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ORIGINAL RESEARCH

Combination of niacin extended-release and simvastatin results in a less atherogenic lipid profile than atorvastatin monotherapy

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Objective: To compare the effects of combination niacin extended-release + simvastatin (NER/S) versus atorvastatin alone on apolipoproteins and lipid fractions in a post hoc analysis from SUPREME, a study which compared the lipid effects of niacin extended-release + simvastatin and atorvastatin in patients with hyperlipidemia or mixed dyslipidemia.

Patients and methods: Patients (n = 137) with dyslipidemia (not previously receiving statin therapy or having discontinued any lipid-altering treatment 4–5 weeks prior to the study) received NER/S (1000/40 mg/day for four weeks, then 2000/40 mg/day for eight weeks) or atorvastatin 40 mg/day for 12 weeks. Median percent changes in apolipoprotein (apo) A-1, apo B, and the apo B:A-I ratio, and nuclear magnetic resonance lipoprotein subclasses from baseline to week 12 were compared using the Wilcoxon rank-sum test and Fisher's exact test.

Results: NER/S treatment produced significantly greater percent changes in apo A-I and apo B:A-I, and, at the final visit, apo B $<$ 80 mg/dL was attained by 59% versus 33% of patients, compared with atorvastatin treatment ($P = 0.003$). NER/S treatment resulted in greater percent reductions in calculated particle numbers for low-density lipoprotein (LDL, 52% versus 43%; $P = 0.022$), small LDL (55% versus 45%; $P = 0.011$), very low-density lipoprotein (VLDL) and total chylomicrons (63% versus 39%; $P < 0.001$), and greater increases in particle size for LDL (2.7% versus 1.0%; $P = 0.007$) and VLDL (9.3% versus 0.1%; $P < 0.001$), compared with atorvastatin.

Conclusion: NER/S treatment significantly improved apo A-I levels and the apo B:A-I ratio, significantly lowered the number of atherogenic LDL particles and VLDL and chylomicron particles, and increased the mean size of LDL and VLDL particles, compared with atorvastatin.

Keywords: niacin, simvastatin, atorvastatin, dyslipidemia, lipid particles, diameter, number, size

Introduction

Elevated levels of low-density lipoprotein cholesterol (LDL-C) have been shown to be directly associated with increased risk for development of atherosclerotic cardiovascular disease and related deaths. Current prevention guidelines from the National Cholesterol Education Program (NCEP) recommend measurement of LDL-C to estimate lipoprotein-related risks for cardiovascular disease and form the basis of treatment recommendations for patients.[1] However, recent studies suggest that the quantity and size of LDL particles is a better predictor of cardiovascular disease risk and atherosclerosis than LDL-C levels,[2,3] because patients with the same level of LDL-C may have higher or lower numbers of LDL particles, and, as a result, may differ in terms of cardiovascular disease risk.[4] Because measurement of LDL-C apolipoprotein B (apo B) reflects atherogenic lipoprotein burden in serum, multiple US and international

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groups now include it in their treatment guidelines, in addition to measuring standard lipid levels.[5–7]

The atherogenicity of LDL particles is influenced by the characteristics of various subclasses, which can differ in size, density, buoyancy, chemical composition, and physiologic behavior.[8] Increased levels of small, dense LDL particles are associated with increased cardiovascular risk,[9,10] whereas an inverse relationship exists between large high-density lipoprotein (HDL) particle levels and cardiovascular disease risk.[11] Therefore, an increased number of small, dense LDL particles (LDL subclass pattern B) and decreased concentrations of large HDL particles appear to be proatherogenic, while large, buoyant LDL particles (LDL subclass pattern A) and increased levels of large HDL particles appear to be antiatherogenic.[2,3,12] The combination of small LDL particles and decreased levels of large HDL particles has been termed the atherogenic lipoprotein profile.[13] Furthermore, studies have shown that increasing the levels of apolipoprotein A-I (apo A-I), the major protein constituent of HDL cholesterol (HDL-C), is associated with decreased cardiovascular risk,[14] whereas increased levels of apo B are associated with increased cardiovascular risk.[15,16]

Niacin has a long-standing history as an effective lipid-altering therapeutic agent with well established clinical benefits.[17–22] Niacin is the most effective agent marketed for raising HDL-C and has also been shown to lower LDL-C, non-HDL-C, lipoprotein(a) (Lp(a)), and triglycerides, all factors believed to be associated with increased cardiovascular risk.[17,19–21] In addition to its beneficial effects on standard lipoprotein levels, niacin has shown further benefits in patients with coronary artery disease by significantly increasing HDL and LDL particle size.[22,23]

HMG-CoA reductase inhibitors (statins) are commonly used for treatment of dyslipidemia and have been shown to be the most effective available agents for decreasing LDL-C.[24–26] In addition, statins have been shown to have a variable response in their ability to reduce the number of small, dense LDL particles and increase their size.[27–29]

SUPREME was a study that compared the effects of a once-daily combination tablet of niacin extended-release (NER, Niaspan®, Abbott) and simvastatin (NER/S, Simcor®, Abbott) with atorvastatin monotherapy in patients with mixed dyslipidemia.[30] Compared with atorvastatin, combination NER/S treatment resulted in superior improvements in HDL-C, triglycerides, and Lp(a); both treatments had equivalent responses in lowering LDL-C and non-HDL-C.[30] We tested the hypothesis that a post hoc analysis would show that NER/S compared with atorvastatin monotherapy produces additional favorable changes in the levels of apo A-1 and apo B, and in the numbers and sizes of LDL and very low-density lipoprotein (VLDL) particles.

Methods

Study design

SUPREME was a prospective, randomized, open-label, blinded-endpoint 12-week Phase IIIB clinical trial conducted at clinical centers in the US.[30] The study consisted of two periods, ie, a screening period and a treatment period. The study was designed and monitored in accordance with the ethical principles of good clinical practice, as required by the major regulatory authorities, and in accordance with the Declaration of Helsinki. The institutional review board for each study site approved the study protocol, and all participants provided written informed consent before enrollment.

All patients were instructed to adopt the NCEP Therapeutic Lifestyle Changes (TLC) diet for a minimum of four weeks during the screening period and to be willing to maintain compliance with this diet throughout the study. Patients discontinued any pretrial lipid treatments for at least four weeks (washout period). Following the four-week TLC diet and washout of any pretrial lipid treatments, eligible patients were randomized centrally in the ratio of 3:2 to one of two treatment regimens (Figure 1): NER/S 1000/40 mg/day for four weeks, followed by NER/S 2000/40 mg/day for eight weeks, or atorvastatin 40 mg/day alone for 12 weeks.

Inclusion criteria

Patients included men and women aged $\geq$ 21 years of age. Following compliance with the TLC diet and washout of lipid drugs for a minimum of four weeks prior to randomization, eligible patients were defined as having primary Type II hyperlipidemia or mixed dyslipidemia if their LDL-C levels were 130–250 mg/dL, HDL-C $<$ 40 mg/dL for men or $<$ 50 mg/dL for women, and triglycerides $<$ 350 mg/dL. Baseline fasting lipid measurements for LDL-C and HDL-C, drawn at two final screening/washout visits 7 $\pm$ 3 days apart, were required to be within 15% of each other at the end of the screening period.

Exclusion criteria

Exclusion criteria included allergy, hypersensitivity, or intolerance to niacin, statins, or their derivatives. Women needed not to be pregnant or breast-feeding, should not be planning to become pregnant or breast-feed, and should be committed to using preventative measures against pregnancy. Patients should not have used an investigational study medication or participated in an investigation within 30 days prior to the screening period, taken a prohibited medication within four weeks of signing the informed consent form, had active gallbladder disease within the preceding 12 months, had

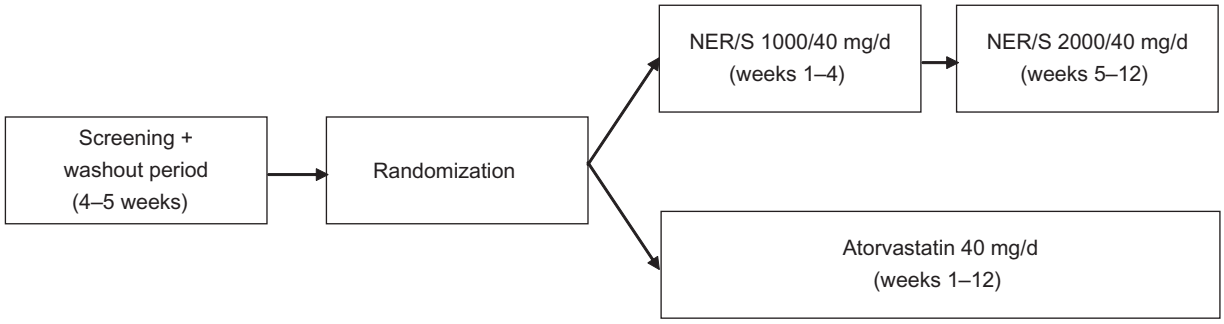


Figure 1 Study design.
Abbreviation: NER/S, niacin extended-release/simvastatin.

chronic pancreatitis or acute pancreatitis within the preceding six months, have persistent, uncontrolled hypertension, have unstable endocrine diseases, or had poorly controlled Type 1 or 2 diabetes. Patients with the following laboratory values were also excluded: creatine phosphokinase $\geq 3 \times$ upper limit of normal; alanine aminotransferase or aspartate aminotransferase $\geq 1.3 \times$ upper limit of normal; calculated creatinine clearance < 30 mL/min; glycosylated hemoglobin $\geq 9\%$; or uric acid levels $\geq 1.3 \times$ upper limit of normal.

Lipoprotein analyses

Fasting serum levels of apo A-I and apo B were measured by the Core Laboratory for Clinical Studies (CLCS, St. Louis, MO) using turbidimetric immunoassays, Autokit Apo A1 and Autokit Apo B, on a Hitachi 917 analyzer (Wako Chemicals, Richmond, VA). Central laboratory services analyzed all clinical laboratory samples, including lipids. Samples were collected, distributed, processed, and shipped according to the procedures established by the CLCS and described in the laboratory manual.

Lipid particle concentration and diameter analyses

This was a post hoc analysis of patients who completed the study and who had particle size and particle number results at baseline and week 12 by the nuclear magnetic resonance (NMR) method (LipoProfile Test®, LipoScience Inc., Raleigh, NC). Patients' fasting plasma samples were analyzed to determine the diameter (size) and number of lipoproteins present by the NMR LipoProfile-II Test®.[31–33] The particle concentrations of the different sized lipoprotein subclasses in blood plasma are determined by the measured amplitudes of the characteristic lipid methyl group NMR signals they emit. The subclass signal amplitudes are extracted from the composite lipid methyl group signal envelope of each plasma sample using a spectral deconvolution algorithm of particle subspecies actually present in the plasma. Neighboring subpopulations are grouped empirically into a smaller number of subclass categories of diameter (small, medium, and large) so that the summed amplitudes of the individual subpopulation signals give acceptable measurement precision (coefficient of variation $< 10\%$). Concentrations of seven subclass categories of diameter are reported: intermediate density LDL (IDL, 23–27 nm), large LDL (21.2–23 nm), medium small LDL (19.8–21.2 nm), very small LDL (18–19.8 nm), large VLDL and chylomicrons (> 60 nm), medium VLDL (35–60 nm), and small VLDL (27–35 nm). Mean particle diameters (nm) are computed as the sum of the diameters of the individual subpopulations multiplied by their relative mass percentages, as estimated from the amplitudes of their methyl NMR signals.

The shift in lipoprotein profiles of subclass pattern A versus subclass pattern B was compared between treatment groups. Subclass pattern A is characterized by increased large, buoyant LDL and is also associated with increased HDL particles and decreased small LDL particles and triglycerides. Subclass pattern B is characterized by the predominance of small, dense, atherogenic LDL particles and is also associated with decreased HDL-C concentrations and increased triglycerides.

Safety

Safety data were collected at each study visit, including the last visit. Safety endpoints included the change from baseline to each postbaseline visit in safety laboratory parameters and vital sign measurements. Safety was also evaluated based on data collected for adverse events coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 9.1, physical examination findings, pregnancy tests (for women of childbearing potential only), and information on flushing.

Statistical analyses

Median percent changes in apo A-1, apo B, and the apo B:A-I ratio from baseline to week 12 were compared

between treatment arms by the Wilcoxon rank-sum test. The percent changes in LDL-C, HDL-C, non-HDL-C, and total cholesterol:HDL-C from baseline to week 12 were compared between treatment groups using a repeated-measures mixed model, with baseline lipids and site as covariates and treatment as the main factor. The percent changes in triglycerides, Lp(a), as well as particle sizes of VLDL and LDL and particle numbers of LDL and its subclasses from baseline to week 12 were compared between treatment groups using the Wilcoxon rank-sum test. The proportions of patients with large LDL particles at week 12 were compared between treatment groups using the Cochran-Mantel-Haenszel method, adjusting for the proportion of patients with predominantly large LDL particles at baseline. LDL particle size was dichotomized to large (20.6–23.0 nm) and small (18.0–20.5 nm) groups.[2,3] The proportion of patients who achieved an LDL particle number as defined by apo B $<$ 80 mg/dL (guidelines set by the American Diabetes Association[34]) and an NMR estimated particle number of $<$ 1000 nmol/L at week 12 was compared between treatment groups using Fisher's exact test; recent treatment guidelines suggest an LDL particle number goal of $<$ 1000 nmol/L for high-risk patients.[15,35]

Results

Study population

This was a post hoc analysis of 137 patients (n = 74 for NER/S, n = 63 for atorvastatin) from the SUPREME efficacy population (152 patients; n = 82 for NER/S, n = 70 for atorvastatin) who completed the study and who had NMR particle size and particle number results at baseline and week 12. This subset was reflective of the total patient population from the SUPREME study.[30] The characteristics of the two treatment groups were reasonably well matched at baseline. Baseline demographics and clinical characteristics are summarized in Table 1.

Lipid efficacy

In patients with dyslipidemia, combination NER/S 2000/40 mg/day treatment resulted in superior improvements, compared with atorvastatin 40 mg/day, in HDL-C (30% versus 9%; $P < 0.001$), triglycerides (–46% versus –37%; $P < 0.05$), total cholesterol:HDL-C (–47% versus –40%; $P < 0.05$), and Lp(a), (–18% versus +16%; $P < 0.001$). A subgroup analysis of covariance for HDL-C by gender confirmed that NER/S increased HDL-C significantly at week 12 compared with atorvastatin in both males and females. Additionally, at week 12, more patients in the NER/S group achieved the HDL-C target of ≥ 40 mg/dL (males) or 50 mg/dL (females) compared with atorvastatin. Specifically, 77.8% of males and 61.7% of females in the NER/S group had week 12 HDL-C values equal to or greater than their respective targets compared with 18.8% and 19.4% of males and females, respectively, in the atorvastatin group (P values for both comparisons < 0.0001). There were no significant differences between treatment arms in the changes in non-HDL-C and LDL-C (Figure 2).

Apo A-I and Apo B

Baseline serum apolipoprotein levels that were assessed following adherence to a TLC diet and washout of lipid-modifying drugs for at least four weeks were typical of patients with mixed dyslipidemia (Table 1). At the final visit, 59% (44/74) of patients in the NER/S treatment arm achieved an apo B $<$ 80 mg/dL in contrast with 33% (21/63) of patients in the atorvastatin treatment arm ($P = 0.003$, NER/S versus atorvastatin, Figure 3). NER/S treatment produced significantly greater improvements in apo A-I and apo B:A-I compared with atorvastatin monotherapy (Figure 4) when evaluated by percent change from baseline.

Lipid particle number and diameter

Combination NER/S 2000/40 mg/day treatment resulted in greater increases in particle diameter for LDL (2.7% versus 1.0%; $P = 0.007$) and VLDL (9.3% versus 0.1%; $P < 0.001$), compared with atorvastatin monotherapy (Figure 5). NER/S treatment also attenuated the decrease in large LDL, large VLDL, and chylomicrons, compared with atorvastatin monotherapy (–13% and –45% versus –29% and –53%, respectively).

Combination NER/S treatment produced statistically significant reductions in atherogenic particle numbers compared with atorvastatin 40 mg/day monotherapy, as evidenced by median percent changes for total LDL (–52% versus –43%; $P < 0.05$), IDL (–91% versus –66%; $P < 0.05$), small LDL (–55% versus –45%; $P < 0.05$), and very small LDL (–57% versus –45%; $P < 0.05$, Figure 6A), and VLDL and total chylomicrons (–63% versus –39%; $P < 0.001$), medium VLDL (–61% versus –35%; $P < 0.05$), and small VLDL (–61% versus –36%; $P < 0.001$, Figure 6B). A greater proportion of patients in the NER/S group achieved an LDL particle number of less than 1000 nmol/L compared with the atorvastatin monotherapy group (46% versus 21%; $P = 0.002$).

In this study, 25% more patients with large, more buoyant LDL particles (pattern A, antiatherogenic) were observed at week 12 after combination NER/S treatment, compared with

Table 1 Demographics and baseline characteristics

Parameter	Statistic	NER/S (n = 74)	Atorvastatin (n = 63)
Age (years)	Mean (SD)	55.0 (12.5)	51.9 (10.8)
Male	n (%)	27 (37)	32 (51)
Caucasian	n (%)	66 (89)	59 (94)
Weight (kg)	Mean (SD)	90.4 (24.2)	88.3 (23.7)
Women	Mean (SD)	86.6 (24.0)	82.0 (23.4)
Men	Mean (SD)	97.1 (23.3)	94.4 (22.7)
BMI (kg/m^2)[a]			
<18.5 (underweight)	n (%)	1 (1)	0 (0)
18.5–24.9 (normal)	n (%)	8 (11)	9 (14)
≥25 (overweight)	n (%)	18 (24)	27 (43)
>30	n (%)	47 (64)	27 (43)
Current smoker	n (%)	13 (18)	12 (19)
Diabetes mellitus	n (%)	14 (19)	7 (11)
Hypertension	n (%)	39 (53)	24 (38)
CHD risk category[b]			
0–1 risk factors	n (%)	25 (34)	25 (40)
≥2 risk factors	n (%)	27 (37)	26 (41)
CHD or CHD risk equivalent	n (%)	22 (30)	12 (19)
CHD disease	n (%)	6 (8)	2 (3)
Concomitant cardiac medications			
ACE inhibitors/ARBs	n (%)	23 (31)	14 (22)
Beta-blockers	n (%)	11 (15)	8 (13)
Aspirin	n (%)	22 (30)	16 (25)
Lipids at baseline (mg/dL)			
Total-C:HDL-C ratio	Mean (SD)	6.1 (1.1)	6.7 (1.4)
Non-HDL-C	Mean (SD)	199.0 (28.0)	205.8 (31.1)
LDL-C	Mean (SD)	162.4 (23.5)	168.0 (29.6)
HDL-C	Mean (SD)	39.9 (6.1)	37.6 (6.4)
TG	Median [Q1, Q3]	174.3 [135.5, 222.5]	175.5 [139.5, 235.5]
Lp(a)	Median [Q1, Q3]	15.3 [6.5, 30.5]	14.5 [8.0, 41.5]
Apo A-I	Median [Q1, Q3]	123.9 [115.9, 134.5]	121.7 [114.3, 131.2]
Apo B	Median [Q1, Q3]	130.3 [118.3, 146.9]	133.8 [124.1, 147.2]
Apo B:A-I ratio	Median [Q1, Q3]	1.0 [0.95, 1.2]	1.1 [0.98, 1.3]

Notes: [a]Based on NIH BMI index guidelines; [b]Based on the NCEP ATP III (2004) definition of risk factors.

Abbreviations: NER/S, niacin extended-release/simvastatin; CHD, coronary heart disease; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; SD, standard deviation; [Q1, Q3], [25th percentile, 75th percentile]; NIH, National Institutes of Health; BMI, body mass index; NCEP ATP, National Cholesterol Education Program Adult Treatment Panel; total-C, Total cholesterol; HDL-C, high-density lipoprotein cholesterol; Non-HDL-C, non-high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; Lp(a), lipoprotein(a); Apo, apolipoprotein.

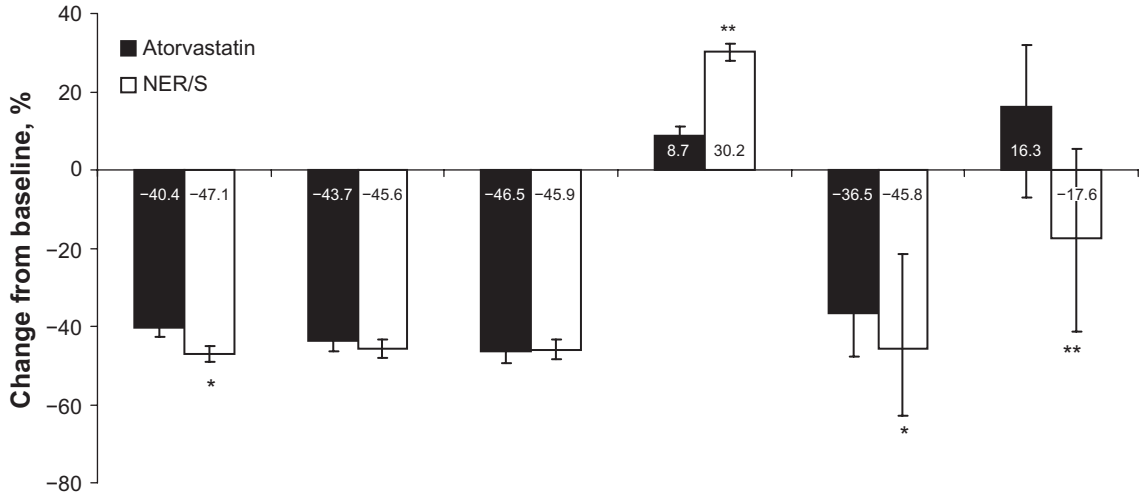
atorvastatin monotherapy (69% versus 44%; $P = 0.005$, based on Cochran-Mantel-Haenszel test, Figure 7).

Safety

Safety analyses included only results from patients used for this post hoc analysis. Overall, NER/S treatment and atorvastatin monotherapy were consistent with the established profiles of these medications (Table 2) and that reported for the overall population from the SUPREME study.[30] Eighty-two percent of patients in the NER/S group and 41% of patients in the atorvastatin group experienced treatment-emergent adverse events, defined as those events with onset dates that were on or after the study medication start dates ($P < 0.001$, Fisher's exact test); the adverse event of flushing primarily accounted for the higher percentage of patients in the NER/S group. A full detailed account of the safety results from the entire patient population can be found in the original SUPREME publication.[30]

Discussion

The focus of lipid-altering therapies has been largely on their abilities to lower LDL-C and triglyceride levels and raise HDL-C levels. This study demonstrates that in addition to these effects, combination NER/S treatment also provides additional significant benefit above atorvastatin monotherapy treatment in numerous measures of the atherogenic lipoprotein profile. Treatment with combination NER/S 2000/40 mg/day produced superior improvements in HDL-C, triglycerides, and Lp(a), compared with atorvastatin



Baseline, mg/dL:	Total-C:HDL	Non-HDL-C	LDL-C	HDL-C	TG	Lp(a)
■ Atorvastatin	6.7	205.8	168.0	37.6	175.5	14.5
□ NER/S	6.1	199.0	162.4	39.9	174.3	15.3

Figure 2 Lipid efficacy from baseline to week 12. For total-C:HDL, non-HDL-C, LDL-C and HDL-C: Bars represent least square means, error bars are standard errors; For TG and Lp(a): Bars represent medians, error bars are [Q1, Q3].
Notes: *$P = 0.05$; **$P < 0.001$; repeated measures of covariance (ANCOVA) for total HDL-C, non-HDL-C, LDL-C, and HDL-C; Wilcoxon rank-sum test for TG and Lp(a).
Abbreviations: Total-C, total cholesterol; HDL-C, high-density lipoprotein cholesterol; Non-HDL-C, non-high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; Lp(a), lipoprotein(a); NER/S, niacin extended-release/simvastatin; [Q1, Q3], [25th percentile, 75th percentile].

40 mg/day monotherapy, and additionally resulted in significant improvement in LDL particle number and prevalence of small LDL particles. Following just 12 weeks of treatment, NER/S significantly decreased total numbers of atherogenic LDL, VLDL, and chylomicron particles, and increased the mean diameter of LDL and VLDL particles.

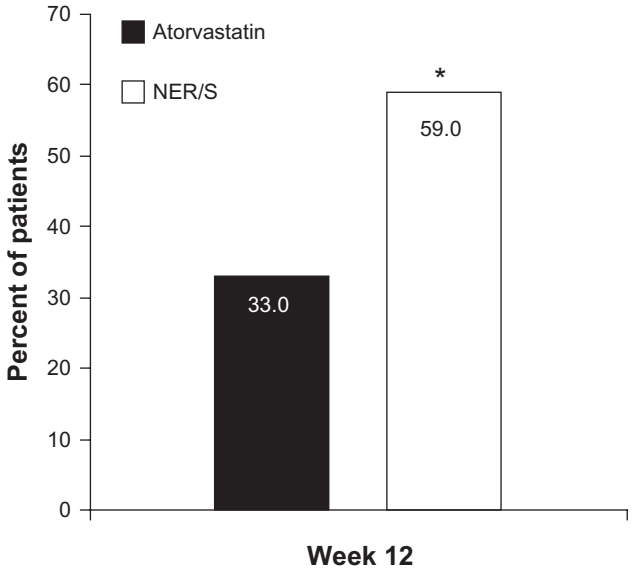
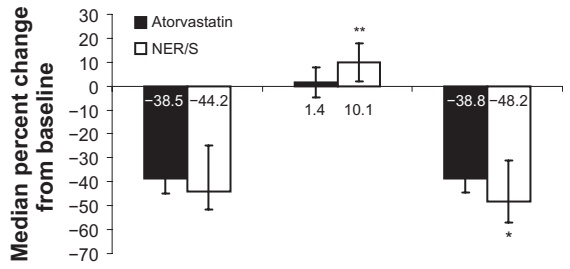


Figure 3 Percent of patients who attained Apo B < 80 mg/dL at week 12.
Note: *$P = 0.003$ versus atorvastatin, Fisher's exact test.
Abbreviations: NER/S, niacin extended-release/simvastatin; Apo, apolipoprotein.

NER/S treatment also significantly shifted the lipoprotein profile towards subclass pattern A, consisting of large, buoyant LDL, whereas this shift did not occur after 12 weeks of atorvastatin monotherapy. Lastly, greater improvements in apo B, apo A-I, and apo B:A-I were observed with NER/S treatment compared with atorvastatin monotherapy. Thus, different lipid agents appeared to cause substantially different quantitative and qualitative effects on lipoproteins, beyond the conventionally measured responses observed in serum lipid subfractions.



Baseline, mg/dL:	Apo B	Apo A-1	Apo B:A-1 ratio
■ Atorvastatin	133.8	121.7	1.1
□ NER/S	130.3	123.9	1.0

Figure 4 Median percent change in Apo A-1, Apo B, and the Apo B:A-I ratio at final visit. Error bars are [Q1, Q3].
Notes: *$P < 0.01$, **$P < 0.001$ versus atorvastatin, Wilcoxon rank-sum test.
Abbreviations: NER/S, niacin extended-release/simvastatin; Apo, apolipoprotein.

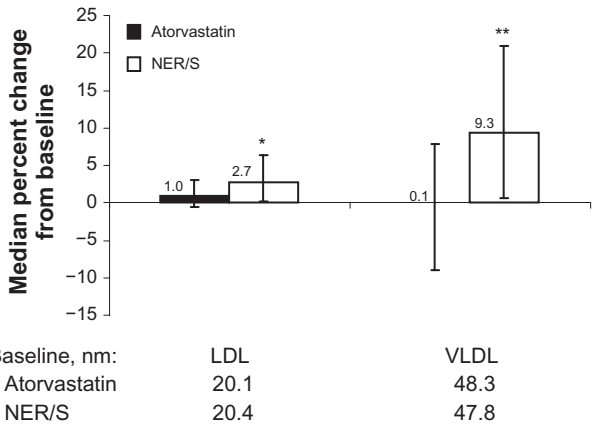


Figure 5 Median percent change in LDL and VLDL particle size from baseline to week 12. Error bars are [Q1, Q3].
Notes: *$P < 0.01$; **$P < 0.001$, Wilcoxon rank-sum test.
Abbreviations: LDL, low-density lipoprotein; VLDL, very low-density lipoprotein; NER/S, niacin extended-release/simvastatin; [Q1, Q3], [25th percentile, 75th percentile].

The number and size of circulating lipid particles, in addition to the total level of cholesterol, are increasingly recognized as important for better assessment of cardiovascular risk.[5,36–38] The size and number of lipid particles may be a better predictor of cardiovascular risk than LDL-C. Patients with the same levels of LDL-C may have substantially different LDL particle numbers and size distribution, and hence may be different in terms of cardiovascular risk, ie, those with greater LDL particle numbers, or smaller LDL size, incurring a greater risk for a cardiovascular event.[4] Thus, favorable changes in lipoprotein number, size, and composition may all contribute to the reduction in cardiovascular risk.

The apo B content of the lipid profile can also differ substantially in response to interventions, because this measurement provides an estimate of atherogenic (non-HDL) particle number because apo B is present at a fixed ratio of one molecule per particle and does not exchange between particles as the other apolipoproteins do. Several studies, including AMORIS (Apolipoprotein-related Mortality Risk)[39] and 4S (Scandinavian Simvastatin Survival Study),[40] have shown that apo B is a significant predictor of cardiovascular events, and this measurement is now often used to provide a measure of LDL or non-HDL particle concentration.[41] In addition, therapies that result in lowering apo B levels can translate into lower risk of cardiovascular disease.[42–44]

Several studies have shown that LDL particle levels are consistently more predictive of cardiovascular events compared with other lipid parameters, including VA-HIT (Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial),[10] the Women's Health Study,[45,46] and the Framingham Heart Study.[47,48] The Framingham Heart Study also demonstrated that cardiovascular event rates among patients with low LDL particle numbers were significantly reduced in contrast with patients having low LDL-C,[47] suggesting that cardiovascular risk is in part mediated by LDL particle burden, as well as particle composition.

The benefits of combination lipid-modifying agents on lipid particle size and number have not been well characterized until recently, although the modification of complementary lipid pathways may be advantageous beyond conventional statin monotherapy. Niacin has a long history as a pleiotropic lipid therapy; in particular, it

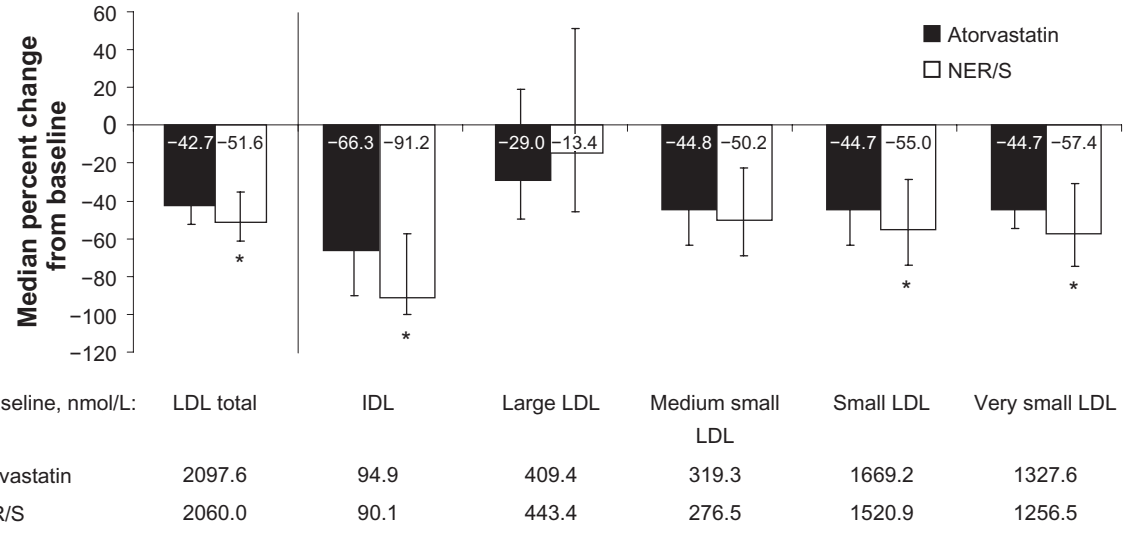


Figure 6A Median percent change in LDL particle numbers from baseline to week 12. Error bars are [Q1, Q3].
Note: *$P < 0.05$, Wilcoxon rank-sum test.
Abbreviations: LDL, low-density lipoprotein; IDL, intermediate-density lipoprotein; NER/S, niacin extended-release/simvastatin; [Q1, Q3], [25th percentile, 75th percentile].

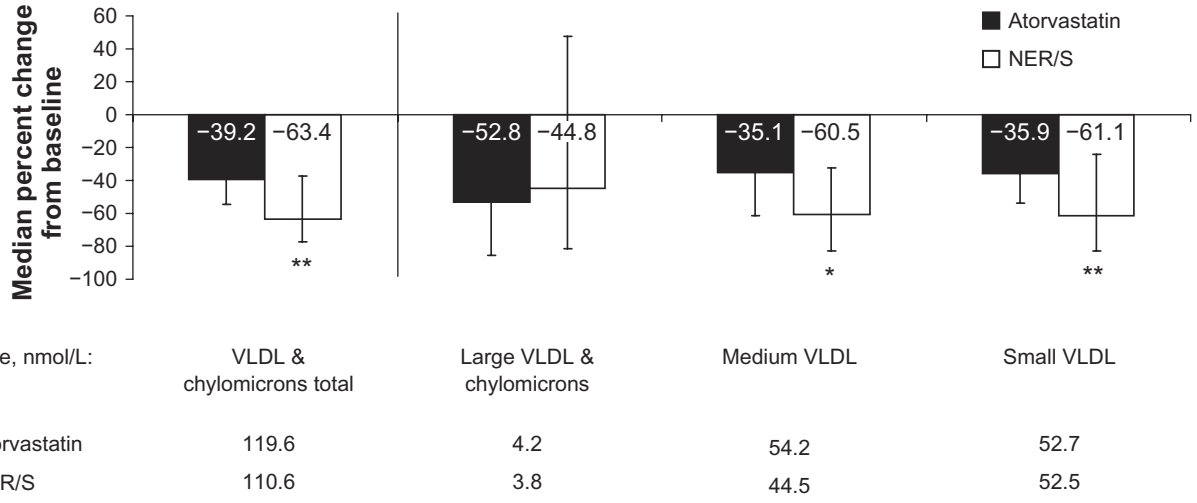


Figure 6B Median percent change in VLDL particle numbers from baseline to week 12. Error bars are [Q1, Q3].
Notes: *$P < 0.05$; **$P < 0.001$, Wilcoxon rank-sum test.
Abbreviations: VLDL, very low-density lipoprotein; NER/S, niacin extended-release/simvastatin; [Q1, Q3], [25th percentile, 75th percentile].

is the most effective agent marketed for raising HDL-C, while also improving LDL-C and triglyceride levels.[17,19–21] NER decreases atherogenic, small, dense LDL and VLDL particles, while increasing levels of large HDL subclasses in patients with primary hypercholesterolemia.[49] Several studies have examined the effects of NER on LDL particle number and density in patients with stable coronary artery disease who were already treated at baseline with a statin to an NCEP LDL-C goal of <100 mg/mL.[22,49,50] Jafri et al[50] found that after three months of NER treatment, the mean number of medium and small LDL particles was significantly decreased in patients with stable coronary artery disease compared with placebo-treated patients. Furthermore, NER favorably altered the mean number of HDL particles typically associated with an atherogenic profile, decreasing the small HDL particles and increasing the large HDL particles.[50] Kuvin et al[22] found that NER treatment in patients with stable coronary artery disease significantly increased both HDL and LDL particle size. Superko et al[23] reported that NER monotherapy favorably shifted LDL particle size and distribution, with a greater increase in mean LDL peak particle diameter and larger reductions in the proportions of

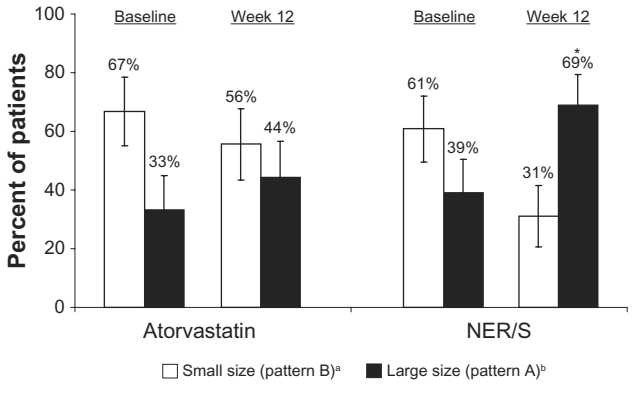


Figure 7 Shift in LDL particle size from baseline to week 12. Error bars are 95% confidence intervals.
Notes: *$P = 0.005$ versus atorvastatin based on Cochran-Mantel-Haenszel test. [a]subclass pattern B: predominance of small, dense LDL particles, triglycerides, and depressed HDL-cholesterol concentrations; [b]subclass pattern A: increased large LDL and HDL particles, and decreased small LDL particles and triglycerides.
Abbreviations: LDL, low-density lipoprotein; HDL, high-density lipoprotein; NER/S, niacin extended-release/simvastatin.

Table 2 Summary of adverse events

	NER/S n = 74	Atorvastatin n = 63	*P* value[a]
Patients, n (%)			
Any TEAE[b]	61 (82.4)	26 (41.3)	<0.001
Any AE possibly drug-related[c]	52 (70.3)	9 (14.3)	<0.001
Any serious AE[d]	2 (2.7)	1 (1.6)	1.000
TEAEs in order of frequency occurring in ≥5% of patients in either treatment group, n (%)			
Flushing	49 (66.2)	7 (11.1)	<0.001
Nausea	7 (9.5)	0 (0.0)	0.015
Vomiting	6 (8.1)	0 (0.0)	0.031
Diarrhea	5 (6.8)	1 (1.6)	0.218
Headache	5 (6.8)	1 (1.6)	0.218
Constipation	5 (6.8)	0 (0.0)	0.062

Notes: [a]*P* values are based on Fisher's exact test; [b]including flushing; [c]possible, probable, or definite relationship to treatment based on investigator assessment; [d]a serious adverse event is defined as any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, is a medically important event or reaction that may not be immediately life-threatening or results in death or hospitalization, but may jeopardize the patient or require intervention to prevent any of the other outcomes listed above.
Abbreviations: NER/S, niacin extended-release/simvastatin; TEAE, treatment-emergent adverse event; AE, adverse event.

smaller LDL subclasses in patients exhibiting the atherogenic LDL subclass pattern B. These findings, in the context of the results of the present study, are congruent with the further reduction of cardiovascular risk with the addition of niacin to background therapy, even in patients whose cholesterol levels were managed to NCEP goals.

The findings of this study, in favorably modifying the lipoprotein profile, including lipid particle diameter and number, over that of statin monotherapy, are clinically pertinent, because the small, dense LDL subfractions are associated with atherosclerotic burden and progression, measured either early, by magnetic resonance imaging or ultrasound as carotid intima-media thickness, or later, by arteriography as arterial plaque.[51,52]

Because atherosclerotic development and progression spans a pathologic and temporal spectrum,[53] there is considerable potential for this combination therapy to impact the process over a cross-section of patients. In a healthy community-based population, Norata et al[54] correlated carotid intima-media thickness with an atherogenic lipoprotein pattern, providing further evidence to consider measurements supplementary to conventional cholesterol fractions in discerning cardiovascular risk.

Notably, niacin-based regimens have demonstrated regression of the atherosclerosis process with the different imaging modalities, vide supra, in contrast with statin monotherapies, which, at best, have shown only delayed progression.[55–57] This has been observed by Taylor et al[58,59] and most recently by Lee et al.[60] Consonant with these results from adding niacin to background therapy, Airan-Javia et al[61] found over 12 months that the coadministration of NER 2000 mg/day plus simvastatin 20 mg/day produced a greater reduction in the proportion of patients with small, atherogenic LDL pattern B, compared with patients treated with simvastatin 20 mg or 80 mg monotherapy.

The mechanistic bases of how these modifications in the lipoprotein subfractions affect atherosclerosis has not been defined, although the contribution of these fractions to endothelial dysfunction[16] and inflammation[54] has been noted. With a combination therapy that produces improvements in the lipoprotein profile and lipid particle size and number, this study provides a basis for generating testable hypotheses of the interaction of these fractions with the artery wall in the development of atherosclerotic plaques.

Accumulating evidence demonstrates that the combination of NER with simvastatin also favorably modulates inflammatory pathways. Kuvin et al[22] showed that NER/S decreases high-sensitivity C-reactive protein (hsCRP) levels, while significantly increasing HDL and LDL particle size, consistent with the salutary effects of niacin. A post hoc analysis from OCEANS (Open-Label Evaluation of the Safety and Efficacy of a Combination of Niacin ER and SimvAstatin)[62] confirmed that treatment with NER/S significantly decreased hsCRP levels beyond statin monotherapy in patients with elevated baseline hsCRP $\geq$ 2 mg/L (–34.6%; $P < 0.005$ versus baseline).[63] Overall, the combined NER/S treatment has the potential for improved reduction of residual risk of coronary heart disease after statin monotherapy.

The safety profile of combination NER/S therapy in this trial was commensurate with those of the individual medications, in light of the faster dose escalation regimen with NER/S or atorvastatin in the SUPREME study. There are limitations to this study, including a small patient population and a relatively short study duration. However, 12 weeks was sufficient for NER/S to improve the lipid profile and lipoprotein subclass distributions significantly, consistent with previous reports. Given these limitations, the cardiovascular event rates were not different between treatments. However, this relationship will be defined by AIM HIGH (Atherosclerosis Intervention in Metabolic syndrome with low HDL-C High triglyceride and Impact on Global Health outcomes), which is evaluating cardiovascular events in approximately 3300 patients treated with NER/S or simvastatin monotherapy.

Conclusion

NER/S 2000/40 mg/day compared with atorvastatin 40 mg/day monotherapy provided superior improvements in HDL-C, Lp(a), and triglycerides, and comparable improvements in non-HDL-C and LDL-C. NER/S compared with atorvastatin monotherapy, also produced a shift towards a less atherogenic profile of lipoproteins, based on particle diameter and number, although both regimens achieved similar improvements in total LDL-C levels. This improvement was accompanied by increased apo A-I levels and a reduction in the apo B:A-I ratio. These results are consistent with previously noted improvements in atherosclerosis observed with various imaging modalities, suggesting that combination NER/S treatment may potentially further decrease cardiovascular risk in patients with dyslipidemia beyond that achieved by statin monotherapy.

This study has several major novel features that warrant comment. First, the study adds to our scientific knowledge about effects of treatment upon LDL particle metabolism. It is the first report of a controlled clinical trial comparing NER/S versus atorvastatin for effects upon the particles of the

lipoproteins containing apoB, and their numbers and sizes. Finally, the study demonstrated substantial advantages of NER/S over atorvastatin with regard to the greater efficacy of the combination for reducing small particles and increasing large particles in LDL-C, presumably resulting in a greater reduction of cardiovascular disease risk.

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Disclosure

Abbott is the financial sponsor of the SUPREME clinical trial. WI is a consultant for Abbott Laboratories (previously Kos Pharmaceuticals). PPT is a consultant for Abbott, AstraZeneca, Kowa, Merck and Co., and is on the speakers' bureau for Abbott, AstraZeneca, Kowa, Merck and Co., and Pfizer. RBT, SK, PJ, RAP, and RJP are employees of Abbott.

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