Circulation
Cardiovascular Imaging
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association
Learn and Live

Carotid Atherosclerosis Progression in Familial Hypercholesterolemia Patients : A Pooled Analysis of the ASAP, ENHANCE, RADIANCE 1, and CAPTIVATE Studies

Menno Vergeer, Rong Zhou, Michiel L. Bots, Raphaël Duivenvoorden, Joerg Koglin, Fatima Akdim, Yale B. Mitchel, Roeland Huijgen, Aditi Sapre, Eric de Groot, Eric J.G. Sijbrands, Richard C. Pasternak, Claude Gagné, A. David Marais, Christie M. Ballantyne, Jonathan L. Isaacsohn, Anton F. Stalenhoef and John J.P. Kastelein

Circ Cardiovasc Imaging 2010;3;398-404; originally published online May 21, 2010;
DOI: 10.1161/CIRCIMAGING.109.909655
Circulation: Cardiovascular Imaging is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
 Print ISSN: 1941-9651. Online ISSN: 1942-0080

Carotid Atherosclerosis Progression in Familial Hypercholesterolemia Patients

A Pooled Analysis of the ASAP, ENHANCE, RADIANCE 1, and CAPTIVATE Studies

Menno Vergeer, MD; Rong Zhou, PhD; Michiel L. Bots, MD, PhD; Raphaël Duivenvoorden, MD; Joerg Koglin, MD; Fatima Akdim, MD; Yale B. Mitchel, MD; Roeland Huijgen, MD; Aditi Sapre, PhD; Eric de Groot, MD, PhD; Eric J.G. Sijbrands, MD, PhD; Richard C. Pasternak, MD; Claude Gagné, MD; A. David Marais, MD; Christie M. Ballantyne, MD; Jonathan L. Isaacsohn, MD; Anton F. Stalenhoef, MD, PhD; John J.P. Kastelein, MD, PhD

Background—Until recently, patients with heterozygous familial hypercholesterolemia (HeFH) were considered the best subjects for the assessment of changes in carotid intima-media thickness (cIMT) in randomized intervention trials. Our aims were to investigate whether contemporary statin-treated HeFH patients still show accelerated cIMT increase and to assess the impact of statin treatment, before and after random assignment, on atherosclerosis progression.

Methods and Results—We retrospectively evaluated cIMT change, and prior statin treatment and postbaseline LDL-C change as predictors of cIMT change, in 1513 HeFH patients who were randomly assigned to the statin arms of the early ASAP and more recent RADIANCE 1, CAPTIVATE, and ENHANCE studies. In the 3 recent studies combined, mean cIMT increased at only 33% of the rate of the simvastatin-treated patients in the ASAP study (0.014 mm/2 years [95% confidence interval, −0.0003–0.028] versus 0.041 mm/2 years [95% confidence interval, 0.020–0.061]; $P<0.05$). Patients whose statin therapy could be intensified, as evidenced by an LDL-C decrease after the initiation of on-trial statin therapy, showed cIMT decrease in the first 6 to 12 months and a much lower cIMT increase measured over the full 2 years. In line with this, previously statin-naive HeFH patients showed a lower overall cIMT increase.

Conclusions—Over the years, intensification of statin therapy in HeFH patients has resulted in an impressive decrease in carotid atherosclerosis progression. In studies that assess other antiatherosclerotic modalities, statin therapy may still induce rapid changes in cIMT. For future cIMT studies, our analyses suggest that patient populations other than intensively pretreated HeFH patients should be selected and that the statin regimen should not be changed on study initiation. **(*Circ Cardiovasc Imaging*. 2010;3:398-404.)**

Key Words: imaging ■ familial hypercholesterolemia

B-mode ultrasound carotid intima-media thickness (cIMT) is the most widely used and best validated imaging modality for intervention studies that evaluate the effect of any given treatment on the progression of atherosclerosis.[1,2] Patients with heterozygous familial hypercholesterolemia (HeFH) were often selected for these studies because of their increased risk of premature coronary artery disease and accelerated cIMT increase from childhood onward.[3,4] Indeed, one of the first cIMT trials in HeFH patients, the Atorvastatin versus Simvastatin on Atherosclerosis Progression (ASAP) study, demonstrated a clear benefit of aggressive lipid-lowering with atorvastatin 80 mg versus conventional lipid-lowering with simvastatin 40 mg, on the rate of arterial wall thickening.[5] However, the implementation of active (genetic) screening programs for HeFH has led to earlier diagnosis and thus earlier intervention in the natural course of this disease.[6] Furthermore, the standard of clinical care for patients with HeFH has changed substantially over the past decade: Life-

Received September 17, 2009; accepted May 11, 2010.

From the Department of Vascular Medicine (M.V., R.D., F.A., R.H., E.d.G., J.J.P.K.), Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands; Medpace, Inc (R.Z., J.L.I.), Cincinnati, Ohio; Julius Center for Health Sciences and Primary Care (M.L.B.), University Medical Center Utrecht, Utrecht, The Netherlands; Merck Research Laboratories (J.K., Y.B.M., A.S., R.C.P.), Rahway, NJ; the Department of Internal Medicine (E.J.G.S.), Erasmus University Medical Centre, Rotterdam, The Netherlands; Lipid Research Center (C.G.), Laval University Medical Center, Quebec City, Canada; the Lipidology Division of Internal Medicine and MRC Cape Heart Group (D.M.), University of Cape Town Health Science Faculty, Cape Town, Republic of South Africa; Baylor College of Medicine and Methodist DeBakey Heart and Vascular Center (C.M.B.), Houston, Tex; and Radboud University Nijmegen Medical Center (A.F.S.), Nijmegen, The Netherlands.

The online-only Data Supplement is available at http://circimaging.ahajournals.org/cgi/content/full/CIRCIMAGING.109.909655/DC1.

Correspondence to John J.P. Kastelein, MD, Academic Medical Center, Department of Vascular Medicine, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands. E-mail j.j.kastelein@amc.uva.nl

style interventions, statin therapy, as well as the treatment of other cardiovascular risk factors have all considerably intensified. In fact, in a recent study, the introduction of statin therapy in HeFH patients was demonstrated to have resulted in an 80% reduction of cardiovascular risk.[7]

Clinical Perspective on p 404

This finding may bear relevance to cIMT trials in contemporary HeFH patients because those studies mostly include patients who have been pretreated with statins and routinely use intensive statin therapy in both treatment arms. This raises several questions. First, do HeFH patients still exhibit sufficient atherosclerosis progression for inclusion in cIMT intervention studies? Second, has the intensification of statin treatment in the contemporary HeFH population affected their cIMT readings? More specifically, does intensification of the statin regimen at the beginning of a trial reduce subsequent cIMT change, and, related to this question, does pretreatment with statin therapy result in a different rate of cIMT change? To address these questions, we performed post hoc analyses in the statin arms of 4 randomized controlled cIMT trials that included HeFH patients, namely ASAP, Rating Atherosclerotic Disease Change by Imaging With A New CETP Inhibitor 1 (RADIANCE 1),[8] Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE),[9] and Efficacy and Safety of the ACAT Inhibitor CS-505 (Pactimibe) for Reducing the Progression of Carotid Artery Disease (CAPTIVATE).[10]

Methods

Data Sources

Individual patient data from the statin arms of the ASAP, RADIANCE 1, CAPTIVATE, and ENHANCE studies were merged. Design and results of these studies were published previously. Briefly, ASAP enrolled HeFH patients who were previously untreated or treated for up to 1 year or who had low-density lipoprotein cholesterol (LDL-C) levels above 173 mg/dL. Patients were then randomized to receive treatment with either atorvastatin 80 mg or simvastatin 40 mg. The primary end point was the change in mean cIMT over 2 years. Both treatment arms were included in the present analyses. RADIANCE 1 enrolled HeFH patients, and titrated with atorvastatin to target low-density lipoprotein cholesterol (LDL-C) levels according to NCEP ATP-III criteria or to a maximally tolerated dose.[11] Patients were then randomly assigned to receive torcetrapib or placebo on top of this atorvastatin regimen. The primary end point was the annualized rate of change in the maximum cIMT of 12 predefined carotid segments. Data from the atorvastatin monotherapy arm were included in the present analysis. CAPTIVATE enrolled HeFH patients who were randomly assigned to receive pactimibe or placebo on top of standard lipid-lowering therapy. The primary end point of this study was the change in mean cIMT over 2 years. The study was prematurely terminated after the development of pactimibe was halted. Data from the standard lipid-lowering therapy arm were included in our analysis. CAPTIVATE differs from the other studies in the fact that besides the addition of pactimibe or placebo, lipid-lowering therapy was not changed at the start of the trial. ENHANCE included HeFH patients who were randomly assigned to receive simvastatin 80 mg and ezetimibe 10 mg or simvastatin 80 mg monotherapy. The primary end point was 2-year change in mean cIMT, which was defined as the average of the means of the far-wall intima-media thickness of the right and left common carotid arteries, carotid bulbs, and internal carotid arteries. Only the monotherapy arm was included in the present analysis.

Extraction of Data

We extracted segment level cIMT data and calculated mean cIMT for each patient at each available time point for all segments, using measures of the far walls of the left and right common carotid artery, left and right internal carotid artery and the left and right carotid bulb. We specifically did not strive to replicate the originally published cIMT results but instead chose to construct a measure of cIMT, homogeneous across all studies. We extracted baseline data on prior statin use and on the variables age, sex, body mass index (BMI), presence/absence of coronary artery disease (CAD), diabetes mellitus, (treated) hypertension, total cholesterol, LDL-C, high-density lipoprotein cholesterol (HDL-C), and triglycerides. We also extracted data on LDL-C at end-of-study.

End Points

End points of our analysis were 1-year and 2-year change of mean cIMT of all segments and 1-year and 2-year change of the mean intima-media thickness of both common carotid arteries, which will be referred to as CCA-IMT. The latter measure has been used as a primary end point in a number of recent trials.[12–17]

Data Analyses

Analyses were performed in subjects with complete data, or, alternatively, missing data for cIMT (112 subjects, ≈7%) were imputed using multiple imputation according to the Markov chain Monte Carlo method. First, to assess differences in carotid atherosclerosis progression between contemporary patients and the early HeFH population, mean cIMT changes in the control arms of the ENHANCE, CAPTIVATE, and RADIANCE 1 trial were compared with mean cIMT change in the ASAP simvastatin arm. The analysis included a fixed effect for each of the studies and inferred on the average difference between the three contemporary studies and ASAP.

Second, we assessed whether intensification of statin therapy at the start of the trial affects on subsequent cIMT change. We could evaluate this in all studies that incorporated a switch in statin therapy at their initiation (ASAP, ENHANCE, and RADIANCE 1). Because the impact of a new statin regimen on LDL-C can be expected to differ between patients, and because a quantitative comparison of the potency of different statins in different dosages is impossible, we decided to select the change in LDL-C as a proxy for the change in intensity of statin therapy. We divided patients into 2 groups: those who showed a decrease of LDL-C levels after initiation of on-trial statin therapy (end-of-study LDL-C $<$screening visit LDL-C) versus those who showed no decrease of LDL-C after the start of study (end-of-study LDL-C $\geq$screening visit LDL-C). The first group ("LDL decrease") was assumed to have received more intensive statin therapy during the trial than before the trial; the second group ("no LDL decrease") was assumed to have received less or equally intensive statin therapy during the trial compared with before the trial.

Third, to assess the potential of prior statin use as an independent predictor for all cIMT change end points, a 2-level random-effects regression analysis was conducted adjusting for all baseline variables mentioned under the heading "extraction of data," incorporating study as a random effect. The likelihood ratio test was used to compare deviance statistics for nested models, with the significance level set at a probability value of 0.10. We chose not to adjust for baseline cIMT because this might have resulted in a considerable bias related to measurement error, as described elsewhere.[18–20] Results are presented as mean change in cIMT with corresponding standard error and probability value. Analyses were performed using SAS, version 9.2.

Results

We extracted data from four different cIMT trials that enrolled HeFH patients. More than 70% of patients in the more recent trials had received intensive lipid-lowering therapy before enrollment as compared with 41% in the earlier

Table 1. Statin Therapy Before and During cIMT Progression Trials in HeFH Patients

	n	Year of Publication	Pretreatment, n (%)		Control Arm Therapy
			Any Statin	Intensive Therapy	
Early					
ASAP	325	2001	221 (68)	134 (41)	Simvastatin 40 mg
Contemporary					
RADIANCE 1	454	2007	390 (86)	331 (73)	Atorvastatin mean 57 mg
CAPTIVATE	371	2008	357 (96)	299 (81)	Same as pretreatment
ENHANCE	363	2008	295 (81)	257 (71)	Simvastatin 80 mg

Six to 7 years after ASAP, both pretreatment and on-trial treatment with lipid-lowering therapy had intensified considerably.

Intensive therapy was defined as simvastatin ≥40 mg or atorvastatin ≥20 mg, or any statin in combination with other lipid-lowering therapy.

ASAP study. In all contemporary studies, statin therapy during the trial was more intensive than in the ASAP simvastatin arm. Differences in statin treatment before and during the trial for each contemporary study, compared with the ASAP study, are shown in Table 1.

Table 2 shows the baseline characteristics of all 1513 subjects. We compared mean cIMT change in contemporary studies with mean cIMT change in the ASAP simvastatin arm. After 2 years, cIMT increase in recent studies was 33% of that in the earlier ASAP study (0.014 mm [95% confidence interval (CI), −0.0003–0.028] versus 0.041 mm [95% CI, 0.020–0.061], $P<0.05$). Interestingly, in both ASAP and the newer studies, cIMT increased faster in the second year than in the first year (Figure 1).

Next, we assessed whether intensification of statin therapy at the start of the trial reduces subsequent cIMT change. To

Table 2. Baseline Characteristics of the Studied Populations at Screening

	ASAP (n=325)	RADIANCE 1 (n=454)	CAPTIVATE (n=371)	ENHANCE (n=363)	All Studies (n=1513)
Age, y	49±11	45±13	54±9	46±10	48±11
Sex, n (%)					
Female	197 (60.6)	222 (48.9)	145 (39.1)	184 (50.7)	748 (49.4)
History of CAD, n (%)					
Presence	48 (14.8)	99 (21.8)	116 (31.3)	9 (2.5)	272 (18.0)
Absence	277 (85.2)	355 (78.2)	255 (68.7)	354 (97.5)	1241 (82.0)
Diabetes mellitus, n (%)					
Presence	7 (2.2)	19 (4.2)	22 (5.9)	5 (1.4)	53 (3.5)
Absence	318 (97.8)	435 (95.8)	349 (94.1)	358 (98.6)	1460 (96.5)
Hypertension, n (%)					
Presence	32 (9.8)	114 (25.1)	104 (28.0)	52 (14.3)	302 (20.0)
Absence	293 (90.2)	340 (74.9)	267 (72.0)	311 (85.7)	1211 (80.0)
BMI ≥30 kg/m^2					
Yes	34 (10.5)	107 (23.6)	94 (25.3)	83 (22.9)	318 (21.0)
No	291 (89.5)	346 (76.2)	275 (74.1)	278 (76.6)	1190 (78.7)
Unknown	0 (0.0)	1 (0.2)	2 (0.5)	2 (0.6)	5 (0.3)
Current smoker					
Yes	101 (31.1)	95 (20.9)	51 (13.7)	104 (28.7)	351 (23.2)
No	224 (68.9)	359 (79.1)	320 (86.3)	259 (71.3)	1162 (76.8)
Cholesterol, mg/dL					
LDL	223±56	167±60	143±36	225±64	187±66
HDL	48±13	53±13	53±14	51±16	51±14
Triglycerides, mg/dL, median (interquartile range)	112 (80–162)	102 (80–142)	118 (90–161)	121 (89–162)	113 (83–158)
Mean cIMT, mm	0.936±0.222	0.950±0.284	0.807±0.172	0.698±0.142	0.856±0.244
CCA-IMT, mm	0.874±0.208	0.821±0.216	0.770±0.175	0.681±0.163	0.788±0.207

Values are means±SD unless otherwise indicated.

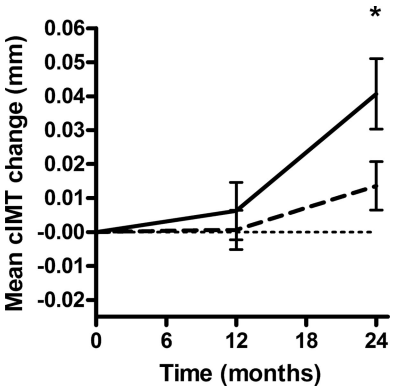

Figure 1. Mean cIMT change in the statin monotherapy arms of contemporary studies (striped line) versus the ASAP simvastatin arm (solid line). In both instances, cIMT increase is more pronounced in the second year than in the first year. In the newer studies (RADIANCE 1, ENHANCE, and CAPTIVATE), cIMT change is more than 3 times lower after 2 years. Error bars represent standard errors. *$P<0.05$.

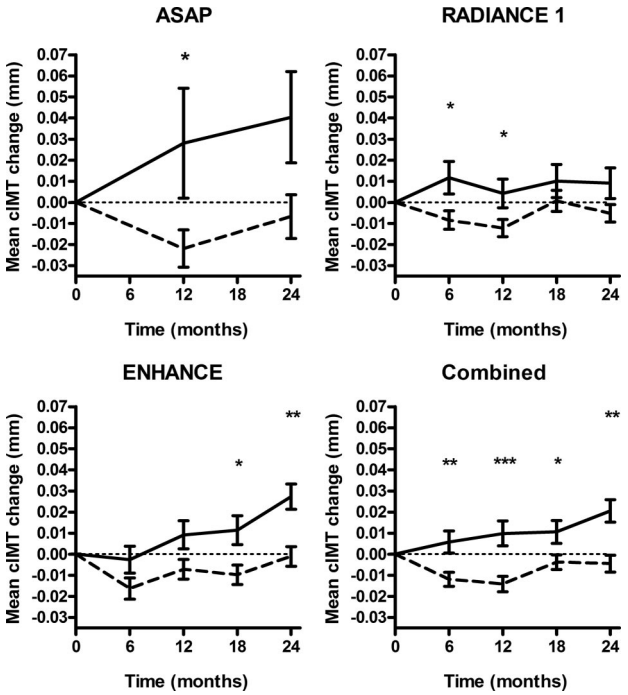

Figure 2. Mean cIMT change in patients according to change in LDL. In ASAP, ENHANCE, and RADIANCE 1, cIMT progression was lower in patients with an LDL decrease (striped line; n=235, n=218, and n=260, respectively) after initiation of on-trial intensive statin therapy than in patients without an LDL decrease (solid line; n=41, n=95, and n=127, respectively). In all studies, cIMT tended to rapidly regress in the first 6 to 12 months in case of an LDL decrease. Error bars represent standard errors. Probability values are for the difference between groups. *$P<0.05$, **$P<0.01$, ***$P<0.001$.

this end, we evaluated whether patients who had a postbaseline decrease in LDL-C showed a different cIMT change from patients who did not. In CAPTIVATE there was no meaningful difference between on-trial LDL-C and baseline LDL-C because patients were continued on their own statin therapy. However, in the studies that switched to a different statin regimen at baseline—ASAP, RADIANCE 1, and ENHANCE—those patients with a decrease of plasma LDL-C after study initiation showed less carotid atherosclerosis progression than patients whose LDL-C did not decrease (Figure 2). Furthermore, patients with a decrease in LDL-C showed a rapid regression of carotid atherosclerosis during the first 6 to 12 months compared with baseline (−0.012 mm [95% CI, −0.018−−0.005] at 6 months and −0.013 mm [95% CI, −0.020−−0.005] at 12 months in the combined analysis; both different from zero with $P<0.0005$ and $P<0.001$, respectively). These data suggest that intensification of statin therapy at the start of the study retards the progression of carotid atherosclerosis.

We hypothesized that such an effect would mainly occur in statin-naive patients. To test this hypothesis, we assessed the association between prior statin use and subsequent cIMT change, as defined by different criteria (1-year mean cIMT change, 2-year mean cIMT change, 1-year CCA-IMT change, and 2-year mean CCA-IMT change), adjusting for age, sex, BMI $\geq$30 kg/m^2, history of CAD, history of diabetes, history of hypertension, and LDL-C, HDL-C, and triglycerides at screening. All variables were entered into the models, and only those with a $P<0.10$ were retained. Final models are depicted in Table 3. Prior statin use was positively associated with cIMT change (ie, previously statin-naive patients, whose statin therapy was first initiated as part of the trial, had a lower subsequent cIMT increase). In line with this, baseline triglycerides were negatively associated with cIMT change. Age and smoking were positively associated with cIMT change. In exploratory analyses we found that imputation of missing cIMT data did not materially change the results. Furthermore, the direction of association between prior statin use and cIMT change was consistent in ASAP, RADIANCE 1, and ENHANCE, ruling out confounding by study (Supplemental Table). However, the association was approximately 6-fold weaker in CAPTIVATE than in the other studies (parameter estimate for association with 2-year change in mean cIMT, 0.0034 mm [standard error, 0.1271], $P=0.98$), suggesting that prior statin use is only an important predictor of cIMT change if the statin regime is changed at the start of the study.

Discussion

In the current analysis, we demonstrate that the rate of cIMT change in intensively treated contemporary HeFH patients is a third of that in the less intensively treated HeFH population of the early ASAP trial. Also within studies, a reduction of carotid atherosclerosis progression occurred in patients whose statin therapy was intensified. In fact, these patients even showed regression of atherosclerosis in the first 6 to 12 months, also while they were randomly assigned to the control arm of these studies. In contrast, patients who did not exhibit an LDL-C reduction on trial medication did not show regression of carotid atherosclerosis and had a higher overall cIMT increase. In line with this, previously statin-naive HeFH patients, who received statin therapy for the first time during the trial, showed a lower overall cIMT increase, indicating that these patients have a particularly strong statin-induced suppression of cIMT increase. These data demonstrate that the intensification of statin therapy that

Table 3. Multivariate Analyses Into Baseline Determinants of cIMT Change End Points

	Parameter Estimate (mm)	Standard Error	*P* Value
1-Year mean cIMT change			
Prior statin use	0.01943	0.00794	0.015
Age	0.00055	0.00028	0.053
Baseline TG	−0.00009	0.00004	0.054
Smoking	0.01465	0.00753	0.052
2-Year mean cIMT change			
Prior statin use	0.01975	0.00982	0.045
Age	0.00077	0.00035	0.027
Baseline TG	−0.00013	0.00006	0.022
Smoking	0.01999	0.00933	0.032
1-Year CCA-IMT change			
Prior statin use	0.02819	0.00768	<0.001
2-Year CCA-IMT change			
Prior statin use	0.02059	0.00943	0.029

In these models, the variables prior statin use, age, sex, BMI ≥30 kg/m^2, history of CAD, history of diabetes, history of hypertension, and LDL-C, HDL-C, and triglycerides (TG) at screening were entered into the models and only those with a $P<0.10$ were retained. Negative parameter estimates indicate a negative association between the variable and the end point. Intercepts are not shown.

HeFH patients have witnessed over the past decade has substantially slowed down atherosclerosis progression. Furthermore, they suggest that at least part of the effect of statin therapy on carotid atherosclerosis is rapidly achieved.

Statins Retard Progression of Carotid Atherosclerosis

After the publication of the ENHANCE study, which showed no benefit of adding ezetimibe to simvastatin 80 mg on cIMT change despite a substantial additional LDL-C reduction,[9] its failure has been subject of intense debate.[21,22] Proposed explanations broadly fell into 3 categories: First, the measurement of cIMT change may not have accurately reflected changes in atherosclerotic burden; second, the compound ezetimibe may lack vascular benefit; and third, cIMT change may have been too low in contemporary HeFH patients to detect a difference between control and intervention arm.[9]

In the current study, we found evidence to support the last explanation: cIMT change in contemporary HeFH patients is considerably lower than in patients who used simvastatin 40 mg in ASAP. Further analyses confirmed that statin treatment remains an important determinant of cIMT change in HeFH patients: Patients who received more intensive statin therapy during the study than before the study exhibited a reduced cIMT increase compared with other patients. Thus, as may have been expected, statin intensification suppresses carotid atherosclerosis progression. In line with this, this effect is mainly observed in previously statin-naive patients, whom we found to display the lowest cIMT increase during the trials.

Rapid Effect of Statins

In addition, we found that intensification of statin therapy is associated with regression of carotid atherosclerosis in the first 6 to 12 months, suggesting rapid statin-induced carotid wall changes. This finding is supported by other recent studies that showed that the initiation of statin therapy leads to a rapid delipidation of carotid plaque: After treating patients with pravastatin for 12 weeks, atherosclerotic plaques removed from their carotid arteries through endarterectomy showed a significantly diminished lipid content, as well as decreased lipid oxidation and inflammation parameters.[23] Rapid statin-induced plaque delipidation has not only been demonstrated by histology but also by MRI. A mere 6 months after the initiation of simvastatin therapy, plaque volume reduction was observed in the thoracic aorta.[24] Indeed, in the ASAP trial as well as in the ASAP extension study, carotid atherosclerosis regression was most prominent during the first year of therapy with atorvastatin 80 mg, supporting the notion that delipidation of the vessel wall may be attained quite rapidly.[5,25] In line with this, findings from the recent METEOR study show an effect on cIMT change after 12 months of rosuvastatin therapy.[26]

Similar results have been observed after a single infusion of reconstituted high-density lipoprotein: Lipid content, macrophage size, and measures of inflammation in plaques from femoral arteries were reduced.[27] Our data show that rapid statin-induced vessel wall delipidation also plays a role in trials that were in fact not designed to assess the effects of statins.

Clinical Implications

After the ASAP study, which showed a large difference in cIMT change between HeFH patients treated with simvastatin 40 mg and HeFH patients treated with atorvastatin 80 mg,[5] these individuals were considered an ideal population to assess novel therapeutic strategies. However, as more potent lipid-lowering therapies became available in recent years, treatment of HeFH patients has improved and cIMT characteristics of this population have changed significantly. The results of the present study imply that contemporary HeFH patients exhibit only a very modest progression of arterial wall thickening because of intensive statin therapy before as well as during trials. This indicates that the current HeFH patient population is less suited for inclusion in cIMT trials that evaluate novel therapeutic strategies on top of (intensive) statin therapy and suggests that other patient populations should be considered for such trials. In this respect, patients with mixed dyslipidemia may be a better choice. RADIANCE 2 assessed the effects of torcetrapib/atorvastatin on cIMT change in this patient population.[28] Two-year mean cIMT change in patients who received atorvastatin monotherapy was 0.0461 mm (standard error, 0.009), which is comparable to that of the HeFH patients in the ASAP simvastatin arm.

In HeFH patients, a high plasma LDL-C is the single most prominent risk factor for the development of cardiovascular disease. Statins address this risk factor very efficiently in the causal pathway of disease. Our data are in line with the recently reported strong improvement in cardiovascular disease risk in HeFH patients.[7] Although one might speculate that the advent of high-dose statin and additional lipid-lowering therapy may effectively have provided a "cure" for HeFH, we emphasize that our results do not lend themselves

for such extrapolation. Although cIMT crudely reflects the atherosclerotic process, the complications of atherosclerosis also depend on other physical properties of the artery and the degree of inflammation, which will also determine the likelihood of rupture and thrombosis.

cIMT Remains a Useful Surrogate End Point

It has consistently been shown, more than for any other vascular imaging technique, that cIMT progression findings parallel outcomes of clinical studies with similar interventions.[1] Although the results from the ENHANCE study[9] have led some to believe that a change in cIMT measurements may not accurately reflect altered cardiovascular risk, the current results consistently show that cIMT change remains sensitive to changes in LDL-C levels. This reinvigorates the notion that cIMT trials are very well equipped to provide an early indication of the antiatherosclerotic efficacy of novel compounds.

The response of carotid atherosclerosis progression to a change in statin therapy also suggests that future cIMT trials should ideally refrain from changing the statin regimen at the start of the study, as to not influence subsequent cIMT readings. A strong statin-induced cIMT decrease may obscure the effects of the novel therapy assessed in that particular study. In this respect, it is interesting to note that both ENHANCE[9] and RADIANCE 1[8] switched statin therapy at the start of the study and found no difference in cIMT change between their 2 treatment arms (simvastatin/ezetimibe versus simvastatin alone, and torcetrapib/atorvastatatin versus atorvastatin alone, respectively), whereas CAPTIVATE[10] did not switch statins and did find a significant difference in cIMT change between the 2 arms (pactimibe versus placebo).

Study Limitations

Some aspects of our analysis merit caution. Data on cIMT were extracted from different studies that used different ultrasound equipment and ultrasound protocols to obtain cIMT measurements. Although we constructed a homogeneous measure of cIMT from the available data, it cannot be excluded that these differences have negatively affected between-trial comparability of cIMT readings at single time points. However, the sole use of cIMT change values instead of single cIMT measurements in this study can be expected to mitigate such risk. In addition, our estimates of the determinants of cIMT change in different analyses rely on the assumption that variability is similarly explained across the individual studies; these assumptions are consistent with—although not proven by—similar analysis results in the individual studies. Finally, this study carries all inherent limitations of a post hoc analysis and its conclusions should be considered hypothesis generating.

Conclusion

B-mode ultrasound cIMT has proven to be a sensitive marker for the assessment of lipid altering pharmacotherapy. The rate of cIMT change in contemporary HeFH patients has slowed dramatically in relation to the use of intensive statin therapy both before and during cIMT trials. This finding suggests both a strong improvement in cardiovascular risk in HeFH patients as well as a diminished suitability for inclusion in cIMT trials that evaluate novel cardiovascular pharmacotherapy. In the design of future cIMT studies, the occurrence of rapid statin-induced vessel wall delipidation should be taken into consideration.

Acknowledgments

We are indebted to all investigators and patients who participated in the trials we analyzed. We would like to acknowledge Pfizer, Schering-Plough, Merck, and Sankyo for making the data of these trials available. Drs Vergeer and Kastelein had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Disclosures

Dr Bots received consulting and lecture fees and grant support from Pfizer, AstraZeneca, and Servier. Drs Koglin, Mitchel, Pasternak, and Sapre are employed by Merck. Dr de Groot received lecture fees from Astra-Zeneca and Pfizer and consulting fees from Wyeth, Roche, and Merck. Dr Marais received consulting and lecture fees from Abbott, AstraZeneca, Pfizer, and Merck. Dr Ballantyne received support from, has been consultant for, or received honorarium from Abbott, AstraZeneca, Bristol-Myers/Squibb, GlaxoSmithKline, KOWA, Merck, Metabasis, Novartis, Pfizer, Sanofi-Synthelabo, Schering-Plough, and Takeda. Dr Stalenhoef received grant support from Pfizer and Merck and delivered lectures for AstraZeneca. Dr Kastelein received consulting fees and lecture fees from Pfizer, AstraZeneca, Merck, and Schering-Plough and grant support from Pfizer and AstraZeneca. Dr Gagné received grant support, and/or lecture fees, and/or consulting fees from Astra-Zeneca, Isis, Merck-Frosst, Merck-Schering, Pfizer, Roche, Sankyo, Sanofi-Avertis, and Takeda. No other potential conflict of interest relevant to this article was reported.

References

1. Duivenvoorden R, Nederveen AJ, de Groot E, Kastelein JJ. Atherosclerosis imaging as a benchmark in the development of novel cardiovascular drugs. *Curr Opin Lipidol*. 2007;18:613–621.
2. Lorenz MW, Markus HS, Bots ML, Rosvall M, Sitzer M. Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis. *Circulation*. 2007;115:459–467.
3. Rader DJ, Cohen J, Hobbs HH. Monogenic hypercholesterolemia: new insights in pathogenesis and treatment. *J Clin Invest*. 2003;111:1795–1803.
4. Wiegman A, de Groot E, Hutten BA, Rodenburg J, Gort J, Bakker HD, Sijbrands EJG, Kastelein JJP. Arterial intima-media thickness in children heterozygous for familial hypercholesterolaemia. *Lancet*. 2004;363:369–370.
5. Smilde TJ, van Wissen S, Wollersheim H, Trip MD, Kastelein JJ, Stalenhoef AF. Effect of aggressive versus conventional lipid lowering on atherosclerosis progression in familial hypercholesterolaemia (ASAP): a prospective, randomised, double-blind trial. *Lancet*. 2001;357:577–581.
6. Huijgen R, Vissers MN, Defesche JC, Lansberg PJ, Kastelein JJ, Hutten BA. Familial hypercholesterolemia: current treatment and advances in management. *Exp Rev Cardiovasc Ther*. 2008;6:567–581.
7. Versmissen J, Oosterveer DM, Yazdanpanah M, Defesche JC, Basart DC, Liem AH, Heeringa J, Witteman JC, Lansberg PJ, Kastelein JJ, Sijbrands EJ. Efficacy of statins in familial hypercholesterolaemia: a long term cohort study. *BMJ*. 2008;337:a2423.
8. Kastelein JJ, van Leuven SI, Burgess L, Evans GW, Kuivenhoven JA, Barter PJ, Revkin JH, Grobbee DE, Riley WA, Shear CL, Duggan WT, Bots ML. Effect of torcetrapib on carotid atherosclerosis in familial hypercholesterolemia. *N Engl J Med*. 2007;356:1620–1630.
9. Kastelein JJ, Akdim F, Stroes ES, Zwinderman AH, Bots ML, Stalenhoef AF, Visseren FL, Sijbrands EJ, Trip MD, Stein EA, Gaudet D, Duivenvoorden R, Veltri EP, Marais AD, de Groot E. Simvastatin with or without ezetimibe in familial hypercholesterolemia. *N Engl J Med*. 2008;358:1431–1443.
10. Meuwese MC, de Groot E, Duivenvoorden R, Trip MD, Ose L, Maritz FJ, Basart DCG, Kastelein JJP, Habib R, Davidson MH, Zwinderman AH, Schwocho LR, Stein EA, for the CAPTIVATE Investigators. ACAT

inhibition and progression of carotid atherosclerosis in patients with familial hypercholesterolemia: the CAPTIVATE randomized trial. *JAMA*. 2009;301:1131–1139.
11. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation*. 2002;106:3143–3421.
12. Hedblad B, Wikstrand J, Janzon L, Wedel H, Berglund G. Low-dose metoprolol CR/XL and fluvastatin slow progression of carotid intima-media thickness: main results from the β-Blocker Cholesterol-Lowering Asymptomatic Plaque Study (BCAPS). *Circulation*. 2001;103:1721–1726.
13. Salonen RM, Nyyssonen K, Kaikkonen J, Porkkala-Sarataho E, Voutilainen S, Rissanen TH, Tuomainen TP, Valkonen VP, Ristonmaa U, Lakka HM, Vanharanta M, Salonen JT, Poulsen HE. Six-year effect of combined vitamin c and e supplementation on atherosclerotic progression: the Antioxidant Supplementation in Atherosclerosis Prevention (ASAP) Study. *Circulation*. 2003;107:947–953.
14. Taylor AJ, Kent SM, Flaherty PJ, Coyle LC, Markwood TT, Vernalis MN. ARBITER: Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol: a randomized trial comparing the effects of atorvastatin and pravastatin on carotid intima medial thickness. *Circulation*. 2002;106:2055–2060.
15. Taylor AJ, Sullenberger LE, Lee HJ, Lee JK, Grace KA. Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER) 2: a double-blind, placebo-controlled study of extended-release niacin on atherosclerosis progression in secondary prevention patients treated with statins. *Circulation*. 2004;110:3512–3517.
16. Devine PJ, Turco MA, Taylor AJ. Design and rationale of the ARBITER 6 Trial (Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol)-6-HDL and LDL Treatment Strategies in Atherosclerosis (HALTS). *Cardiovasc Drugs Ther*. 2007;21:221–225.
17. Taylor AJ, Lee HJ, Sullenberger LE. The effect of 24 months of combination statin and extended-release niacin on carotid intima-media thickness: ARBITER 3. *Curr Med Res Opin*. 2006;22:2243–2250.
18. Campbell MJ, Machin D. Common pitfalls in medical statistics: plotting change against initial value. In: *Medical Statistics: A Commonsense Approach.* 2nd ed. New York, NY: John Wiley & Sons; 1993:130–132.
19. Vollmer WM. Comparing change in longitudinal studies: adjusting for initial value. *J Clin Epidemiol*. 1988;41:651–657.
20. Yanez ND, Kronmal RA, Shemanski LR, Psaty BM, for the Cardiovascular Health Study. A regression model for longitudinal change in the presence of measurement error. *Ann Epidemiol*. 2002;12:34–38.
21. Brown BG, Taylor AJ. Does ENHANCE diminish confidence in lowering LDL or in ezetimibe? *N Engl J Med*. 2008;358:1504–1507.
22. Stein EA. After ENHANCE: is more LDL cholesterol lowering even better? *Clin Chem*. 2008;54:940–942.
23. Crisby M, Nordin-Fredriksson G, Shah PK, Yano J, Zhu J, Nilsson J. Pravastatin treatment increases collagen content and decreases lipid content, inflammation, metalloproteinases, and cell death in human carotid plaques: implications for plaque stabilization. *Circulation*. 2001;103:926–933.
24. Lima JAC, Desai MY, Steen H, Warren WP, Gautam S, Lai S. Statin-induced cholesterol lowering and plaque regression after 6 months of magnetic resonance imaging-monitored therapy. *Circulation*. 2004;110:2336–2341.
25. van Wissen S, Smilde TJ, Trip MD, Stalenhoef AF, Kastelein JJ. Long-term safety and efficacy of high-dose atorvastatin treatment in patients with familial hypercholesterolemia. *Am J Cardiol*. 2005;95:264–266.
26. Bots ML, Palmer MK, Dogan S, Plantinga Y, Raichlen JS, Evans GW, O'Leary DH, Grobbee DE, Crouse JR III. Intensive lipid lowering may reduce progression of carotid atherosclerosis within 12 months of treatment: the METEOR study. *J Intern Med*. 2009;265:698–707.
27. Shaw JA, Bobik A, Murphy A, Kanellakis P, Blombery P, Mukhamedova N, Woollard K, Lyon S, Sviridov D, Dart AM. Infusion of reconstituted high-density lipoprotein leads to acute changes in human atherosclerotic plaque. *Circ Res*. 2008;103:1084–1091.
28. Bots ML, Visseren FL, Evans GW, Riley WA, Revkin JH, Tegeler CH, Shear CL, Duggan WT, Vicari RM, Grobbee DE, Kastelein JJ. Torcetrapib and carotid intima-media thickness in mixed dyslipidaemia (RADIANCE 2 study): a randomised, double-blind trial. *Lancet*. 2007;370:153–160.

CLINICAL PERSPECTIVE

Patients with familial hypercholesterolemia, a hereditary disorder with severely elevated low-density lipoprotein cholesterol levels, were once the individuals with the highest possible risk for an early heart attack. This was reflected by the fact that the thickness of their carotid artery walls as well as their coronary angiograms showed the highest progression over time when left untreated. This, however, was the situation before the introduction of statin therapy, and that has dramatically changed the cause of disease and life for those unfortunate individuals. The results of the current study suggest that with potent statin therapy, progression rates have come down to one third of what was previously reported. This is a great improvement but by no means the solution for these patients. Familial hypercholesterolemia heterozygotes are often far from low-density lipoprotein cholesterol goals and still require a lot of medical attention. We have also identified in our study that patients with familial hypercholesterolemia who have been aggressively treated for many years and have responded with regression of artery wall abnormalities are no longer ideal subjects for clinical studies into other antiatherosclerotic modalities. These issues are relevant when designing clinical trials in this patient population.

SUPPLEMENTAL MATERIAL

Carotid Atherosclerosis Progression in Familial Hypercholesterolemia Patients
A Pooled Analysis of the ASAP, ENHANCE, RADIANCE 1 and CAPTIVATE Studies

Menno Vergeer, MD[1]; Rong Zhou, PhD[2]; Michiel L Bots, MD, PhD[3]; Raphaël Duivenvoorden, MD[1]; Joerg Koglin, MD[4]; Fatima Akdim, MD[1]; Yale B Mitchel, MD[4]; Roeland Huijgen, MD[1]; Aditi Sapre, PhD[4]; Eric de Groot, MD, PhD[1]; Eric JG Sijbrands, MD, PhD[5]; Richard C Pasternak, MD[4]; Claude Gagné, MD[6]; A David Marais, MD[7]; Christie M Ballantyne, MD[8]; Jonathan L Isaacsohn, MD[2]; Anton F Stalenhoef, MD, PhD[9] and John JP Kastelein, MD, PhD[1]

Table. **Analyses into baseline determinants of 2 year mean cIMT change, by study**

	Parameter estimate (mm)	Standard error	p-value
ASAP			
Prior statin use	0.02149	0.02000	0.283
Age	0.00013	0.00096	0.176
Baseline TG	-0.00019	0.00013	0.161
Smoking	-0.00714	0.02199	0.746
RADIANCE 1			
Prior statin use	0.01758	0.01840	0.340
Age	0.00039	0.00049	0.426
Baseline TG	-0.00006	0.00009	0.550
Smoking	0.03465	0.01518	0.023
ENHANCE			
Prior statin use	0.01862	0.00945	0.049
Age	-0.00018	0.00037	0.622
Baseline TG	0.00006	0.00006	0.287
Smoking	0.00116	0.00791	0.884
CAPTIVATE			
Prior statin use	0.00341	0.12710	0.979
Age	0.00224	0.00135	0.010
Baseline TG	-0.00034	0.00016	0.039
Smoking	0.08330	0.03231	0.011

The direction of association between prior statin use and 2 year mean cIMT change is consistent across studies, if the statin regime is changed at the start of sthe study (i.e. in ASAP, RADIANCE 1 and ENHANCE). Negative parameter estimates indicate a negative association between the variable and the endpoint. Intercepts are not shown.