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Extended-Release Niacin or Ezetimibe and Carotid Intima–Media Thickness

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ABSTRACT

BACKGROUND

Treatment added to statin monotherapy to further modify the lipid profile may include combination therapy to either raise the high-density lipoprotein (HDL) cholesterol level or further lower the low-density lipoprotein (LDL) cholesterol level.

METHODS

We enrolled patients who had coronary heart disease or a coronary heart disease risk equivalent, who were receiving long-term statin therapy, and in whom an LDL cholesterol level under 100 mg per deciliter (2.6 mmol per liter) and an HDL cholesterol level under 50 mg per deciliter for men or 55 mg per deciliter for women (1.3 or 1.4 mmol per liter, respectively) had been achieved. The patients were randomly assigned to receive extended-release niacin (target dose, 2000 mg per day) or ezetimibe (10 mg per day). The primary end point was the between-group difference in the change from baseline in the mean common carotid intima–media thickness after 14 months. The trial was terminated early, on the basis of efficacy, according to a prespecified analysis conducted after 208 patients had completed the trial.

RESULTS

The mean HDL cholesterol level in the niacin group increased by 18.4% over the 14-month study period, to 50 mg per deciliter ($P<0.001$), and the mean LDL cholesterol level in the ezetimibe group decreased by 19.2%, to 66 mg per deciliter (1.7 mmol per liter) ($P<0.001$). Niacin therapy significantly reduced LDL cholesterol and triglyceride levels; ezetimibe reduced the HDL cholesterol and triglyceride levels. As compared with ezetimibe, niacin had greater efficacy regarding the change in mean carotid intima–media thickness over 14 months ($P=0.003$), leading to significant reduction of both mean ($P=0.001$) and maximal carotid intima–media thickness ($P\leq0.001$ for all comparisons). Paradoxically, greater reductions in the LDL cholesterol level in association with ezetimibe were significantly associated with an increase in the carotid intima–media thickness ($R=-0.31$, $P<0.001$). The incidence of major cardiovascular events was lower in the niacin group than in the ezetimibe group (1% vs. 5%, $P=0.04$ by the chi-square test).

CONCLUSIONS

This comparative-effectiveness trial shows that the use of extended-release niacin causes a significant regression of carotid intima–media thickness when combined with a statin and that niacin is superior to ezetimibe. (ClinicalTrials.gov number, NCT00397657.)

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Treatment with 3-hydroxy-3-methylglutaryl–coenzyme A reductase inhibitors reduces low-density lipoprotein (LDL) cholesterol levels and results in clinically significant reductions in the relative risk of major cardiovascular events.[1] However, because of the residual cardiovascular risk seen with statin monotherapy, treatment may be intensified with the use of combination therapy, aimed at either further reducing the LDL cholesterol level or at altering levels of other lipids, such as high-density lipoprotein (HDL) cholesterol.

Progressive lowering of the LDL cholesterol level through intensification of statin therapy leads to a 16% reduction in the odds of cardiovascular events and death from cardiovascular causes.[2] This approach has also been shown to yield improvement in atherosclerosis, measured as the carotid intima–media thickness[3] or on coronary ultrasonography.[4] Although the use of ezetimibe in combination with a statin reduces the LDL cholesterol level, data on its clinical value are lacking. Alternatively, low levels of HDL cholesterol may be treated as a secondary lipid target through niacin-based combination therapy. This approach has led to potentially clinically significant reductions in the relative risk of a clinical coronary event in generally small studies,[5] as well as resulting in the stabilization or regression of atherosclerosis.[6-11]

To our knowledge, no clinical trial has directly compared the clinical effectiveness of treatment strategies using the two common secondary agents niacin and ezetimibe combined with a statin. The ARBITER 6–HALTS (Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 6–HDL and LDL Treatment Strategies) trial compared the effects of two combination therapies — either niacin or ezetimibe added to long-term statin therapy — on carotid intima–media thickness over a 14-month period.[12]

METHODS

STUDY POPULATION

This prospective, randomized, parallel-group, open-label study involving the blinded evaluation of end points was conducted at two centers: Walter Reed Army Medical Center, a university-affiliated, suburban, tertiary care military medical center in Washington, DC, and the Washington Adventist Hospital, a private tertiary care hospital located in Takoma Park, Maryland. The institutional review boards of each facility approved the study, and all patients provided written informed consent. We enrolled men and women 30 years of age or older who had either known atherosclerotic coronary or vascular disease (279 patients) or a coronary heart disease risk equivalent, including diabetes mellitus (38 patients); a 10-year Framingham risk score (estimating the risk of coronary heart disease) of 20% or more (26 patients); or a coronary calcium score above 200 for women or 400 for men (20 patients). All participants were required to have been treated with statin monotherapy at a consistent dose, with a lipid panel obtained within 3 months before enrollment that showed both an LDL cholesterol level under 100 mg per deciliter (2.6 mmol per liter) and an HDL cholesterol level under 50 mg per deciliter for men or 55 mg per deciliter for women (1.3 or 1.4 mmol per liter, respectively).

RANDOMIZATION

From November 16, 2006, through June 4, 2009, 363 patients were enrolled in the trial. The follow-up of patients throughout the trial is shown in Figure 1 in the Supplementary Appendix (available with the full text of this article at NEJM.org).

Eligible patients were randomly assigned, in a blinded manner, to receive open-label treatment with either extended-release niacin at a target dose of 2000 mg per day (Abbott) or ezetimibe at a dose of 10 mg per day (Merck–Schering-Plough Pharmaceuticals). The niacin dose was increased from an initial dose of 500 mg at bedtime, by 500 mg every other week, to the maximum tolerated dose (up to 2000 mg at bedtime). Niacin was provided by the sponsor, as was ezetimibe, after it was acquired by the sponsor from a commercial source. Randomization was performed by means of a computer-generated sequence of random numbers. There were no protocol-directed changes in statin medications or doses during the study.

END POINTS

The predefined primary end point was the between-group difference in the change in mean carotid intima–media thickness after 14 months. The four secondary end points were the change in lipid values, a composite end point consisting of major adverse cardiovascular events (myocardial infarction, myocardial revascularization, admission to the hospital for an acute coronary syndrome, and death from coronary heart disease),

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discontinuation of a study drug owing to adverse effects, and health-related quality of life.[13] Clinical cardiovascular end points were adjudicated by means of a consensus between two members of the independent data advisory committee who were unaware of the treatment assignments.

B-MODE ULTRASONOGRAPHY OF THE CAROTID ARTERIES

Carotid ultrasonography was performed with the use of an ultrasonography system equipped with a broadband linear-array probe (13 MHz Micromaxx, Sonosite). Patients underwent three ultrasonographic examinations during the study: at baseline, at 8 months, and at 14 months. Except for the first 20 subjects enrolled at the Washington Adventist site, for whom another sonographer performed the initial ultrasonographic examination, a single ultrasonographer performed all ultrasonographic examinations.

The images obtained were of the far wall of the distal 1 cm of the right and left common carotid arteries, in the anterior and lateral views. A total of eight images (two complete sets of four separate images) were obtained with the use of standardized ultrasonography settings. The baseline carotid ultrasonographic examinations were used to localize the site of interest in subsequent images. Digitized still images from an electrocardiographically defined diastolic frame were quantitated offline. A single observer who was unaware of the treatment assignments and the identities of the patients measured the mean and maximal carotid intima–media thicknesses. Focal atherosclerotic plaque was excluded from the measurements. All measurements were performed in duplicate, with the use of an automated border-detection algorithm (see Fig. 2 in the Supplementary Appendix). No scans were excluded on the basis of image quality, and measurements of the carotid intima–media thickness were available for all patients except one, for whom ultrasonography at 8 months was not completed.

For mean carotid intima–media thickness, the variability between the two sets of images taken for each patient was 0.0011±0.0125 mm ($r=0.997$, $P<0.001$). The intraobserver variability was 0.0001± 0.0055 mm ($r=0.999$, $P<0.001$). The reproducibility of measurements by the single observer over time was evaluated with the use of a standard set of 10 images of carotid intima–media thickness obtained from various patients, which the observer serially quantified every 6 months. The maximum difference at any time point among the mean carotid intima–media thicknesses obtained from these 10 images was 0.001 mm or less.

CARDIOVASCULAR RISK VARIABLES

After an overnight fast, laboratory measurements were obtained for serum total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, C-reactive protein, liver-associated enzymes, and glucose — at baseline and at 2, 8, and 14 months. LDL cholesterol was measured with the use of a direct assay. C-reactive protein was measured by means of a high-sensitivity, commercially available immunoturbidimetric assay that uses monoclonal antibodies against C-reactive protein (Integra, Roche Cobas).

FUNDING AND ROLE OF THE SPONSOR

Abbott was the study sponsor (after acquiring Kos Pharmaceuticals, the original sponsor). Abbott provided an unrestricted, investigator-initiated research grant administered by the Henry M. Jackson Foundation for the Advancement of Military Medicine. The monitoring of the study, maintenance of the trial database, measurement of all study end points, end-point adjudication, and statistical analysis were performed by the authors, without involvement of the sponsor. The manuscript was drafted by the principal investigator and revised by the coauthors. The sponsor's medical department commented on the completed manuscript, but the final decisions regarding the content and publication were made by the authors, who vouch for the completeness and accuracy of the data and analyses.

STATISTICAL ANALYSIS

The primary end point was the change in mean common carotid intima–media thickness from baseline and 14 months, compared between the niacin group and the ezetimibe group. On the basis of a minimum sample size of 150 per group, the trial had a statistical power of 80% to detect a difference between the two groups in the change in carotid intima–media thickness of 0.02±0.06 mm per year, with an alpha level of 0.05. Clinical and carotid-imaging data were held in separate databases for the duration of the trial. Between-group data for continuous variables were assessed with the use of a t-test for independent variables or a Mann–Whitney U test, as appropriate. A chi-

Table 1. Baseline Characteristics of the 208 Study Patients Who Completed the 14-Month Assessment of Carotid Intima–Media Thickness, According to Treatment Group.*

Characteristic	Ezetimibe (N=111)	Niacin (N=97)	P Value
Male sex — no. (%)	91 (82)	76 (78)	0.51
Age — yr	65±11	64±11	0.49
Diabetes mellitus — no. (%)	44 (40)	31 (32)	0.25
Hypertension — no. (%)	96 (86)	82 (85)	0.69
Tobacco use — no. (%)	5 (5)	6 (6)	0.86
Family history of coronary heart disease — no. (%)	42 (38)	48 (49)	0.09
History of coronary heart disease — no. (%)			
Angina with documented ischemia	41 (37)	34 (35)	0.78
Angiographic coronary disease	70 (63)	63 (65)	0.78
Myocardial infarction	37 (33)	27 (28)	0.32
Percutaneous coronary revascularization	49 (44)	29 (30)	0.05
Coronary bypass surgery	26 (23)	25 (26)	0.69
Medications — no. (%)			
Beta-blocker	83 (75)	69 (71)	0.55
Aspirin, at baseline and during trial	104 (94)	94 (97)	0.28
Clopidogrel	31 (28)	31 (32)	0.53
Angiotensin-converting–enzyme inhibitor	65 (59)	61 (63)	0.52
Statin therapy — no. (%)			
Simvastatin	43 (39)	52 (54)	0.09
Atorvastatin	63 (57)	39 (40)	
Pravastatin	2 (2)	4 (4)	
Rosuvastatin	3 (3)	2 (2)	
Lovastatin	0	0	
Mean daily statin dose — mg	42±24	42±25	0.98
Duration of statin use — yr	6.1±5.2	5.2±4.6	0.18
Body-mass index†	31.0±5.4	30.8±6.7	0.90
Waist circumference — in.	41.0±4.8	40.8±5.8	0.81
Blood pressure — mm Hg			
Systolic	136±18	132±15	0.11
Diastolic	75±10	74±10	0.70
Cholesterol — mg/dl			
Total cholesterol	146.6±23.3	145.6±24.0	0.74
LDL	83.7±19.9	80.5±17.2	0.22
HDL	43.3±8.5	42.5±8.6	0.48
Triglycerides — mg/dl			0.56
Median	122	126	
Interquartile range	87–162	94–163	
Glucose — mg/dl	104.0±27.8	100.1±18.9	0.25
High-sensitivity CRP — mg/liter			0.51
Median	1.9	1.3	
Interquartile range	0.8–3.5	0.8–4.0	

* Plus–minus values are means ±SD. To convert values for waist circumference to centimeters, multiply by 2.54. To convert values for cholesterol to millimoles per liter, multiply by 0.02586. To convert values for triglycerides to millimoles per liter, multiply by 0.01129. To convert values for glucose to millimoles per liter, multiply by 0.05551. CRP denotes C-reactive protein, HDL high-density lipoprotein, and LDL low-density lipoprotein.

† The body-mass index is the weight in kilograms divided by the square of the height in meters.

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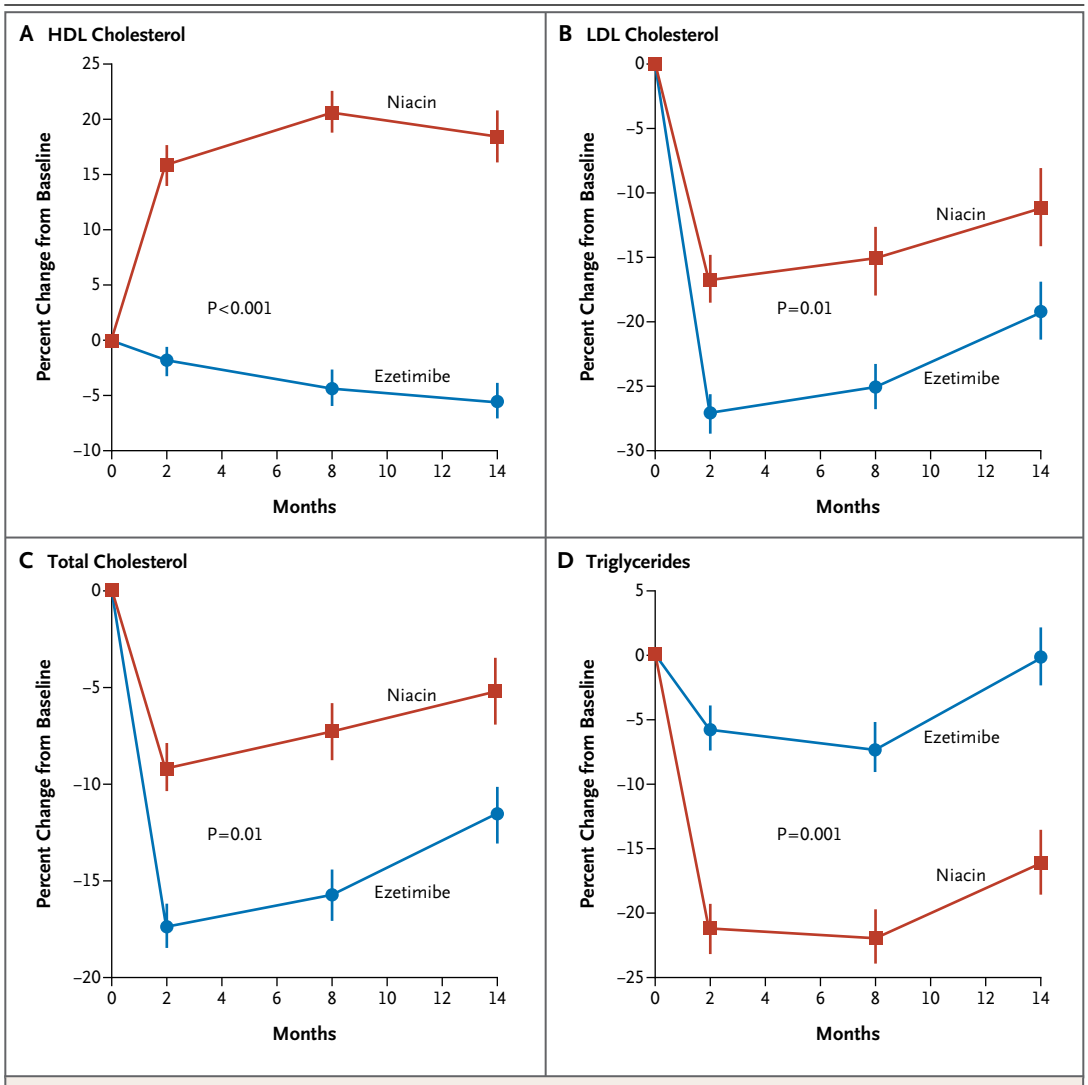

Figure 1. Mean Percent Changes in Cholesterol and Triglyceride Levels over the 14-Month Study Period among the 208 Patients Who Completed the Study, According to Treatment Group.

P values are given for the comparison between the two treatment groups at 14 months. The vertical bars indicate the standard errors. HDL denotes high-density lipoprotein, and LDL low-density lipoprotein.

square test was used to evaluate categorical variables. A general linear model was used to analyze repeated measures of carotid intima–media thickness for the comparison of effects between the two groups. Kaplan–Meier survival analysis was performed with the use of the log-rank test. All statistical analyses were performed with SPSS software (version 16). Values are reported as means and standard deviations or standard errors or, for non-normal distributions, as medians and interquartile ranges. A two-sided P value of 0.05 or less was considered to indicate statistical significance.

The study design prespecified the performance of a blinded, interim analysis, according to the conservative method of O'Brien and Fleming, with an alpha spending function.[14] This analysis was conducted after 180 patients (60% of the planned sample size) had completed the study (in March 2009). On June 4, 2009, an independent data advisory committee evaluated the end-point data without knowledge of the treatment assignments. No formal, a priori stopping boundaries were set for the trial. On the basis of efficacy as measured in terms of the primary end point — the consistency of findings at 8 and 14 months in both mean and maximum carotid intima–media thicknesses,

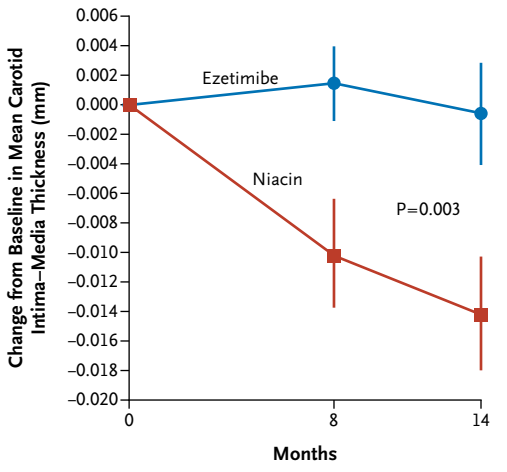

Figure 2. Changes in the Mean Carotid Intima–Media Thickness over the 14-Month Study Period, According to Treatment Group.

The carotid intima–media thickness is the thickness of the far wall of the bilateral distal common carotid arteries, measured in millimeters. The P value is given for the comparison of repeated measures of the carotid intima–media thickness over the 14-month period. The vertical bars indicate the standard errors.

results of sensitivity analyses regarding the statistical stability of the findings, and other secondary analyses showing potentially paradoxical effects of ezetimibe — the committee unanimously recommended that the trial should be terminated. After termination, final visits were conducted, which resulted in 208 patients having 14-month end-point data. These data are described herein.

RESULTS

The baseline characteristics of the 208 patients who had completed the trial at the time of its termination were similar between the two treatment groups (Table 1). In the study population, a total of 80% of patients were male, the mean (±SD) age was 65±11 years, and all patients had received a statin — simvastatin or atorvastatin in 95% of patients — at a mean dose of 42±25 mg for 6±5 years. The baseline level of total cholesterol was 146.1±23.6 mg per deciliter (3.8±0.7 mmol per liter); LDL cholesterol, 82.1±23.1 mg per deciliter (2.1±0.6 mmol per liter); HDL cholesterol, 42.4±8.5 mg per deciliter (1.1±0.2 mmol per liter); and triglycerides, 137±67 mg per deciliter (2±1 mmol per liter). The mean and maximum carotid intima–media thicknesses at baseline were 0.8978±0.1516 mm and 1.0078±0.1653 mm, respectively.

The final change in LDL cholesterol level in the ezetimibe group was –17.6±20.1 mg per deciliter (0.5±0.5 mmol per liter), as compared with –10.0±24.5 mg per deciliter (0.3±0.6 mmol per liter) in the niacin group (P=0.01) (Fig. 1, and Table 2 in the Supplementary Appendix). The final change in HDL cholesterol level in the ezetimibe group was –2.8±5.7 mg per deciliter (0.1±0.1 mmol per liter), as compared with 7.5±9.2 mg per deciliter (0.2±0.2 mmol per liter) in the niacin group (P<0.001). Significant reductions in the triglyceride level were observed in both groups.

Niacin showed superior efficacy to ezetimibe regarding the change in the mean carotid intima–media thickness at both 8 and 14 months (Fig. 2), with similar findings for the maximal thickness (Table 2, and Fig. 3 in the Supplementary Appendix). The change from baseline to 14 months in the mean carotid intima–media thickness was significantly different between the niacin group and the ezetimibe group (P=0.003 for the repeated-measures analysis). Niacin therapy caused a significant reduction in the mean and maximal carotid intima–media thicknesses at both 8 and 14 months. Significant reduction of the mean carotid intima–media thickness was observed in the niacin group between 8 and 14 months (P=0.02). No significant net changes in the carotid intima–media thickness were seen with ezetimibe.

In a post hoc analysis, we explored the bivariate relationships between changes in LDL cholesterol levels and mean carotid intima–media thickness. There was a significant inverse relationship between the changes in LDL cholesterol level and the carotid intima–media thickness in the ezetimibe group (R=−0.31, P<0.001), such that a paradoxical increase in the carotid intima–media thickness was seen in patients with greater reductions in LDL cholesterol. Such a relationship was not observed in the niacin group (R=−0.01, P=0.92) (Fig. 4 in the Supplementary Appendix).

Major adverse cardiovascular events occurred at a significantly higher incidence in the ezetimibe group (9 of 165 patients [5%]) than in the niacin group (2 of 160 patients [1%]) (P=0.04 by the chi-square test) (Fig. 3, and Table 3 in the Supplementary Appendix). The effects of niacin on the mean carotid intima–media thickness were consistent across the prespecified subgroups: those stratified according to sex, presence or absence of diabetes, quartile of baseline HDL cholesterol level, and me-

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Table 2. Data on Carotid Intima–Media Thickness in the 208 Study Subjects Who Completed the Study, According to Treatment Group.*

	Ezetimibe (N=111)	Niacin (N=97)	P Value
Baseline			
Mean thickness (mm)	0.8957±0.1484	0.9001±0.1558	0.83
Maximal thickness (mm)	1.0065±0.1548	1.0092±0.1650	0.90
Change from baseline to 8 mo			
Mean thickness (mm)	0.0014±0.0020	–0.0102±0.0030	0.001
P value for change from baseline	0.48	0.001	
Maximal thickness (mm)	–0.0028±0.0031	–0.0128±0.0043	0.057
P value for change from baseline	0.38	0.004	
Change from baseline to 14 mo			
Mean thickness (mm)	–0.0007±0.0035	–0.0142±0.0041	0.01
P value for change from baseline	0.84	0.001	
Maximal thickness (mm)	–0.0009±0.0039	–0.0181±0.0050	0.006
P value for change from baseline	0.81	<0.001	

* Plus–minus values are means ±SE. Data are missing for one patient in the niacin group at the 8-month time point.

dian cutoff points for baseline carotid intima–media thickness and C-reactive protein level.

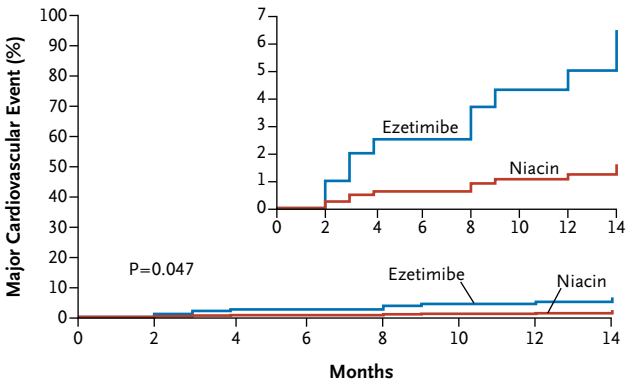
Among 363 patients enrolled in the trial, 44 had left the study by June 4, 2009: 16 of 176 (9%) in the ezetimibe group (of whom 9 had been withdrawn and 7 had died) and 28 of 187 (15%) in the niacin group (of whom 27 had been withdrawn and 1 had died) (P=0.09). There was no significant difference between the 16 patients in the ezetimibe group and the 28 patients in the niacin group with respect to the age, baseline lipid level, or baseline carotid intima–media thickness. Among these 16 and 28 patients, for whom there were laboratory values at 2 months, the change in the LDL level from baseline in the ezetimibe group and the change in the HDL level from baseline in the niacin group were similar to the corresponding changes among the patients who completed the study. Adverse drug effects were cited as the reason for withdrawal in 3 of 9 patients receiving ezetimibe and 17 of 27 patients receiving niacin (P=0.12). Cutaneous flushing was reported in 36% of patients in the niacin group.

There was no significant difference between the two groups in the quality of life at baseline or at 14 months. Adherence to study medication, as measured by means of tablet counts, was 95±8% with ezetimibe versus 88±15% with niacin (P<0.001). The final dose of extended-release niacin was 2000 mg per day in 75%, 1500 mg per day in 3%, 1000 mg per day in 12%, and 500 mg per day in 10%. There was no significant difference between the two groups in the numbers of patients having clinically directed changes in the statin drug or dose during the study.

DISCUSSION

Our study, the ARBITER 6–HALTS trial, demonstrates the superiority of extended-release niacin over ezetimibe when combined with statin therapy. Niacin therapy led to regression of carotid intima–media thickness and fewer clinical cardiovascular events over 14 months among patients with an LDL cholesterol level of less than 100 mg per deciliter and an HDL cholesterol level of less than 50 or 55 mg per deciliter. We found an unexpected paradoxical relationship of a greater degree of atherosclerosis progression in patients with larger, ezetimibe-induced reductions in LDL cholesterol level.

Previous clinical trials with therapeutic strategies based on niacin[6,7,9,10,15-17] and apolipoprotein A-I[18,19] have indicated an association between the use of treatments that increase HDL cholesterol levels and the stabilization of — or, as shown in the ARBITER 6–HALTS trial, the regression in — atherosclerosis. This finding is consistent with the prevailing understanding of HDL cholesterol as a lipoprotein particle that mediates reverse transport of cholesterol through the interaction of apolipoprotein A-I, the principal apolipoprotein



No. at Risk

Ezetimibe	176	174	171	167	160	154	146	143	139	132	126	121	118	113	111
Niacin	187	185	171	163	160	152	138	132	130	116	106	104	101	97	97

Figure 3. Kaplan–Meier Estimates of the Incidence of a Major Cardiovascular Event among the 363 Study Patients, According to Treatment Group.

The P value, calculated with the use of the log-rank test, is given for the comparison between the two treatment groups at 14 months. The inset shows the same data on a magnified scale.

of HDL cholesterol, with cholesterol-transport proteins such as ATP-binding cassette transporters A1 and G1 and scavenger receptor B1.[20,21]

The clinical use of niacin extends over 50 years, with trial data, beginning with data from the Coronary Drug Project,[22] suggesting favorable clinical outcomes. The use of niacin, characterized by the National Cholesterol Education Program as the most potent therapy for favorably altering all lipoprotein abnormalities of the atherogenic dyslipidemic profile,[23] increases the HDL cholesterol level through a diverse mechanism of action including the induction of apolipoprotein A-I production.[24,25] Traditionally, a "low" HDL cholesterol level has been defined as less than 40 mg per deciliter (1.0 mmol per liter), with recent guidelines for women citing an increase in this threshold to less than 50 mg per deciliter.[26] Our trial, through enrollment of men and women with an HDL cholesterol level of less than 50 or 55 mg per deciliter, respectively (the values approximating population means for men and women in the United States),[27] suggests that an even higher treatment threshold of "low" HDL cholesterol — one that is above the current guideline recommendations — may be warranted.

Ezetimibe was licensed by the Food and Drug Administration in 2002 exclusively on the basis of its ability to reduce the LDL cholesterol level while having an acceptable short-term side-effect profile. An understanding of ezetimibe's mechanism of action has subsequently evolved and appears to be increasingly more complex than the purported simple inhibition of cholesterol absorption at the enterocyte and than can be inferred from murine and other animal models.[28] The drug, systemically absorbed and enterohepatically recirculated in a potent glucuronidated form,[29] inhibits multiple, key cholesterol-transport proteins including the primarily intracellular lipid cholesterol transport receptor, Niemann–Pick C1-L1.[30] In addition, ezetimibe has been reported to have diverse actions including mild inhibition of acyl-coenzyme A:cholesterol acyltransferase,[30] a mechanism of action shown to potentially worsen atherosclerosis and clinical cardiovascular events.[31-33] Ezetimibe can inhibit scavenger receptor B1, the high-affinity HDL receptor that may be responsible for up to 50% of HDL binding.[20] This effect, which includes inhibition of the in vitro uptake of cholesterol by means of scavenger receptor B1[34,35] and transcriptional down-regulation of this and other key cholesterol-transport proteins,[36] may disrupt the process of HDL-mediated, reverse transport of cholesterol. Thus, we hypothesize that the seemingly paradoxical association of greater ezetimibe-induced reduction of LDL cholesterol level with a greater increase in carotid intima–media thickness is biologically plausible if it is associated with the unintended disruption of reverse cholesterol transport.

If viewed properly, this hypothesis-generating finding is not an indictment of the overall importance of reducing LDL cholesterol for the purpose of preventing cardiovascular events, as illustrated by therapies based on statins or nonstatins (e.g., bile acid sequestrants).[37] Rather, this adverse relationship may be attributable to the net effect of ezetimibe, a drug with diverse actions, not all of which are measured through its effects on intestinal cholesterol absorption and LDL cholesterol level. Taken together with a preexisting concern regarding the clinical effectiveness of ezetimibe,[38-40] our findings challenge the usefulness of LDL cholesterol reduction as a guaranteed surrogate of clinical efficacy, particularly reduction achieved through the use of novel clinical compounds. For ezetimibe, our results indicate a disconnect between reductions in the LDL cholesterol level and increases in the carotid intima–media thickness in patients with dyslipidemia who are receiving statin therapy. Thus, we believe that prudent clinical practice currently favors the avoidance of ezetimibe, with consideration of further

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restriction on its use in lieu of clinically validated regimens, until its net effect on clinical outcomes can be fully ascertained.

A limitation of this comparative-effectiveness study is that it used carotid intima–media thickness as a surrogate for clinical end points. The finding of a clinical benefit in cardiovascular outcome with niacin, although based on a small number of events, provides additional support for the validity of this imaging end point and is consistent with outcome effects seen in other trials.[6-8] Further clinical certainty regarding ezetimibe and niacin will require data from ongoing clinical trials. The trial could not be conducted in a completely blinded manner because of the use of drugs acquired by the sponsor from a commercial source and their disparate side-effect profiles; therefore, the trial was designed to include the blinded evaluation of end points and automated border-detection methods for quantitation of the carotid intima–media thickness. The reproducibility of measurements of the carotid intima–media thickness in the ARBITER 6–HALTS study is among the highest ever achieved in a clinical trial.

The ARBITER 6–HALTS trial shows regression of carotid intima–media thickness when extended-release niacin was combined with statin therapy in patients with coronary heart disease, or a coronary heart disease risk equivalent, and an LDL cholesterol level of less than 100 mg per deciliter and an HDL cholesterol level of less than 50 or 55 mg per deciliter. This approach was more efficacious for both carotid intima–media thickness and clinical cardiovascular events than was the combination of ezetimibe and statin therapy. The use of ezetimibe led to a paradoxical increase in the degree of atherosclerosis in association with greater reduction in LDL cholesterol, an effect we hypothesize may stem from unintended biologic effects of this agent.

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The opinions or assertions herein are the private views of the authors and are not to be construed as reflecting the views of the Department of the Army or the Department of Defense.

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