The ARBITER 6-HALTS Trial
(Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 6– HDL and LDL Treatment Strategies in Atherosclerosis)

Final Results and the Impact of Medication Adherence, Dose, and Treatment Duration

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Objectives This report describes the final results of the ARBITER 6-HALTS (Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 6–HDL and LDL Treatment Strategies in Atherosclerosis) trial.

Background The ARBITER 6-HALTS trial was terminated early on the basis of a pre-specified interim analysis showing superiority of niacin over ezetimibe on change in carotid intima-media thickness (CIMT). After termination, an additional 107 subjects completed a close-out assessment.

Methods Patients with coronary heart disease (CHD) or CHD equivalent with low-density lipoprotein cholesterol <100 mg/dl and high-density lipoprotein cholesterol <50 mg/dl for men or 55 mg/dl for women while receiving stable statin treatment were randomly assigned to ezetimibe (10 mg/day) or extended-release niacin (target dose, 2,000 mg/day). The primary end point was change in mean CIMT, analyzed according to a last observation carried forward method. The relationships of study medication adherence, dosage, and cumulative exposure (product of adherence, dose, and time) with change in CIMT were explored.

Results Results in 315 patients included 208 with 14-month follow-up and 107 after mean treatment of 7 ± 3 months. Niacin (n = 154) resulted in significant reduction (regression) in mean CIMT (-0.0102 ± 0.0026 mm; $p < 0.001$) and maximal CIMT (-0.0124 ± 0.0036 mm; $p = 0.001$), whereas ezetimibe (n = 161) did not reduce mean CIMT (-0.0016 ± 0.0024 mm; $p = 0.88$) or maximal CIMT (-0.0005 ± 0.0029 mm; $p = 0.88$) compared with baseline. There was a significant difference between ezetimibe and niacin treatment groups on mean changes in CIMT, favoring niacin, for both mean CIMT ($p = 0.016$) and maximal CIMT ($p = 0.01$). Increased cumulative drug exposure was related to regression of CIMT with niacin, and progression of CIMT with ezetimibe.

Conclusions Niacin induces regression of CIMT and is superior to ezetimibe for patients taking statins. (Comparative Study of the Effect of Ezetimibe Versus Extended-Release Niacin on Atherosclerosis; NCT00397657) (J Am Coll Cardiol 2010;55:2721–6) © 2010 by the American College of Cardiology Foundation

Despite significant reductions in major cardiovascular events, lipid abnormalities and residual risk in patients receiving statin monotherapy are prevalent (1). We conducted a comparative-efficacy trial examining the addition of ezetimibe or extended-release niacin (ERN) on carotid intima-media thickness (CIMT) in high-risk patients on stable, chronic statin monotherapy (2). Results within the initial 208 patients completing the 14-month trial demon-

**Abbreviations
and Acronyms**

CHD = coronary heart
disease

CI = confidence interval

CIMT = carotid intima-
media thickness

ERN = extended-release
niacin

HDL-C = high-density
lipoprotein cholesterol

hsCRP = highly-sensitive
C-reactive protein

IQR = interquartile range

LDL-C = low-density
lipoprotein cholesterol

strated superiority of ERN over ezetimibe in the change in CIMT, and the trial was stopped early in a pre-specified interim analysis (3). Herein, we extend our initial report with results on final CIMT imaging among all patients enrolled in the ARBITER 6-HALTS (Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 6–HDL and LDL Treatment Strategies) trial. These results include an analysis of the last-observed CIMT assessment for the full trial sample, and the effect on CIMT of study medication adherence, dose optimization, and treatment duration.

Methods

Patient population. The rationale, design, and primary results of the ARBITER 6-HALTS study have been described (2,3). Briefly, inclusion criteria were as follows: 1) patients at least 30 years of age with known atherosclerotic cardiovascular disease or coronary heart disease (CHD) equivalent; 2) currently taking statin monotherapy at a consistent dose; 3) low-density lipoprotein cholesterol (LDL-C) <100 mg/dl (2.6 mmol/l); and 4) high-density lipoprotein cholesterol (HDL-C) <50 mg/dl in men or <55 mg/dl in women (1.3 or 1.4 mmol/l, respectively), documented on a lipid panel within 3 months of enrollment.

Eligible patients were randomly assigned to open-label therapy with either ezetimibe (10 mg/day) or ERN (target dose 2,000 mg/day). The ERN was initiated at 500 mg/day taken at bedtime, and increased by 500 mg every other week to the maximum tolerated dose. There were no protocol-directed changes in statin medications or dosage throughout the study. Adherence to study medication was determined through tablet counts. The primary end point was the between-group difference in the change in mean CIMT after 14 months.

B-mode ultrasonography of the carotid arteries. Carotid ultrasound examinations were performed at baseline, 8 months, and 14 months. We have previously described the protocol for CIMT assessment utilized in this study (2,3). In summary, mean and maximal diastolic CIMT of the distal 1 cm of the far wall of the right and left common carotid arteries was measured by a single, blinded, trained observer utilizing an automated border-detection algorithm. All images were obtained in duplicate, and no scans were excluded on the basis of image quality.

Statistical analysis. Between-group data for continuous variables were evaluated using a *t* test for independent variables or a Mann-Whitney *U* test, as appropriate. Categorical variables were evaluated using the chi-square test.

Within-group comparisons of continuous variables were performed using a paired *t* test or Wilcoxon signed-rank test, as appropriate. A 2-sided p value ≤0.05 was considered statistically significant. The SPSS for Windows version 16 software (SPSS Inc., Chicago, Illinois) was used for all statistical analyses. On the basis of a minimum sample size of 150 per group, the trial had an 80% power to detect a difference of CIMT change between agents of 0.02 ± 0.06 mm/year ($\alpha = 0.05$).

As previously described (2,3), the study design pre-specified the performance of a blinded, interim analysis according to the conservative method of O'Brien and Fleming (4) with an alpha spending function, to be conducted after 180 subjects (60% of the planned sample size) had completed the trial. After the interim analysis (March 2009), an independent data advisory committee (June 4, 2009) evaluated the primary end point data without knowledge of treatment assignment, and based upon the trial findings, unanimously recommended that the trial should be terminated.

After study termination on June 4, 2009, all actively enrolled patients were contacted and returned for final collection of clinical variables, laboratory data, and blinded CIMT assessment. Among the 363 patients initially enrolled in the trial, 208 patients had completed the entire 14 months of the study period at the time of their final visit (111 ezetimibe, 97 ERN), and 44 had left the study. Final ultrasound examinations could not be obtained in 4 additional subjects after termination of the study (total of 48 participants dropped out), leaving 315 patients for this analysis. In 107 of the 315 patients analyzed, final achieved lipid values and CIMT measurements were performed after study termination at a mean treatment duration of 7 ± 3 months, and these values are included in the primary end point (a last observation carried forward analysis).

Results

The baseline characteristics of the 363 patients enrolled in the trial were similar between the 2 treatment groups (Table 1). A majority of the patients were male (80%), hypertensive (87%), age 65 ± 11 years, and had taken a statin (atorvastatin or simvastatin by 95%) at a mean dose of 42 mg for 6 ± 5 years. There was no difference with respect to age, baseline lipid values, and CIMT between the 48 participants who did not complete the trial and the remainder of the trial participants. In addition, there was no significant difference among baseline covariates, including demographics, blood pressure, lipid levels, baseline therapies, or baseline CIMT between patients who completed the entire 14-month trial (n = 208) and patients who completed the trial after study termination (n = 107). Baseline and final lipid and biomarker values in the 315 patients who completed the trial are shown in Table 2. Significant reductions in baseline LDL-C and triglycerides were seen with both

Table 1	Baseline Characteristics of 363 Patients Randomly Assigned to Ezetimibe or Extended-Release Niacin		
	Ezetimibe (n = 176)	Niacin (n = 187)	p Value
Male	144 (81.8)	147 (78.6)	0.44
Age, yrs	65 ± 11	65 ± 10	0.63
Diabetes mellitus	72 (40.9)	73 (39.0)	0.71
Hypertension	154 (87.5)	163 (87.2)	0.92
Tobacco use	9 (5.1)	13 (7.0)	0.68
Family history of CHD	65 (36.9)	88 (47.3)	0.05
History of coronary heart disease			
Angina with documented ischemia	65 (36.9)	58 (31.2)	0.25
Angiographic coronary disease	109 (61.9)	116 (62.0)	0.98
Myocardial infarction	59 (33.5)	54 (28.9)	0.34
Percutaneous coronary revascularization	70 (39.8)	58 (31.0)	0.08
Coronary bypass surgery	44 (25.0)	48 (25.7)	0.88
Medications			
Beta-blocker	125 (71.0)	125 (67.6)	0.48
Aspirin	165 (93.8)	176 (94.1)	0.88
Clopidogrel	32 (24.8)	30 (27.0)	0.70
ACE inhibitor	100 (56.8)	96 (51.9)	0.35
Statin therapy			
Simvastatin	70 (39.8)	78 (41.7)	0.18
Atorvastatin	96 (54.5)	88 (47.1)	0.22
Pravastatin	5 (2.8)	9 (4.8)	
Rosuvastatin	5 (2.8)	8 (4.3)	
Lovastatin	0 (0)	4 (2.1)	
Mean daily statin dose, mg	42 ± 24	42 ± 24	0.95
Duration of statin use, yrs	6.5 ± 5.6	6.1 ± 4.9	0.40
BMI, kg/m^2	30.8 ± 5.6	31.3 ± 6.4	0.43
Waist circumference, inches	40.9 ± 5.0	41.6 ± 5.9	0.27
Systolic blood pressure, mm Hg	137 ± 18	134 ± 18	0.08
Diastolic blood pressure, mm Hg	74 ± 10	75 ± 11	0.82
CIMT mean thickness, mm	0.8957 ± 0.1484	0.9001 ± 0.1558	0.83
CIMT maximal thickness, mm	1.0065 ± 0.1548	1.0092 ± 0.1650	0.90

Values are n (%) or mean ± SD.

ACE = angiotensin-converting enzyme; BMI = body mass index; CHD = coronary heart disease; CIMT = carotid intima-media thickness.

ezetimibe and ERN. As compared with ERN, patients treated with ezetimibe achieved significantly lower total cholesterol, LDL-C, and HDL-C, and had higher triglyceride values. There was no difference in baseline or final fasting glucose values between the study groups. There was no significant difference between groups in clinically directed changes in the statin drug or dose during the study. Mean study drug adherence rates over the duration of the study exceeded 80% in each arm, and were significantly higher with ezetimibe as compared with ERN (87.5 ± 15.3% vs. 82.1 ± 17.2%, respectively; p = 0.005).

Primary end point. The primary end point was assessed among all randomized subjects (n = 315) who completed a final CIMT measurement after either 14 months (n = 208) or after <14 months of treatment (n = 107) among subjects who had not yet completed the study at the time of its termination (Table 3). Treatment with niacin (n = 154) resulted in significant reduction (regression) in mean CIMT (−0.0102 ± 0.0026 mm; p < 0.001) and maximal CIMT (−0.0124 ± 0.0036 mm; p = 0.001) compared to baseline.

Treatment with ezetimibe (n = 161) had no effect on mean CIMT (−0.0016 ± 0.0024 mm; p = 0.88) or maximal CIMT (−0.0005 ± 0.0029 mm; p = 0.88) compared to baseline. There was a significant difference between the ezetimibe and niacin treatment groups on the change in CIMT, favoring niacin for both mean CIMT (p = 0.016) and maximal CIMT (p = 0.01) among the 315 patients completing the trial. Imputing baseline CIMT as the final CIMT (last observation of baseline CIMT carried forward) in the 48 patients who did not complete the trial resulted in no change in the primary outcome.

Impact of cumulative drug exposure. Based on differences in study medication adherence, ERN dosage achieved and treatment duration (due to early trial termination) between trial participants, we performed an exploratory analysis to assess the impact of these variables on change in CIMT among niacin and ezetimibe treatment groups. The product of study drug adherence, dosage, and treatment duration was calculated to estimate cumulative exposure to study drug as an integrated measure of drug effect (5). The

Table 2	Serum Biomarkers at Baseline and Study Completion				
	Baseline (n = 315)			Final Values (n = 315)	
	Ezetimibe (n = 161)	Niacin (n = 154)		Ezetimibe (n = 161)	Niacin (n = 154)
Total cholesterol, mg/dl	147.3 ± 28.5	147.2 ± 24.8		127.5 ± 24.8	137.6 ± 30.5
p value, between groups		0.96			0.002
p value, change from baseline				<0.001	<0.001
HDL-C, mg/dl	43.0 ± 8.8	42.0 ± 8.3		41.1 ± 8.5	49.7 ± 11.5
p value, between groups		0.32		<0.001	
p value, change from baseline				<0.001	<0.001
LDL-C, mg/dl	84.5 ± 23.8	83.2 ± 19.4		65.5 ± 20.0	72.7 ± 25.9
p value, between groups		0.59			0.007
p value, change from baseline				<0.001	<0.001
Triglycerides, mg/dl	118 (87–160)	129 (89–166)		111 (82–144)	91 (69–134)
p value, between groups		0.24			0.012
p value, change from baseline				0.025	<0.001
Fasting glucose, mg/dl	104.0 ± 27.1	103.9 ± 29.2		111.2 ± 33.8	111.5 ± 41.0
p value, between groups		0.97			0.96
p value, change from baseline				0.03	0.001
hsCRP, mg/l	1.6 (0.7–3.2)	1.3 (0.8–3.7)		1.0 (0.5–2.9)	1.0 (0.4–2.3)
p value, between groups		0.71			0.21
p value, change from baseline				<0.001	0.06

Values are mean ± SD or median (interquartile range).

HDL-C = high-density lipoprotein cholesterol; hsCRP = highly-sensitive C-reactive protein; LDL-C = low-density lipoprotein cholesterol.

relationships between increasing cumulative drug exposure (lowest, quartile 1 to highest, quartile 4) and change in mean CIMT for all subjects using the method of last observation carried forward are shown in Table 4 and Figure 1. Increased cumulative drug exposure resulted in regression of CIMT with niacin, and progression of CIMT with ezetimibe. Specifically, comparing participants treated optimally (best-case comparison), defined as those with the highest quartile of study drug adherence and those reaching the target 2,000 mg/day in the niacin group (quartile 4) for the entire 14 months of the study, patients treated with ERN had significant reduction (regression) of mean CIMT from baseline (−0.0128 ± 0.0078 mm), whereas patients treated with ezetimibe experienced CIMT progression (0.0067 ± 0.0059 mm).

Discussion

We recently demonstrated that ERN leads to significant regression of CIMT and was superior to ezetimibe when added to chronic statin therapy among 208 high-risk patients who had completed 14 months of randomized, open-label, parallel group treatment in the ARBITER 6-HALTS trial (3). This comparative-efficacy trial was stopped before all enrolled patients completing the intended 14 months of drug treatment after a planned interim analysis clearly demonstrated the superiority of ERN over ezetimibe in the effect on CIMT. In the current analysis, we extend our original observations by examining the effect of the study treatments on CIMT within a last observation carried forward and therapy optimization analysis.

Table 3	Change From Baseline CIMT by Treatment Group for Completing Subjects and for All Subjects With the Last Observation Carried Forward			
CIMT	Ezetimibe	Niacin	p Value (Ezetimibe vs. Niacin)	
Completing subjects	(n = 111)	(n = 97)		
Mean thickness, mm	−0.0007 ± 0.0035	−0.0142 ± 0.0041	0.01	
p value, change from baseline	0.84	0.001		
Maximal thickness, mm	−0.0009 ± 0.0039	−0.0181 ± 0.0050	0.006	
p value, change from baseline	0.81	<0.001		
Last observation carried forward	(n = 161)	(n = 154)		
Mean thickness, mm	−0.0016 ± 0.0024	−0.0102 ± 0.0026	0.016	
p value, change from baseline	0.52	<0.001		
Maximal thickness, mm	−0.0005 ± 0.0029	−0.0124 ± 0.0036	0.01	
p value, change from baseline	0.88	0.001		

Data shown as mean ± SE.

CIMT = carotid intima-media thickness.

Table 4	**Change From Baseline CIMT Stratified by Quartiles of Increasing Cumulative Drug Exposure* to Ezetimibe and Niacin**				
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	ANOVA p Value
Ezetimibe					
Adherence, %	71 ± 22	87 ± 8	94 ± 1	98 ± 1	<0.001
Maximum dose, mg/day	9 ± 2	10	10	10	
Treatment duration, months	6.9 ± 2.6	13.2 ± 1.4	14	14	<0.001
Change in mean CIMT, mm	−0.0071 ± 0.0031	−0.0051 ± 0.0036	−0.0009 ± 0.0067	0.0067 ± 0.0059	0.05
Niacin					
Adherence, %	63 ± 19	80 ± 14	87 ± 6	98 ± 1	<0.001
Maximum dose, mg/day	1271 ± 690	1700 ± 441	2,000	2,000	<0.001
Treatment duration, months	8.2 ± 4.1	11.0 ± 2.7	13.8 ± 0.7	14	<0.001
Change in mean CIMT, mm	−0.0052 ± 0.0041	−0.0073 ± 0.0027	−0.0148 ± 0.0060	−0.0128 ± 0.0078	0.23
CIMT p value, ezetimibe vs. niacin within quartile	0.71	0.63	0.13	0.048	

*Cumulative drug exposure = (adherence × dose × treatment duration). Adherence, dose, and treatment duration expressed as mean ± SD; CIMT expressed as mean ± SE.

ANOVA = analysis of variance; CIMT = carotid intima-media thickness.

Consistent with the results seen for patients completing 14 months of treatment, among the entire study group (n = 315) including 208 subjects treated for the full study duration and 107 subjects treated for a mean of 7 months, therapy with ERN led to significant regression of baseline CIMT among statin-treated patients with an LDL-C <100 mg/dl and an HDL-C <50 or 55 mg/dl. Treatment with ezetimibe did not significantly change CIMT. Comparatively, there was a significant difference between the effect of niacin and ezetimibe on changes in CIMT, favoring niacin. These results strengthen the findings from the interim analysis through the inclusion of patients treated for shorter times (last observation carried forward analysis), which might have been expected to reduce the magnitude of

effect between the 2 treatment strategies originally observed. This is a noteworthy possibility within the trial design of ARBITER 6-HALTS with an 8-week titration period for ERN to the target dose of 2,000 mg/day, as opposed to ezetimibe, which was initiated at the maximal clinical dose. Final results confirm the difference in the primary outcome and preserved magnitude of CIMT regression among patients taking ERN. In addition, the magnitude of effect of ERN on mean CIMT, producing regression (−0.0142 ± 0.0041 mm), over 14 months of treatment in the relatively high risk ARBITER 6-HALTS study population is noteworthy in comparison with other contemporaneous lipid-lowering trials using similar CIMT methodology. In the METEOR (Measuring Effects of Intima-Media Thickness:
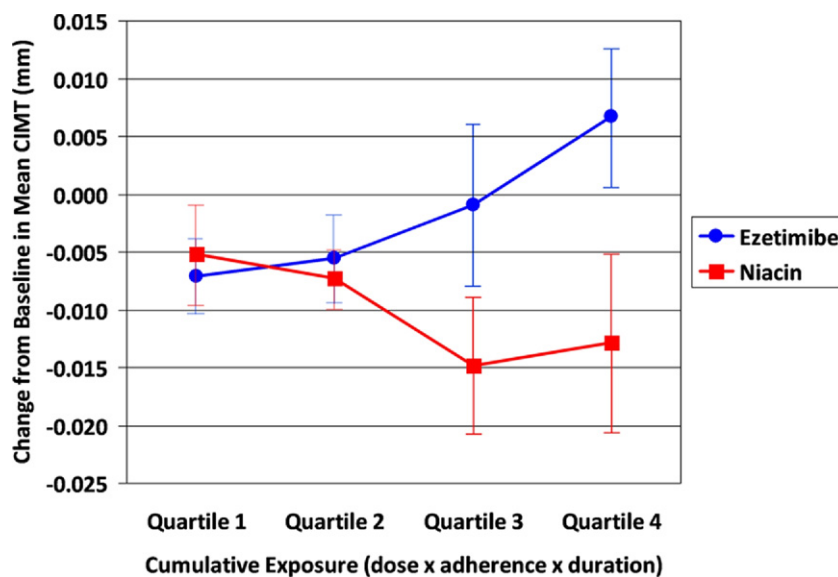

Figure 1   Relationship Between Quartiles of Cumulative Drug Exposure to Ezetimibe and Niacin and Change in CIMT

Cumulative drug exposure was calculated as the product of mean study drug adherence, dose, and time in the study. The relationship between quartiles of drug exposure (lowest, quartile 1, to highest, quartile 4) and change in mean carotid intima-media thickness (CIMT) for all subjects using the method of last observation carried forward is shown. The relationship between quartiles of cumulative drug exposure and change in CIMT is shown separately for ezetimibe **(blue line)** (analysis of variance [ANOVA] p = 0.05), and niacin **(red line)** (ANOVA p = 0.23).

An Evaluation of Rosuvastatin) trial, treatment for 24 months with high-potency statin monotherapy (rosuvastatin 40 mg; mean final LDL 78 mg/dl) in a low-risk population resulted in a change in mean common CIMT of 0.0004 mm (95% confidence interval: −0.0011 to 0.0019 mm), as compared to placebo 0.0088 mm (95% confidence interval: 0.0064 to 0.0112 mm) (6).

The observation that the CIMT response was related to niacin adherence, dose, and increased treatment duration, calculated as cumulative drug exposure, is consistent with a drug effect as shown in prior studies demonstrating a favorable impact of niacin on clinical events and atherosclerosis (7–9). A prior study has shown regression of CIMT when ERN adherence rates are high, even when the dose was <2,000 mg/day (8,9). Additional studies examining the optimal and minimal effective dose of ERN on atherosclerosis, and ultimately clinical events, are warranted.

The relationship between cumulative drug exposure and the CIMT effect of ERN supports an expected, direct relationship between increasing intensity of drug exposure (through a composite of dose, adherence, and time) and its effect on atherosclerosis. In contrast, findings with ezetimibe showing an unexpected inverse relationship between intensity of drug exposure and CIMT draw further attention to a growing body of evidence on the diverse effects of ezetimibe on cholesterol transport mechanisms, such as interference with the pivotal HDL receptors SRB-1, and ABCA1 (10,11). Although the net health impact of ezetimibe's described off-target receptor effects are yet to be fully understood, this evolving science clearly indicates that the pharmacologic effects of ezetimibe extend beyond the simple inhibition of enteric cholesterol absorption, and reduction of LDL-C.

Study limitations. A limitation of this study is the use of CIMT as a surrogate for clinical end points. While the preponderance of studies demonstrate the validity of CIMT as a surrogate for cardiovascular events (3,12–14), the ultimate net health impact of therapeutics requires clinical end point trials. Additionally, our analysis evaluating cumulative drug exposure is post-hoc and exploratory in nature. Sample size is limited within ERN subjects who did not achieve the 2,000 mg/day target dose, and such subjects also were less adherent to the therapy. Prior studies in highly adherent subjects treated for 1 to 2 years at the 1,000 mg/day dose showed regression of CIMT (8,9). Dose-ranging studies would be useful to further elucidate dose response effects of ERN on CIMT.

Conclusions

Final results from the ARBITER 6-HALTS trial confirm the superiority of extended-release niacin over ezetimibe for the end point of change in CIMT and the ability of niacin to induce CIMT regression. Increased cumulative drug exposure was related to regression of CIMT with niacin, and progression of CIMT with ezetimibe.

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