughnessy, M.D., and Peter Ganz, M.D., for the Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) Investigators*

ABSTRACT

BACKGROUND

Recent trials have demonstrated better outcomes with intensive than with moderate statin treatment. Intensive treatment produced greater reductions in both low-density lipoprotein (LDL) cholesterol and C-reactive protein (CRP), suggesting a relationship between these two biomarkers and disease progression.

METHODS

We performed intravascular ultrasonography in 502 patients with angiographically documented coronary disease. Patients were randomly assigned to receive moderate treatment (40 mg of pravastatin orally per day) or intensive treatment (80 mg of atorvastatin orally per day). Ultrasonography was repeated after 18 months to measure the progression of atherosclerosis. Lipoprotein and CRP levels were measured at baseline and follow-up.

RESULTS

In the group as a whole, the mean LDL cholesterol level was reduced from 150.2 mg per deciliter (3.88 mmol per liter) at baseline to 94.5 mg per deciliter (2.44 mmol per liter) at 18 months ($P < 0.001$), and the geometric mean CRP level decreased from 2.9 to 2.3 mg per liter ($P < 0.001$). The correlation between the reduction in LDL cholesterol levels and that in CRP levels was weak but significant in the group as a whole ($r = 0.13$, $P = 0.005$), but not in either treatment group alone. In univariate analyses, the percent change in the levels of LDL cholesterol, CRP, apolipoprotein B-100, and non-high-density lipoprotein cholesterol were related to the rate of progression of atherosclerosis. After adjustment for the reduction in these lipid levels, the decrease in CRP levels was independently and significantly correlated with the rate of progression. Patients with reductions in both LDL cholesterol and CRP that were greater than the median had significantly slower rates of progression than patients with reductions in both biomarkers that were less than the median ($P = 0.001$).

CONCLUSIONS

For patients with coronary artery disease, the reduced rate of progression of atherosclerosis associated with intensive statin treatment, as compared with moderate statin treatment, is significantly related to greater reductions in the levels of both atherogenic lipoproteins and CRP.

From the Cleveland Clinic Foundation, Cleveland (S.E.N., E.M.T., P.S., T.C.); Pfizer, New York (W.J.S., J.T., J.O.); Ohio State University Medical Center, Columbus (R.D.M.); North Ohio Heart Care, Elyria (C.O.); and Brigham and Women's Hospital, Boston (P.G.). Address reprint requests to Dr. Nissen at the Department of Cardiovascular Medicine, Cleveland Clinic Foundation, 9500 Euclid Ave., Cleveland, OH 44195, or at nissens@ccf.org.

*The REVERSAL Investigators are listed in the Appendix.

N Engl J Med 2005;352:29-38.

Copyright © 2005 Massachusetts Medical Society.

TWO RECENT TRIALS DEMONSTRATED that intensive lipid-lowering therapy with statins improved clinical outcomes¹ and reduced the progression of atherosclerosis.² Many authorities attributed the greater benefits of intensive statin therapy, as compared with moderate statin therapy, to greater reductions in the levels of atherogenic lipoproteins, particularly low-density lipoprotein (LDL) cholesterol.³ However, statins have a wide range of biologic effects in addition to lipid lowering, including reductions in the levels of C-reactive protein (CRP), a phenomenon commonly termed a “pleiotropic effect.”⁴⁻⁶ In both recent comparisons, at the conclusion of the trials, CRP levels were 30 to 40 percent lower after intensive statin therapy than after moderate treatment.⁴ This finding raises a provocative scientific question: Do reductions in CRP represent an independent factor influencing the benefits of more intensive statin therapy?

Large observational studies have established a strong relationship between CRP levels and the morbidity and mortality associated with coronary

disease.⁷⁻⁹ However, the precise mechanism underlying the association between CRP levels and adverse outcomes remains incompletely described. Theoretically, by decreasing the levels of atherogenic lipoproteins, statins could decrease systemic inflammation, thereby reducing CRP levels. An alternative hypothesis proposes that statins have direct antiinflammatory effects, independent of their lipid-lowering capabilities. In this model, CRP plays a more direct role in the pathogenesis of atherosclerosis, and a statin-mediated reduction in inflammation contributes directly to reduced disease activity. Because statins decrease the levels of both LDL cholesterol and CRP, it is difficult to determine whether CRP is an indirect biomarker reflecting the benefits of statins or a direct participant in atherogenesis.

Intravascular ultrasonography is a useful technique for assessing the effect of therapies on the vascular wall, providing a precise and continuous measure of the progression of atherosclerosis. In the Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) trial, intensive therapy with 80 mg of atorvastatin per day slowed the pro-

Table 1. Laboratory Values at Baseline and Follow-up and Change in Values from Baseline.*

Characteristic	Both Groups (N=502)	Pravastatin Group (N=249)	Atorvastatin Group (N=253)	P Value†
Baseline				
Total cholesterol (mg/dl)	232.2±34.2	232.6±34.1	231.8±34.2	0.80
LDL cholesterol (mg/dl)	150.2±26.9	150.2±25.9	150.2±27.9	0.99
HDL cholesterol (mg/dl)	42.6±10.7	42.9±11.4	42.3±9.9	0.51
Non-HDL cholesterol (mg/dl)	189.6±32.5	189.7±32.3	189.5±32.7	0.96
Triglycerides (mg/dl)	197.4±100.6	197.7±105.6	197.2±95.7	0.96
Apo B-100 (mg/dl)	152.7±23.4	153.0±22.4	152.4±24.3	0.79
CRP (mg/liter)‡				0.46
Geometric mean	2.9	3.0	2.8	
Interquartile range	1.4 to 6.1	1.4 to 6.1	1.3 to 6.3	
18-Mo follow-up				
Total cholesterol (mg/dl)	169.2±40.0	187.5±32.2	151.3±38.9	<0.001
LDL cholesterol (mg/dl)	94.5±32.2	110.4±25.8	78.9±30.2	<0.001
HDL cholesterol (mg/dl)	43.8±11.3	44.6±11.3	43.1±11.3	0.15
Non-HDL cholesterol (mg/dl)	125.4±39.6	142.9±32.2	108.1±38.6	<0.001
Triglycerides (mg/dl)	157.0±93.8	165.8±92.1	148.4±94.9	0.04
Apo B-100 (mg/dl)	104.8±29.1	118.1±24.0	91.8±27.9	<0.001
CRP (mg/liter)‡				<0.001
Geometric mean	2.3	2.9	1.8	
Interquartile range	0.9 to 5.4	1.3 to 6.2	0.8 to 4.3	

gression of atherosclerosis more than did moderate treatment with 40 mg of pravastatin per day.² We applied statistical methods to examine the relationship between the reductions in LDL cholesterol and CRP levels and the rate of disease progression measured by intravascular ultrasonography.

METHODS

STUDY DESIGN

The institutional review board of each participating center approved the protocol, and all patients provided written informed consent. Intravascular ultrasonography was performed in a single vessel in patients who had a clinical indication for coro-

nary angiography and had stenosis of at least 20 percent on angiography. Eligible patients had to have an LDL cholesterol level of 125 to 210 mg per deciliter (3.23 to 5.43 mmol per liter) after a statin-free washout period of 4 to 10 weeks. Patients were randomly assigned to receive either 40 mg of pravastatin or 80 mg of atorvastatin orally daily. The patients and all study personnel were unaware of the treatment assignments or the results of laboratory measurements.

INTRAVASCULAR ULTRASONOGRAPHY

Investigators performed intravascular ultrasonography in the longest and least angulated target vessel that met the inclusion criteria. After the adminis-

Table 1. (Continued.)

Characteristic	Both Groups (N=502)	Pravastatin Group (N=249)	Atorvastatin Group (N=253)	P Value†
Change from baseline				
Total cholesterol				<0.001
Mean (mg/dl)	-63±44	-45±37	-81±43	
Percent	-26.3	-18.4	-34.1	
LDL cholesterol				<0.001
Mean (mg/dl)	-56±37	-40±29	-71±37	
Percent	-35.8	-25.2	-46.3	
HDL cholesterol				0.11
Mean (mg/dl)	1.2±7.9	1.6±7.7	0.8±8.0	
Percent	4.2	5.6	2.9	
Non-HDL cholesterol				<0.001
Mean (mg/dl)	-64±43	-47±35	-81±43	
Percent	-33.0	-23.6	-42.2	
Triglycerides				0.002
Mean (mg/dl)	-40±96	-32±94	-49±98	
Percent	-13.5	-6.8	-20.0	
Apo B-100				<0.001
Mean (mg/dl)	-48±30	-35±25	-61±30	
Percent	-30.6	-22.0	-39.1	
CRP‡				<0.001
Geometric mean (mg/liter)	-0.2	0.2	-0.7	
Interquartile range (mg/liter)	-1.9 to 0.8	-1.5 to 1.6	-2.8 to 0.1	
Percent	-22.4	-5.2	-36.4	

* Plus-minus values are means ±SD. To convert values for cholesterol to millimoles per liter, multiply by 0.02586. To convert values for triglycerides to millimoles per liter, multiply by 0.01129.

† P values were calculated by means of the two-sample t-test.

‡ CRP levels were not available for six patients at baseline or follow-up (one in the pravastatin group and five in the atorvastatin group).

tration of intracoronary nitroglycerin, the transducer was positioned in the distal vessel and withdrawn at a rate of 0.5 mm per second (the “pullback”) with the use of a motor drive. A core laboratory evaluated the image quality of each ultrasonogram, and only patients whose ultrasonograms met prespecified image-quality requirements were eligible for randomization. After an 18-month treatment period, patients again underwent intravascular ultrasonography under identical conditions. This method of intravascular ultrasonography has been described previously in detail.^{2,10,11}

CORE LABORATORY MEASUREMENTS

Personnel who were unaware of the patients’ clinical characteristics and treatment assignments used manual planimetry to measure, on a computer screen, a series of cross-sections of ultrasonographic images selected exactly 1.0 mm apart along the long axis of the vessel. Measurements were performed in accordance with the standards of the American College of Cardiology and the European Society of Cardiology.¹² For each cross-section analyzed, the operator measured the area of the external elastic membrane and the lumen. The accuracy and reproducibility of this method have been reported previously.^{2,13}

CALCULATION OF END POINTS

The average area of atheroma per cross-section was calculated as follows:

$$\frac{\sum(\text{EEM}_{\text{CSA}} - \text{LUMEN}_{\text{CSA}})}{n}$$

where EEM_{CSA} is the cross-sectional area of the external elastic membrane, $\text{LUMEN}_{\text{CSA}}$ is the cross-sectional area of the lumen, and n is the number of cross-sections in the pullback. To compensate for pullbacks of differing lengths, the total atheroma volume for each patient was calculated as the average area of atheroma multiplied by the median number of cross-sections in the pullbacks for all patients in the study. The efficacy variable “change in normalized total atheroma volume” (TAV) was calculated as $\text{TAV}_{18 \text{ months}} - \text{TAV}_{\text{baseline}}$. The percent atheroma volume (PAV) was calculated with the use of the following formula:

$$\left[\frac{\sum(\text{EEM}_{\text{CSA}} - \text{LUMEN}_{\text{CSA}})}{\sum \text{EEM}_{\text{CSA}}} \right] \times 100.$$

The efficacy variable “change in PAV” was calculated as $\text{PAV}_{18 \text{ months}} - \text{PAV}_{\text{baseline}}$.

LABORATORY TESTS

A central laboratory performed all biochemical determinations (Medical Research Laboratory, Highland Heights, Ky.).

STATISTICAL ANALYSIS

For continuous variables with a normal distribution, means \pm SD are reported. For CRP levels, the geometric means and interquartile ranges are reported. Because the ultrasonographic end points were not normally distributed, we applied an analysis-of-covariance model to rank-transformed data to determine P values. Correlations between variables are described with the use of Spearman rank-correlation coefficients, and multivariate regression analyses based on rank-transformed data were used to obtain partial correlation coefficients adjusted for the effects of covariates.¹⁴ The ultrasonographic variable served as the dependent variable; the independent variables consisted of the change in CRP coupled with the change in non-high-density lipoprotein (non-HDL) cholesterol, LDL cholesterol, or apolipoprotein B-100 (apo B-100). For a further description of bivariate relationships with ultrasonographic end points, we used the locally weighted scatterplot smoothing (LOWESS) technique.¹⁵ This technique is designed to produce a smooth fit to the data and reduces the influence of extreme outliers. Analyses were performed with the use of SAS software, version 6.12.

RESULTS

PATIENT POPULATION

Between June 1999 and September 2001, 502 patients were enrolled at 34 U.S. centers and underwent intravascular ultrasonography at both baseline and 18 months of follow-up that could be evaluated (249 in the pravastatin group and 253 in the atorvastatin group). The average age was 56 years, 72 percent were men, 89 percent were white (race was recorded by the study coordinators on the case-report form), 26 percent were current smokers, 69 percent had a history of hypertension, and 19 percent had a history of diabetes.²

LABORATORY FINDINGS AND RESULTS OF INTRAVASCULAR ULTRASONOGRAPHY

Table 1 summarizes laboratory values at baseline and at the completion of the study (18 months) for the entire population and each treatment group. For

all 502 patients, the mean baseline LDL cholesterol level was 150.2 mg per deciliter (3.88 mmol per liter), the non-HDL cholesterol level was 189.6 mg per deciliter (4.90 mmol per liter), and the geometric mean CRP level was 2.9 mg per liter. After 18 months of treatment, the mean LDL cholesterol level was 94.5 mg per deciliter (2.44 mmol per liter), the non-HDL cholesterol level was 125.4 mg per deciliter (3.24 mmol per liter), and the geometric mean CRP level was 2.3 mg per liter. There were greater reductions in LDL cholesterol, non-HDL cholesterol, and CRP levels in the atorvastatin group than in the pravastatin group ($P < 0.001$ for each comparison).²

Table 2 summarizes measures of disease burden as determined by intravascular ultrasonography at baseline and the completion of the study for the entire population and the two treatment groups. Both measures of the progression of atherosclerosis — total atheroma volume and percent atheroma volume — reflected a slower rate of progression in the

group that received intensive treatment with atorvastatin than in the group that received moderate treatment with pravastatin.

CORRELATION BETWEEN REDUCTIONS IN LIPOPROTEIN AND CRP

There was a weak but significant correlation between the percent reductions in LDL cholesterol and in CRP levels only for the study group as a whole ($r = 0.13$, $P = 0.005$) — not for the pravastatin group alone ($r = -0.008$, $P = 0.90$) or the atorvastatin group alone ($r = 0.09$, $P = 0.17$). Changes in other atherogenic lipoproteins, such as apo B-100 and non-HDL cholesterol, had similarly weak correlations with the reduction in CRP levels in the regression analysis.

EFFECT OF CHANGES IN CRP AND LIPIDS ON PROGRESSION

Table 3 summarizes the correlations between the changes in the levels of atherogenic lipoproteins, CRP, and HDL cholesterol and the rate of progres-

Table 2. Baseline and Follow-up Values for Intravascular Ultrasonographic End Points and Change in Values from Baseline.*

Atheroma Volume	Both Groups (N=502)		Pravastatin Group (N=249)		Atorvastatin Group (N=253)		P Value†
	Mean ±SD	Median	Mean ±SD	Median	Mean ±SD	Median	
Baseline							
Total (mm ³)	189.4±115.3	165.9 (113.8 to 238.9)	194.5±114.8	168.6 (117.4 to 246.2)	184.4±115.7	161.9 (111.0 to 228.2)	0.20
Normalized total (mm ³)‡	184.1±83.1	174.5 (122.1 to 232.3)	189.1±86.5	187.2 (122.1 to 239.1)	179.1±79.4	166.6 (122.4 to 226.6)	0.26
Percent	38.9±11.0	38.9 (32.2 to 46.2)	39.5±10.8	40.0 (32.5 to 46.3)	38.4±11.3	38.2 (31.7 to 45.8)	0.18
18-Mo follow-up							
Total (mm ³)	191.7±110.7	169.9 (113.3 to 244.0)	199.6±112.3	180.0 (125.5 to 255.3)	183.9±108.8	160.9 (107.4 to 240.3)	0.04
Normalized total (mm ³)‡	186.5±81.5	175.7 (124.5 to 239.2)	194.2±86.0	179.7 (128.9 to 248.2)	178.9±76.2	170.5 (119.8 to 222.2)	0.08
Percent	40.2±10.5	39.9 (33.8 to 47.1)	41.4±10.0	41.8 (35.0 to 47.7)	39.0±10.8	38.7 (31.6 to 45.7)	<0.001
Change from baseline							
Total (mm ³)	2.3±31.7	1.4 (-14.4 to 19.5)	5.1±31.4	4.4 (-13.3 to 21.9)	-0.4±31.8	-0.9 (-14.5 to 13.8)	0.04
Normalized total (mm ³)‡	2.4±29.4	1.5 (-15.3 to 20.1)	5.1±27.6	4.1 (-13.2 to 23.5)	-0.2±31.0	-0.9 (-17.9 to 15.3)	0.03
Percent	1.3±5.1	0.9 (-1.9 to 4.4)	1.9±4.9	1.6 (-1.6 to 4.7)	0.6±5.1	0.2 (-2.5 to 3.9)	0.002

* Values in parentheses are interquartile ranges.

† P values were calculated with the use of the Wilcoxon rank-sum test.

‡ Values were adjusted for pullbacks of different lengths by multiplying the average area of atheroma volume for each patient by the median number of cross-sections in the pullbacks for all patients in the study.

Table 3. Relationships between Changes in Laboratory Measures and Intravascular Ultrasonographic End Points.

Laboratory Measure	Percent Atheroma Volume		Total Atheroma Volume	
	Correlation Coefficient*	P Value	Correlation Coefficient*	P Value
Univariate analysis				
LDL cholesterol				
Change	0.10	0.03	0.09	0.04
Percent change	0.14	0.002	0.12	0.005
HDL cholesterol				
Change	-0.04	0.40	-0.01	0.84
Percent change	-0.04	0.42	-0.01	0.78
Triglycerides				
Change	0.05	0.23	0.06	0.19
Percent change	0.08	0.08	0.08	0.09
Non-HDL cholesterol				
Change	0.09	0.05	0.07	0.10
Percent change	0.13	0.004	0.10	0.02
apo B-100				
Change	0.09	0.05	0.08	0.06
Percent change	0.13	0.004	0.12	0.008
CRP				
Change	0.11	0.01	0.11	0.02
Percent change	0.11	0.01	0.11	0.02
Multivariate analysis (adjusted for changes in CRP and non-HDL cholesterol)				
Percent change in non-HDL cholesterol	0.11	0.01	0.08	0.06
Percent change in CRP	0.09	0.04	0.09	0.05
Multivariate analysis (adjusted for changes in CRP and LDL cholesterol)				
Percent change in LDL cholesterol	0.12	0.008	0.11	0.02
Percent change in CRP	0.09	0.04	0.08	0.06
Multivariate analysis (adjusted for changes in CRP and apo B-100)				
Percent change in apo B-100	0.11	0.01	0.10	0.03
Percent change in CRP	0.09	0.05	0.08	0.07

* Values are Spearman rank-correlation coefficients.

sion of atherosclerosis for both end points assessed by means of intravascular ultrasonography. Univariate analysis revealed significant correlations between ultrasonographic measures of disease progression and laboratory measures of atherogenic lipoproteins, including LDL cholesterol, apo B-100, and non-HDL cholesterol. The percent change in the LDL cholesterol level had the closest correlation

with progression, with a correlation coefficient of 0.12 for total atheroma volume ($P=0.005$) and of 0.14 for percent atheroma volume ($P=0.002$).

The correlations between the reduction in CRP levels and the rates of progression on intravascular ultrasonography were also significant and similar in strength to the relationships observed for the atherogenic lipoproteins. Univariate analysis yielded a correlation coefficient of 0.11 for both total and percent atheroma volume ($P=0.02$ and $P=0.01$, respectively). Most correlations between the rates of progression on ultrasonography and the percent change in non-HDL cholesterol, LDL cholesterol, and CRP levels remained significant on multivariate analysis but were weaker than those obtained by univariate analyses (Table 3).

As shown in Figure 1, greater reductions in LDL cholesterol levels were associated with slower rates of progression on intravascular ultrasonography. Figure 2 shows this same relationship for the reduction in CRP levels. Patients with the largest reductions in CRP levels had regression of atheroma, as evidenced by progression rates of less than zero.

Table 4 shows the rates of progression of atherosclerosis on ultrasonography for subgroups defined according to whether the reductions in LDL cholesterol or CRP levels were greater than or less than the median decreases. For both efficacy measures, the highest rates of progression were in the subgroup in which decreases in both LDL cholesterol and CRP levels were less than the median. Significantly lower progression rates were observed in the subgroup with decreases in both LDL cholesterol and CRP levels that were greater than the median ($P=0.001$ for both efficacy measures).

DISCUSSION

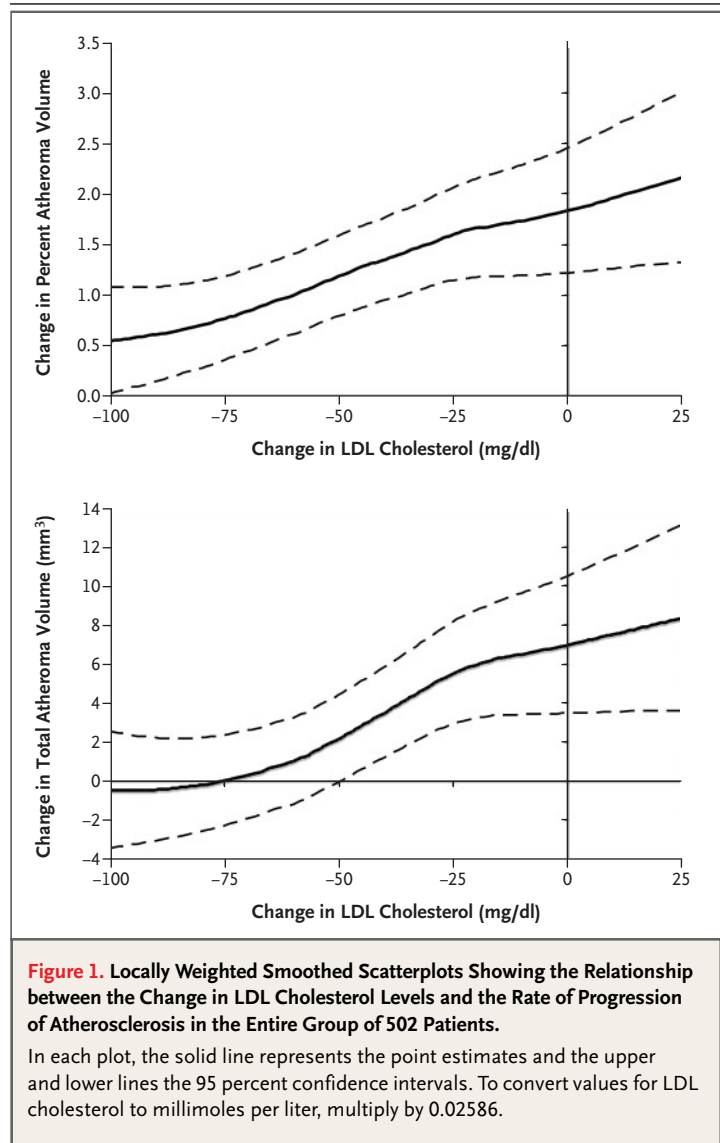
Epidemiologic evidence has established a strong relationship between elevated levels of atherogenic lipoproteins, particularly LDL cholesterol, and the risk of death and complications from cardiovascular causes. Placebo-controlled trials of statins have demonstrated that pharmacologic therapies that reduce LDL cholesterol levels also proportionally decrease cardiovascular risk.¹⁶⁻¹⁹ Accordingly, the clinical benefits of statin therapy have largely been attributed to reductions in the levels of atherogenic lipoproteins. However, observational studies have also established a strong relationship between the levels of CRP, the most stable and reliable laboratory measure of systemic inflammation, and adverse

cardiovascular outcomes. Statins have a variety of pleiotropic properties, including their ability to induce dose-dependent decreases in the levels of CRP and other inflammatory biomarkers.^{5,6} Since statins reduce the levels of both LDL cholesterol and CRP, it is difficult to determine the relative contribution of the reduction in each of these biomarkers to the observed clinical benefits.

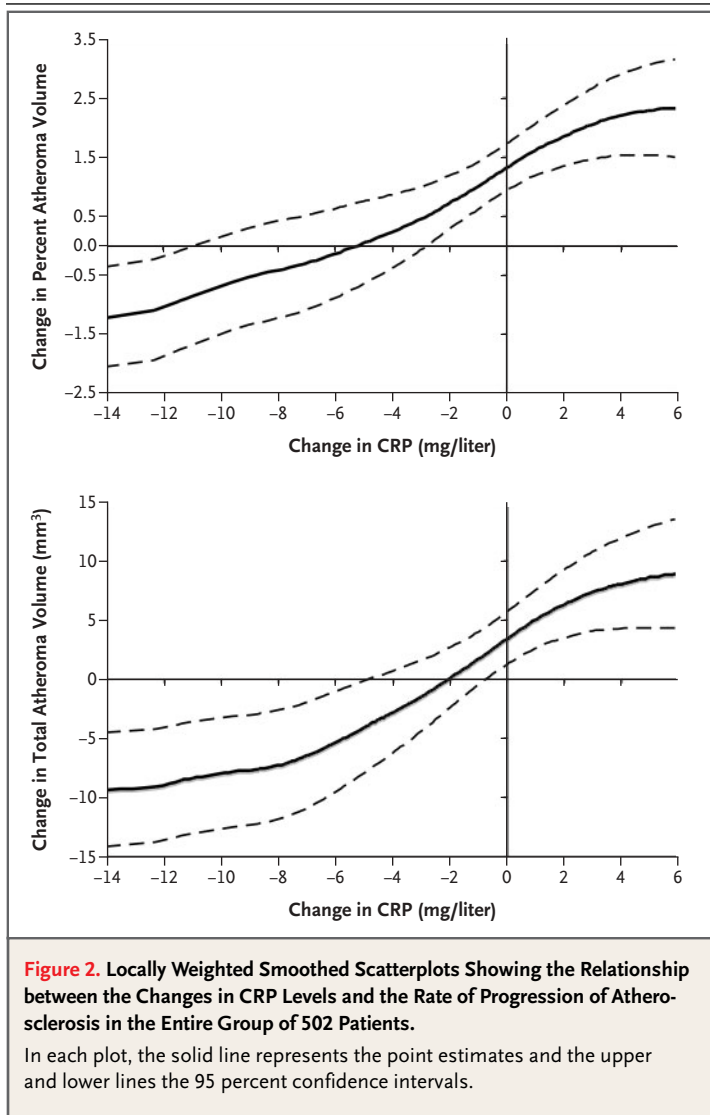
We sought to close this gap in knowledge by analyzing the correlation among lipid levels, CRP levels, and the rate of progression of atherosclerosis, using intravascular ultrasonography to measure disease progression in patients who were being treated with statins.² Intravascular ultrasonography is a useful technique for assessing the effect of therapies on the vascular wall, providing a precise and continuous measure of disease progression.²⁰ In the REVERSAL trial, intensive therapy with 80 mg of atorvastatin per day slowed the rate of progression of atherosclerosis more than did moderate treatment with 40 mg of pravastatin per day. Because we studied two different intensities of statin therapy, we evaluated a broad range of reductions in LDL cholesterol and CRP, permitting a post hoc analysis of the relationship between these two biomarkers and the rate of progression of atherosclerosis across a clinically important range of values.

Correlation analysis revealed that reductions in the levels of atherogenic lipoproteins were not closely correlated with reductions in CRP levels. There was a weak but significant correlation between the reduction in LDL cholesterol levels and the reduction in CRP levels for the overall group of 502 patients ($r=0.13$, $P=0.005$), but not in either treatment group alone. These data demonstrate that statin-mediated reductions in CRP are largely unrelated to the decrease in LDL cholesterol levels. These findings confirm the work of other investigators and strongly suggest that the statin-mediated reduction in CRP is unlikely to be a secondary consequence of a reduction in LDL cholesterol but, rather, is potentially mediated by independent pathways.²¹

Analysis of the relationship among lipoprotein levels, CRP levels, and the rate of progression of atherosclerosis yielded particularly informative results. Reductions in both LDL cholesterol and CRP levels were significantly correlated to the rate of progression. In univariate analyses, both ultrasonographic measures of progression—the change in the normalized total atheroma volume and the change in percent atheroma volume—correlated significantly with the reduction in the levels of ath-



erogenic lipoproteins, including LDL cholesterol, non-HDL cholesterol, and apo B-100. The closest correlation was between the LDL cholesterol level and the percent atheroma volume ($r=0.14$, $P=0.002$). However, similar correlations were observed for the relationship between the reduction in CRP levels and the rate of progression on intravascular ultrasonography ($r=0.11$, $P=0.01$). Substituting non-HDL cholesterol for LDL cholesterol, to account for the broad range of atherogenic lipoproteins, did not increase the correlation. Since the levels of both CRP and LDL cholesterol showed relatively weak correlations with the ultrasonographic end points (r values of 0.11 to 0.14), this analysis



demonstrates that biomarkers can account for only a small fraction of the observed progression rate.

To determine whether the reduction in CRP levels represented an independent factor influencing the progression of atherosclerosis, we adjusted the CRP correlations for the effects of atherogenic lipoproteins. In this multivariate analysis, CRP remained significant in most analyses, regardless of which measure of atherogenic lipoproteins was used — LDL cholesterol, apo B-100, or non-HDL cholesterol. Patients with reductions in the levels of both LDL cholesterol and CRP that were greater than the median reduction had significantly lower progression rates than patients in whom the reductions were less than the median decrease ($P=0.001$). These data

provide evidence that the reduction in CRP levels plays an independent role in the beneficial effects of statins on the progression of coronary atherosclerosis.

Since measures of progression reflected by intravascular ultrasonography are not normally distributed, we used LOWESS methods to illustrate the relationships between the reductions in LDL cholesterol and CRP levels and the rates of progression determined by ultrasonography (Fig. 1 and 2). These plots demonstrated a continuous relationship between the magnitude of reduction in either LDL cholesterol or CRP levels and the rates of progression of atherosclerosis for both measures of efficacy. Atherosclerosis regressed in patients with the greatest reduction in CRP levels, but not in those with the greatest reduction in LDL cholesterol levels. Although the data are not provided in this article, LOWESS plots showed slower rates of progression in the intensively treated atorvastatin subgroup across a broad range of reductions in lipids and CRP. The slower rate of progression in the atorvastatin group for any magnitude of reduction in LDL cholesterol levels can be partially explained by the additional effects of treatment on the reduction in CRP levels, just as the differences in the CRP plots can be partially explained by the additional reduction in LDL cholesterol levels effected by atorvastatin therapy. Thus, the effects of the reductions in both LDL cholesterol and CRP levels must be considered to explain the observed differences in progression between atorvastatin and pravastatin treatment.

Our findings have important implications for understanding the pathogenesis of the progression of atherosclerosis and the mechanism of benefit of statin therapy. The Pravastatin or Atorvastatin and Infection Therapy (PROVE IT) trial demonstrated improved outcomes¹ and the REVERSAL trial demonstrated reduced rates of progression of atherosclerosis² after intensive, as compared with moderate, statin therapy. Although a single trial had previously shown that the effects of statins are evident within 16 weeks,²² the rapidity of the divergence in results between the treatment groups in both trials was unexpected.⁴ In most earlier placebo-controlled trials, differences between statins and placebo were not evident for the first two years after randomization.¹⁶⁻¹⁸ However, in both the REVERSAL and PROVE IT trials, CRP levels were 30 to 40 percent lower at the conclusion of the trial in the intensively treated patients than in the group that received moderate treatment, which may ex-

Table 4. Rates of Progression According to the Change in LDL Cholesterol and CRP Levels.*

Subgroup	No. of Patients	Percent Atheroma Volume [†]			Total Atheroma Volume (mm ³) [†]		
		Median	95% CI	Mean ±SD	Median	95% CI	Mean ±SD
Reduction in LDL cholesterol and CRP both greater than median	141	0.24 (-2.8 to 3.5) [‡]	-0.77 to 0.54	0.33±5.3	-1.98 (-23.0 to 10.8) [‡]	-6.26 to 3.67	-2.41±31.6
Reduction in LDL cholesterol greater than median, reduction in CRP less than median	106	0.81 (-2.0 to 4.8)	-0.32 to 1.81	1.62±4.7	2.06 (-12.8 to 21.5)	-3.26 to 6.41	4.04±28.7
Reduction in LDL cholesterol less than median, reduction in CRP greater than median	108	1.21 (-2.0 to 4.0)	-0.31 to 2.08	0.91±4.9	-1.04 (-18.6 to 22.5)	-6.78 to 8.74	1.42±29.2
Reduction in LDL cholesterol and CRP both less than median	141	1.82 (-1.5 to 5.1)	1.0 to 2.84	2.25±5.0	8.21 (-11.8 to 27.5)	0.40 to 13.05	7.49±27.5

* CRP levels were not available for six patients at baseline or follow-up. The subgroups were formed on the basis of the median percent change in LDL cholesterol of -37.1 percent and the median percent change in CRP of -21.4 percent.

[†] Values in parentheses are interquartile ranges. Confidence intervals (CIs) are for the medians.

[‡] P=0.001 for the comparison with the subgroup in which the reduction in the levels of both LDL cholesterol and CRP was less than the median reduction (by Wilcoxon's rank-sum test).

plain the magnitude and unexpectedly rapid divergence of outcomes reported by Ridker et al. elsewhere in this issue of the *Journal*.²³

Our findings are consistent with a variety of experimental observations that suggest a direct role for CRP in the pathogenesis of atherosclerosis. CRP renders oxidized LDL more susceptible to uptake by macrophages, induces the expression of vascular-cell adhesion molecules, stimulates the production of tissue factor, and impairs the production of nitric oxide.²⁴⁻²⁷ Children with elevated CRP levels have increased carotid intimal medial thickness and reduced vasodilatation mediated by brachial-artery flow.²⁸ A recent study suggested that the presence of above-average levels of CRP attenuates the benefits of intensive statin therapy with respect to the carotid intimal media thickness.²⁹

Evidence of a dual mechanism of benefit for statins — lipid lowering and a reduction in inflammation — has important implications for current and future treatment of atherosclerosis. Current guidelines emphasize the use of lipid-lowering therapies to reach target levels of LDL cholesterol, non-HDL cholesterol, or both. However, individual agents differ in their ability to reduce the levels of inflammatory biomarkers. Accordingly, our study raises the provocative question of whether the effects of statins on CRP, as well as LDL cholesterol, should be considered in decisions regarding therapy.

Our study has important limitations. It is a hypothesis-generating post hoc analysis examining the effect of a single inflammatory marker on disease progression, not morbidity or mortality. Nonetheless, our findings suggest that the level of CRP may ultimately represent an important therapeutic target. We do not believe that these data are sufficient to recommend routine serial measurement of CRP in order to modulate statin therapy, but further study is warranted. An ongoing clinical trial is assessing the use of CRP levels to guide therapy in patients who do not have elevated LDL cholesterol levels.³⁰ Since approaches to the reduction of LDL cholesterol levels that do not involve statins have uncertain antiinflammatory effects, the ability of such therapies to improve the outcome requires testing in clinical trials.³¹

Funded by Pfizer.

Dr. Nissen reports having served as a consultant to AstraZeneca, Atherogenics, Lipid Sciences, Wyeth, Novartis, Pfizer, Sankyo, Takeda, Kowa, Sanofi, Novo-Nordisk, Eli Lilly, Kos Pharmaceuticals, GlaxoSmithKline, Forbes Medi-tech, and Merck-Schering Plough; having served as a lecturer for AstraZeneca and Pfizer; and having received funding from AstraZeneca, Takeda, Sankyo, Pfizer, Atherogenics, and Lipid Sciences for ongoing clinical trials. Dr. Tuzcu reports having received lecture fees from AstraZeneca, Merck, Pfizer, and Takeda and grant support from Pfizer. Mr. Crowe reports owning Pfizer stock. Drs. Sasiela, Tsai, and Orazem are employees of Pfizer. Dr. Magorien reports having served as a consultant to Bristol-Myers Squibb and owning stock in Merck. Dr. Ganz reports having served as a consultant for AstraZeneca and Pfizer and a lecturer for Pfizer.

APPENDIX

In addition to the authors, the following investigators participated in this study: Wake Forest University, Winston-Salem, N.C., M. Kutcher; University of Colorado Health Sciences Center, Denver, J. Burchenal; University of Texas—San Antonio, San Antonio, S. Bailey; Heart Institute at Borgess, Kalamazoo, Mich., T. Fischell; University of Florida, Gainesville, R. Kerensky; Heart Care Center, Blue Island, Ill., R. Iafaldano; University of Chicago, Chicago, J. Lopez; William Beaumont Hospital, Royal Oak, Mich., C. Grines; University of California, San Diego, San Diego, A. DeMaria; UCLA Medical Center for Health Sciences, Los Angeles, J. Tobis; LeBauer Cardiovascular Research Foundation, Greensboro, N.C., B. Brodie; University of Washington Medical Center, Seattle, D. Linker; Cedars-Sinai Medical Center, Los Angeles, J. Forrester; University of North Carolina, Chapel Hill, S. Smith; Androsoggin Cardiology Research, Auburn, Me., R. Weiss; Medical College of Ohio, Toledo, C. Cooper; Rhode Island Hospital, Providence, B. Sharaf; East Carolina University, Greenville, N.C., M. Miller; Buffalo Cardiology and Pulmonary Associates, Buffalo, N.Y., J. Corbelli; Heart Care Group, Allentown, Pa., J. Kleaveland; University of Arkansas for Medical Sciences, Little Rock, L. Garza; University of Louisville, Louisville, Ky., M. Leesar; Capital Cardiology Associates, Albany, N.Y., A. DeLago; Cardiology of Georgia—Piedmont Hospital, Atlanta, C. Wickliffe; New England Medical Center, Boston, J. Kavin; Kramer & Crouse Cardiology, Kansas City, Mo., P. Kramer; Miriam Hospital, Providence, R.I., P. Gordon; Mount Sinai Hospital, New York, S. Sharma; Oklahoma Heart Institute, Tulsa, W. Leimbach; Eastlake Cardiovascular Associates, St. Clair Shores, Mich., R. Cleary, Jr.; University Hospitals of Cleveland, R. Nair.

REFERENCES

- Cannon CP, Braunwald E, McCabe CH, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med* 2004;350:1495-504.
- Nissen SE, Tuzcu EM, Schoenhagen P, et al. Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomized controlled trial. *JAMA* 2004;291:1071-80.
- Sacks FM. High-intensity statin treatment for coronary heart disease. *JAMA* 2004;291:1132-4.
- Topol EJ. Intensive statin therapy — a sea change in cardiovascular prevention. *N Engl J Med* 2004;350:1562-4.
- Liao JK. Isoprenoids as mediators of the biological effects of statins. *J Clin Invest* 2002;110:285-8.
- Albert MA, Danielson E, Rifai N, Ridker PM. Effect of statin therapy on C-reactive protein levels: the pravastatin inflammation/CRP evaluation (PRINCE): a randomized trial and cohort study. *JAMA* 2001;286:64-70.
- Ridker PM, Rifai N, Rose L, Buring JE, Cook NR. Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. *N Engl J Med* 2002;347:1557-65.
- Ridker PM. Clinical application of C-reactive protein for cardiovascular disease detection and prevention. *Circulation* 2003;107:363-9.
- Ridker PM, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. *N Engl J Med* 2000;342:836-43.
- Nissen SE, Tsunoda T, Tuzcu EM, et al. Effect of recombinant ApoA-I Milano on coronary atherosclerosis in patients with acute coronary syndromes: a randomized controlled trial. *JAMA* 2003;290:2292-300.
- Eisen HJ, Tuzcu EM, Dorent R, et al. Everolimus for the prevention of allograft rejection and vasculopathy in cardiac-transplant recipients. *N Engl J Med* 2003;349:847-58.
- Mintz GS, Nissen SE, Anderson WD, et al. American College of Cardiology clinical expert consensus document on standards for acquisition, measurement and reporting of intravascular ultrasound studies (IVUS): a report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. *J Am Coll Cardiol* 2001;37:1478-92.
- Schoenhagen P, Sapp SK, Tuzcu EM, et al. Variability of area measurements obtained with different intravascular ultrasound catheter systems: impact on clinical trials and a method for accurate calibration. *J Am Soc Echocardiogr* 2003;16:277-84.
- Neter J, Wasserman W, Kutner MH. Applied linear regression models. Homewood, Ill.: R.D. Irwin, 1983.
- Chambers JM, Cleveland WS, Kleiner B, Tukey PA. Graphical methods for data analysis. Boston: Duxbury Press, 1983.
- Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *N Engl J Med* 1996;335:1001-9.
- Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;344:1383-9.
- Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002;360:7-22.
- Sever PS, Dahlof B, Poulter NR, et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet* 2003;361:1149-58.
- Nissen SE, Yock P. Intravascular ultrasound: novel pathophysiological insights and current clinical applications. *Circulation* 2001;103:604-16.
- Plenge JK, Hernandez TL, Weil KM, et al. Simvastatin lowers C-reactive protein within 14 days: an effect independent of low-density lipoprotein cholesterol reduction. *Circulation* 2002;106:1447-52.
- Schwartz GG, Olsson AG, Ezekowitz MD, et al. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial. *JAMA* 2001;285:1711-8.
- Ridker PM, Cannon CP, Morrow D, et al. C-reactive protein levels and outcomes after statin therapy. *N Engl J Med* 2005;352:20-8.
- Zouki C, Beauchamp M, Baron C, Filep JG. Prevention of in vitro neutrophil adhesion to endothelial cells through shedding of L-selectin by C-reactive protein and peptides derived from C-reactive protein. *J Clin Invest* 1997;100:522-9.
- Torzewski M, Rist C, Mortensen RF, et al. C-reactive protein in the arterial intima: role of C-reactive protein receptor-dependent monocyte recruitment in atherosclerosis. *Arterioscler Thromb Vasc Biol* 2000;20:2094-9.
- Cermak J, Key NS, Bach RR, Balla J, Jacob HS, Vercellotti GM. C-reactive protein induces human peripheral blood monocytes to synthesize tissue factor. *Blood* 1993;82:513-20.
- Verma S, Wang CH, Li SH, et al. A self-fulfilling prophecy: C-reactive protein attenuates nitric oxide production and inhibits angiogenesis. *Circulation* 2002;106:913-9.
- Jarvisalo MJ, Harmoinen A, Hakanen M, et al. Elevated serum C-reactive protein levels and early arterial changes in healthy children. *Arterioscler Thromb Vasc Biol* 2002;22:1323-8.
- Kent SM, Taylor AJ. Usefulness of lowering low-density lipoprotein cholesterol to <70 mg/dl and usefulness of C-reactive protein in patient selection. *Am J Cardiol* 2003;92:1224-7.
- Ridker PM. Rosuvastatin in the primary prevention of cardiovascular disease among patients with low levels of low-density lipoprotein cholesterol and elevated high-sensitivity C-reactive protein: rationale and design of the JUPITER trial. *Circulation* 2003;108:2292-7.
- Abramowicz M. Cholesterol rethink for high-risk patients. *Med Lett Drugs Ther* 2004;46:37-8.

Copyright © 2005 Massachusetts Medical Society.