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

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Background—Niacin reduces coronary heart disease morbidity and mortality when taken either alone or in combination with statins; however, the incremental impact of adding niacin to background statin therapy is unknown.

Methods and Results—This was a double-blind randomized placebo-controlled study of once-daily extended-release niacin (1000 mg) added to background statin therapy in 167 patients (mean age 67 years) with known coronary heart disease and low levels of high-density lipoprotein cholesterol (HDL-C; <45 mg/dL). The primary end point was the change in common carotid intima-media thickness (CIMT) after 1 year. Baseline CIMT (0.884±0.234 mm), low-density lipoprotein cholesterol (89±20 mg/dL), and HDL-C (40±7 mg/dL) were comparable in the placebo and niacin groups. Adherence to niacin exceeded 90%, and 149 patients (89.2%) completed the study. HDL-C increased 21% (39 to 47 mg/dL) in the niacin group. After 12 months, mean CIMT increased significantly in the placebo group (0.044±0.100 mm; P<0.001) and was unchanged in the niacin group (0.014±0.104 mm; P=0.23). Although the overall difference in IMT progression between the niacin and placebo groups was not statistically significant (P=0.08), niacin significantly reduced the rate of IMT progression in subjects without insulin resistance (P=0.026). Clinical cardiovascular events occurred in 3 patients treated with niacin (3.8%) and 7 patients treated with placebo (9.6%; P=0.20).

Conclusions—The addition of extended-release niacin to statin therapy slowed the progression of atherosclerosis among individuals with known coronary heart disease and moderately low HDL-C. (Circulation. 2004;110:3512-3517.)

Key Words: atherosclerosis ■ risk factors ■ lipids

S tatin-mediated reductions in low-density lipoprotein cholesterol (LDL-C) form the cornerstone of treatment of hyperlipidemia to reduce cardiovascular morbidity and mortality. Low-serum concentrations of high-density lipoprotein cholesterol (HDL-C) are one of the major risk factors for adverse events related to coronary atherosclerosis and are highly prevalent among patients with acute coronary syndromes. Epidemiological studies suggest that an ≈1-mg/dL increase in HDL-C is associated with a 2% to 4% reduction in coronary heart disease (CHD) outcomes. Accordingly, low levels of HDL-C (<40 mg/dL) are identified as a coronary risk factor within the guidelines for treatment of hyperlipidemia as put forth by the National Cholesterol Education Program.

Niacin is the most effective therapy available for the treatment of low HDL-C, with a nonlinear dose-related increase in HDL-C of ≈20% observed with modest drug doses (≈1 g per day). Compared with the vast clinical trial database supporting the use of statin monotherapy in the prevention of CHD, clinical trial data supporting an effect of niacin monotherapy on cardiovascular outcomes are sparse, and no study has examined the incremental effect of niacin added to statin therapy on cardiovascular outcomes or their surrogates. Related to this uncertainty, there are no established HDL-C treatment goals recommended in the present lipid treatment guidelines. Accordingly, we conducted a randomized, double-blind, placebo-controlled trial of niacin on carotid intima-media thickness (CIMT), a validated surrogate cardiovascular end point, in patients with known CHD already being treated with statin monotherapy.

Methods

Study Background and Population
This trial was a single-center study conducted at Walter Reed Army Medical Center, a university-affiliated, suburban, tertiary care military medical center. The institution’s Department of Clinical Inves-
tigation approved the study. Reporting follows the recommendations of the revised Consolidated Standards of Reporting Trials. Volunteer research subjects were recruited from the cardiology and general medicine services. The study included men and women >30 years old with known coronary vascular disease. All subjects were required to be currently treated with a statin drug, with documented LDL-C <130 mg/dL and HDL-C >45 mg/dL. Subjects with known intolerance to niacin, a history of liver disease (cirrhosis, chronic hepatitis), or abnormal liver associated enzymes (>3 times the upper laboratory reference value) were excluded.

Randomization

After providing informed consent, subjects were randomized (allocation concealed) in a 1:1 fashion to receive either extended-release niacin (Niaspan) or a matching placebo, both provided by Kos Pharmaceuticals. Randomization was performed with a computer-generated sequence of random numbers. Participants were assigned a unique study identification that was used by a central research pharmacy to dispense the study medication. Only the research pharmacist was aware of the study drug assignment. Study medication was initiated at a daily dose of 300 mg for 30 days, which was then increased to 1000 mg for the duration of the 12-month study period. The study medication was taken at night, and it was recommended that it be taken with the subjects’ usual daily dose of aspirin. All patients taking either vitamin C or vitamin E were strongly encouraged to discontinue their use of these supplements during the study to avoid possible interference with the response to niacin. No protocol-directed changes in statin doses occurred during the study. Four subjects had their statin doses changed: A decrease in statin dose occurred in 2 patients (1 in each group), and an increase in the statin dose was instituted in 2 patients (both in the niacin group). Clinical pharmacists, who also were blinded to the study drug assignment, assessed drug education and study medication compliance using pill counts. Between December 2001 and May 2003, 167 patients were enrolled in the trial, and the final follow-up was completed in May 2004. Patients were individually unblinded to their study medication assignment after completion of their 12-month end point assessment.

End Points

The predefined primary end point of this study was the change in mean common CIMT after 1 year, assessed within each study medication group via a paired t test. Secondary end points included changes in serum lipid concentrations, adverse events including liver-associated enzyme elevations, and a composite of clinical cardiovascular events including any hospitalization for an acute coronary syndrome (eg, unstable angina, myocardial infarction), stroke, an arterial revascularization procedure (percutaneous coronary revascularization, coronary bypass surgery, or peripheral vascular revascularization), or sudden cardiac death.

Carotid B-Mode Ultrasound

Measurements were obtained from the far wall of the distal common carotid arteries (immediately proximal to the carotid bulb) and referenced as the mean value for the right-left measurement. This location was chosen because of its demonstrated reproducibility as compared with the measurement of CIMT at other sites. All studies were performed on a single ultrasound machine (SonoSite) with a linear array 8-MHz probe. Ultrasound studies were performed in standard fashion by a single sonographer specifically trained to perform the prescribed study examination. All sonograms were obtained with patients in the supine position with heads turned slightly to the contralateral side. Digital images from a diastolic frame of the cine-loop recording were electronically stored and transferred via a serial port transfer protocol to an offline workstation for quantification. Each ultrasound examination was performed as an independent study without knowledge of the previous CIMT results. Images from an individual patient’s previous ultrasound exams were not used to guide their follow-up evaluations.

A single independent observer blinded to the treatment group and trained in the interpretation of CIMT images performed offline analyses of B-mode ultrasound images using a custom script for IMT analysis (ProSolv Echo Analyzer, Problem Solving Concepts). The near-field (intimal-luminal surface) and far-field (medial-adventitial) arterial wall borders were manually traced to measure mean CIMT. The mean segment length of arterial wall evaluated was 1.67±0.37 cm, which was similar in the placebo and niacin groups. These methods have been previously validated in our laboratory as having a high degree of reproducibility.

Cardiovascular Risk Variables

All laboratory values were measured after an overnight fast. Laboratory measurements included serum total cholesterol, LDL-C, HDL-C, triglycerides, C-reactive protein (CRP), liver-associated enzymes, and glucose at baseline and 12 months. LDL-C was measured using a direct assay. Non–HDLC was calculated as the difference between total cholesterol and HDL-C. CRP was measured with a high-sensitivity, commercially available immunoturbidimetric assay, which uses monoclonal antibodies to CRP (Roche COBAS). Blood pressure and waist girth were measured to determine the prevalence of the metabolic syndrome.

Statistical Analysis

The prespecified primary efficacy end point was the change in mean IMT values over 12 months. Both an unpaired t test for independent groups (the basis of sample size calculations) and a within-group paired analysis were planned. The trial was powered to detect a mean difference between study groups (n = 70/group) in the change in IMT of 0.02±0.06 mm (power=0.8, α=0.05). No specific subgroup analyses of the primary efficacy end point were prespecified. Prespecified secondary end points were changes in lipid parameters, adverse effects, and composite clinical cardiovascular events, although the trial was not specifically powered for these end points. Between-group data for continuous variables were assessed with a t test for independent variables or ANOVA. The χ² test or Fisher’s exact test as appropriate was used for categorical variables. Normality of the study data was tested with a 1-sample Kolmogorov-Smirnov test to indicate the appropriateness of parametric testing. Data were analyzed on an intention-to-treat principle. All statistical analyses were performed with SPSS software (version 12.0.1, SPSS Inc). Values are reported as mean±SD, except where indicated. A 2-sided probability value of ≤0.05 was considered statistically significant.

Results

The mean patient age was 67±10 years, and 91% of patients were men. Known CHD was present in all 167 patients, with a history of myocardial infarction reported in 83 (49.7%), percutaneous coronary revascularization in 77 (46.1%), and coronary bypass surgery in 68 (40.7%). Mean lipid concentration included a total cholesterol of 157±27 mg/dL, LDL-C of 89±20 mg/dL, HDL-C of 40±7 mg/dL, and triglycerides of 161±91 mg/dL. All patients were receiving statin drugs on entry to the study, with a mean duration of treatment of 4.8±4.3 years. Most of the patients (n = 156, 93.4%) were being treated with simvastatin, and the majority (n = 160, 95.8%) were receiving a daily dose of ≥20 mg.

Subjects randomized to either placebo (n = 80) or niacin (n = 87) had similar baseline characteristics (Table 1). The 2 groups had similar cardiac risk factors and a history of CHD. No differences were found between groups in the use of other cardiovascular medications, including β-blockers, aspirin, angiotensin-converting enzyme inhibitors, and hypoglycemic agents, either at the beginning or the end of the study. Baseline lipid concentrations and CIMT were similar in the 2
study groups (Table 2). Both treatment groups had well-controlled LDL-C, with mean values <100 mg/dL. Of the 167 patients randomized, 149 (89.2%) completed the 12-month study period and were included in the primary end point analysis. After 12 months, HDL-C rose significantly in the niacin group, from 39 ± 16 mg/dL to 47 ± 16 mg/dL (P = 0.002), and was unchanged in the placebo group (Figure 1). Triglycerides also decreased significantly in the niacin group.

TABLE 1. Baseline Characteristics of 167 Patients Randomly Assigned to Either Placebo or Extended-Release Niacin

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Niacin</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender, n (%)</td>
<td>74 (92.5)</td>
<td>78 (89.7)</td>
<td>0.52</td>
</tr>
<tr>
<td>Age, mean ± SD</td>
<td>68 ± 10</td>
<td>67 ± 10</td>
<td>0.64</td>
</tr>
<tr>
<td>Type 2 diabetes mellitus, n (%)</td>
<td>22 (27.5)</td>
<td>24 (27.6)</td>
<td>0.99</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>61 (76.3)</td>
<td>64 (73.6)</td>
<td>0.69</td>
</tr>
<tr>
<td>Tobacco use, n (%)</td>
<td>5 (6.3)</td>
<td>12 (13.8)</td>
<td>0.23</td>
</tr>
<tr>
<td>Family history of CHD, n (%)</td>
<td>39 (48.8)</td>
<td>33 (37.9)</td>
<td>0.16</td>
</tr>
<tr>
<td>Metabolic syndrome, n (%)</td>
<td>42 (52.5)</td>
<td>43 (49.4)</td>
<td>0.69</td>
</tr>
<tr>
<td>History of CHD, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td>42 (52.5)</td>
<td>41 (47.1)</td>
<td>0.49</td>
</tr>
<tr>
<td>Percutaneous coronary revascularization</td>
<td>35 (43.8)</td>
<td>42 (48.8)</td>
<td>0.51</td>
</tr>
<tr>
<td>CABG</td>
<td>28 (35.0)</td>
<td>40 (46.0)</td>
<td>0.15</td>
</tr>
<tr>
<td>Angina with documented ischemia</td>
<td>27 (33.8)</td>
<td>26 (29.9)</td>
<td>0.59</td>
</tr>
<tr>
<td>Medications, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-Blocker</td>
<td>63 (78.8)</td>
<td>69 (79.3)</td>
<td>0.93</td>
</tr>
<tr>
<td>Aspirin</td>
<td>68 (85.0)</td>
<td>75 (86.2)</td>
<td>0.82</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitor</td>
<td>42 (57.5)</td>
<td>54 (62.1)</td>
<td>0.21</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>14 (17.5)</td>
<td>22 (25.3)</td>
<td>0.22</td>
</tr>
<tr>
<td>Vitamin C</td>
<td>8 (10)</td>
<td>10 (11.5)</td>
<td>0.81</td>
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</table>

The increase in CIMT in the niacin group was 0.014 ± 0.104 mm, compared with 0.044 ± 0.100 mm in the placebo group (P = 0.08). On paired analysis, the increase in CIMT progression in the niacin group (0.893 ± 0.259 mm to 0.907 ± 0.235 mm) was not statistically significant (P = 0.23). The increase in CIMT observed in the placebo group (0.868 ± 0.207 mm to 0.912 ± 0.202 mm) was significant (P < 0.001; Figure 2). An intent-to-treat analysis imputing the mean group change in IMT for the 18 subjects who did not complete the 12-month study end point showed that the mean change in IMT was significantly greater with placebo (P = 0.048). The progression of CIMT during treatment with niacin was related to the presence of both diabetes and the metabolic syndrome. In a nonprespecified subgroup analysis in 88 subjects with insulin resistance (diabetes or the metabolic syndrome), the lowest progression rate was observed in niacin-treated patients with normal glycemic status (Figure 3; ANOVA P = 0.037). Placebo-treated patients had the greatest CIMT progression, regardless of insulin-resistance status.

TABLE 2. Comparison of Baseline and 12-Mo Serologic Results for Patients Completing the Study Who Were Randomly Assigned to Either Placebo or Extended-Release Niacin

<table>
<thead>
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<th>Niacin (n = 78)</th>
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<td>Total cholesterol</td>
<td>161 ± 29</td>
<td>154 ± 27</td>
<td>0.13</td>
</tr>
<tr>
<td>LDL-C</td>
<td>91 ± 22</td>
<td>87 ± 17</td>
<td>0.19</td>
</tr>
<tr>
<td>HDL-C</td>
<td>40 ± 7</td>
<td>39 ± 7</td>
<td>0.52</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>172 ± 104</td>
<td>154 ± 82</td>
<td>0.25</td>
</tr>
<tr>
<td>Non-HDL-C</td>
<td>121 ± 27</td>
<td>115 ± 26</td>
<td>0.15</td>
</tr>
<tr>
<td>CRP*</td>
<td>3.0 ± 4.7</td>
<td>3.8 ± 4.3</td>
<td>0.21</td>
</tr>
<tr>
<td>CIMT, mm</td>
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Within-Group Comparison (Baseline–12 Months)

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Units of reporting: lipid values, mg/dL; CRP, mg/L. Abbreviations are as in text.

*Subjects with acute-phase reactant levels (>2 mg/L) of CRP excluded from this analysis.
in the placebo group withdrew because of concern about adverse drug effects, compared with 2 of 9 in the niacin group \((P=NS)\). At the conclusion of the study, skin flushing was reported to have occurred in the majority of patients treated with niacin (54 of 78, 69.2%) compared with 9 of 71 patients treated with placebo (12.7%, \(P<0.001)\).

**Discussion**

Currently, the treatment of lipid abnormalities is characterized by the primary use of statins to reduce serum levels of LDL-C. Despite the substantial reductions in cardiovascular morbidity and mortality that have been achieved with statins, the protection afforded by these drugs is incomplete; thus, combination therapies directed at also increasing HDL-C are an attractive but unproved approach. This study is the first demonstration of an incremental independent effect of combination therapy with statin and niacin compared with statin monotherapy to retard the progression of atherosclerosis. Given the prevalent nature of dyslipidemia and low HDL-C, these findings have implications for the approach to the treatment of lipids in a substantial proportion of the population with CHD.

Niacin has been in clinical use for 4 decades and is the most effective treatment currently available to increase low levels of HDL-C. The current understanding of its place in an era of potent therapies directed at LDL-C is limited by a lack of studies assessing its incremental effect on atherosclerosis and coronary outcomes. The Coronary Drug Project, the only sufficiently powered placebo-controlled study of the effect of niacin monotherapy on CHD outcomes, demonstrated a significant early reduction in nonfatal myocardial infarction\(^{16}\) and a late reduction in 15-year mortality,\(^{17}\) an effect that is postulated to result from the slowing of the progression of atherosclerosis.\(^{18}\) Beyond this single study, all of the other placebo-controlled studies assessing the effect of niacin on either atherosclerosis progression or outcomes have tested an initial rather than a stepwise approach to combination therapy.\(^{19,20}\) Such studies have led to a global approach to treating lipid abnormalities but are unable to discriminate among the individual effects of the multiple agents studied. The most recent demonstration of this was the HDL-Atherosclerosis Treatment Study (HATS).\(^{21}\) This placebo-controlled study of combined low-dose simvastatin (10 to 20 mg/d) and high-dose niacin (2 to 4 mg/d) showed the ability of combination therapy to largely stabilize coronary atherosclerosis with an associated substantial \(\geq 13\%\) absolute risk reduction (up to 90% relative risk reduction) for cardiovascular outcomes. The absence of a statin monotherapy control group and the use of relatively high doses of niacin, however, limit the capacity to extrapolate the data to a stepwise additive approach to combination therapy in clinical practice that might typically use lower doses of niacin.

The data from ARBITER 2 extend our understanding of the potential benefit of combination therapy with statin and niacin in patients with known CHD and moderately low levels of HDL-C beyond multiple previous studies that have included niacin as a component of combination therapy.\(^{19,20}\) We observed a significant progression of CIMT in the placebo (statin monotherapy) group, despite a mean LDL-C

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**Figure 2.** Serial mean CIMT measurements from the far wall of the bilateral common carotid arteries at baseline and 12 months during treatment with either placebo or extended-release niacin (Niaspan) added to stable statin therapy. Progression rates in the 2 groups were 0.044±0.011 mm (placebo; \(P<0.001)\) and 0.014±0.011 mm (Niaspan, \(P=0.23)\).

**Figure 3.** Change in IMT across 12 months in patients treated with placebo and extended-release niacin in presence or absence of metabolic syndrome or type 2 diabetes mellitus.
<100 mg/dl, a result that is consistent with previous placebo-controlled studies of statin monotherapy and atherosclerosis progression.22–28 Such progression of atherosclerosis in the setting of a statin administered long term differs from the observed initial results of statin administration, likely from the influence of other lipid (eg, low HDL-C) and nonlipid risk factors. This is supported further by our subgroup analysis showing a significantly lower progression of CIMT in niacin-treated patients without type 2 diabetes mellitus or the metabolic syndrome. This analysis was not prespecified, however, and thus should be the subject of further investigation. The present study was not powered to detect a difference in cardiovascular event rates, although the observed nonsignificant trend toward a lower event rate in the niacin group is consistent with the results of both the Cholesterol Lowering Atherosclerosis Study (CLAS) and HATS, in which slower rates of atherosclerosis progression were associated with lower cardiovascular event rates during treatment when niacin was combined with colestepl (CLAS19) or a statin (HATS21).

The tolerability, compliance, lipid, and CIMT results observed in this study are strictly generalizable to the dose and preparation of niacin studied, specifically extended-release niacin at 1000 mg/d. This dose was selected as an intermediate dose of niacin that would balance adverse effects (eg, flushing) and the expected nonlinear increase in HDL-C. This dose was well tolerated; however, flushing, a well-known side effect of niacin, did occur. Practical advice to patients, such as bedtime dosing with concurrent aspirin administration, and a commitment to the therapy on the part of patients and providers can lead to a high rate of successful compliance with niacin therapy.

The effect of niacin, which is similar to all lipid-lowering agents, is potentially mediated by simultaneous changes in multiple-lipid parameters, including reductions in the potentially atherogenic components of non–HDL-C and increased HDL-C. Thus, in ARBITER 2, the treatment group likely benefited from both the observed 21% increase in HDL-C and the concomitant reduction in triglyceride concentration. Slowed progression of atherosclerosis in the setting of increased HDL-C is consistent with the current paradigm in which HDL participates as the acceptor particle in the process of reverse cholesterol transport.27 Proof of this concept in human subjects was seen recently in a small clinical trial that showed the regression of atherosclerosis during treatment with a man-made nascent HDL particle with apoA1 Milano,28 a variant of the principal apoprotein of HDL.

Definitive clinical implications for statin-controlled studies of combination therapy must await sufficiently powered clinical event trials. Until such data are available, therapeutic lifestyle change, optimal treatment of LDL-C, and an individualized approach to combination therapy are recommended.1 Additional data, such as those in ARBITER 2, will be required before lipid treatment guidelines can more clearly point patients and providers toward combination therapy with drugs such as niacin to increase HDL-C. Nevertheless, the measurement of atherosclerosis progression via CIMT as a validated surrogate end point provides an important preliminary measure of the potential gains to be achieved.

Acknowledgment

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Disclosure

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 US Department of Defense.

The study was investigator initiated. Monitoring of the study, maintenance of the trial database, measurement of all study end points, and statistical analysis were performed by the investigating institution. The manuscript was prepared solely by the authors. The sponsor’s medical department was permitted to review the manuscript and provide comment, but the final decision about content was retained exclusively by the authors.

References

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/content/111/24/e446.full.pdf

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In the article by Taylor et al, “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,” which appeared in the December 7, 2004, issue of the journal (*Circulation*. 2004;110:3512–3517), an error appears on page 3515. In the right-hand column, sixteenth line up from the bottom, there was a mistake in the dosage noted. The sentence read, “...dose niacin (2 to 4 mg/d) showed the ability of combination. ...” The sentence should read, “...dose niacin (2 to 4 g/d) showed the ability of combination. ...”

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