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ORIGINAL ARTICLE

The effect of 24 months of combination statin and extended-release niacin on carotid intima–media thickness: ARBITER 3*

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ABSTRACT

Objective: The ARBITER 2 trial showed that extended-release niacin (ERN) when added to statin monotherapy slowed the progression of carotid atherosclerosis over 12 months. Whether longer treatment with ERN would have a greater effect on carotid intima–media thickness (CIMT) is unknown.

Research design and methods: We examined the long-term effects of ERN on high density lipoprotein (HDL-C) cholesterol and CIMT during 12–24 months treatment with ERN in ARBITER 2 participants who were either continued or were crossed over (from placebo) to ERN 1000 mg daily.

Main outcome measures: Among 149 subjects completing ARBITER 2, 130 (88%) enrolled in ARBITER 3. The prespecified primary endpoints were the within-group change in CIMT and HDL-C in patients receiving placebo for 12 months (n = 71), ERN for 12 months (comprised of subjects from ERN treatment during ARBITER 2 (n = 78) and those crossed over to ERN from placebo after ARBITER 2 (n = 47)), and ERN for 24 months spanning ARBITER 2 and 3 (n = 57). Five subjects discontinued the study due to flushing side effects. The study was completed by 104 subjects (47 crossed over from placebo; 57 with ERN continued from ARBITER 2).

Results: HDL-C increased in the ERN group from 39.5 ± 6.7 to 48.6 ± 13.3 mg/dl ($p < 0.001$) along with modest reductions in LDL-C and TG. Among 125 participants treated with ERN for 12 months, there was a net regression of CIMT of –0.027 ± 0.011 mm ($p < 0.001$ vs. placebo). Among 57 participants treated with ERN for 24 months, there was additional significant regression of CIMT of –0.041 ± 0.021 mm ($p = 0.001$ vs. placebo). Controlling for changes in LDL and triglycerides, only changes in HDL-C were independently associated with regression of CIMT ($\beta = -0.25$; $p = 0.001$).

Conclusion: When added to statin therapy, ERN significantly increases HDL-C and induces atherosclerosis regression measured by CIMT over 24 months. Limitations to this study include its open-label design and the inability to relate CIMT effects to clinical outcomes.

Introduction

A large body of epidemiological evidence shows a consistent association between low high-density lipoprotein cholesterol (HDL-C) levels, atherosclerosis extent[1–4] and incident coronary heart disease[5]. A consistent finding in the scientific literature on HDL-C is its role in the process of reverse cholesterol transport,

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in which apolipoprotein A1 (apoA1), the principal apoprotein of HDL particles, acts as an acceptor particle for cholesterol removed from cells through cell membrane transporters such as ATP-binding cassette transporter A1 (ABCA1)[6] and ATP-binding cassette transporter G1 (ABCG1)[7]. Through this and other mechanisms, a strategy of pharmacologically raising HDL-C, such as through the use of prescription niacin[8,9], has the potential to induce atherosclerosis regression. Furthermore, such a strategy may extend the important but limited reduction in clinical coronary heart disease events within a prevention strategy solely focused on the reduction of LDL-C through statin monotherapy[10].

To test the hypothesis that a strategy of targeting low levels of HDL-C would extend the effects of statin monotherapy on atherosclerosis burden, the Arterial Biology for the Investigation of the Treatment Effects of Reducing cholesterol trial 2 (ARBITER 2) was conducted. ARBITER 2 was a 12-month, double-blind, placebo controlled study of extended-release niacin (Niaspan*, 1000 mg/day) on carotid intima–media thickness (CIMT) among patients with known coronary heart disease and good control of their LDL-C during statin monotherapy, but moderately low HDL-C[11]. The study found significant progression of CIMT among placebo-treated patients (n = 71; statin monotherapy), whereas extended release niacin (n = 78; ERN) in combination with continued statin therapy resulted in a 21% increase in HDL-C and stabilized CIMT progression. To extend these findings, ARBITER 3, described in this manuscript, was a prespecified extension study of ARBITER 2 in which subjects completing the blinded 12-month endpoint assessment were followed for an additional 12 months on open-label ERN. The endpoint was the effect on mean common carotid intima–media thickness, an endpoint shown to be related to the risk for subsequent coronary heart disease events[12].

Methods

Study 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 Investigation approved the study. Volunteer research subjects who successfully completed the 12-month CIMT assessment of ARBITER 2[11] were eligible. ARBITER 2 included male and female patients, greater than 30 years old, with known coronary heart disease. All subjects were required to be currently treated with a statin drug with documented LDL cholesterol < 130 mg/dl (according to published guidelines at the time of study initiation, the National Cholesterol Education Program Adult Treatment Panel II[13]) and HDL cholesterol < 45 mg/dl. Statin medications were not changed by study protocol, but could be altered by attending physicians as clinically indicated.

Treatment

After the final endpoint assessment for ARBITER 2, subjects were unblinded to their original study group (ERN 1000 mg or matching placebo). On the basis of completing ARBITER 2 (n = 149), these subjects were eligible and offered voluntary enrollment in ARBITER 3. Consenting subjects received open-label treatment for an additional 12 months with either continued prescription of ERN 1000 mg (subjects who received ERN during ARBITER 2), or, for subjects who had received placebo during ARBITER 2, ERN was initiated as in ARBITER 2 (starting dose of 500 mg for 30 days, and then increased to 1000 mg nightly). Between December 2002 and May 2004, 130 of 149 eligible subjects were enrolled in the trial and the final follow-up was completed in May 2005. Serum lipids, blood glucose, high sensitivity C-reactive protein (CRP), and liver-associated enzymes were measured at 3 months and at the conclusion of the study. A compliance assessment was performed consisting of a review of pharmacy records to determine the proportion of ERN prescriptions filled during the 12 months study.

Endpoints and CIMT analysis

The predefined primary endpoint of this study was the time-dependent change in mean CIMT in subjects treated with ERN for up to 24 months compared to treatment with placebo for 12 months during ARBITER 2. The two time-points examined during ERN therapy were 12 and 24 months. The 12-month group was comprised of subjects treated with ERN during the 12-month blinded phase of ARBITER 2 (n = 78), and subjects crossed over to open-label ERN from placebo treatment during ARBITER 2 (n = 61 of whom 47 completed the additional 12-month study). The 24-month group was comprised of subjects treated with blinded ERN for 12 months during ARBITER 2, who continued on open-label ERN during ARBITER 3 for a total of 24 months (n = 69 of whom 57 completed the additional 12-month study). Carotid intima–media thickness measurements were obtained from the far wall of the distal common carotid arteries (immediately proximal to the carotid bulb) and reported as the

* Niaspan is a registered trademark of Kos Pharmaceuticals, Inc., Cranbury, NJ, USA

average value for the bilateral measurement. This location was chosen because of its demonstrated reproducibility compared to measurement of CIMT at other sites[14,15]. All studies were performed on a single ultrasound machine (Sonosite Inc., Bothell, WA, USA) using a linear array broadband 10 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, and their head 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 off-line workstation for quantitation. Each ultrasound exam was performed as an independent study, without knowledge of the previous CIMT results. Images from an individual patient's prior ultrasound exams were not used to guide their follow-up evaluations.

A single independent observer, trained in the interpretation of CIMT images, performed off-line analysis of B-mode ultrasound images using a custom script for IMT analysis (Prosolv Echo Analyzer, Problem Solving Concepts, Indianapolis, IN, USA). The near (intimal–luminal surface) and far (medial–adventitial) field arterial wall borders were manually traced for measurement of mean CIMT. Ultrasound images from ARBITER 3 were analyzed independently without knowledge of drug assignment or prior CIMT measurements from ARBITER 2, and laboratory values. The personnel performing CIMT analysis were unaware of the subject's assigned treatment group. Rigorous quality control for image quality and consistency in analysis were employed including analysis of a subset of images by a second observer to determine inter-reader reliability. Among a randomly selected 10% subgroup of cases undergoing evaluation by a second interpreter, the intraclass correlation coefficient was 0.95 ($p < 0.001$) for the change in mean CIMT from the baseline assessment of ARBITER 2 and the final CIMT assessment of ARBITER 3, similar to previous results from our laboratory[16].

Statistical analysis

The prespecified analysis was the time-dependent change in CIMT comparing the change in CIMT after a total of up to 24 months of exposure to ERN. This endpoint was comprised of three separate groups (Figure 1) including the initial 12 months of exposure to placebo from ARBITER 2, initial exposure for 12 months to ERN from a composite of ARBITER 2 and placebo conversions to ERN in ARBITER 3, and lastly the cumulative 24-month continuous treatment with ERN comprised of ARBITER 2 subjects treated with ERN who continued on ERN for the 12 subsequent months of ARBITER 3. Clinical values used for comparison of baseline characteristics were those at the time of entry to ARBITER 2, unless otherwise specified. Between-group changes in laboratory and CIMT measurements were performed using a *t*-test for independent groups or ANOVA as appropriate. Bivariate correlations between the change in HDL-C and change in CIMT observed during the trial were sought. For a further description of the bivariate relationships between the CIMT endpoint and HDL-C, we used the locally weighted scatterplot smoothing (LOESS) technique fitting 95% of the datapoints. This technique is designed to produce a smooth fit to the data and reduces the influences of extreme outliers. We performed multivariable linear regression using the change in CIMT as the independent variable. Dependent variables, including the change in HDL-C, LDL-C and triglycerides, were entered into the model using both forward and backward entry. Models were tested for influential datapoints using leverage and collinearity diagnostics. All statistical analyses were performed using SPSS software (version 13.0, SPSS Inc., Chicago, IL). Values are reported as mean ± standard deviation, except where indicated. A two-sided *p*-value of ≥0.05 was considered statistically significant.

Results

Among the 149 eligible subjects from ARBITER 2, 130 consented to participate in the 12-month extension phase (ARBITER 3). This was comprised of 61 of 71 eligible subjects from the placebo arm, and 69 of 78 eligible subjects from the ERN arm of ARBITER 2. The baseline characteristics (at the time of initiation of ARBITER 2) of the 19 subjects who declined participation were similar to the 130 subjects that entered the trial. The mean patient age was 67 ± 10 years and 92.3% were men (Table 1). Known coronary heart disease was present in all 130 subjects, and all

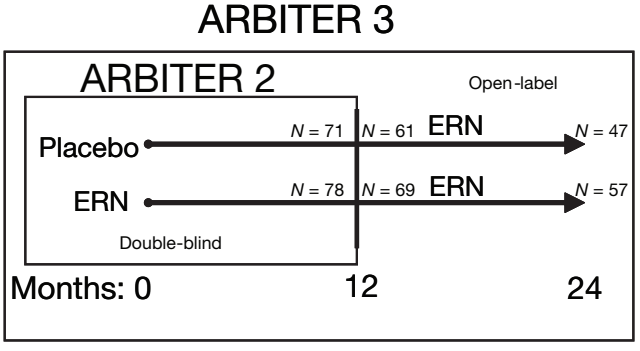

Figure 1. *Schematic of the study sequence from ARBITER 2 and 3*

patients were treated with a statin medication (simvastatin 92.3%; mean dose 36 ± 21 mg) as specified by the original study design and inclusion criteria. The study group had been chronically treated with statin medications with a mean duration of statin therapy prior to the beginning of ARBITER 2 of 4.8 ± 4.3 years. The prevalence of metabolic syndrome (31.5%) and diabetes mellitus (27.7%) was similar to ARBITER 2.

A total of 104 subjects (80%) completed the extension phase including 57 subjects from the ERN group of ARBITER 2, and 47 of the placebo conversions. Reasons for not completing the study included voluntary study withdrawal in 15 (five due to flushing side-effects, seven were unable to complete the follow-up procedures, one inadvertently stopped study medication, one developed prostate cancer, and one due to a rash), seven moved from the area during the study and were therefore lost to follow-up, and there were four deaths (three noncardiac). Compliance with the prescribed ERN was very high. A total of 103 of 104 subjects filled all four ERN (90-day) prescriptions across 12 months.

Table 2 shows baseline, 12- and 24-month lipid values from ARBITER 2 and 3 stratified by initial drug therapy in ARBITER 2. Aggregate values from ARBITER 3 are shown in Table 3. Baseline labs at the time of entry to ARBITER 2 included a mean LDL-C of 87.6 ± 22.0 mg/dl and an HDL-C of 39.5 ± 6.7 mg/dl. After 24 months, LDL-C decreased by a mean of 8.8 mg/dl, HDL-C increased by 9.1 mg/dl (Figure 2), and triglycerides decreased by 33 mg/dl ($p < 0.001$ for all). There were no significant changes in blood glucose, or CRP.

At the conclusion of the 12-month extension phase, subjects converted from placebo to ERN (n = 47) had experienced significant regression of CIMT of –0.095 ± 0.019 mm ($p < 0.001$ vs. placebo phase). The subjects had significant regression in CIMT, which was quantitatively greater than that observed during the 12-month experience with ERN during ARBITER 2. Notable differences between baseline characteristics of the 47 cross-over subjects compared to the ARBITER 2 ERN subjects include nonsignificant trends to lower frequency of diabetes (23.4 vs. 33.3%), greater initial increases in HDL-C (8.8 vs. 7.0 mg/dl) and greater reductions in LDL-C (9.7 mg/dl vs. 7.0 mg/dl). Pooling the 12-month effects of ERN on CIMT from ARBITER 2 (n = 78) and the ARBITER 3 extension phase (n = 47), there was net regression of CIMT of –0.027 ± 0.011 mm (n = 125, $p < 0.001$ vs. placebo) (Figure 3). Continued treatment with ERN in subjects converted from blinded to open-label ERN (n = 57; ERN treatment duration 24 months) was associated with significant regression of CIMT of –0.041 ± 0.021 mm ($p = 0.001$ vs. placebo phase). The between-group differences for the placebo phase, first 12 months of ERN, and total 24-month ERN treatment groups were significant ($p < 0.001$ by ANOVA). However, there was no significant difference between 12- (–0.027 ± 0.011 mm; n = 125) and 24-month (–0.041 ± 0.021 mm; n = 47) change in CIMT (t-test for independent groups). After 12–24 months of ERN in subjects with either diabetes mellitus or the metabolic syndrome (n = 62), HDL-C increased by 9.6 ± 12.5 mg/dl and this group showed significant regression of CIMT (–0.046 ± .131 mm; $p < 0.001$ vs. placebo phase).

There was a statistically significant inverse correlation between change in CIMT and change in HDL-C (r = –0.23; $p = 0.002$; Figure 4). Multiple linear regression controlling for changes in HDL-C, LDL-C and triglycerides showed that changes in CIMT were

Table 1. *Baseline characteristics*

N	130
Male gender	120 (92.3%)
Age, mean ± SD (years)	67 ± 10
Body mass index (kg/m^2)	29.2 ± 5.9
Hypertension, *n* (%)	98 (75.4%)
Metabolic syndrome, *n* (%)	41 (31.5%)
Diabetes mellitus, *n* (%)	36 (27.7%)
Tobacco use, *n* (%)	12 (9.2%)
Pharmacotherapies	
Mean statin dose (mg)	37 ± 20
β-blockers, *n* (%)	108 (83.1%)
ACEI	78 (60%)
ASA	110 (84.6%)

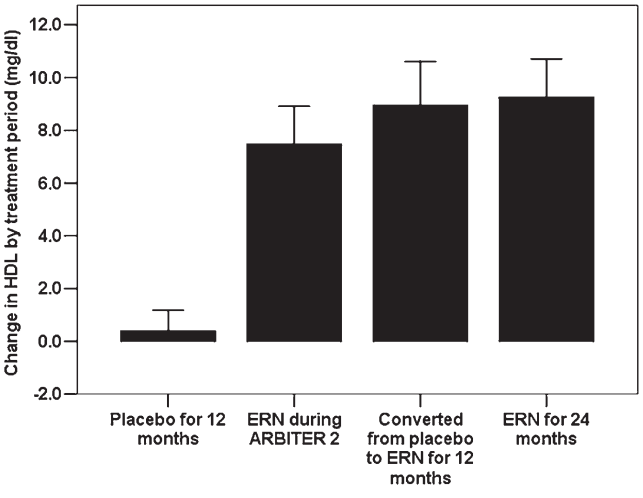

Figure 2. *Changes in HDL-C among ARBITER 3 participants during the treatment phases of both ARBITER 2 and 3 (placebo,* p = *NS; extended-release niacin* p < *0.001 for all comparisons with baseline HDL-C)*

Table 2. *Lipid, CRP, and CIMT effects in subjects enrolled in ARBITER 3 at baseline, 12 and 24 months stratified by treatment group*

	Placebo during ARBITER 2			ERN during ARBITER 2		
	Baseline	12 months on placebo, prior to ERN	Post-placebo, 12 months on ERN	Baseline	12 months on ERN, prior to open-label	Post-24 months of ERN
N		61	47		69	57
LDL-C (mg/dl)	90.5 ± 23.3	85.2 ± 20.7 $p = 0.056$	79.2 ± 26.0 $p = 0.012$	85.9 ± 17.8	82.8 ± 25.0 $p = 0.29$	78.4 ± 17.8 $p = 0.012$
HDL-C (mg/dl)	39.2 ± 6.7	39.4 ± 7.7 $p = 0.78$	48.5 ± 12.9 $p < 0.001$	39.4 ± 7.0	47.4 ± 16.3 $p < 0.001$	48.6 ± 13.8 $p < 0.001$
Triglycerides (mg/dl)	180.4 ± 107.2	171.0 ± 86.5 $p = 0.35$	120.5 ± 58.6 $p = 0.001$	154.2 ± 84.2	127.2 ± 80.0 $p = 0.001$	120.5 ± 58.6 $p = 0.001$
Glucose (mg/dl)	106.4 ± 24.8	114.4 ± 2.3 $p = 0.05$	111.9 ± 27.5 $p = 0.68$	108.2 ± 36.0	122.5 ± 45.9 $p = 0.04$	111.9 ± 27.5 $p = 0.68$
C-reactive protein (mg/L)	3.0 ± 3.5	3.5 ± 4.9 $p = 0.10$	3.4 ± 9.0 $p = 0.62$	5.0 ± 6.8	4.2 ± 5.9 $p = 0.39$	4.0 ± 9.0 $p = 0.60$
CIMT (mm)	0.862 ± 0.216	0.910 ± 0.215 $p < 0.001$	0.829 ± 0.209 $p = 0.055$	0.887 ± 0.271	0.899 ± 0.243 $p = 0.35$	0.829 ± 0.209 $p = 0.055$

Values are mean ± SD
CIMT = carotid intima–media thickness

only related to the change in HDL-C (standardized β = –0.25; $p = 0.001$). Standardized regression coefficients for the change in LDL-C (standardized β = 0.08; $p = 0.28$) and triglycerides (standardized β = –0.04; $p = 0.56$) were not significant.

Statin medications (agent and daily dose) were unchanged during the 24-month study in 93 of the 104 (89.4%) subjects completing ARBITER 3. In the other 11 subjects, clinically-directed conversions to a different statin were identified. Specifically, four were changed from simvastatin to atorvastatin, three were changed from atorvastatin to simvastatin, four were changed from simvastatin to pravastatin. Compared to subjects without statin conversions, these 11 subjects showed a nonsignificant trend towards greater reductions in LDL-C (–15.7 ± 25.0 mg/dl vs. –7.6 ± 19.5 mg/dl; $p = 0.21$), greater increases in HDL-C (11.6 ± 17.6 mg/dl vs. 8.8 ± 10.2 mg/dl; $p = 0.420$) and greater reductions in CIMT (–0.064 ± 0.025 vs. –0.038 ± 0.017 mm; $p = 0.58$) after 24 months.

During the open-label extension phase (12–24 months), four patients experienced cardiovascular events including one myocardial infarction, one sudden death in an elderly woman with end-stage renal disease and a valvular cardiomyopathy, and two elective percutaneous coronary revascularization procedures. There were no significant (>3× above upper limit of normal) changes in liver-associated enzymes and no subject experienced myopathy.

Discussion

ARBITER 3 shows that, in the setting of well-controlled LDL-C (≈80 mg/dl) on statin monotherapy, ERN increased HDL-C by 23% and induced significant regression of CIMT after 12–24 months. Greater increases in HDL-C were independently associated with superior effects on CIMT, consistent with the prevailing biologic understanding of the role of HDL-C in reverse cholesterol transport and delipidation of plaque[6,17]. Considering consistent evidence from angiographic[18], coronary intravascular ultrasound[19] and CIMT[12] studies linking atherosclerosis stabilization and regression with protection from cardiovascular events, ARBITER 3 supports the potential for combination therapy targeting both LDL-C and HDL-C to extend the outcomes benefit of aggressive statin therapy to low LDL-C targets.

A large body of clinical trial evidence has defined the modest, approximately 30% reduction in cardiovascular events achieved with moderate LDL-C reductions on statin monotherapy[20]. Recent clinical trials have extended our understanding of the potential benefit of further reductions in LDL-C to even lower targets by

Table 3. *Lipid, CRP, and CIMT effects in 104 subjects completing ARBITER representing 12–24 month effects of extended-release niacin*

	Baseline	24 months	*p*-value
N	104	104	
LDL-C (mg/dl)	87.6 ± 22.0	79.3 ± 21.5	< 0.001
HDL-C (mg/dl)	39.5 ± 6.7	48.6 ± 13.3	< 0.001
Triglycerides (mg/dl)	165 ± 84	132 ± 82	0.001
Glucose (mg/dl)	108 ± 33	113 ± 32	0.20
C-reactive protein (mg/L)	3.7 ± 5.1	3.6 ± 6.9	0.86
CIMT (mm)	0.869 ± 0.245	0.829 ± 0.212	0.008

CIMT = carotid intima–media thickness

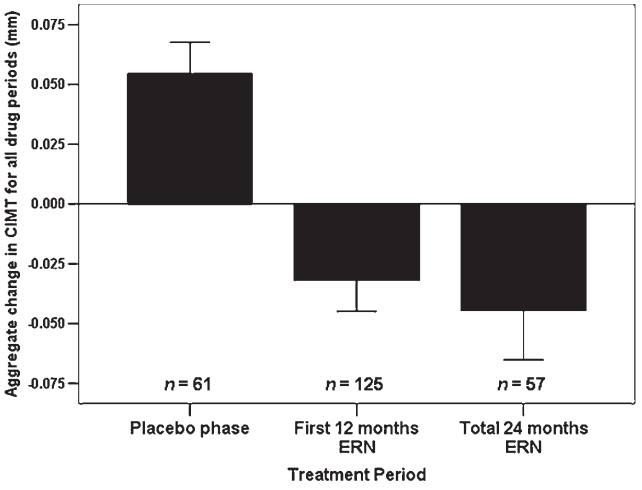

Figure 3. *IMT change across 12 months in placebo (n = 61), 12 months of extended-release niacin (n = 125) and 24 months of extended-release niacin (n = 57) (p < 0.001)*

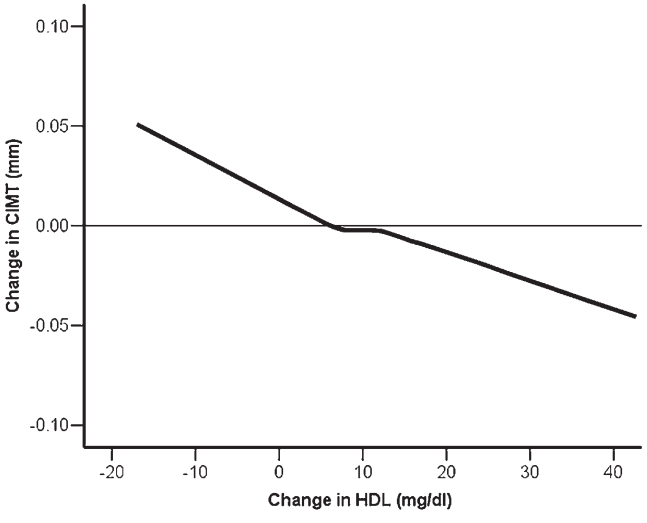

Figure 4. *Locally weighted smooth scatterplot showing the relationship between changes in HDL-C and CIMT in the 104 subjects who completed ARBITER 3 (r = –0.23; p = 0.002)*

demonstrating the incremental but limited benefit of intensive statin monotherapy[21–24]. By contrast, low levels of HDL-C are prevalent[25] and have been consistently and independently associated with increased coronary heart disease risk[5] even among statin-treated patients[26]. Thus, combination drug therapy that includes a focus on raising HDL-C is available as an adjunctive approach to further reduce cardiovascular risk. Existing small studies show that an additional relative risk reduction of 30–60% in incident coronary heart disease event rates[9,27,28] may be achievable through pharmacological treatment of multiple components of the dyslipidemic profile.

These clinical observations are underscored by an expanding understanding of the biologic role of HDL-C in atherogenesis. HDL particles remove esterified cholesterol via the liver in the process of reverse cholesterol transport through the interaction of apoA1, the principal apoprotein of HDL, with the membrane cholesterol transporters, such as ABCA1[6,17] and ABCG1[7]. Extending from these basic science observations, experimental studies in animals, for example, have shown that HDL particles and apoA1 are anti-atherogenic[29]. Recently, the first demonstration in humans with exogenously administered phospholipids–apoA1 particles showed short-term effects on regression of coronary atherosclerosis[30]. Thus it is biologically plausible that niacin, which leads to dose-dependent increases in both HDL-C and apoA1 levels via interaction with the recently identified nicotinic acid receptor[31] and delayed clearance of apoA1, can stimulate atherosclerosis regression.

The data from ARBITER 3, together with prior observations from ARBITER 2, show definite regression of CIMT after 12–24 months, a finding compatible with the expanding biologic understanding of the beneficial role of HDL-C in atherogenesis. Importantly, CIMT regression in ARBITER 3 was observed not only in the participants treated with ERN for 24 months,

but also in the expanded 12-month ERN exposure experience from ARBITER 2 (n = 78) to ARBITER 3 (n = 125). Similar short and long-term effects on coronary atherosclerosis regression by increasing HDL-C through the use of niacin have been previously demonstrated in combination with colestipol in several trials including FATS[32], CLAS I after 2 years[28], CLAS II after 4 years[33] and the recently reported Armed Forces Regression Study[9]. However, the findings from ARBITER 2 and ARBITER 3 are particularly notable and relevant to current clinical practice through the demonstration of the incremental impact of niacin added to background statin therapy at clinically-proven doses of statin medications through which LDL-C was well-controlled. We found an inverse relationship between increase in HDL-C and regression of CIMT (r = –0.23). Although the strength of this correlation is modest, similar findings were reported in the HDL Atherosclerosis Treatment study, in which a similar strength relationship (r = –0.235) was observed for the relationship between the change in quantitative coronary angiography and the change in α-subparticles of HDL with simvastatin–niacin[34]. In a cross-sectional study[35], a similar inverse correlation was also observed between CIMT and HDL-C (r = –0.117 (unadjusted) and r = –0.268 (adjusted).

Niacin has been in clinical use for four decades with an established safety and tolerability profile, including its use as a component of combination therapy with statins. For example, safety data from combination therapy with lovastatin with extended-release niacin shows no excess in the rate of liver toxicity or rhabdomyolysis over statin monotherapy[36]. Clinical tolerability can be highly successful with simple maneuvers to overcome the time-limited, harmless side-effect of flushing, including patient awareness, co-administration of aspirin, bedtime dosing, taking the medication with a low-fat snack, and the use of low doses of a non-steroidal anti-inflammatory drug as abortive therapy when flushing occurs.

Limitations

The data presented here are pooled from both the blinded and open-label extension phase of a clinical trial treated with the same dose and duration of ERN. However, data from the open-label phase may include subjects preferentially self-selected to be adherent to the prescribed therapy, possibly as suggested by the greater increase in HDL-C observed in placebo-ERN conversions and the large reductions in CIMT in this group. These differences, along with other non-significant between-group differences, such as the lower prevalence of diabetes and slight differences in LDL-C changes, may have contributed to the larger observed CIMT effects. We used the 12-month placebo-controlled CIMT progression rates from ARBITER 2 for comparison with the 12 and 24 months CIMT changes during ERN. By study design, there was not a concurrent placebo control during ARBITER 3. However, because 1-year CIMT progression observed during placebo treatment in ARBITER 2 was consistent with the expected response with chronic statin monotherapy, it is probable that CIMT progression would have continued during prolonged (>12 months) observation. This study cannot determine the impact of combination therapy to increase HDL-C on clinical cardiovascular events. However, this is the subject of a recently initiated National Heart Lung and Blood Institute outcome study entitled **A**therothrombosis **I**ntervention in **M**etabolic Syndrome with Low **H**DL-C/High Triglyceride and **I**mpact on **G**lobal **H**ealth Outcomes (AIM HIGH) comparing ERN to placebo in the setting of statin therapy and well-controlled LDL-C.

Conclusions

ARBITER 3 extends the findings of ARBITER 2, demonstrating that a therapeutic strategy of treating low HDL-C with extended-release niacin leads to sustained increases in HDL-C, and regression of atherosclerosis, consistent with the prevailing biologic understanding of the role of HDL-C in reverse cholesterol transport. Translation of these findings to understand their implications for clinical outcomes is under investigation through dedicated clinical trials.

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