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Simvastatin with or without Ezetimibe in Familial Hypercholesterolemia

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ABSTRACT

BACKGROUND

Ezetimibe, a cholesterol-absorption inhibitor, reduces levels of low-density lipoprotein (LDL) cholesterol when added to statin treatment. However, the effect of ezetimibe on the progression of atherosclerosis remains unknown.

METHODS

We conducted a double-blind, randomized, 24-month trial comparing the effects of daily therapy with 80 mg of simvastatin either with placebo or with 10 mg of ezetimibe in 720 patients with familial hypercholesterolemia. Patients underwent B-mode ultrasonography to assess the intima-media thickness of the walls of the carotid and femoral arteries. The primary outcome measure was the change in the mean carotid-artery intima-media thickness, 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.

RESULTS

The primary outcome, the mean (\pm SE) change in the carotid-artery intima-media thickness, was 0.0058 ± 0.0037 mm in the simvastatin-only group and 0.0111 ± 0.0038 mm in the simvastatin-plus-ezetimibe (combined-therapy) group ($P=0.29$). Secondary outcomes (consisting of other variables regarding the intima-media thickness of the carotid and femoral arteries) did not differ significantly between the two groups. At the end of the study, the mean (\pm SD) LDL cholesterol level was 192.7 ± 60.3 mg per deciliter (4.98 ± 1.56 mmol per liter) in the simvastatin group and 141.3 ± 52.6 mg per deciliter (3.65 ± 1.36 mmol per liter) in the combined-therapy group (a between-group difference of 16.5%, $P<0.01$). The differences between the two groups in reductions in levels of triglycerides and C-reactive protein were 6.6% and 25.7%, respectively, with greater reductions in the combined-therapy group ($P<0.01$ for both comparisons). Side-effect and safety profiles were similar in the two groups.

CONCLUSIONS

In patients with familial hypercholesterolemia, combined therapy with ezetimibe and simvastatin did not result in a significant difference in changes in intima-media thickness, as compared with simvastatin alone, despite decreases in levels of LDL cholesterol and C-reactive protein. (ClinicalTrials.gov number, NCT00552097.)

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A REDUCTION IN LEVELS OF LOW-DENSITY lipoprotein (LDL) cholesterol constitutes one of the cornerstones in the prevention of cardiovascular disease. In recent trials comparing various statins or the same statin at various doses, aggressive therapy to lower LDL cholesterol levels was associated with a reduction in rates of cardiovascular events.¹⁻⁴ However, administration of the highest approved statin dose offers only limited additional lowering of LDL cholesterol at the expense of an increased incidence of side effects.⁵ Therefore, novel compounds that further reduce LDL cholesterol levels when added to statin therapy are of interest. A recently introduced compound, ezetimibe, selectively inhibits cholesterol absorption by binding to the Niemann–Pick C1-like 1 (NPC1L1) protein. The latter is located at the brush-border membrane of the enterocyte, where it contributes substantially to the intestinal uptake and cellular transport of cholesterol and noncholesterol sterols.^{6,7} Combined therapy with ezetimibe and a statin provides an incremental reduction in LDL cholesterol levels of 12 to 19%.^{8,9}

In this study, we sought to determine whether the daily administration of 10 mg of ezetimibe in combination with 80 mg of simvastatin could reduce the progression of atherosclerosis in patients with familial hypercholesterolemia, as assessed by measurement of arterial intima–media thickness. The rationale for studying patients with familial hypercholesterolemia is that such patients have a greatly increased risk of premature coronary artery disease¹⁰ and an increased rate of progression of intima–media thickness starting in childhood.¹¹ In our study, called the Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) trial, we used B-mode ultrasonographic imaging of the intima–media thickness in the carotid and femoral arteries as a surrogate measure to assess the progression of atherosclerosis.

METHODS

STUDY DESIGN

Our prospective, randomized, double-blind, active-comparator, multicenter study was designed by academic investigators in collaboration with the study sponsors, Merck and Schering-Plough. The image database was generated and housed in the Core Echo Laboratory at the Academic Medical

Center in Amsterdam, and the clinical database was maintained by the sponsors. All data were analyzed independently by an investigator at the Department of Clinical Epidemiology and Biostatistics at the Academic Medical Center. Although the authors allowed the sponsors to review the manuscript, all data analyses and interpretation of the results are those of the academic investigators.

Patients provided written informed consent, and the study's protocol was approved by the institutional review board at each center. The study was conducted at 18 ambulatory care centers in the United States, Canada, South Africa, Spain, Denmark, Norway, Sweden, and the Netherlands between August 2002 and April 2006. Men and women between the ages of 30 and 75 years were eligible to participate in the study if familial hypercholesterolemia had been diagnosed either by genotyping or by their having met the diagnostic criteria outlined by the World Health Organization.¹² Patients were enrolled regardless of their previous treatment with lipid-lowering drugs. Untreated levels of LDL cholesterol had to be 210 mg per deciliter (5.43 mmol per liter) or more. Patients who were receiving lipid-lowering therapy and who had an LDL cholesterol level of less than 210 mg per deciliter at the time of screening were permitted to undergo randomization if their LDL cholesterol level was 210 mg per deciliter or more after the placebo run-in period.

Major exclusion criteria included high-grade stenosis or occlusion of the carotid artery, a history of carotid endarterectomy or carotid stenting, homozygous familial hypercholesterolemia, New York Heart Association class III or IV congestive heart failure, cardiac arrhythmia, angina pectoris, or recent cardiovascular events.

The study consisted of three periods: a screening phase, a single-blind placebo run-in period of 6 weeks, and a double-blind study period with a scheduled duration of 24 months. At baseline, informed consent was obtained, after which laboratory testing and a screening evaluation of the carotid artery were performed. (For details, see the Supplementary Appendix, available with the full text of this article at www.nejm.org.)

At the end of the run-in period, during which all lipid-lowering drugs were discontinued, baseline measurements of lipoprotein variables and intima–media thickness were recorded. Patients were randomly assigned in a 1:1 ratio to receive

daily therapy with 80 mg of simvastatin either with placebo or with 10 mg of ezetimibe. Randomization, which was based on computer-generated codes provided to the clinical centers by a central randomization service, was stratified according to clinical center. Visits were scheduled on day 1, at months 1 and 3, and thereafter at 3-month intervals, with ultrasonographic measurements scheduled for visits at baseline and at 6, 12, 18, and 24 months.

All authors contributed to the manuscript and can vouch for the accuracy and completeness of the data. The study contract specified that after the database was locked, a copy of the completed study database should be provided to the coordinating center for independent analysis. The academic authors had full and unrestricted rights to analyze, interpret, and publish the results.

MEASURES OF CAROTID INTIMA-MEDIA THICKNESS

All patients underwent ultrasonography of the carotid and femoral arteries to assess the intima-media thickness.¹³ Replicate scans were performed within a week of each other at baseline and at 24 months to decrease any variation in measurement, to increase the statistical power, and to preserve the quality control of image acquisition. At each visit, a scan was performed with image acquisition at one predefined angle of the far wall of six carotid segments: the right and left common carotid arteries, carotid bifurcations, and internal carotid arteries. B-mode scans of the right and left common femoral arteries were also performed. All images were transferred to the ultrasonography core laboratory at the Academic Medical Center. Standardized equipment and operating procedures were used to process stored images.

The original training protocol for image readers was amended in April 2006. The change that was proposed was the transition from a single image on the screen to a multiple-image (synchronous) reading process. Images were arranged in electronic folders, with each folder containing seven shuffled, masked time points. These were used for anatomic location and image quality and resulted in improvement in reader variability as well as improvement in the intra-observer standard deviation of the means of the repeated measurements (for details, see the Supplementary Appendix).

STUDY OUTCOMES

The predefined primary outcome was the change from baseline in ultrasonographic measurement of the mean carotid-artery intima-media thickness, 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 in the two study groups.

The key secondary outcomes were the proportion of patients with regression in the mean carotid-artery intima-media thickness from baseline, the proportion of patients with new carotid-artery plaques of more than 1.3 mm, the change from baseline in the mean maximal carotid-artery intima-media thickness (which was defined as the average of far wall maximum intima-media thickness of the right and left common carotid arteries, carotid bulbs, and internal carotid arteries), and the change from baseline in the average mean intima-media thickness of the carotid and common femoral arteries. (Additional secondary outcomes are listed in the Supplementary Appendix.) Fasting blood samples were obtained for analysis of lipid measures, as well as laboratory measures of liver aminotransferase levels, renal function, and hematologic values.

STATISTICAL ANALYSIS

A total of 325 patients were required in each study group to provide a statistical power of 90% to detect a difference of 0.05 mm in carotid-artery measures between the two study groups within 2 years, assuming a standard deviation of 0.20 mm and a two-sided alpha of 0.05. We planned to recruit 725 patients to allow for a discontinuation rate of about 12% during the 2-year study period.

To calculate differences between study groups in changes from baseline, we use analysis-of-covariance models that extract effects according to center, treatment, and the baseline mean carotid-artery intima-media thickness. Analyses are two-sided, with a P value of 0.05 considered to indicate statistical significance. All analyses were performed on an intention-to-treat basis.¹⁴ We used the last-observation-carried-forward method for patients who did not complete the study. In addition, we used a longitudinal (repeated-measures) model that extracts effects according to center, treatment, time, and time according to treatment interaction with an unstructured vari-

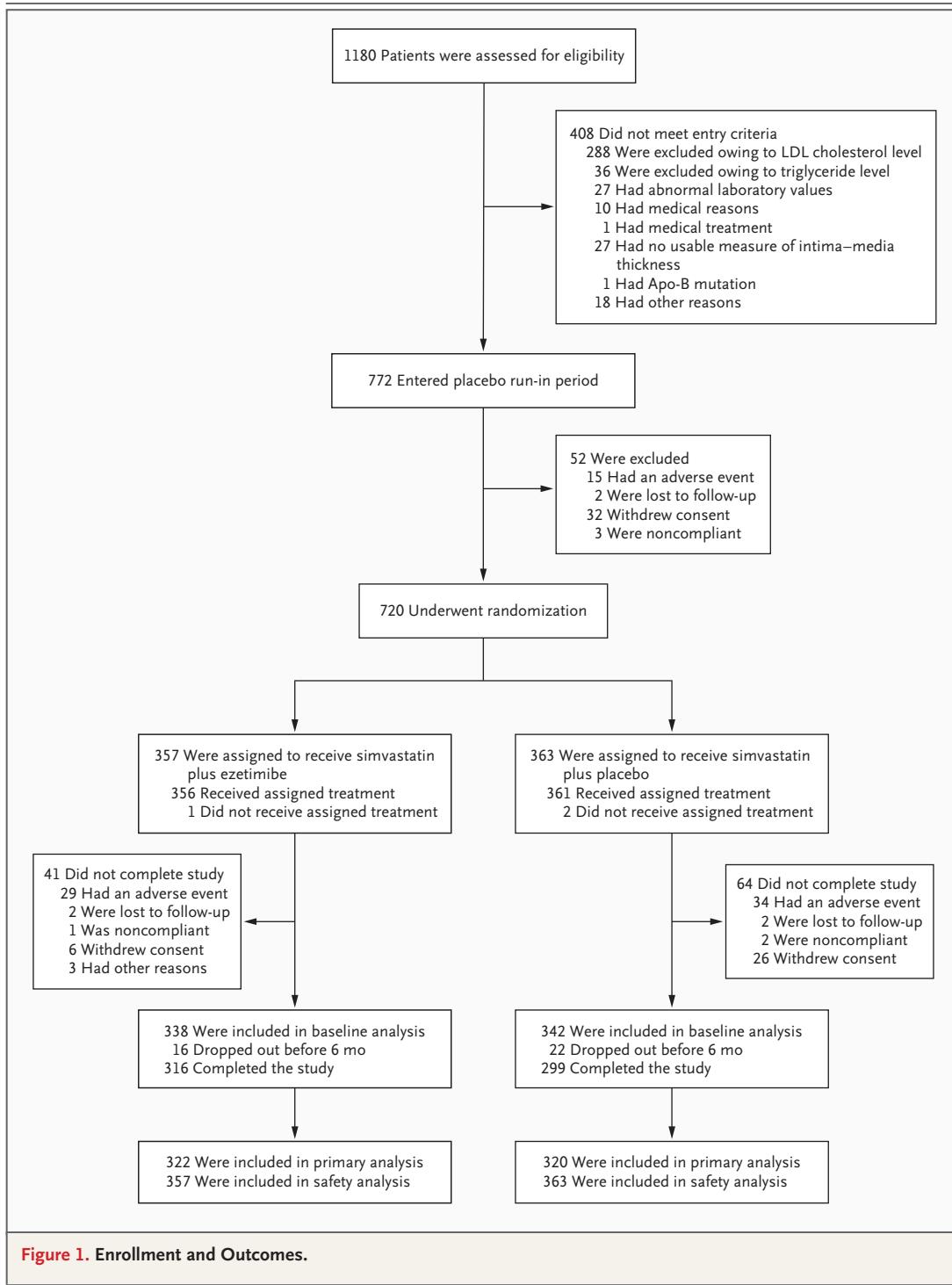


Figure 1. Enrollment and Outcomes.

ance-covariance structure to support the primary analysis. The longitudinal analysis was based on observed data (with time points at 6, 12, 18, and 24 months) and not on the last-observation-carried-forward method.

We used a chi-square test to compare the two study groups with respect to the proportion of patients with a reduction in the mean carotid-artery intima-media thickness from baseline to the end of the study and the proportion of patients

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Simvastatin Monotherapy (N=363)	Simvastatin plus Ezetimibe (N=357)	P Value
Age — yr	45.7±10.0	46.1±9.0	0.69
Male sex — no. (%)	179 (49.3)	191 (53.5)	0.26
Body-mass index	26.7±4.4	27.4±4.6	0.047
Risk factors — no. (%)			
Diabetes	5 (1.4)	8 (2.2)	0.38
Hypertension	51 (14.0)	67 (18.8)	0.09
Current smoking	104 (28.7)	102 (28.6)	0.98
History of myocardial infarction	26 (7.2)	14 (3.9)	0.06
Previous use of statins — no. (%)	297 (81.8)	286 (80.1)	0.56
Blood pressure — mm Hg			
Systolic	124±15	125±15	0.31
Diastolic	78±10	78±9	0.41

* Plus–minus values are means ±SD. The body-mass index is the weight in kilograms divided by the square of the height in meters.

with new carotid-artery plaques, which were defined as an intima–media thickness of more than 1.3 mm. Statistical analyses were performed with SAS software, version 9.1. All exploratory analyses are further outlined in the Supplementary Appendix.

Although the study was not powered to assess clinical outcomes, patients were followed for the occurrence of major adverse cardiovascular events, including death, myocardial infarction, stroke, resuscitated cardiac arrest, and coronary revascularization. It should be noted, however, that none of these events were adjudicated.

RESULTS

PATIENTS

From August 2002 to April 2004, a total of 1180 patients with familial hypercholesterolemia underwent screening. Of these patients, 720 then underwent randomization, with 363 assigned to the simvastatin-only group and 357 assigned to the simvastatin-plus-ezetimibe (combined-therapy) group (Fig. 1). The intention-to-treat population (i.e., patients who underwent post-baseline measurement of carotid-artery intima–media thickness) consisted of 642 patients (320 in the simvastatin-only group and 322 in the combined-therapy group). Of these patients, 64 in the simvastatin-only group

and 41 in the combined-therapy group did not complete the trial.

Demographic and clinical characteristics of the patients are listed in Table 1. The body-mass index was significantly higher in the combined-therapy group ($P=0.047$). Medical-history findings revealed trends toward a higher rate of hypertension ($P=0.09$) and a lower rate of myocardial infarction ($P=0.06$) in the combined-therapy group. Approximately 80% of patients in each group had previously received statins. Compliance with the administration of a study drug (i.e., receipt of at least 70% of a study medication), as measured by tablet count, was 78% in the simvastatin-only group and 84% in the combined-therapy group.

LABORATORY RESULTS

Table 2 summarizes laboratory values for all patients in the intention-to-treat analysis. After 24 months, mean levels of LDL cholesterol decreased from 317.8 ± 66.1 mg per deciliter (8.22 ± 1.71 mmol per liter) to 192.7 ± 60.3 mg per deciliter (4.98 ± 1.56 mmol per liter) in the simvastatin-only group and from 319.0 ± 65.0 mg per deciliter (8.25 ± 1.68 mmol per liter) to 141.3 ± 52.6 mg per deciliter (3.65 ± 1.36 mmol per liter) in the combined-therapy group, a between-group difference of 16.5% ($P<0.01$). Reductions in levels of triglycerides and C-reactive protein were significantly higher in the combined-

Table 2. Levels of Lipids, Lipoproteins, Sterols, and C-Reactive Protein at Baseline and after 24 Months of Treatment, with Changes from Baseline.*

Variable	Simvastatin Monotherapy (N=363)	Simvastatin plus Ezetimibe (N=357)	P Value
Level at baseline			
Cholesterol (mg/dl)			
Total	400.0±68.3	400.0±67.5	0.96
LDL	317.8±66.1	319.0±65.0	0.85
HDL	47.4±13.2	46.7±11.3	0.43
Triglycerides (mg/dl)			
Median	160	157	0.84†
Interquartile range	114 to 227	113 to 217	
Apolipoprotein (mg/dl)			
B	254.1±49.3	253.9±47.6	0.93
A1	145.1±28.7	144.9±26.1	0.53
C-reactive protein (mg/liter)			
Median	1.70	1.70	0.86†
Interquartile range	0.80 to 4.10	0.80 to 3.85	
Level at 24 mo			
Cholesterol (mg/dl)			
Total	270.6±61.5	217.3±56.4	<0.01‡
LDL	192.7±60.3	141.3±52.6	<0.01‡
HDL	50.7±14.7	50.9±12.8	0.78‡
Triglycerides (mg/dl)			
Median	120	108	<0.01†
Interquartile range	89 to 164	82 to 148	
Apolipoprotein (mg/dl)			
B	168.8±44.3	134.6±39.1	<0.01‡
A1	153.3±28.2	152.8±26.1	0.86‡
C-reactive protein (mg/liter)			
Median	1.20	0.90	<0.01†
Interquartile range	0.60 to 2.40	0.50 to 1.90	
Percent change from baseline			
Cholesterol§			
Total	-31.9±0.8	-45.3±0.8	<0.01
LDL	-39.1±0.9	-55.6±0.9	<0.01
HDL	7.8±0.9	10.2±1.0	0.05
Triglycerides			
Median	-23.2	-29.8	<0.01†
Interquartile range	-37.0 to 1.7	-43.5 to 11.5	
Apolipoprotein§			
B	-33.1±0.9	-46.7±0.9	<0.01
A1	6.9±0.8	6.3±0.8	0.56

Table 2. (Continued.)

Variable	Simvastatin Monotherapy (N=363)	Simvastatin plus Ezetimibe (N=357)	P Value
C-reactive protein			<0.01†
Median	-23.5	-49.2	
Interquartile range	-55.9 to 18.2	-66.7 to -7.4	

* Plus-minus values are means \pm SD, unless otherwise indicated. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. HDL denotes high-density lipoprotein, and LDL low-density lipoprotein.

† The P value was calculated from analysis of covariance on rank-transformed data, with the last observation carried forward.

‡ The P value was calculated from analysis of variance, with the last observation carried forward for 24-month follow-up variables.

§ Percent changes from baseline are given as least-square means \pm SE.

therapy group than in the simvastatin-only group (Table 2 and Fig. 2).

IMAGE QUALITY FOR INTIMA-MEDIA THICKNESS

Intraclass correlation coefficients, indicating the reproducibility of the measurements between replicate scans at baseline (for 572 patients) and at the end of the study (for 548 patients), were 0.92 and 0.93, respectively. These estimates included differences within and between visits, within and between sonographers, and within and between reader-variability components. The standard deviations between the paired measurements at baseline and at the end of the study were 0.053 mm and 0.056 mm, respectively.

Completeness of the data for the primary outcome measure (i.e., information regarding four segments or more at baseline and at the end of the study) was 88.0% for patients who had at least one end-of-study visit. In addition, completeness of the data for the intima-media thickness of the common carotid artery was 96.6% for patients who were seen at baseline and at the end of the study. For the intima-media thickness of the carotid bulb and internal carotid artery, these proportions were 84.9% and 84.1%, respectively.

CAROTID ULTRASONOGRAPHY

Table 3 summarizes the results of measurement of the intima-media thickness of the carotid and femoral arteries. The full analysis set incorporated all patients with at least one measurement of intima-media thickness after the baseline assessment: 320 patients (88.1%) in the simvastatin-only group and 322 patients (90.2%) in the combined-therapy group.

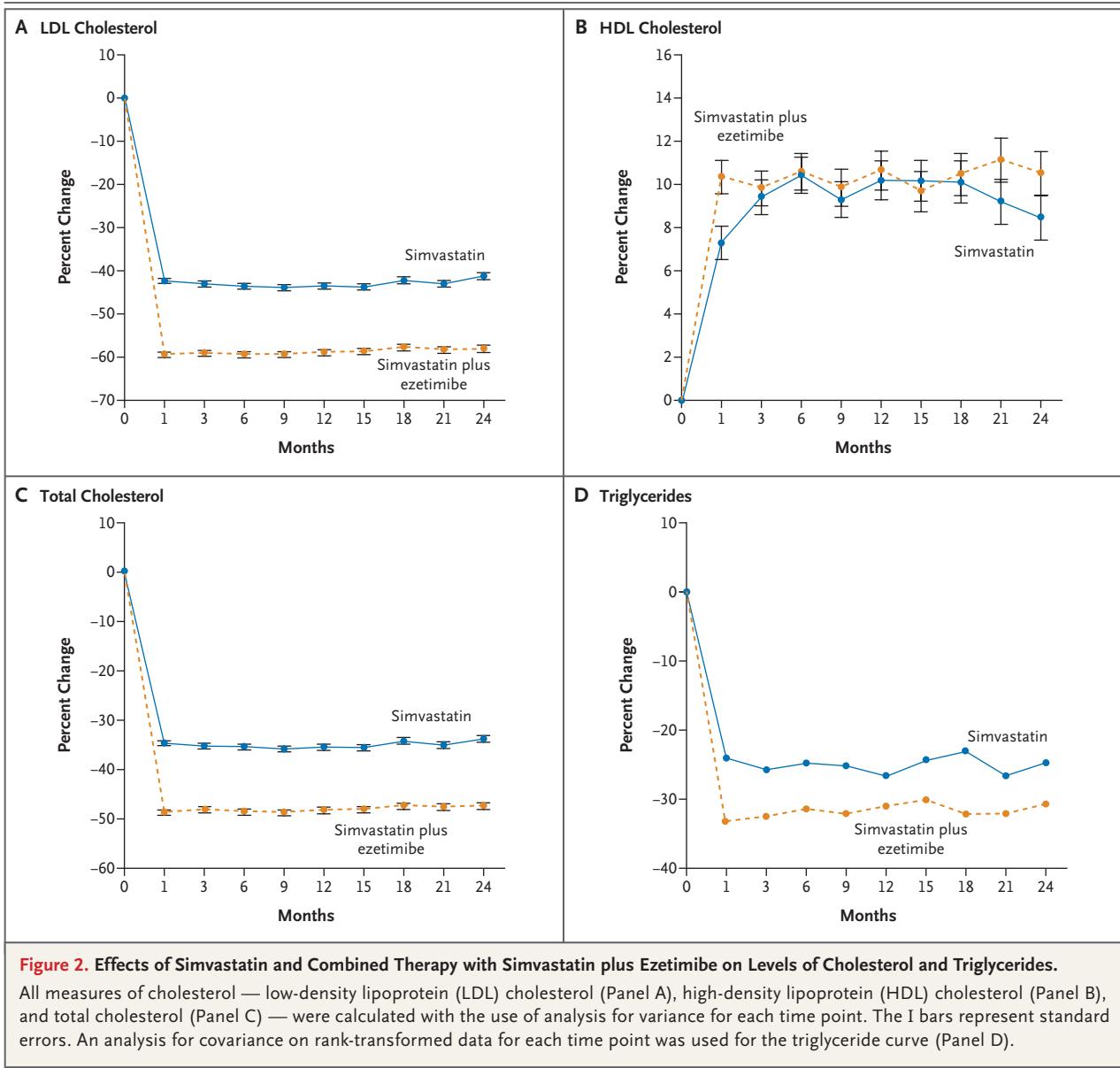
Primary Outcome Measure

The primary outcome measure, the change from baseline in the mean (\pm SE) intima-media thickness of the carotid artery, was 0.0058 ± 0.0037 mm in the simvastatin-only group and 0.0111 ± 0.0038 mm in the combined-therapy group. This difference (0.0053 mm) did not reach statistical significance ($P=0.29$). The exclusion from the statistical analyses of patients with missing data or biologically implausible measures of the carotid-artery intima-media thickness (defined as a difference of >0.1 mm between visits) did not change the primary or secondary outcome results (data not shown).

The results of the longitudinal, repeated-measures model were in line with the primary outcome measure (Fig. 3). The change in the average intima-media thickness over time did not differ significantly between the two study groups ($P=0.17$ for the interaction between treatment and time). There was a slight increase in the mean intima-media thickness over time in both groups; at 2 years, estimates were 0.0095 ± 0.0040 mm in the simvastatin-only group ($P=0.02$) and 0.0121 ± 0.0038 mm in the combined-therapy group ($P<0.01$).

Secondary Outcome Measures

Regression in the mean carotid-artery intima-media thickness was seen in 142 of 320 patients (44.4%) in the simvastatin-only group and in 146 of 322 patients (45.3%) in the combined-therapy group ($P=0.92$). New plaque formation (which was defined as an intima-media thickness of more than 1.3 mm) was seen in 9 of 320 patients (2.8%) in the simvastatin-only group and in 15 of 322



patients (4.7%) in the combined-therapy group ($P=0.20$). No significant change was observed in the mean maximum carotid-artery intima-media thickness, an increase of 0.0103 ± 0.0049 mm in the simvastatin-only group and 0.0175 ± 0.0049 mm in the combined-therapy group ($P=0.27$). Finally, no significant changes were observed between study groups regarding mean measures of the intima-media thickness of the common carotid artery ($P=0.93$), the carotid bulb ($P=0.37$), the internal carotid artery ($P=0.21$), and the femoral artery ($P=0.16$), nor in the average of the mean

values for intima-media thickness in the carotid and femoral arteries ($P=0.15$) (Table 3).

ADVERSE EVENTS

Adverse events that were considered to be related to treatment were similar in the two groups and occurred in 107 of 363 patients (29.5%) in the simvastatin-only group and in 122 of 357 patients (34.2%) in the combined-therapy group ($P=0.18$). Likewise, the rates of discontinuation owing to adverse events were similar: 34 of 363 patients (9.4%) in the simvastatin-only group and 29 of 357

Table 3. Measures of Intima–Media Thickness in Carotid and Femoral Arteries at Baseline and at 24 Months and Changes from Baseline.*

Variable	Simvastatin Monotherapy	Simvastatin plus Ezetimibe	P Value
At baseline			
No. of patients	342	338	
Mean intima–media thickness of carotid artery (mm)			
Average of 6 segments†	0.70±0.13	0.69±0.13	0.64
Common carotid artery	0.68±0.16	0.67±0.16	0.45
Carotid bulb	0.80±0.20	0.79±0.22	0.51
Internal carotid artery	0.61±0.17	0.62±0.17	0.42
Maximum‡	0.80±0.16	0.80±0.17	0.94
Mean intima–media thickness of femoral artery (mm)			
Average of mean intima–media thickness of carotid and femoral arteries (mm)	0.75±0.22	0.73±0.19	0.18
At 24 mo§			
No. of patients	320	322	
Mean intima–media thickness of carotid artery (mm)			
Average of 6 segments†	0.70±0.14	0.71±0.15	0.29
Common carotid artery	0.68±0.15	0.68±0.16	0.93
Carotid bulb	0.81±0.22	0.81±0.23	0.37
Internal carotid artery	0.62±0.17	0.64±0.17	0.21
Maximum‡	0.81±0.17	0.82±0.18	0.27
Mean intima–media thickness of femoral artery (mm)			
Average of mean intima–media thickness of carotid and femoral arteries (mm)	0.76±0.23	0.75±0.22	0.15
Difference from baseline at 24 mo¶			
Mean intima–media thickness of carotid artery (mm)			
Average of 6 segments†	0.0058±0.0037	0.0111±0.0038	0.29
Common carotid artery	0.0024±0.0043	0.0019±0.0044	0.93
Carotid bulb	0.0062±0.0069	0.0144±0.0070	0.37
Internal carotid artery	–0.0007±0.0064	0.0099±0.0065	0.21
Maximum‡	0.0103±0.0049	0.0175±0.0049	0.27
Mean intima–media thickness of femoral artery (mm)			
Average of mean intima–media thickness of carotid and femoral arteries (mm)	0.0033±0.0079	0.0182±0.008	0.15

* Plus–minus values are means ±SD, unless otherwise indicated.

† This value was defined as the average of the means of the far wall intima–media thickness of at least two of six segments: the right and left common carotid arteries, carotid bulbs, and internal carotid arteries.

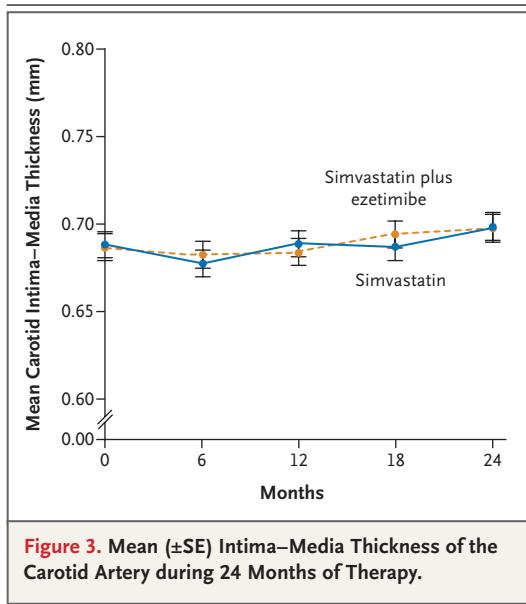
‡ This value was defined as the average of far wall maximum intima–media thickness of at least two of six segments: the right and left common carotid arteries, carotid bulbs, and internal carotid arteries.

§ Values were calculated by the last-observation-carried-forward method.

¶ Differences from baseline are given as least-square means ±SE.

patients (8.1%) in the combined-therapy group (P=0.56). Eight of 360 patients (2.2%) in the simvastatin-only group and 10 of 356 patients (2.8%) in the combined-therapy group had to discontinue

treatment because of consecutive elevations of more than three times the upper limit of the normal range (ULN) in alanine aminotransferase, aspartate aminotransferase, or both (P=0.62). There



was one case of possible hepatitis in the simvastatin-only group. Furthermore, 8 of 360 patients (2.2%) in the simvastatin-only group and 4 of 356 patients (1.1%) in the combined-therapy group had an increase in the level of creatine kinase of more than 10 times the ULN ($P=0.25$). Myopathy (which was defined as a creatine kinase level ≥ 10 times the ULN, with associated muscle symptoms) occurred in one patient in the simvastatin-only group and in two patients in the combined-therapy group. In all patients, increased levels of alanine aminotransferase, aspartate aminotransferase, or both and elevations in creatine kinase levels were transient. No clinically important treatment-related changes were observed for vital signs or measures on electrocardiography.

Investigator-reported cardiovascular events were noted in 7 patients in the simvastatin group (including 1 death from a cardiovascular cause, 2 nonfatal myocardial infarctions, 1 nonfatal stroke, and 5 coronary revascularization procedures) and in 10 patients in the combined-therapy group (including 2 deaths from cardiovascular causes, 3 nonfatal myocardial infarctions, 1 nonfatal stroke, and 6 coronary revascularizations).

DISCUSSION

The results of our study showed that the addition of ezetimibe to the highest recommended dose of simvastatin did not reduce the intima-media

thickness of the carotid-artery wall in this cohort of patients with familial hypercholesterolemia, despite significant incremental reductions in levels of both LDL cholesterol and C-reactive protein. The primary outcome, the change in the mean intima-media thickness, did not differ significantly between the two study groups, nor did the secondary outcome measures.

There are at least three possible explanations for the absence of an incremental reduction in the intima-media thickness in patients receiving ezetimibe: the lack of vascular benefit conferred by ezetimibe despite the observed reduction in LDL cholesterol level, the inability of the measurement technique to accurately reflect changes in atherosclerotic burden, and the possibility that the study population had too low a risk, which would limit our ability to detect a differential response to the two interventions.

The first explanation to consider is that the lowering of LDL cholesterol levels by a drug other than a statin might be ineffective for slowing atherosclerosis. Thus, the fact that ezetimibe-induced lowering of LDL cholesterol levels was not associated with an incremental effect on carotid-artery intima-media thickness could be due to the different mechanisms of action of ezetimibe, as compared with those of statins. In addition to the capacity of statins to lower LDL cholesterol levels, the inhibition of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase also leads to a plethora of lipid-independent effects involving antiinflammatory action and improvement in endothelial function.¹⁵ A direct comparison between ezetimibe and statins revealed differential effects on endothelial function favoring statin therapy despite similar reductions in LDL cholesterol,^{16,17} although this finding has not been consistent in all studies.¹⁸ Also, dose intensification of statins in patients with familial hypercholesterolemia resulted in a further reduction in the progression of intima-media thickness in the carotid artery.¹⁹ Thus, it can be argued that certain lipid-independent effects of statins that are not shared by ezetimibe are involved in the production of a vascular benefit.

However, several facts argue against the concept that ezetimibe-induced lowering of LDL cholesterol levels does not produce additional vascular benefit beyond that of statins. First, a recent regression meta-analysis showed that the lipid-

independent effects of statins did not confer an additional risk reduction beyond that expected from the degree of the lowering of the LDL cholesterol level.²⁰ Second, data from the Program on Surgical Control of the Hyperlipidemias (POSCH) trial showed that reductions in levels of LDL cholesterol after ileocecal bypass were associated with significant reductions in cardiovascular mortality and event rates similar to those observed in statin-prevention trials.^{21,22} In view of the controversy regarding the lipid-independent effects of statins, the results of ongoing clinical trials comparing statins with combined therapy with ezetimibe and a statin are eagerly awaited to resolve this issue.

Large epidemiologic studies have provided strong associations between intima-media thickness and stroke, angina pectoris, and myocardial infarction.^{10,11} In the Atherosclerosis Risk in Communities (ARIC) study involving 15,800 adults, an increase of 0.2 mm in the mean carotid-artery intima-media thickness was associated with an increase in relative risk for myocardial infarction and stroke of 33% and 28%, respectively.²³ This close relationship between intima-media thickness and cardiovascular risk has subsequently been corroborated in several other studies.²⁴

One of the principal determinants of atherosclerosis progression has proved to be LDL cholesterol levels, as confirmed by the linear relationship between the level of LDL cholesterol and intima-media thickness.²⁵ This finding is further supported by the observation that progression in intima-media thickness is significantly attenuated in statin intervention studies in both adult and pediatric patients with familial hypercholesterolemia.^{11,19,26-32} On the basis of this information, the measurement of intima-media thickness can be considered as a validated surrogate marker for atherosclerotic vascular disease. Also, in view of the precision of the measurements in our study, as exemplified by the high intraclass correlation coefficient and the small standard deviations, it seems unlikely that we were unable to detect a truly significant change in arterial-wall measures using our measurement technique.

Patients with familial hypercholesterolemia are known to be at greatly increased risk for premature coronary artery disease,¹⁰ accompanied by accelerated progression of intima-media thickness starting in childhood.¹¹ However, the treatment of

patients with familial hypercholesterolemia has witnessed profound changes. Currently, the majority of patients with familial hypercholesterolemia are treated with high-dose statins starting at an early age. Such therapy can be expected to attenuate the progression of intima-media thickness, as was shown in the Atorvastatin versus Simvastatin on Atherosclerosis Progression (ASAP) study.¹⁹ Thus, it is not unexpected that the baseline carotid intima-media thickness in our study was lower than that observed in earlier trials involving patients with familial hypercholesterolemia³³ and in most other previous lipid-modifying trials,^{26,27,31} with the exception of the Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 1 (ARBITER-1) study.³¹ Among patients who received 80 mg of simvastatin only in our study, the progression of intima-media thickness was 0.0029 mm per year, as compared with 0.018 mm per year in patients with familial hypercholesterolemia who received 40 mg of simvastatin in the ASAP study — a reduction by a factor of 6 among patients receiving the higher dose. In further support of the influence of previous statin therapy, progression of intima-media thickness in the carotid artery decreased to 0.005 mm per year during long-term daily therapy with 80 mg of atorvastatin in the ASAP extension study,³⁴ a finding that contrasts with the substantial reductions in intima-media thickness seen during the first 2 years of the trial. In the Rating Atherosclerotic Disease Change by Imaging with a New CETP [Cholesteryl Ester Transfer Protein] Inhibitor (RADIANCE 1) study,³⁵ the most recent study involving a similar group of patients with familial hypercholesterolemia, the pattern of change in intima-media thickness after a mean daily dose of 57 mg of atorvastatin was very similar to that observed in both groups in our study. These data raise the possibility that there may be limits to the extent to which the lowering of LDL cholesterol levels can result in a further decrease in the progression of intima-media thickness in the context of previous statin therapy and a modest baseline intima-media thickness.

In conclusion, the reduction of LDL cholesterol by the addition of ezetimibe to simvastatin did not reduce intima-media thickness of the carotid-artery wall in patients with familial hypercholesterolemia in our study. The reason for the failure

to observe an incremental effect on intima-media thickness despite a reduction in levels of LDL cholesterol remains unknown.

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APPENDIX

In addition to the authors, the following investigators participated in the ENHANCE trial: *Hospital Universitario Reina Sofia, Cordoba, Spain: F. Perez Jimenez; Fundacion Jimenez Diaz, Madrid: P. Mata; Centre Cardiovasculaire de Laval, Quebec, QC, Canada: R. Habib; St. Paul's Hospital, Vancouver, BC, Canada: J. Frohlich; Centre Hospitalier Université Laval, Quebec, QC, Canada: C. Gagne; Institute of Pathology, Pretoria, South Africa: I. Ker; Midrand Medical Center, Midrand Gauteng, South Africa: A. Jacovides; Aarhus Amtssygehus University Hospital, Aarhus C, Denmark: E. Madsen; University of Oslo, Oslo: L. Ose, K. Retterstoel; Center for Metabolism, Stockholm: M. Eriksson; University Medical Center, Nijmegen, the Netherlands: J. de Graaf; University Hospital, Groningen, the Netherlands: A.J. Smit.*

REFERENCES

- MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002;360:7-22.
- Cannon CP, Braunwald E, McCabe CH, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med* 2004;350:1495-504. [Erratum, *N Engl J Med* 2006;354:778.]
- LaRosa JC, Grundy SM, Waters DD, et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med* 2005;352:1425-35.
- Pedersen TR, Faergeman O, Kastelein JJ, et al. High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial. *JAMA* 2005;294:2437-45. [Erratum, *JAMA* 2005;294:3092.]
- Armitage J. The safety of statins in clinical practice. *Lancet* 2007;370:1781-90.
- Altmann SW, Davis HR Jr, Zhu LJ, et al. Niemann-Pick C1 Like 1 protein is critical for intestinal cholesterol absorption. *Science* 2004;303:1201-4.
- Davis HR Jr, Hoos LM, Tetzloff G, et al. Deficiency of Niemann-Pick C1 Like 1 prevents atherosclerosis in ApoE^{-/-} mice. *Arterioscler Thromb Vasc Biol* 2007;27:841-9.
- Ballantyne CM, Houry J, Notarbartolo A, et al. Effect of ezetimibe coadministered with atorvastatin in 628 patients with primary hypercholesterolemia: a prospective, randomized, double-blind trial. *Circulation* 2003;107:2409-15.
- Davidson MH, McGarry T, Bettis R, et al. Ezetimibe coadministered with simvastatin in patients with primary hypercholesterolemia. *J Am Coll Cardiol* 2002;40:2125-34.
- Rader DJ, Cohen J, Hobbs HH. Monogenic hypercholesterolemia: new insights in pathogenesis and treatment. *J Clin Invest* 2003;111:1795-803.
- Wiegman A, de Groot E, Hutten BA, et al. Arterial intima-media thickness in children heterozygous for familial hypercholesterolemia. *Lancet* 2004;363:369-70.
- Familial hypercholesterolaemia (FH): report of a WHO consultation. Geneva: World Health Organization, 1998. (Accessed March 11, 2008, at http://whqlibdoc.who.int/hq/1998/WHO_hgn_fh_CONS_98.7.pdf.)
- Kastelein JJ, Sager PT, de Groot E, Veltri E. Comparison of ezetimibe plus simvastatin versus simvastatin monotherapy on atherosclerosis progression in familial hypercholesterolemia: design and rationale of the Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) trial. *Am Heart J* 2005;149:234-9.
- Espeland MA, Craven TE, Miller ME, D'Agostino R Jr. 1996 Remington Lecture: modeling multivariate longitudinal data that are incomplete. *Ann Epidemiol* 1999;9:196-205.
- Schönbeck U, Libby P. Inflammation, immunity, and HMG-CoA reductase inhibitors: statins as antiinflammatory agents? *Circulation* 2004;109:Suppl II:II-18-II-26.
- Landmesser U, Bahlmann F, Mueller M, et al. Simvastatin versus ezetimibe: pleiotropic and lipid-lowering effects on endothelial function in humans. *Circulation* 2005;111:2356-63.
- Fichtlscherer S, Schmidt-Lucke C, Bojunga S, et al. Differential effects of short-term lipid lowering with ezetimibe and statins on endothelial function in patients with CAD: clinical evidence for 'pleiotropic' functions of statin therapy. *Eur Heart J* 2006;27:1182-90.
- Bulut D, Hanefeld C, Bulut-Streich N, Graf C, Mügge A, Spiecker M. Endothelial function in the forearm circulation of patients with the metabolic syndrome — effect of different lipid-lowering regimens. *Cardiology* 2005;104:176-80.
- 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;357:77-81.
- Robinson JG, Smith B, Maheshwari N, Schrott H. Pleiotropic effects of statins: benefit beyond cholesterol reduction? A meta-regression analysis. *J Am Coll Cardiol* 2005;46:1855-62.
- Buchwald H, Varco RL, Matts JP, et al. Effect of partial ileal bypass surgery on mortality and morbidity from coronary heart disease in patients with hypercholesterolemia: report of the Program on the Surgical Control of the Hyperlipidemias (POSCH). *N Engl J Med* 1990;323:946-55.
- Buchwald H, Varco RL, Boen JR, et al. Effective lipid modification by partial ileal bypass reduced long-term coronary heart disease mortality and morbidity: five-year posttrial follow-up report from the POSCH. *Arch Intern Med* 1998;158:1253-61.
- Howard G, Sharrett AR, Heiss G, et al. Carotid artery intimal-medial thickness distribution in general populations as evaluated by B-mode ultrasound. *Stroke* 1993;24:1297-304.
- Bots ML, Hoes AW, Koudstaal PJ, Hofman A, Grobbee DE. Common carotid intima-media thickness and risk of stroke and myocardial infarction: the Rotterdam Study. *Circulation* 1997;96:1432-7.
- Amarenco P, Labreuche J, Lavallée P, Touboul PJ. Statins in stroke prevention and carotid atherosclerosis: systematic review and up-to-date meta-analysis. *Stroke* 2004;35:2902-9.
- Crouse JR III, Grobbee DE, O'Leary DH, et al. Measuring Effects on intima

- media Thickness: an Evaluation Of Rosuvastatin in subclinical atherosclerosis — the rationale and methodology of the METEOR study. *Cardiovasc Drugs Ther* 2004;18:231-8.
27. de Groot E, Jukema JW, Montauban van Swijndregt AD, et al. B-mode ultrasound assessment of pravastatin treatment effect on carotid and femoral artery walls and its correlations with coronary arteriographic findings: a report of the Regression Growth Evaluation Statin Study (REGRESS). *J Am Coll Cardiol* 1998;31:1561-7.
28. 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 Beta-Blocker Cholesterol-Lowering Asymptomatic Plaque Study (BCAPS). *Circulation* 2001;103:1721-6.
29. Hodis HN, Mack WJ, LaBree L, et al. Reduction in carotid arterial wall thickness using lovastatin and dietary therapy: a randomized controlled clinical trial. *Ann Intern Med* 1996;124:548-56.
30. MacMahon S, Sharpe N, Gamble G, et al. Effects of lowering average of below-average cholesterol levels on the progression of carotid atherosclerosis: results of the LIPID Atherosclerosis Substudy. *Circulation* 1998;97:1784-90. [Erratum, *Circulation* 1996;97:2479.]
31. 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;106:2055-60.
32. 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;110:3512-7. [Errata, *Circulation* 2004;110:3615, 2005;111(24):e446.]
33. de Groot E, Hovingh GK, Wiegman A, et al. Measurement of arterial wall thickness as a surrogate marker for atherosclerosis. *Circulation* 2004;109:Suppl III:III-33–III-38.
34. 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;95:264-6.
35. Kastelein JJP, van Leuven SI, Burgess L, et al. Effect of torcetrapib on carotid atherosclerosis in familial hypercholesterolemia. *N Engl J Med* 2007;356:1620-30.

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