ACAT Inhibition and Progression of Carotid Atherosclerosis in Patients With Familial Hypercholesterolemia: The CAPTIVATE Randomized Trial

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ACAT Inhibition and Progression of Carotid Atherosclerosis in Patients With Familial Hypercholesterolemia

The CAPTIVATE Randomized Trial

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Context Inhibition of acyl coenzyme A:cholesterol acyltransferase (ACAT), an intracellular enzyme involved in cholesterol accumulation, with pactimibe was developed to assist in the prevention of cardiovascular disease.

Objective To evaluate the efficacy and safety of pactimibe in inhibition of atherosclerosis.

Design, Setting, and Patients A prospective, randomized, stratified, double-blind, placebo-controlled study (Carotid Atherosclerosis Progression Trial Investigating Vascular ACAT Inhibition Treatment Effects [CAPTIVATE]) of 892 patients heterozygous for familial hypercholesterolemia conducted at 40 lipid clinics in the United States, Canada, Europe, South Africa, and Israel between February 1, 2004, and December 31, 2005. Study was terminated on October 26, 2005.

Intervention Participants received either 100 mg/d of pactimibe (n=443) or matching placebo (n=438), in addition to standard lipid-lowering therapy.

Main Outcome Measures Carotid atherosclerosis, assessed by ultrasound carotid intima-media thickness (CIMT), at baseline, 12, 18, and 24 months. Maximum CIMT was the primary end point and mean CIMT the secondary end point.

Results Because pactimibe failed to show efficacy in the intravascular coronary ultrasound ACTIVATE study, the CAPTIVATE study was terminated prematurely after a follow-up of 15 months. After 6 months of treatment with pactimibe, low-density lipoprotein cholesterol increased by 7.3% (SD, 23%) compared with 1.4% (SD, 28%) in the placebo group (P=.001). The carotid ultrasonographic scans of the 716 patients with at least 2 scans and obtained at least 40 weeks apart were analyzed. Maximum CIMT measurements did not show a pactimibe treatment effect (difference, 0.004 mm; 95% confidence interval [CI], –0.023 to 0.015 mm; P=.64); however, the less variable mean CIMT measurement revealed an increase of 0.014 mm (95% CI, –0.027 to 0.000 mm; P=.04) in patients administered pactimibe vs placebo. Major cardiovascular events (cardiovascular death, myocardial infarction, and stroke) occurred more often in patients administered pactimibe vs placebo (10/443 [2.3%] vs 1/438 [0.2%]; P=.01).

Conclusions In patients with familial hypercholesterolemia, pactimibe had no effect on atherosclerosis as assessed by changes in maximum CIMT compared with placebo but was associated with an increase in mean CIMT as well as increased incidence of major cardiovascular events.

Trial Registration clinicaltrials.gov Identifier: NCT00151788

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CARDIOVASCULAR DISEASE (CVD) remains a leading cause of death in the Western world despite current treatment modalities. Cholesterol-lowering therapy, especially with statins, has been clearly demonstrated to be the single most effective, cost-effective, and safest method to reduce CVD risk and events, and as such has become the cornerstone of prevention of CVD.[1] However, reducing circulating low-density lipoprotein cholesterol (LDL-C), although effective in stabilizing plaque and reducing clinical events, has limitations and requires long-term, intensive treatment to demonstrate plaque regression by imaging techniques.[2] Therefore, research efforts continue to be directed at additional targets for treatment. One potential target is the inhibition of the intracellular enzyme acyl coenzyme A:cholesterol acyltransferase (ACAT), which is key to controlling the accumulation of cholesterol

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within cells, including macrophages and the arterial wall.

ACAT esterifies free cholesterol in a variety of cells. Two isoforms of ACAT have been identified (ACAT-1 and ACAT-2). ACAT-1 is present in many cell types, including macrophages, and ACAT-2 is active in the intestine and liver.[3,4] In these intestinal cells, it promotes incorporation of dietary cholesterol into chylomicrons for transport to the liver. In hepatocytes, esterification of free cholesterol precedes its incorporation into very low-density lipoprotein particles. In theory, inhibition of ACAT-1 could prevent the transformation of macrophages into foam cells in the vessel wall and thereby slow the progression of atherosclerosis and prevent the development of vulnerable plaque. In addition, inhibition of ACAT-2 could decrease serum lipid levels by reducing the synthesis of lipoproteins.

Pactimibe (CS-505) is a potent inhibitor of both ACAT-1 and ACAT-2. Treatment with ACAT inhibitors showed promising results for the prevention of atherosclerosis in various animal models.[5-8] However, some results were ambiguous. Deletion of ACAT-1 in atherosclerosis-prone mice was both reported to lead to an increase as well as to an attenuation of atherosclerosis in different studies.[9-11] Also, deletion of ACAT-2 in mice on a normal diet did not result in lipid or lipoprotein changes.[12] Furthermore, the first human trials evaluating the effects of ACAT inhibition on coronary atherosclerosis, measured by intravascular coronary ultrasound (ie, the A-PLUS [avasimibe] and ACTIVATE [pactimibe] trials), did not show any beneficial effect of ACAT inhibition on coronary atherosclerosis.[13,14]

Parallel to the phase 2 ACAT Intravascular Atherosclerosis Treatment Evaluation (ACTIVATE) trial,[14] the Carotid Atherosclerosis Progression Trial Investigating Vascular ACAT Inhibition Treatment Effects (CAPTIVATE) study was conducted. Herein, we report the results of this phase 2 and 3, randomized, stratified, double-blind, placebo-controlled clinical trial assessing the efficacy and safety of pactimibe in reducing progression of atherosclerosis as measured by carotid intima-media thickness (CIMT) in patients heterozygous for familial hypercholesterolemia.

METHODS

Study Design

The CAPTIVATE study was a prospective, randomized, stratified, double-blind, placebo-controlled study that compared 100 mg/d of pactimibe (CS-505) with matching placebo in addition to usual care in patients with heterozygous familial hypercholesterolemia and carotid atherosclerosis. This was an investigator-initiated protocol and the final trial protocol was designed in collaboration with the study sponsors. The protocol was reviewed and approved by the institutional review board at each of the participating centers and all participants provided written informed consent before entry into the trial.

The Cleveland Clinic Cardiovascular Coordinating Center in Cleveland, Ohio, acted as the clinical events committee that independently reviewed suspected events to confirm all cardiovascular secondary end points. The clinical events committee reviewed and provided comments on the study protocol and adjudicated the clinical end points of the study based on rigorous definitions specified in the protocol. A data safety and monitoring board, which was independent of the clinical events committee, monitored the safety of participants in both treatment groups during the study as described in the data safety and monitoring board charter developed for CAPTIVATE.

The study was conducted at 40 lipid clinics in the United States, Canada, Europe, South Africa, and Israel between February 1, 2004, and December 31, 2005. The treatment was discontinued on October 26, 2005, when the parallel ACTIVATE study failed to demonstrate efficacy of pactimibe vs placebo.[14] The planned study duration was 24 months.

Main inclusion criteria included age 40 to 75 years (for men) or age 45 to 75 years (for women); a diagnosis of heterozygous familial hypercholesterolemia either by genotyping or by having met the diagnostic criteria outlined by the World Health Organization; an LDL-C level of more than 100 mg/dL (to convert to millimoles per liter, multiply by 0.0259) and triglycerides of less than 500 mg/dL (to convert to millimoles per liter, multiply by 0.0113) while receiving usual and stable lipid-lowering therapy; and evidence of carotid atherosclerosis (defined as the presence of a maximum CIMT in any wall of the common carotid arteries >0.7 mm on B-mode carotid ultrasound examination performed at screening, with a maximum of 2.5 mm). Exclusion criteria included high-grade stenosis or occlusion of the carotid artery, symptomatic heart failure, or a cardiovascular event in the 3 months before randomization and uncontrolled hypertension or diabetes mellitus.

The study consisted of 2 periods. First, a period of up to 4 weeks in which patients continued on their usual prescription medication and diet. Then, if they met the entry criteria, they were randomized. Subsequently, a double-blind treatment period commenced with a scheduled duration of 104 weeks. In the lead-in period, patients continued their usual medication, including lipid-lowering treatment. At the conclusion of the lead-in period, patients were assigned randomly in a 1:1 fashion to receive either 100-mg/d pactimibe or matching placebo tablets. The study randomization was performed by using random permuted blocks within strata. Because statin use is known to influence the progression of atherosclerosis, patient randomization was stratified according to the duration of prior statin treatment (<24 months vs ≥ 24 months). Visits were scheduled at day 1 and 1, 3, 6, 9, 12, 15, 18, and 24 months after randomization.

Laboratory Test Results

All laboratory tests were performed in a certified, central clinical laboratory (Medical Research Laboratory International Inc, Highland Heights, Kentucky, and Zaventem, Belgium). Lipid

and lipoprotein levels were determined every 3 months. Routine laboratory safety testing included extensive chemistry testing (liver and renal function tests, creatinine, creatine kinase, glucose), hematological measurements, and urinalysis. Inflammatory markers, such as serum high-sensitivity C-reactive protein, were measured at baseline and after 3 months. (To convert serum C-reactive protein from milligrams per liter to nanomoles per liter, multiply by 9.524.) We present 6-month LDL-C results as they reflect on (experimental) therapy LDL-C level. End-of-study visits were performed at variable intervals (days to weeks) after discontinuation of therapy in December 2005, when the effect of the experimental therapy may have waned.

B-Mode Ultrasound CIMT Measurements

All patients underwent B-mode ultrasound imaging for CIMT measurements. Duplicate scans were performed at baseline and at 12 months to increase the power of the trial and for quality control of image acquisition. Three carotid arterial segments were assessed: the common carotid (1 cm proximal to the bulb), the carotid bulb (between the dilatation and flow divider), and the internal carotid (1 cm distal to the flow divider). Of each segment, the near and the far walls of the left and right carotid artery segments were imaged at 2 different angles; a total of 22 views. The best image of each view was selected by the sonographer as a high resolution still frame in 2×2 cm regional expansion selection mode. To provide the image analyst with dynamic information of the vessel wall for each view, an associated video clip was obtained. Acuson Aspen ultrasound instruments (Siemens, Erlangen, Germany) were equipped with L7 linear array broadband (5-12 MHz) transducers. The change in luminal diameter and wall compliance of the common carotid artery was measured by M-mode ultrasound. All images were saved in digital imaging and communications in medicine (DICOM) database format and saved to magnetic optical disks for transfer to the ultrasound core laboratory located at the Academic Medical Center (Academic Medical Center Vascular Imaging, Department of Vascular Medicine, Amsterdam, the Netherlands).

Standardized equipment and protocols were used for image and data management. Qualitative and quantitative image analyses were performed with in-house developed CAPTIVATE trial dedicated image analysis software (eTrack, Academic Medical Center, Amsterdam, the Netherlands). On each image, analysts selected a region of interest. In the far wall, the analyst positioned cursors along the leading edges of the lumen-intima and the media-adventitia interfaces. In near walls, the cursors were positioned along the trailing edges of the (estimated) adventitia-media and intima-lumen interfaces. The cursors of each of the given interfaces were splined by the image analysis software program. The maximum distance of the intima-media thickness, defined as "maximum IMT," and the mean distance, defined as the "mean IMT" parameter, between the splines were calculated for each view.

Also, at a single point, the distal common carotid lumen diameter was measured continuously for at least 3 heartbeats, from the leading edge of the intima-lumen interface of the near wall to the intima-lumen interface of the far wall using M-mode ultrasound. The change in lumen diameter and the change in pulse pressure were used to calculate the wall compliance from end diastole to peak systole. At time of efficacy assessment, readers were blinded to site, treatment allocation, sonographer, and time point of the scan. To ensure quality of image acquisition and image analyses, all sonographers and readers were trained and certified for the study. Quality control was implemented regularly during the trial and qualitative and quantitative feedback was given to sonographers and readers on their performance. Meetings of sonographers and readers and recurring site visits were also performed to safeguard standardization of protocols.

Study End Points

Our objective was to demonstrate the effect of pactimibe vs placebo when added to usual medical care on CIMT in patients with heterozygous familial hypercholesterolemia and carotid atherosclerosis. Treatment effect was to be assessed as the change in CIMT from baseline after 24 months, measured by B-mode carotid ultrasound. The primary efficacy measure was the change in maximum CIMT of a given arterial wall of all patients of which scans are available at least 40 weeks apart, comparing those randomized to pactimibe with those allocated to placebo using an intention-to-treat comparison. The secondary efficacy measure was the annual progression of the mean CIMT. Maximum and mean CIMTs were defined and calculated as the per scan aggregate of the maximum and mean CIMTs of available views.

In statistical analyses, the difference in progression in the CIMTs between treatment groups was assessed. A priori, based on previous study data and assuming α=.05 and β=.10 (a power of 90%), it was calculated that 398 patients per treatment group were required to detect a 0.04-mm maximum CIMT difference between groups after 2 years of treatment. A recent meta-analysis showed that the age-adjusted and sex-adjusted overall estimate of the relative risk of myocardial infarction (MI) is 1.15 (95% confidence interval [CI], 1.12-1.17) per 0.10-mm common CIMT difference in the general population.[15] A common standard deviation of 0.16 mm and a dropout rate of 15% were assumed. Intraclass correlation coefficients were 0.92 for maximum CIMT and 0.94 for mean CIMT for the average of duplicate baseline measurements in 719 patients. The standard deviations of the paired differences in maximum and mean CIMT between the duplicate baseline scans were 0.12 mm and 0.09 mm, respectively.

Intersonographer, interreader, and natural variances were all included in the calculated variance between visits. After premature discontinuation, intrial reproducibility showed that the available B-mode ultrasound scans

would meet the a priori set requirements to detect a relative change in maximum CIMT of at least 0.04 mm.

Secondary objective outcomes were to demonstrate the effects of pactimibe vs placebo over 24 months when added to usual medical care on (1) the lumen diameter and wall compliance of the common carotid arteries, measured by M-mode carotid ultrasound; (2) inflammatory and oxidative markers, such as serum high-sensitivity C-reactive protein, plasma interleukin 6, plasma myeloperoxidase, and serum nitrotyrosine; (3) lipid profiles (LDL-C, total cholesterol, high-density lipoprotein cholesterol (HDL-C), triglycerides, apolipoprotein B, apolipoprotein A-1, and lipoprotein [a]); (4) safety, particularly with respect to the incidence of clinical and laboratory adverse events; and (5) adrenal function, as well as (6) the incidence and the time to first occurrence of cardiovascular events. Due to discontinuation, the observation period was shorter and not all parameters were measured.

Safety Assessments

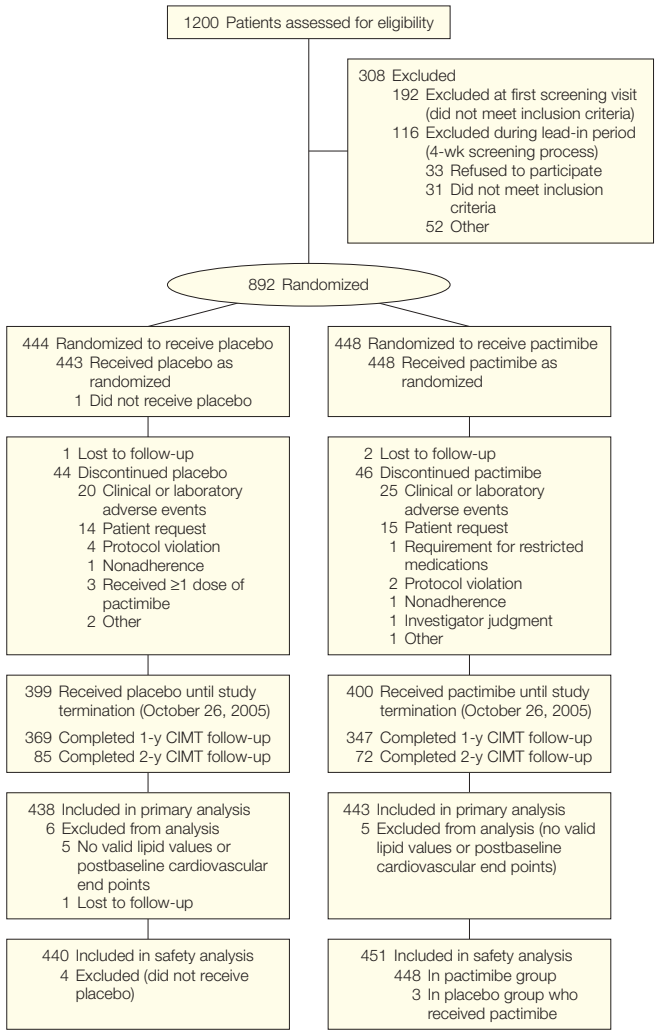
Safety was assessed by vital signs, adverse event reports, laboratory data, including an adrenocorticotropic hormone stimulation test and fecal occult blood test, and electrocardiograms. At baseline, a chest radiograph was made of all participants. Clinical adverse events were reported at each study visit. Clinically significant abnormal physical findings or laboratory values were recorded as adverse events. The incidence and the time to first occurrence of cardiovascular events, defined as the composite of cardiovascular death, nonfatal MI, nonfatal stroke, carotid revascularization, coronary revascularization, and hospitalization for unstable angina or cardiovascular death, nonfatal MI, and stroke, was determined.

All randomized patients who received at least 1 dose of randomized study medication were to be followed up for cardiovascular events for 24 months. The intention-to-treat population included all randomized patients who received at least 1 dose of randomized study medication and had at least 1 postbaseline efficacy assessment.

Statistical Analyses

The statistical analyses were intention-to-treat for all randomized participants. The maximum CIMT values of all available segment walls were averaged per person both for baseline visits and for 12-month visits and termed the maximum CIMT. Similarly, the mean CIMT values of all available segment walls were averaged per person per visit and termed the mean CIMT. Subsequently, the absolute difference between the 12-month value and the baseline value was calculated per person and termed the annual CIMT change. For the statistical analysis, we used covariance analysis with annual CIMT change as the dependent variable, and baseline CIMT and treatment group as independent variables. Because CIMT measurements were not always available from all 22 views, imputation was used to deal with incomplete data. Missing CIMT measurements of arterial segment walls were imputed using a multiple imputation scheme. Missing CIMT measurements were 5 times imputed, and imputations were drawn from the conditional distribution given CIMT measurements of all

Figure. Study Participant Flow Diagram



CIMT indicates carotid intima-media thickness.

other arterial segment walls in all available visits using an MCMC Markov chain Monte Carlo) algorithm.[16] Results from the imputed data sets were averaged.

The incidence of adjudicated cardiovascular events was defined as the composite of cardiovascular death, nonfatal MI, nonfatal stroke, coronary revascularization, carotid revascularization, and hospitalization for unstable angina or cardiovascular death, nonfatal MI, and stroke. The incidence of adjudicated cardiovascular events was compared between the pactimibe and placebo groups by using the Fisher exact test, and by the difference in composite end point proportions and the 2-tailed 95% CI for this difference.

Additional continuous variable analyses included end point and time point treatment comparisons of the following lipid and lipoprotein parameters: LDL-C, total cholesterol, HDL-C, triglycerides, apolipoprotein B, and apolipoprotein A-1. Percentage change from baseline in lipid and lipoprotein levels was assessed by using *t* test. Safety data were analyzed with the use of a linear model with terms for baseline value, hypertensive status, age, sex, race, smoking status, history of diabetes mellitus, body mass index (calculated as weight in kilograms divided by height in meters squared), creatinine clearance, and treatment. Statistical analyses were performed by using SPSS version 15.0 (SPSS Inc, Chicago, Illinois). $P < .05$ was defined as statistically significant.

RESULTS

Patient Enrollment and Characteristics

Between February 1, 2004, and February 28, 2005, 1200 patients with familial hypercholesterolemia were screened and 892 were randomized (FIGURE). Of those 892 patients, 448 received pactimibe and 443 received placebo on top of usual care. In each group, 5 patients were excluded from the analysis because of the lack of lipid values or information on postbaseline cardiovascular end points. A total of 46 patients discontinued pactimibe treatment (10%) and 44 patients discontinued placebo (10%). At the end of the study on October 26, 2005, the mean (SD) follow-up was 15 (5) months. A total of 716 of 892 patients underwent carotid ultrasonography both at baseline and after at least 40 weeks of follow-up.

Baseline characteristics and cardiovascular medical history of the participants are shown in TABLE 1. Approximately 96% of participants received statin therapy during the study, which mostly consisted of atorvastatin (48%), rosuvastatin (22%), or simvastatin (21%). Baseline characteristics of all 892 randomized patients, as well as the 716 patients for whom CIMT assessment is available, were well balanced between the 2 groups.

Effect of Pactimibe on Lipid and Lipoprotein Levels

TABLE 2 shows the lipid and lipoprotein levels at baseline and after 6 months of treatment for the 2 groups. After 6 months of treatment with pactimibe, the mean (SD) percentage change from baseline of LDL-C significantly increased by 7.3% (23%) compared with 1.4% (28%) in the placebo group ($P = .001$). This modest increase in LDL-C, accompanied by an increase in apolipoprotein B, was observed throughout the study and disappeared after discontinuation of study medication. The median high-sensitivity C-reactive protein level at baseline was 1.0 mg/L (interquartile range [IQR], 0.5-1.9 mg/L) in the placebo group and 1.0 mg/L (IQR, 0.5-2.2 mg/L) in the pactimibe group. These results did not change significantly after 3 months and were 1.1 mg/L (IQR, 0.5-2.1 mg/L) and 1.1 mg/L (IQR, 0.5-2.1 mg/L) in the placebo and pactimibe groups, respectively. Furthermore, there were no significant differences between the groups in HDL-C or triglycerides levels.

Table 1. Baseline Characteristics and Medical History of Cardiovascular Disease[a]

Characteristics	No. (%) of Patients	
	Placebo (n = 438)	Pactimibe (n = 443)
Age, mean (SD), y	54.7 (8.5)	55.5 (8.5)
Male sex	258 (58.9)	281 (63.4)
Smoking[b]		
Never	198 (45.2)	176 (39.7)
Former	180 (41.1)	186 (42.0)
Current	60 (13.7)	81 (18.3)
Body mass index, mean (SD)	27.6 (4.3)	27.6 (4.1)
Blood pressure, mean (SD), mm Hg		
Systolic	128 (15)	128 (17)
Diastolic	78 (9)	78 (10)
Statin use, mo		
None or <24	86 (19.6)	80 (18.1)
≥24	352 (80.4)	363 (81.9)
Medical history of cardiovascular disease		
Any cardiovascular medical history[c]	425 (97)	438 (97)
Hypertension	124 (28)	136 (30)
Stable angina	73 (17)	86 (19)
Unstable angina	29 (7)	23 (5)
Myocardial infarction	69 (16)	59 (13)
Coronary artery bypass graft	70 (16)	66 (15)
Percutaneous transluminal coronary angioplasty	42 (10)	53 (12)
Stroke	2 (0.5)	7 (2)
Transient ischemic attack	4 (0.9)	12 (3)
Peripheral artery disease	16 (4)	16 (4)
Diabetes mellitus	24 (6)	19 (4)

[a] Baseline is the last measurement on or before the date of the first dose of randomized study medication. Body mass index is calculated as weight in kilograms divided by height in meters squared.
[b] Smoking is not otherwise specified.
[c] Other than heterozygous familial hypercholesterolemia.

Table 2. Lipid and Lipoprotein Levels at Baseline and After 6 Months of Treatment[a]

Lipid and Lipoprotein Levels, mg/dL	Mean (SD)								
	Baseline			6 Months			% Change From Baseline		
	Placebo (n = 438)	Pactimibe (n = 443)	*P* Value	Placebo (n = 420)	Pactimibe (n = 412)	*P* Value	Placebo (n = 420)	Pactimibe (n = 412)	*P* Value
Total cholesterol	219 (45.0)	219 (46.6)	.99	217 (50.6)	224 (48.6)	.02	0.7 (18)	3.5 (17)	.02
LDL-C	139 (42.0)	141 (41.7)	.48	138 (47.1)	148 (44.0)	.002	1.4 (28)	7.3 (23)	.001
HDL-C	52 (14)	51 (15)	.31	52 (15)	51 (15)	>.99	0.6 (13)	−0.5 (14)	.23
Triglycerides	136 (70.8)	135 (78.2)	.84	138 (72.3)	127 (61.3)	.02	6.1 (36)	2.8 (35)	.18
Apolipoprotein B	135 (32.9)	137 (32.6)	.37	133 (35.8)	139 (15.7)	.002	−0.1 (20)	3.0 (18)	.02
Apolipoprotein A-1	157 (29.6)	155 (30.9)	.33	155 (29.6)	150 (29.4)	.01	0.1 (12)	−2.6 (12)	.001

Abbreviations: HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.
SI conversions: To convert total cholesterol, LDL-C, and HDL-C values to millimoles per liter, multiply by 0.0259; triglycerides to millimoles per liter, multiply by 0.0113; and apolipoprotein B and apolipoprotein A-1 to g/L, multiply by 0.01.
[a]Baseline is the last measurement on or before the date of the first dose of randomized study medication. If the day 1 measurement is nonfasting, then screening (fasting) measurement will be used for baseline. Data after 6 months of treatment are presented as they reflect lipid profiles on study therapy and a sufficient number of data points is available.

Table 3. Baseline, 12-Months' Follow-up, and Change From Baseline for Maximum and Mean CIMT

Variable	Mean (SD), mm			*P* Value
	Placebo	Pactimibe	Difference (95% CI)	
Baseline				
Maximum CIMT	0.927 (0.185)	0.937 (0.224)	−0.010 (−0.040 to 0.020)	.51
Mean CIMT	0.775 (0.141)	0.785 (0.167)	0.010 (−0.032 to 0.013)	.41
12-mo follow-up				
Maximum CIMT	0.940 (0.199)	0.955 (0.223)	0.015 (−0.046 to 0.016)	.36
Mean CIMT	0.781 (0.146)	0.804 (0.165)	0.023 (−0.046 to 0.000)	.05
Difference from baseline at 12 mo				
Maximum CIMT	0.013 (0.123)	0.017 (0.140)	0.004 (−0.023 to 0.015)	.64
Mean CIMT	0.005 (0.085)	0.019 (0.099)	−0.014 (−0.027 to 0.000)	.04

Abbreviations: CI, confidence interval; CIMT, carotid intima-media thickness.

Effect of Pactimibe on CIMT

The results for primary and secondary efficacy parameters assessed by carotid ultrasonography are shown in TABLE 3. The annual progression of maximum CIMT showed no difference between groups (difference from baseline at 12 months, 0.004 mm; 95% CI, −0.023 to 0.015 mm; *P* = .64). However, the annual progression of the mean CIMT showed a significant difference between groups as relative mean CIMT increase was observed in patients receiving pactimibe (difference, −0.014 mm; 95% CI, −0.027 to 0.000 mm; *P* = .04). Mean CIMT progressed significantly in the pactimibe group within 1 year (mean [SD], 0.019 [0.099] mm; 95% CI, 0.0081 to 0.029 mm), whereas only minor progression of mean CIMT was observed in the placebo group (0.005 [0.085] mm; 95% CI, −0.004 to 0.013 mm). No significant changes were observed in wall compliance in either treatment group.

Clinical Adverse Events and Cardiovascular End Points

Adverse events were reported in 363 of 451 patients (80.5%) in the pactimibe group and 348 of 440 patients (79.1%) in the placebo group (*P* = .62) (TABLE 4). Liver function abnormalities (increased alanine aminotransferase or aspartate aminotransferase occurring in 7/451 patients [1.6%] and 3/440 patients [0.7%], respectively; *P* = .34) were one of the more common reasons that led to discontinuation from the trial. In all but 1 patient, transaminase elevations returned to near normal limits at the time of the final study visit. No clinically important treatment-related changes were observed for vital signs, electrocardiographic parameters, fecal occult blood tests, or an adrenocorticotropic hormone stimulation. Serious adverse events were reported more frequently by patients in the pactimibe group than in the placebo group (45/451 [10.0%] vs 34/440 [7.7%]; *P* = .24).

TABLE 5 shows the incidence of cardiovascular events. Nonfatal MI occurred more frequently in patients receiving pactimibe than in patients receiving placebo (6/443 [1.4%] vs 0%; *P* = .03). Furthermore, the composite end point of all cardiovascular events (28/443 [6.3%] vs 15/438 [3.4%]; *P* = .06) as well as the composite of cardiovascular death, MI, and stroke (10/443 [2.3%] vs 1/438 [0.2%]; *P* = .01) occurred more frequently in patients receiving pactimibe vs placebo.

COMMENT

Our study shows that administration of pactimibe in addition to usual lipid-lowering therapy does not reduce carotid atherosclerosis progression in patients with familial hypercholesterolemia. Although we observed no significant difference in maximum CIMT between treatment groups, mean CIMT increased at a significantly higher rate in patients receiving pactimibe. In addition and in line with the mean CIMT findings, LDL-C levels and the incidence of cardiovascular events increased as well compared with placebo.

Our study is the third in a series of vascular imaging trials to show that ACAT inhibition does not decrease atherosclerosis

rosis and the first, to our knowledge, to suggest that it may even promote atherogenesis. In the parallel ACTIVATE study,[14] the effects of pactimibe were studied in a group of patients with established coronary disease using intravascular coronary ultrasound. Although the primary efficacy variable defined as the change in percentage atheroma volume was neutral, both major secondary efficacy measures showed that less progression of atherosclerosis was present in the placebo group than in pactimibe group. The A-PLUS study,[13] with a similar design to the ACTIVATE study, investigated the effect of the ACAT-inhibitor avasimibe. Avasimibe tended to modestly increase plaque burden and significantly increased LDL-C by 8% to 11%. Neither intravascular coronary ultrasound trial found an increase, or trend toward increase, in cardiovascular events.

Taken together, the consistent negative findings in these surrogate marker imaging trials, along with the increase in actual CVD clinical end points observed in CAPTIVATE, mitigate the promise and further development of this class of drugs for cardiovascular prevention. Furthermore, the small increase in LDL-C levels, observed in both the A-PLUS (avasimibe) and the CAPTIVATE study, does not support a beneficial effect of ACAT-2 inhibition on lipid levels and, therefore, of development of selective ACAT-2 inhibitors.

The mechanisms underlying the proatherogenic effects of ACAT inhibition in humans as well as the discrepancy between promising animal studies[5-8] and the negative human trials remain uncertain, but several explanations have been suggested. A plausible explanation is that inhibition of ACAT-1 leads to accumulation of free cholesterol to toxic levels in macrophages, leading to cell death.[17] Second, ACAT-2 may be present in lower amounts in humans than in other species and its relative contribution to plasma cholesterol levels may be smaller.[18] Third, ACAT-2 has also been reported to be up-regulated in macrophages of atherosclerotic lesions, where it could contribute to the toxic effect of free cholesterol accumulation.[19] These would explain a limited or even pernicious effect of ACAT-2 inhibition. In addition, lipid metabolism and lesion biology differ between animals and humans. In fact, most animal studies were performed against a background of very high cholesterol levels. Another explanation could be that most animal models have a much faster rate and capacity of reverse cholesterol transport than humans. On the other hand, some animal studies, such as those by Fazio et al[3] who demonstrated that ACAT-1 deficiency in macrophages

Table 4. Clinical and Laboratory Adverse Events

Adverse Events	No. (%) of Patients		*P* Value[a]
	Placebo (n = 440)	Pactimibe (n = 451)	
≥1 Clinical or laboratory	348 (79.1)	363 (80.5)	.62
≥1 Serious clinical or laboratory	34 (7.7)	45 (10.0)	.24
Most commonly reported[b]			
Influenza	40 (9.1)	30 (6.7)	.21
Nasopharyngitis	27 (6.1)	27 (6.0)	>.99
Diarrhea[c]	19 (4.3)	27 (6.0)	.29
Myalgia	19 (4.3)	25 (5.5)	.44
Back pain	19 (4.3)	20 (4.4)	>.99
Headache	29 (6.6)	19 (4.2)	.14
Arthralgia	25 (5.7)	19 (4.2)	.35
Chest pain	18 (4.1)	19 (4.2)	>.99
Dizziness	13 (3.0)	19 (4.2)	.37
Upper respiratory tract infection[c]	25 (5.7)	17 (3.8)	.21
Hypertension[c]	15 (3.4)	17 (3.8)	.86
Nausea	12 (2.7)	17 (3.8)	.45
Influenza like illness	14 (3.2)	16 (3.5)	.85
Cough	12 (2.7)	15 (3.3)	.70
Sinusitis[c]	10 (2.3)	15 (3.3)	.42
Bronchitis[c]	8 (1.8)	15 (3.3)	.20
Pain in extremity	12 (2.7)	13 (2.9)	>.99
Muscle cramp	11 (2.5)	12 (2.7)	>.99
Fatigue	15 (3.4)	11 (2.4)	.43
Urinary tract infection[c]	11 (2.5)	11 (2.4)	>.99
Tendonitis	5 (1.1)	11 (2.4)	.21
Angina pectoris	10 (2.3)	10 (2.2)	>.99
Rash[c]	7 (1.6)	10 (2.2)	.63
Edema peripheral	18 (4.1)	9 (2.0)	.08

[a] By Fischer exact test.
[b] Most commonly (<2%) reported clinical and laboratory adverse events.
[c] Not otherwise specified.

Table 5. Incidence of Cardiovascular Events

Cardiovascular Events	No. (%) of Patients		*P* Value[a]
	Placebo (n = 438)	Pactimibe (n = 443)	
Cardiovascular death	1 (0.2)	3 (0.7)	.62
Nonfatal myocardial infarction	0	6 (1.4)	.03
Nonfatal stroke	0	1 (0.2)	>.99
Coronary revascularization	10 (2.3)	14 (3.2)	.54
Carotid revascularization	1 (0.2)	0	.48
Hospitalization for unstable angina[b]	3 (0.7)	4 (0.9)	>.99
Incidence of first cardiovascular events[b]	12 (2.7)	20 (4.5)	.20
Incidence of all cardiovascular events	15 (3.4)	28 (6.3)	.06
Cardiovascular death, myocardial infarction, and stroke[b]	1 (0.2)	10 (2.3)	.01

[a] By Fisher exact test.
[b] Every patient only counted once.

causes larger atherosclerotic lesions in LDL-receptor knockout mice, a model of homozygous familial hypercholesterolemia, do support our results.

Furthermore, our study underscores the supportive role of CIMT imaging in assessing the effect of therapies on the atherosclerotic disease process. The extent of carotid atherosclerosis measured by CIMT as a predictive test for cardiovascular morbidity and mortality has been validated in a number of prospective epidemiological studies.[20] Mean CIMT has proved to be a robust surrogate end point. In our study, baseline and end-of-study visits were performed in duplicate to enhance power and provide information on within-sonographer reproducibility. The intraclass correlation coefficient of mean CIMT exceeded the intraclass correlation coefficient of maximum CIMT. Because the mean CIMT data describe the intima-media complex in a more reproducible fashion than maximum CIMT and the majority of arterial wall segments did not exhibit plaques, the mean CIMT can be considered the more sensitive efficacy measure.

CIMT has also been shown in evaluations of the efficacy of lipid-modifying medication,[21-23] antihypertensive drugs,[24] estrogens,[25] and antioxidants[26] to be consistent with the clinical outcome of subsequent morbidity and mortality trials with these therapies.[27] This was recently illustrated by the RADIANCE 1 CIMT trial,[23] which assessed increased HDL-C with the cholesterol ester transfer protein–inhibitor torcetrapib. This trial was prematurely discontinued because of increased mortality in the active treatment group in the parallel clinical end point trial ILLUMINATE.[28] The design of the RADIANCE 1 CIMT trial was comparable with that of the CAPTIVATE study in that it compared the effect of the cholesterol ester transfer protein–inhibitor torcetrapib with placebo in addition to usual care in a similar group of patients with familial hypercholesterolemia. Indeed, in line with the ILLUMINATE trial, a significant difference in annual mean CIMT progression of 0.0052 mm in favor of placebo was observed along with a significant increase in CVD end points. To put our findings in perspective, the difference observed in our study was twice as large as that observed in the RADIANCE 1 CIMT trial. These results emphasize the potential value of performing small and relatively short imaging trials before exposing large numbers of patients to new drugs in large and prolonged morbidity and mortality trials.

Recently, another CIMT study in a similar patient group with heterozygous familial hypercholesterolemia was published.[29] Against expectations, the ENHANCE trial[29] did not show a difference in change in mean CIMT between patients treated with simvastatin only compared with combined therapy with simvastatin and ezetimibe. In the CAPTIVATE trial, mean CIMT did increase at a significantly faster rate in patients receiving pactimibe compared with patients receiving placebo. One of the explanations for this difference is that ACAT inhibition may have adverse effect, as discussed above, whereas ezetimibe may not. Moreover, in our study, presence of carotid atherosclerosis was a prerequisite. This was accompanied by a higher pace of atherosclerosis progression (CAPTIVATE: 0.005 mm [placebo] and 0.019 mm [pactimibe] in 1 year vs ENHANCE: 0.0058 mm [simvastatin only] and 0.0111 and 0.0038 [simvastatin and ezetimibe] in 2 years).

Our study has important limitations. Premature termination of our study resulted in a limited efficacy analysis based on CIMT. The annual progression in maximum CIMT did not show a statistically significant difference between groups, whereas mean CIMT progression did. The difference in outcome between the 2 ultrasound parameters is most likely due to the more robust, less variable nature of the mean CIMT measurement compared with the maximum CIMT values. Second, although there was a statistically significant difference in the incidence of cardiovascular events between treatment groups, our study was not powered to assess effects on clinical outcomes. Finally, our study investigated the effect of pactimibe only in patients with familial hypercholesterolemia. Although the results were in line with the ACTIVATE study in patients with coronary artery disease, we caution generalization to nonfamilial hypercholesterolemia populations.

In conclusion, in patients with familial hypercholesterolemia, pactimibe had no effect on atherosclerosis as assessed by changes in maximum CIMT compared with placebo but was associated with an increase in mean CIMT as well as increased incidence of major cardiovascular events.

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