

ORIGINAL ARTICLE

## Effect of ACAT Inhibition on the Progression of Coronary Atherosclerosis

Steven E. Nissen, M.D., E. Murat Tuzcu, M.D., H. Bryan Brewer, M.D., Ilke Sipahi, M.D., Stephen J. Nicholls, M.B., B.S., Ph.D., Peter Ganz, M.D., Paul Schoenhagen, M.D., David D. Waters, M.D., Carl J. Pepine, M.D., Tim D. Crowe, B.S., Michael H. Davidson, M.D., John E. Deanfield, M.D., Lisa M. Wisniewski, R.N., James J. Hanyok, Pharm.D., and Laurent M. Kassalow, M.S., for the ACAT Intravascular Atherosclerosis Treatment Evaluation (ACTIVATE) Investigators\*

### ABSTRACT

#### BACKGROUND

The enzyme acyl-coenzyme A:cholesterol acyltransferase (ACAT) esterifies cholesterol in a variety of tissues. In some animal models, ACAT inhibitors have antiatherosclerotic effects.

#### METHODS

We performed intravascular ultrasonography in 408 patients with angiographically documented coronary disease. All patients received usual care for secondary prevention, including statins, if indicated. Patients were randomly assigned to receive the ACAT inhibitor pactimibe (100 mg per day) or matching placebo. Ultrasonography was repeated after 18 months to measure the progression of atherosclerosis.

#### RESULTS

The primary efficacy variable analyzing the progression of atherosclerosis — the change in percent atheroma volume — was similar in the pactimibe and placebo groups (0.69 percent and 0.59 percent, respectively;  $P=0.77$ ). However, both secondary efficacy variables assessed by means of intravascular ultrasonography showed unfavorable effects of pactimibe treatment. As compared with baseline values, the normalized total atheroma volume showed significant regression in the placebo group ( $-5.6 \text{ mm}^3$ ,  $P=0.001$ ) but not in the pactimibe group ( $-1.3 \text{ mm}^3$ ,  $P=0.39$ ;  $P=0.03$  for the comparison between groups). The atheroma volume in the most diseased 10-mm subsegment regressed by  $3.2 \text{ mm}^3$  in the placebo group, as compared with a decrease of  $1.3 \text{ mm}^3$  in the pactimibe group ( $P=0.01$ ). The combined incidence of adverse cardiovascular outcomes was similar in the two groups ( $P=0.53$ ).

#### CONCLUSIONS

For patients with coronary disease, treatment with an ACAT inhibitor did not improve the primary efficacy variable (percent atheroma volume) and adversely affected two major secondary efficacy measures assessed by intravascular ultrasonography. ACAT inhibition is not an effective strategy for limiting atherosclerosis and may promote atherogenesis. (ClinicalTrials.gov number, NCT00268515.)

From the Cleveland Clinic Foundation, Cleveland (S.E.N., E.M.T., I.S., S.J.N., P.S., T.D.C., L.M.W.); Medstar Research Institute—Washington Hospital Center, Washington, D.C. (H.B.B.); Brigham and Women's Hospital, Boston (P.G.); San Francisco General Hospital, San Francisco (D.D.W.); the University of Florida, Gainesville (C.J.P.); Radiant Research, Chicago (M.H.D.); the University of London, London (J.E.D.); and Sankyo Pharma, Edison, N.J. (J.J.H., L.M.K.). 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.

\*Participants in the ACTIVATE trial are listed in the Appendix.

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THE INTRODUCTION OF 3-HYDROXY-3-methylglutaryl coenzyme A reductase inhibitors (statins) nearly two decades ago marked a turning point in the effort to develop pharmacologic agents to reduce morbidity and mortality from coronary disease. However, despite the development of increasingly potent statins capable of markedly lowering cholesterol levels, coronary disease remains the leading cause of death in Western societies.<sup>1</sup> Basic research has clarified the metabolic pathways underlying the accumulation and removal of lipids from the vascular wall. Accordingly, drug-discovery efforts have focused on targeted therapeutic approaches. One promising target is the enzyme acyl-coenzyme A:cholesterol acyltransferase (ACAT), which esterifies cholesterol in a variety of cells and tissues.<sup>2,3</sup>

Two forms of ACAT have been identified: ACAT1, present in many tissues, including macrophages, and ACAT2, present in intestinal epithelial cells and hepatocytes (Fig. 1).<sup>4,5</sup> Theoretically, inhibition of ACAT1, by blocking the esterification of cholesterol, could prevent the transformation of macrophages into foam cells and slow the progression of atherosclerosis.<sup>6</sup> Inhibition of ACAT2 would be expected to decrease serum lipid levels. In some animal models, ACAT inhibitors are remarkably effective in reducing the formation of atheromas.<sup>6-10</sup> However, some studies involving genetically engineered mice have suggested that the inhibition of ACAT1 may promote atherosclerosis.<sup>11-13</sup> Interspecies differences in ACAT activity limit the ability of studies in animals to predict the effects of such agents in humans.<sup>14</sup>

Therefore, we conducted the ACAT Intravascular Atherosclerosis Treatment Evaluation (ACTIVATE) trial, a phase 3 clinical trial assessing the effects of pactimibe, a nonselective ACAT inhibitor with approximately equipotent effects on both ACAT1 and ACAT2. Recently, intravascular ultrasonography has been used successfully to study therapies for atherosclerosis.<sup>15-19</sup> We used intravascular ultrasonography to assess the disease burden in patients with established coronary disease before and after 18 months of treatment with pactimibe or placebo.

## METHODS

### STUDY DESIGN AND BASELINE INTRAVASCULAR ULTRASONOGRAPHY

The study was designed by the Cleveland Clinic Cardiovascular Coordinating Center and the steering

committee (listed in the Appendix) in consultation with the study sponsor. The institutional review boards of participating centers approved the protocol, and all patients provided written informed consent. Intravascular ultrasonography was performed in patients who had clinical indications for coronary angiography. Eligible patients had to have at least one vessel with stenosis of at least 20 percent on angiography.

The methods used for intravascular ultrasonography in trials evaluating regression and progression of atherosclerosis have been described recently.<sup>15-19</sup> Briefly, a target vessel was identified by the interventional operator. This vessel could not have undergone revascularization or have more than 50 percent luminal narrowing throughout a target segment, which had to be at least 30 mm long. After the intracoronary administration of 100 to 300  $\mu$ g of nitroglycerin, a 40-MHz intravascular-ultrasonography catheter (Atlantis, Boston Scientific Scimed) was advanced into the target vessel and the transducer positioned distal to a side branch. The transducer was then withdrawn at a speed of 0.5 mm per second with the use of a motor drive ("pullback"). During this pullback, images were obtained at a rate of 30 frames per second and recorded on videotape. The image quality of each videotape was assessed in a core laboratory at the Cleveland Clinic Foundation, and only patients whose videotape met prespecified requirements for image quality were eligible to undergo randomization. Patients were randomly assigned to receive either 100 mg of pactimibe daily or matching placebo. The patients and all study personnel were unaware of the treatment assignments.

### FOLLOW-UP INTRAVASCULAR ULTRASONOGRAPHY AND ANALYSIS

After an 18-month treatment period, patients who received at least one dose of study drug underwent repeated intravascular ultrasonography. The operator placed the ultrasonographic catheter in the vessel originally examined and positioned the transducer distal to the original branch site. The motorized pullback was repeated under conditions identical to those in the baseline study. The resulting videotapes were then analyzed by the core laboratory. A technician selected the distal branch site as the beginning point for analysis. Subsequently, every 60th image was analyzed, representing cross-sections spaced 1.0 mm apart. Measurements were performed in accordance

with the standards of the American College of Cardiology.<sup>20</sup> Using customized software (ImageJ, version 1.29w), the technician performed a calibration by measuring 1-mm grid marks in the image. Manual planimetry was used to trace the leading edges of the lumen and external elastic membrane. The accuracy and reproducibility of this method have been reported previously.<sup>21</sup>

#### CALCULATION OF INTRAVASCULAR-ULTRASONOGRAPHY EFFICACY VARIABLES

The atheroma volume, expressed as a percentage (the percent atheroma volume [PAV]), the primary efficacy variable, was calculated with the use of the following equation:

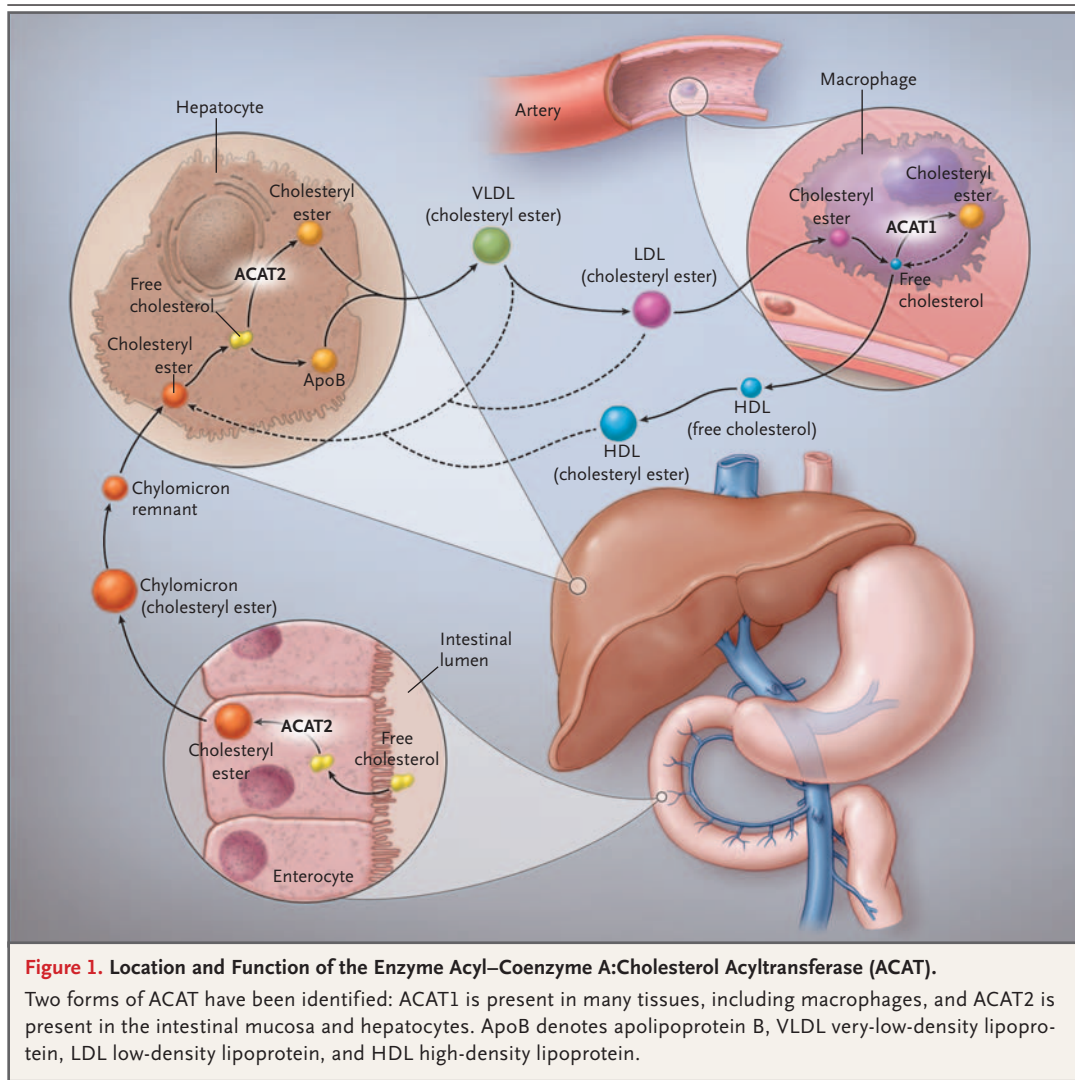
$$\text{PAV} = \frac{\sum(\text{EEM}_{\text{CSA}} - \text{lumen}_{\text{CSA}})}{\sum \text{EEM}_{\text{CSA}}} \times 100$$

where  $\text{EEM}_{\text{CSA}}$  is the cross-sectional area of the external elastic membrane and  $\text{lumen}_{\text{CSA}}$  is the cross-sectional area of the lumen. For each patient, the change in the percent atheroma volume was computed as the percent atheroma volume at the end of the study minus the percent atheroma volume at baseline.

The change in the normalized total atheroma volume, the secondary efficacy variable, was calculated by first determining the average area of atheroma per cross-section:

$$\text{Average atheroma area} = \frac{\sum(\text{EEM}_{\text{CSA}} - \text{lumen}_{\text{CSA}})}{n}$$

where  $n$  is the number of cross-sections in the pullback. To compensate for pullbacks of different lengths, the normalized total atheroma volume for each patient was calculated as the aver-



age atheroma area multiplied by the mean number of cross-sections in pullbacks that could be evaluated for all study patients. The change in normalized total atheroma volume was calculated as the normalized total atheroma volume at follow-up minus the normalized total atheroma volume at baseline.

The efficacy variable change in atheroma volume in the most diseased 10-mm subsegment was calculated by determining the atheroma volume for every possible contiguous 10-mm segment of the vessel that underwent intravascular ultrasonography. For each patient, the 10-mm subsegment with the greatest atheroma volume at baseline was examined at follow-up and the change in atheroma volume determined.

#### LABORATORY TESTS AND CLINICAL OUTCOMES

The patients had scheduled clinic visits every three months. A central laboratory performed all biochemical determinations (Medical Research Laboratory). Patients were followed for adverse cardiovascular outcomes, including death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina, and coronary and carotid revascularization. Investigator-reported events were independently verified by an adjudication team at the coordinating center, whose members were unaware of patients' treatment assignments.

#### STATISTICAL ANALYSIS

Statistical analyses were performed by the sponsor and confirmed independently by a biostatistician at the Cleveland Clinic. The manuscript was written by the lead author in consultation with coauthors. The sponsor was permitted to review the manuscript and make suggestions, but the steering committee determined the final content.

We estimated that 208 patients would need to be enrolled in each group for the study to have a statistical power of 90 percent (assuming a standard deviation of 4.7 percent) to detect an absolute difference of 1.5 percent in the primary efficacy variable with a 5 percent type I error rate for a two-sided test. With an anticipated dropout rate of 20 percent, enrollment of 260 patients per group was required to provide an adequate number of patients with results that could be evaluated.

Demographic and laboratory characteristics are summarized for all randomized patients, and

P values were calculated from uncorrected Pearson chi-square analysis of categorical variables. For normally distributed continuous variables, P values were calculated with the use of one-way analysis of variance, with treatment group as a factor. For variables that were not normally distributed, the Wilcoxon rank-sum test was used. For the efficacy analyses of percent atheroma volume and normalized total atheroma volume, the least-square mean and P values were calculated from an analysis-of-covariance model with percent atheroma volume at baseline as the covariate and center and treatment group as factors. For atheroma volume in the most diseased 10-mm subsegment, the median values are reported and P values were obtained from a stratified rank analysis of the covariance model, with the baseline value as the covariate and center as a stratification factor. The time to a first adverse cardiovascular event was analyzed with the use of the Cox regression model. Analyses were performed with the use of SAS software (version 8.2).

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## RESULTS

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#### PATIENT POPULATION

Between December 2002 and January 2004, 534 patients underwent randomization at 52 U.S. centers and 526 received the study drug. The baseline demographic and laboratory characteristics of the study population are reported in Table 1. All baseline characteristics were similar in the pactimibe and placebo groups, although the pactimibe group had a slightly higher high-density lipoprotein (HDL) cholesterol level than the placebo group (P=0.04) and had a slightly higher percentage of patients with a history of hypertension (P=0.03). A total of 408 patients (206 in the pactimibe group and 202 in the placebo group) underwent intravascular ultrasonography at both baseline and follow-up and had results that could be evaluated. Of the 126 randomized patients who were not included in the intravascular ultrasonography analysis, 8 never received study drug, 29 withdrew because of an adverse event, 35 were withdrawn at their own request, 11 were lost to follow-up, and 43 were withdrawn for miscellaneous reasons, including noncompliance and inadequate intravascular ultrasonography at follow-up. There were no significant differences in dropout rates between the two groups.

**Table 1. Baseline Characteristics of the Patients.\***

Characteristic	Placebo (N = 268)	Pactimibe (N = 266)	P Value†
Age — yr	59.6±10.4	58.8±9.8	0.41
Male sex — no. (%)	192 (71.6)	175 (65.8)	0.15
Body-mass index	31.0±5.9	30.9±5.6	0.93
Statin use — no. (%)	212 (79.1)	204 (76.7)	0.50
History of diabetes mellitus — no. (%)	71 (26.5)	77 (28.9)	0.53
History of hypertension — no. (%)	188 (70.1)	208 (78.2)	0.03
Prior myocardial infarction — no. (%)	83 (31.0)	78 (29.3)	0.68
Stable angina — no. (%)	152 (56.7)	152 (57.1)	0.92
Unstable angina — no. (%)	113 (42.2)	98 (36.8)	0.21
Tobacco use — no. (%)	55 (20.5)	58 (21.8)	0.72
Blood pressure — mm Hg			
Systolic	129.5±15.6	127.8±17.0	0.22
Diastolic	75.7±9.9	75.1±9.2	0.49
Cholesterol — mg/dl			
Total	171.5±38.3	173.4±33.3	0.55
Direct LDL	101.5±31.1	101.4±27.7	0.99
Calculated LDL	94.8±31.7	96.0±29.4	0.67
HDL	42.4±11.1	44.6±12.6	0.04
Triglycerides — mg/dl			
Median	150	144	0.53‡
Interquartile range	107–215	107–205	
C-reactive protein — mg/liter			
Median	2.8	3.1	0.68‡
Interquartile range	1.2–6.2	1.3–6.0	

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

The body-mass index is the weight in kilograms divided by the square of the height in meters. To convert the values for triglycerides to millimoles per liter, multiply by 0.0113. LDL denotes low-density lipoprotein, and HDL high-density lipoprotein. A high-sensitivity assay was used to measure C-reactive protein.

† P values for categorical variables were obtained from uncorrected Pearson chi-square analysis. P values for continuous variables were obtained from one-way analysis of variance with treatment group as a factor.

‡ The Wilcoxon rank-sum test was used.

#### LABORATORY RESULTS

Laboratory values at the completion of the study were similar in the two groups. The mean low-density lipoprotein (LDL) cholesterol level was 86.4 mg per deciliter (2.2 mmol per liter) in the placebo group and 91.3 mg per deciliter (2.4 mmol per liter) in the pactimibe group ( $P=0.11$ ). The mean HDL cholesterol level was 42.8 mg per deciliter (1.1 mmol per liter) in the placebo group and 43.8 mg per deciliter (1.1 mmol per liter) in the pactimibe group ( $P=0.22$ ). There were no significant differences between the groups in the levels of triglyceride or C-reactive protein, as measured with the use of a high-sensitivity assay.

#### EFFICACY ANALYSES INVOLVING INTRAVASCULAR ULTRASONOGRAPHY

Table 2 shows the results of the efficacy analyses involving intravascular ultrasonography. The primary efficacy variable, the change in percent atheroma volume, was similar in the pactimibe and placebo groups (0.69 percent and 0.59 percent, respectively;  $P=0.77$ ). However, the change in the normalized total atheroma volume showed a less favorable outcome in the pactimibe group than in the placebo group ( $P=0.03$ ). The normalized total atheroma volume decreased by 5.6 mm<sup>3</sup> in the placebo group ( $P=0.001$  for the comparison with baseline values) and by 1.3 mm<sup>3</sup> in the pac-

**Table 2. Intravascular Ultrasonographic Measures of the Atheroma Burden at Baseline and at the End of the Study.**

Efficacy Variable	Placebo (N=202)	Pactimibe (N=206)	P Value
<b>Percent atheroma volume</b>			
Baseline			
Mean $\pm$ SD	39.3 $\pm$ 9.2	39.8 $\pm$ 8.8	0.53*
Median	39.3	40.2	
Interquartile range	32.5 to 45.9	34.1 to 46.0	
End of study			
Mean $\pm$ SD	39.9 $\pm$ 9.2	40.6 $\pm$ 9.2	0.77†
Median	39.4	41.1	
Interquartile range	34.1 to 46.6	34.7 to 47.0	
Change from baseline			
Least-square mean $\pm$ SE	0.59 $\pm$ 0.25	0.69 $\pm$ 0.25	0.77†
P value	0.02†	0.006†	
<b>Normalized total atheroma volume (mm<sup>3</sup>)</b>			
Baseline			
Mean $\pm$ SD	196.5 $\pm$ 90.4	198.1 $\pm$ 87.0	0.86*
Median	180.2	185.5	
Interquartile range	129.3 to 249.2	139.9 to 237.5	
End of study			
Mean $\pm$ SD	190.9 $\pm$ 87.3	196.8 $\pm$ 85.5	0.03†
Median	179.6	183.9	
Interquartile range	129.0 to 238.7	140.2 to 237.2	
Change from baseline			
Least-square mean $\pm$ SE	-5.6 $\pm$ 1.47	-1.3 $\pm$ 1.47	0.03†
P value	0.001†	0.39†	
<b>Change in most diseased 10-mm subsegment (mm<sup>3</sup>)</b>			
Baseline			
Mean $\pm$ SD	59.5 $\pm$ 28.2	61.9 $\pm$ 27.9	0.40*
Median	55.9	60.7	
Interquartile range	36.6 to 80.2	39.1 to 80.0	
End of study			
Mean $\pm$ SD	56.0 $\pm$ 26.8	60.0 $\pm$ 27.3	
Median	53.0	60.9	0.96‡
Interquartile range	37.1 to 74.0	40.4 to 74.6	
Change from baseline			
Median	-3.2	-1.3	0.01‡
Interquartile range	-8.0 to 1.1	-5.9 to 4.0	
P value§	<0.001	0.02	

\* One-way analysis of variance was used with treatment group as a factor.

† Least-square means and P values were obtained from an analysis-of-covariance model with the baseline value as covariate and center and treatment group as factors.

‡ The P value was obtained with the use of a stratified-rank analysis-of-covariance model with the baseline value as covariate and center as a stratification factor.

§ The P values were obtained with the use of the Wilcoxon signed-rank test.

timibe group ( $P=0.39$  for the comparison with baseline values). With respect to the 10-mm subsegment with the greatest disease severity, the placebo group also had more favorable effects than the pactimibe group. In these segments, the median decrease was  $3.2 \text{ mm}^3$  in the placebo group and  $1.3 \text{ mm}^3$  in the pactimibe group ( $P=0.01$ ). Thus, both secondary efficacy measures showed attenuation in the degree of the regression of atherosclerosis as assessed by intravascular ultrasonography during 18 months of a usual-care regimen, which consisted of statins in most patients.

#### PRESPECIFIED SUBGROUPS

Table 3 shows the results for the primary efficacy measure for 11 prespecified subgroups in the two groups of patients. The results were similar in most subgroups, although a subgroup defined by whether body-mass index (the weight in kilograms divided by the square of the height in meters) was more than 30 or 30 or less at baseline showed heterogeneity ( $P=0.03$ ).

#### ADVERSE EVENTS AND CLINICAL OUTCOMES

Table 4 shows the numbers of patients who had abnormal hepatic and muscle-related laboratory values and adverse clinical outcomes. Figure 2 shows the time to a first adverse cardiovascular event for the combined outcomes of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina, and coronary or carotid revascularization. Adverse cardiovascular events occurred in 26.5 percent of patients in the placebo group, as compared with 23.8 percent of patients in the pactimibe group (relative risk, 0.90;  $P=0.53$ ). A sharp increase in events was observed at the end of the trial, reflecting revascularization procedures prompted by the catheterization required at the end of the study.

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### DISCUSSION

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Despite great advances in prevention and treatment, atherosclerotic cardiovascular disease remains the leading cause of death in Western societies, and its incidence is growing rapidly in the developing world. Since their introduction in 1987, statins have gradually assumed a central role in the primary and secondary prevention of cardiovascular disease. However, statins reduce the risk

of complications and death from cardiovascular causes by only about one third, at best, leaving the remaining two thirds of patients unprotected.<sup>1</sup> Accordingly, the quest for pharmacologic agents that target other steps in atherogenesis has intensified in recent years. ACAT inhibitors have been considered a promising therapeutic agent, and several pharmaceutical companies are developing agents that fall into this class.<sup>22,23</sup> Since most ACAT inhibitors do not substantially alter serum lipid levels in humans, other means are required to determine whether a specific ACAT inhibitor will have antiatherosclerotic effects. Intravascular ultrasonography is particularly well suited to this role, providing precise measures of the progression of atherosclerosis with sufficient statistical power to allow trials of reasonable size and duration.<sup>15-19</sup>

In our phase 3 study, we evaluated the ACAT inhibitor pactimibe in a group of patients with established coronary disease. The results were not encouraging. Although the primary efficacy variable, the change in percent atheroma volume, was neutral (Table 2), both major secondary efficacy measures showed that pactimibe treatment attenuated the regression of atherosclerosis observed in the usual-care group. Furthermore, treatment with pactimibe was associated with unfavorable trends in subgroups at increased risk, such as patients with diabetes (Table 3). Fortunately, with only 18 months of drug exposure in about 500 patients, no adverse effect on the risk of death or complications was observed. Nonetheless, because of the relationship between measures of disease progression or regression and clinical outcome,<sup>24,25</sup> this finding should be considered carefully by pharmaceutical companies and investigators studying other ACAT inhibitors. If other agents in this class are studied in patients with coronary disease, there should be reasonable evidence that their biologic effects differ from those of pactimibe. Clinical trials of other ACAT inhibitors will require warnings in the informed-consent form and close monitoring by an independent data and safety monitoring board.

The mechanisms underlying the potentially proatherogenic effects of ACAT inhibition remain uncertain. By blocking esterification of cholesterol, ACAT1 inhibitors increase the level of free cholesterol. There is credible scientific evidence of a cytotoxic effect of free cholesterol, which is expressed primarily by apoptosis of macrophages

Table 3. Change in Percent Atheroma Volume in Prespecified Subgroups.\*

Subgroup	No. of Patients	Placebo (N=202)	Pactimibe (N=206)	P Value
Statin use at baseline				
None or <12 mo	241	0.63±3.1	0.59±3.9	0.98
≥12 Mo	167	0.60±2.9	0.91±3.7	0.55
Sex				
Male	290	0.33±2.9	0.50±3.8	0.57
Female	118	1.5±3.2	1.2±3.9	0.69
Age				
<65 yr	284	0.34±3.1	0.74±3.9	0.32
≥65 yr	124	1.2±2.6	0.65±3.8	0.33
Diabetes mellitus at baseline				
Present	108	1.1±2.9	2.0±3.9	0.17
Absent	300	0.47±3.0	0.17±3.7	0.46
Metabolic syndrome at baseline				
Present	169	0.95±2.9	1.4±3.5	0.30
Absent	239	0.40±3.0	0.15±4.0	0.61
History of hypertension				
Present	301	0.85±2.6	0.90±3.8	0.88
Absent	107	0.1±3.7	0.04±4.1	0.97
Smoking status at baseline				
Current	84	0.49±3.0	0.93±3.5	0.65
Former or never	324	0.65±3.0	0.65±3.9	0.90
Body-mass index at baseline				
≤30	218	0.62±3.2†	-0.01±4.2†	0.21†
>30	188	0.60±2.8†	1.4±3.4†	0.08†
Baseline LDL cholesterol				
≤100 mg/dl	199	0.86±2.9	0.57±4.1	0.81
>100 mg/dl	189	0.36±3.1	0.82±3.6	0.38
Baseline HDL cholesterol				
≤40 mg/dl	197	0.88±3.0	0.87±3.8	0.95
>40 mg/dl	209	0.37±3.0	0.59±3.9	0.61
Baseline C-reactive protein				
≤3.0 mg/liter	213	0.59±3.0	0.57±3.7	0.97
>3.0 mg/liter	192	0.65±3.0	0.77±4.0	0.79

\* Plus-minus values are means ±SD. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. LDL denotes low-density lipoprotein, and HDL high-density lipoprotein. A high-sensitivity assay was used to measure C-reactive protein.

† Interaction P=0.03 from an analysis-of-covariance model with percent atheroma volume at baseline as the covariate and treatment group and body-mass index as factors.

within atherosclerotic lesions.<sup>26-29</sup> Cellular necrosis within atherosclerotic lesions has been associated with increased activity of the underlying disease process.<sup>29</sup> Fazio et al. demonstrated increased atherosclerosis in LDL-receptor-knockout mice also lacking macrophage ACAT1.<sup>12</sup> Similar findings have been described with pharmacologic inhibition of macrophage ACAT in mouse and rabbit models of atherosclerosis.<sup>13</sup> Thus, although it was hoped that ACAT inhibition would promote re-

verse cholesterol transport (Fig. 1), the cytotoxic effects of free cholesterol may counterbalance any favorable effects. The slightly higher LDL cholesterol level in the pactimibe group than in the placebo group at the end of the study cannot explain differences on intravascular ultrasonography of the magnitude we observed.<sup>19</sup>

One other ACAT inhibitor, avasimibe, was studied in a phase 2 dose-ranging trial that used intravascular ultrasonographic efficacy measures and showed a neutral outcome (with nonsignificant trends toward a greater degree of progression in the ACAT-inhibitor group).<sup>30</sup> However, the results of this study are difficult to interpret. Avasimibe is a potent inducer of cytochrome P-450 3A4, the principal route for the metabolism of many statins.<sup>31</sup> Accordingly, the lipid-lowering effects of their background statin regimen were attenuated in many statin-treated patients exposed to avasimibe. The increase in LDL cholesterol levels among avasimibe-treated patients approached 10 percent, an increase likely to affect progression rates as assessed by intravascular ultrasonography.<sup>30</sup> The avasimibe study was prematurely terminated by the study sponsor, preventing many patients from taking study drug for the intended period. Finally, there were only about 100 patients in each group, thus limiting the statistical power to detect changes in plaque burden by intravascular ultrasonography.

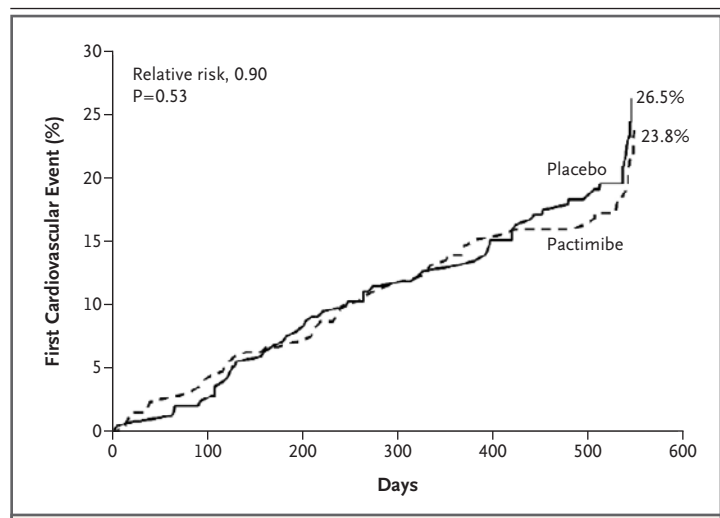
Our study demonstrates the value of intravascular ultrasonography in assessing the effect of therapies on the atherosclerotic disease process. Previous studies have demonstrated the beneficial effects of treatments known to decrease atherosclerosis. These include studies demonstrating the antiatherosclerotic benefits of achieving lower-than-usual LDL cholesterol levels,<sup>17</sup> administration of an HDL cholesterol mimetic,<sup>16</sup> treatment with an antihypertensive-drug regimen,<sup>18</sup> and reductions of C-reactive protein.<sup>19</sup> However, we found that systemic therapy with pactimibe had unfavorable effects on disease progression. This finding is important, because it suggests that intravascular ultrasonography can be used successfully to determine both the benefits and potential hazards of new therapies. The primary efficacy variable — percent atheroma volume — showed progression in both groups, whereas both secondary efficacy variables showed regression. These differences reflect the effect of negative coronary remodeling, which influences the

**Table 4. Laboratory Abnormalities and Adverse Clinical Outcomes.**

Variable	Placebo (N=255)	Pactimibe (N=258)
	<i>no. of patients (%)</i>	
<b>Adverse clinical outcome</b>		
Death from cardiovascular causes	4 (1.6)	2 (0.8)
Nonfatal myocardial infarction	6 (2.4)	4 (1.6)
Nonfatal stroke	1 (0.4)	1 (0.4)
Carotid or coronary revascularization	62 (24.3)	61 (23.6)
Hospitalization for unstable angina	27 (10.6)	20 (7.8)
<b>Laboratory abnormality*</b>		
Alanine aminotransferase >3 times ULN†	0	2 (0.8)
Aspartate aminotransferase >3 times ULN†	0	1 (0.4)
Creatine kinase >10 times ULN	1 (0.4)	0

\* ULN denotes upper limit of normal.

† An abnormal laboratory result was obtained on two consecutive occasions.



**Figure 2. Time to a First Adverse Cardiovascular Event.**

Cardiovascular events included in this composite end point include death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina, and carotid or coronary revascularization. The sharp increase in events at the end of the trial represents revascularization procedures prompted by the required catheterization procedure. The relative risk is for the comparison of the pactimibe group with the placebo group.

end point of percent atheroma volume but not the end point of total atheroma volume.<sup>32</sup>

Our study has important limitations. The relationship between efficacy measures assessed with the use of intravascular ultrasonography and clinical outcomes has not been fully explored. Since our study was not powered to detect a dif-

ference in the rates of adverse cardiovascular events, the clinical effects of any observed pro-atherogenic properties of pactimibe cannot be confirmed. Since ACAT inhibitors do not substantially affect serum lipid levels, the optimal dose of these agents is difficult to determine. We used a dose of pactimibe that was based on studies of animal models of atherosclerosis and cultured macrophages. Thus, theoretically, a lower or higher dose of pactimibe might have produced different effects, and other ACAT inhibitors with different relative effects on ACAT1 and ACAT2 may exert more favorable effects on atherosclerosis.

Nonetheless, several important conclusions are warranted. The strategy of ACAT inhibition did not slow the progression of atherosclerosis as indicated by our measurements and may even have promoted atherogenesis. Accordingly, further study of the therapeutic use of ACAT inhibitors must consider the possibility of adverse effects, and drug-development programs should exercise caution in exposing patients to this class of drugs.

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#### APPENDIX

In addition to the authors, the following persons participated in the ACTIVATE trial: *Data Safety and Monitoring Board*: S.C. Smith (chair), Durham, N.C.; K.L. Lee, Durham, N.C.; G.A. Beller, Charlottesville, Va.; *Intravascular Ultrasonography and Angiographic Core Laboratory Staff*: J. Andrews, E. Balazs, S. Brener, T. Churchill, A. Colagiovanni, K. Emerick, T. Fonk, J. Fox, T. Ivanc, K. King, A. Loyd, B. Magyar, K. McInturff, R. Poliszczuk, R. Regal, T. Schweitzer, A. Winkhart, J. Zhltnik; *Adjudication Committee*: S. Brener, A.M. Lincoff, C. Sila, K. Civello, C. Gring, B. Jefferson, V. Kalahasti, M. Khan; *Investigators*: Baptist Hospital, Pensacola, Fla., G. Aycock; University of Texas—University of Texas Health Science Center, San Antonio, S. Bailey; Montclair Hospital, Birmingham, Ala., J. Jones, III; Albany Medical Center, Troy, N.Y., A. DeLago; Huntsville Hospital, Huntsville, Ala., D. Drenning; Med Central Health System, Mansfield, Ohio, G. Eaton; Borgess Medical Center, Kalamazoo, Mich., T. Fischell; Sacred Heart Hospital, Pensacola, Fla., F.J. Fleischhauer; Cedars-Sinai Medical Center, Los Angeles, R. Makkar; Birmingham Heart Clinic, Birmingham, Ala., R. Foster; University of Florida Health Science Center, Jacksonville, P. Gilmore; St. Vincent Hospital, Indianapolis, J. Hermlinger; Research Medical Center, Kansas City, Mo., E. Hockstad; Christiana Hospital, Newark, Del., J. Hopkins; Charlotte Regional Medical Center, Port Charlotte, Fla., V. Howard; Akron General Medical Center, Akron, Ohio, M. Hughes; Baptist Hospital East, Louisville, Ky., M. Imburgia; Piedmont Hospital, Atlanta, W.C. Jacobs; University of Florida, Gainesville, R. Kerensky; Connecticut Clinical Research, Bridgeport, E. Kosinski; University of Louisville, Louisville, Ky., M. Leesar; Florida Cardiovascular Institute, Tampa, F. Matar; Pitt County Memorial Hospital, Greenville, N.C., M. Miller; Johns Hopkins Hospital, Baltimore, J. Miller; Abbott Northwestern Hospital, Minneapolis, I. Chavez; Lenox Hill Hospital, New York, S. Iyer; Veterans Affairs San Diego Medical Center, San Diego, Calif., W. Penny; Veterans Affairs Medical Center, Memphis, Tenn., K. Ramanathan; Baptist Hospital, Miami, J. Roberts; High Point Regional Health System, High Point, N.C., S. Rohrbeck; Baystate Medical Center, Springfield, Mass., M. Schweiger; Elyria Memorial Hospital, Elyria, Ohio, W.S. Sheldon; Carolinas Medical Center, Charlotte, N.C., G. Kowalchuk; Spectrum Health, Grand Rapids, Mich., H. Singh; Morton Plant Hospital, Clearwater, Fla., D. Spriggs; UCLA Medical Center—Westwood, Los Angeles, J. Tobis; Integris Southwest Medical Center, Oklahoma City, M. Yasin; Arizona Heart Hospital, Phoenix, G. Nseir; Sarasota Memorial Hospital, Sarasota, Fla., S. Culp; Holmes Regional Medical Center, Melbourne, Fla., K. Gibbs; St. Vincent's Medical Center, Jacksonville, Fla., G. Pilcher; Bayonet Pointe Hospital, Hudson, Fla., P. Rossi; Tallahassee Memorial HealthCare, Tallahassee, Fla., J. Katopodis; Prairie Education and Research Cooperative, Springfield, Ill., G. Mishkel; Wake Forest University, Winston-Salem, N.C., T. Baki; Saint Mary's—Duluth Clinic Health System, Duluth, Minn., M. Lucca; Providence Hospital, Mobile, Ala., C. Brown; University of Rochester Medical Center—Strong Memorial Hospital, Rochester, N.Y., F. Ling; Doylestown Hospital, Doylestown, Pa., J. McGarvey, Jr.; Nebraska Heart Institute, Lincoln, P. Dionisopoulos; Heart and Vascular Clinic of Northern Colorado, Fort Collins, D. Cullinane.

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**CORRECTION**

**Effect of ACAT Inhibition on the Progression of  
Coronary Atherosclerosis**

Effect of ACAT Inhibition on the Progression of Coronary Atherosclerosis . On page 1253, the last line of the Abstract should have read, "(ClinicalTrials.gov number, NCT00185042.)," not "(ClinicalTrials.gov number, NCT00268515.," as printed. We regret the error.