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ORIGINAL ARTICLE

Long-term efficacy and safety of ezetimibe/simvastatin coadministered with extended-release niacin in hyperlipidaemic patients with diabetes or metabolic syndrome

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Aims: To assess the efficacy and safety of ezetimibe/simvastatin (*E/S*) plus extended-release niacin (*N*) in hyperlipidaemic patients with diabetes mellitus (DM), metabolic syndrome (MetS) without DM (MetS/non-DM) or neither (non-DM/non-MetS).
Methods: A subgroup analysis of a double-blind, 64-week trial of 1220 randomized patients who received *E/S* (10/20 mg) + *N* (to 2 g) or *E/S* (10/20 mg) for 64 weeks, or *N* (to 2 g) for 24 weeks then *E/S* (10/20 mg) + *N* (2 g) or *E/S* (10/20 mg) for 40 additional weeks. The evaluable populations of this analysis included n = 765 patients at 24 weeks and n = 574 at 64 weeks. Among those receiving *N*, only those who attained the 2-g dose were included in the analysis.
Results: *E/S+N* improved levels of low-density lipoprotein cholesterol, other lipids and lipoprotein ratios compared with *N* and *E/S* at 24 weeks and *E/S* at 64 weeks. The combination increased high-density lipoprotein cholesterol and apolipoprotein AI comparably to *N* and more than *E/S*. *E/S+N* reduced high-sensitivity C-reactive protein (hsCRP) levels more effectively than *N* and similarly to *E/S*. *E/S+N* was generally well tolerated. Discontinuations due to flushing with *N* and *E/S+N* were comparable and greater than *E/S* in all subgroups. Fasting glucose trended higher for *N* vs. *E/S*. Glucose elevations from baseline to 12 weeks were highest for patients with DM (24.9 mg/dl for *N*, 21.2 mg/dl for *E/S+N*, 17.5 mg/dl for *E/S*); fasting glucose then declined to pretreatment levels at 64 weeks in all subgroups. New-onset DM was more frequent among MetS patients than those without MetS during the first 24 weeks and trended higher among those assigned to *N*-containing regimens [n = 5 (5.1%) for *N*, n = 2 (1.7%) for *E/S*, n = 21 (8.8%) for *E/S+N*]; during 24–64 weeks, diabetes was diagnosed in five additional patients in the *E/S* (cumulative incidence of 5.9%) and one in the *E/S+N* (cumulative incidence of 9.2%) groups. Treatment-incident elevations in uric acid levels were increased among subjects assigned to *N*-containing regimens, but there were no effects on symptomatic gout.
Conclusion: Combination *E/S+N* is a safe treatment option for hyperlipidaemic patients including those with DM and MetS, but requires monitoring of glucose and potentially uric acid levels.
Keywords: diabetes, ezetimibe/simvastatin, hyperlipidaemia, niacin

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Introduction

Although reducing low-density lipoprotein cholesterol (LDL-C) levels is the primary target in hyperlipidaemic patients with either type 2 diabetes mellitus (DM) or the metabolic syndrome (MetS), control of non-high-density lipoprotein cholesterol (non-HDL-C) and normalization of the lipid panel are expected to contribute to overall cardiovascular risk reduction in these patients [1–3]. Guidelines recommend combination therapy to achieve optimal LDL-C lowering and broader lipid regulation in high-risk, coronary heart disease (CHD) patients, including those with DM and MetS [1–4].

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Niacin (*N*) is the most effective agent available to increase HDL-C levels, while improving levels of triglycerides (TG), LDL-C, lipoprotein(a) [Lp(a)], and lipoprotein particle size [5,6]. *N*, alone or combined with other lipid-lowering agents, may also reduce cardiovascular events and slow the progression or induce regression of coronary atherosclerosis [5,7–12]. Although *N*-associated flushing may limit its use, this effect can be mitigated through patient counselling and proper administration [5,13]. Of more concern in patients with diabetes and MetS, *N* can be associated with increases in blood glucose levels that necessitate monitoring, and possibly treating, glucose changes [5–15].

Ezetimibe/simvastatin (*E/S*) is effective in lowering levels of LDL-C, non-HDL-C, TG and apolipoprotein (apo) B and modestly increases HDL-C in patients with hypercholesterolaemia or dyslipidaemia [16–19] and in patients with MetS and type 2

DM [20–25]. Combination therapy with *E/S* at 10/20 mg/day and extended-release niacin (Niaspan® [*N*]) at up to 2 g/day was recently shown to provide greater lipid-altering benefits in patients with type IIa and IIb hyperlipidaemia compared with *N* and *E/S* alone, and was generally well-tolerated, aside from *N*-associated flushing, during 24 and 64 weeks [26,27].

The present analysis evaluated the potential to extrapolate these long-term efficacy and safety results for *E/S+N* to subgroups of patients with DM, with MetS without DM (MetS/non-DM) and without either DM or MetS (non-DM/non-MetS). This is one of the most extensive, randomized, controlled trials of *N* therapy since the Coronary Drug Project [12], and it provides an important opportunity to evaluate the effects of *N* and combination *E/S+N* therapies in DM and MetS populations.

Materials and Methods

Study Design and Population

This is a subgroup analysis of a randomized, double-blind, multicentre, 64-week study in patients with type IIa or IIb hyperlipidaemia [26,27]. The protocol (091) was approved by appropriate institutional review boards, and all patients provided informed written consent. The subgroups consisted of those patients with DM, MetS and neither condition at baseline, as defined in Table 1.

In brief, men and women 18–79 years of age with 130–190 mg/dl LDL-C, TG ≤ 500 mg/dl, creatinine < 2 mg/dl, creatinine kinase (CK) ≤2× upper limit of normal (ULN), transaminases ≤1.5× ULN, haemoglobin A1c ≤ 8.0% were eligible for inclusion. After a 4-week wash-out period, eligible patients were randomized (5 : 2 : 2) to treatment with *E/S* (10/20 mg) + *N* (titrated to 2 g), or *E/S* (10/20 mg) or *N* (titrated to 2 g). *N* was increased by 500 mg every 4 weeks up to 2 g/day for 12 weeks from a 500 mg/day starting dose. Patients were counselled to take *N* at bedtime with a low-fat snack, aspirin (325 mg) or ibuprofen (200 mg) 30 min prior to taking *N*, and to avoid alcoholic and hot beverages near the time of taking *N*. Patients were stratified at randomization according to baseline LDL-C (130–159; 160–190 mg/dl) and TG (<200; 201–500 mg/dl) levels.

Efficacy endpoints included changes from baseline in lipids, lipid/lipoprotein ratios and high-sensitivity C-reactive protein (hsCRP). Prespecified safety variables included the incidence of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≥ 3× ULN, CK > 10× ULN with and without muscle symptoms, discontinuation due to flushing, gallbladder-related adverse events, cholecystectomy, change from baseline in fasting glucose, and new onset of diabetes

Table 1. Baseline characteristics.

	FC (n = 770)*†	DM‡ (n = 113)*†	MetS/non-DM (n = 301)*†	non-DM/non-MetS (n = 351)*†
Age mean (years) (s.d.)	57.4 (10.4)	62.0 (8.9)	57.9 (10.0)	55.6 (10.7)
Female (%)	47.1	46.9	47.8	46.7
Race (%)				
White	88.6	77.0	91.7	89.5
Asian	1.3	1.8	1.0	1.4
Black	4.7	11.5	4.0	3.1
Hispanic	4.8	8.8	2.3	5.7
Other	0.6	0.9	1.0	0.3
BMI mean (kg/m^2) (s.d.)	30.0 (5.5)	31.2 (6.2)	32.3 (5.3)	27.7 (4.5)
Fasting glucose mean (mg/dl) (s.d.)	101.9 (17.1)	127.1 (24.5)	101.8 (10.5)	93.7 (9.1)
NCEP risk category (%)				
CHD/CHD risk equivalent§	27.9	100.0	22.3	9.7
CHD	9.4	15.0	10.6	6.3
Other forms of atherosclerosis¶	5.3	11.5	4.7	3.7
High risk with AVD	12.7	22.1	14.0	8.5
High risk without AVD	15.2	77.9	8.3	1.1
≥2 CHD (10-years 10–20%) risk factors	16.4	0.0	24.9	14.5
MetS‖ (%)	50.2	73.5	100.0	0.0

AVD, atherosclerotic vascular disease; BMI, body mass index; CHD, coronary heart disease; DM, diabetes mellitus; FC, full cohort; MetS, metabolic syndrome; NCEP, National Cholesterol Education Program; TG, triglycerides.

*Completers population at 24 weeks, primary efficacy population at 64 weeks.

†Baseline values were similar for 64-week cohorts, n's are 578 for FC, 84 for DM, 235 for MetS/non-DM and 255 for non-DM/non-MetS subgroups; note that n's may vary in the treatment arms of the disease groups and full cohort as there were a few patients who did not qualify for the specified disease subgroup categories.

‡DM defined as baseline fasting glucose ≥126 mg/dl on more than two occasions, a diagnosis of diabetes or use of antidiabetic medications [37].

§Patients with CHD and CHD risk equivalents may be in more than one category of CHD.

¶Other forms of atherosclerosis are peripheral arterial disease, abdominal aortic aneurysm, symptomatic carotid artery disease, TIA, and stroke.

‖MetS defined as having three or more of the following: (i) waist circumference ≥102 cm (males) or ≥88 cm (females); (ii) TG ≥ 150 mg/dl; (iii) HDL-C < 40 mg/dl (males) or <50 mg/dl (females); (iv) blood pressure ≥130/85 mmHg or on antihypertensive medication; (v) fasting glucose ≥100 mg/dl or diabetic [1]. SI unit conversion factors: to convert fasting glucose to mmol/l, multiply by 0.0555; LDL-C to mmol/l, multiply by 0.0259; TG to mmol/l, multiply by 0.113.

(patients who had an adverse event related to a diagnosis of diabetes, initiated an antidiabetic medication during the study or had two consecutive fasting glucose measurements of ≥126 mg/dl).

Statistical Methods

Percent change from baseline in lipids, lipoprotein ratios and hsCRP were assessed in the completers population, which included all patients who received ≥24 weeks of active study therapy and who reached the maximum titrated dose of *N* (2 g) at 24 weeks [26], and in the primary efficacy population, which included all patients randomized to *E/S+N* or *E/S* who continued past 24 weeks into the full 64-week study and had baseline and ≥1 on-treatment measurements between 24 and 64 weeks [27]. Percent change from baseline and treatment group differences *E/S+N* vs. *E/S* and *E/S+N* vs. *N* were derived by an analysis of covariance (ANCOVA) model with terms for treatment; baseline LDL-C and TG levels; gender; DM, MetS/non-DM and non-DM/non-MetS subgroups; and treatment-by-subgroup interaction. For hsCRP, the same model was used except the dependent variable was the logarithm of the post-baseline-to-baseline value ratio. For TG, percent change values were transformed to ranks based on normal scores before analysis and between-treatment group differences were assessed by Hodges–Lehman location shift.

Safety was assessed by clinical and/or statistical review of all safety parameters in the primary safety population, which included those patients originally randomized to *E/S+N* or *E/S* who continued in the study during 64 weeks and received ≥1 dose of study medication [27]. For analysis of change from baseline in safety parameters, patients were also required to have baseline and ≥1 on-treatment measurements. Incidences of prespecified adverse experiences (AEs) were compared by Fisher's exact test for the full cohort. The 64-week safety analysis was cumulative and included 24-week and 24–64-week data for *E/S* and *E/S+N*. Safety was also assessed as above in those who received *N*, *E/S* and *E/S+N* during 24 weeks [26]. Change from baseline in fasting glucose was assessed in the modified intent-to-treat (mITT) population treated with *N*, *E/S* and *E/S+N* during the 24-week phase as described previously [26]; and in the primary safety population treated with *E/S* and *E/S+N* during 64 weeks by an ANCOVA model with terms for treatment; baseline fasting glucose; DM, MetS/non-DM and non-DM/non-MetS subgroups; and treatment-by-subgroup interaction [26,27].

Results

Of the 1220 patients randomized to treatment with *N*, *E/S* and *E/S+N* into the study [26], 765 patients completed 24 weeks with full treatment doses and were included in the 24-week subgroup analysis. Among these 765 patients, 14.8% (n = 113) had DM, 39.3% (n = 301) had MetS without DM, and 45.9% (n = 351) had neither DM nor MetS. Of the patients originally randomized to *E/S* and *E/S+N* who continued on these therapies after 24 weeks for an additional 40 weeks [27], 574 patients were included in the analysis at 64 weeks with overall prevalences of 14.6% (n = 84) for DM, 41.0% (n = 235) for MetS without DM, and 44.4% (n = 255) for neither disorder. The most frequent reasons for study discontinuations were clinical AEs related to *N*-associated flushing in the *N* and *E/S+N* groups during 24 and 64 weeks, as well as low LDL-C levels (<50 mg/dl) in the *E/S* and *E/S+N* groups during 64 weeks [26,27].

The DM, MetS/non-DM and non-DM/non-MetS subgroups differed at baseline in terms of demographics, glucose and lipoprotein levels, and cardiovascular risk. The percentage of black patients with DM was higher (11.5%) than those with MetS (4.0%) and non-DM/non-MetS (3.1%). DM patients had higher CHD risk compared with other patients, and higher fasting glucose levels (127.1 mg/dl) compared with MetS (101.8 mg/dl) and non-DM/non-MetS (93.7 mg/dl) patients. Mean body mass index (BMI) levels were higher in the DM (31.2 kg/m^2) and MetS (32.3 kg/m^2) patients, compared with those with neither disorder (27.7 kg/m^2). Greater proportions of DM (31.1%) and MetS (41.9%) patients had baseline TG levels >200–≤500 mg/dl than those with neither DM or MetS (16.2%), and conversely, higher number of patients with neither disorder (83.8%) had TG levels ≤200 mg/dl than DM (69.9%) and MetS (58.1%) patients.

Baseline values of efficacy parameters were generally comparable among the subgroups, with the exception of TG and hsCRP, where higher levels were observed for all treatments in DM and MetS patients compared with those with neither condition (Table 2). At both 24 and 64 weeks, mean baseline levels of LDL-C ranged from 152 to 158 mg/dl and total cholesterol (TC) from 239 to 246 mg/dl for the full cohort as well as for the subgroups.

Efficacy

The effect of combination *E/S+N* on efficacy variables across patient subgroups (DM, MetS/non-DM and non-DM/non-MetS) was generally consistent with the significantly greater improvements observed in the full study cohort compared with *N* and *E/S* during 24 and 64 weeks [26,27]. This consistency was supported by the lack of significant treatment-by-subgroup interactions observed for any efficacy parameter, and by overlapping 95% confidence intervals for treatment effects among subgroups (not shown). At 24 weeks, *E/S+N* was generally more effective in reducing LDL-C, TG, non-HDL-C and apoB (figures 1 and 2) as well as lipoprotein ratios LDL-C : HDL-C, TC : HDL-C, non-HDL-C : HDL-C, and apoB : apoAI (figure S1) than *N* or *E/S* alone in all subgroups. *E/S+N* was superior to *E/S* in increasing HDL-C and apoAI and comparable with *N* alone in all groups. The effect of *E/S+N* on LDL-C lowering was substantially greater than *N* in all subgroups, and greater than *E/S* in the MetS and non-DM/non-MetS subgroups, while similar to *E/S* in DM patients. Changes in TC were greater with *E/S+N* than *N* and comparable with those observed for *E/S* in all subgroups (data not shown). The triple combination reduced hsCRP levels more than *N* in all groups and comparably with *E/S* in MetS and non-DM/non-MetS patients at 24 weeks as observed in the full cohort, while *E/S* had a considerably more pronounced effect than *E/S+N* in DM patients.

Table 2. Baseline values for efficacy variables.

Efficacy measure, mean (mg/dl)	Full cohort			DM			MetS/non-DM			non-DM/non-MetS		
	N	*E/S*	*E/S+N*	*N*	*E/S*	*E/S+N*	*N*	*E/S*	*E/S+N*	*N*	*E/S*	*E/S+N*
24 weeks*	n = 166	n = 212†	n = 391†	n = 24	n = 31†	n = 58†	n = 56	n = 94†	n = 151†	n = 85	n = 86†	n = 180†
HDL-C	50.5	49.9	50.5	52.4	48.4	49.4	45.4	44.0	45.2	53.4	56.8	55.4
LDL-C	157.1	155.4	156.9	158.4	152.4	158.3	157.0	156.3	157.0	156.7	155.5	156.5
Triglycerides‡	148.0	158.0	159.0	159.0	171.0	160.0	188.5	197.5	192.0	121.0	119.5	126.0
Non-HDL-C	191.0	190.8	190.9	193.9	190.3	194.1	200.7	198.3	197.4	183.7	183.0	184.5
Total C	241.5	240.6	241.4	246.3	238.7	243.5	246.1	242.3	242.6	237.1	239.7	239.9
LDL-C : HDL-C	3.3	3.3	3.3	3.3	3.4	3.4	3.7	3.7	3.6	3.1	2.9	3.0
TC : HDL-C	5.1	5.1	5.0	5.0	5.3	5.2	5.7	5.7	5.6	4.6	4.4	4.5
Non-HDL-C: HDL-C	4.1	4.1	4.0	4.0	4.3	4.2	4.7	4.7	4.6	3.6	3.4	3.5
	n = 163	n = 205§	n = 383§	n = 23	n = 30§	n = 58§	n = 56	n = 91§	n = 146§	n = 83	n = 83§	n = 177§
ApoB	149.9	151.2	151.5	151.1	151.5	154.1	156.0	157.4	156.7	145.3	144.6	146.3
ApoAI	163.9	166.1	165.8	170.3	164.4	161.4	155.8	156.8	158.8	168.0	176.9	173.0
ApoB : apoAI	0.9	0.9	0.9	0.9	1.0	1.0	1.0	1.0	1.0	0.9	0.8	0.9
	n = 162	n = 207¶	n = 381¶	n = 22	n = 30¶	n = 57¶	n = 56	n = 90¶	n = 148¶	n = 83	n = 85¶	n = 174¶
hsCRP (mg/l)‖	2.0	2.1	2.3	2.5	2.7	2.2	3.1	2.7	3.1	1.5	1.5	1.9

apoB, apolipoprotein B; apoAI, apolipoprotein AI; DM, diabetes mellitus; *E/S*, ezetimibe/simvastatin; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; MetS, metabolic syndrome; *N*, niacin; TG, triglycerides.

*Baseline values were similar for *E/S* and *E/S+N* treatment groups assessed during 64 weeks.

†For HDL-C, LDL-C, TG, non-HDL-C, total C, LDL-C : HDL-C, TC : HDL-C, and non-HDL-C : HDL-C, n's were *E/S* (n = 207) and *E/S+N* (n = 369) in full cohort, *E/S* (n = 29) and *E/S+N* (n = 55) in DM subgroup, *E/S* (n = 93) and *E/S+N* (n = 141) in MS/non-DM subgroup, and *E/S* (n = 84) and *E/S+N* (n = 171) in non-DM/non-MetS subgroup at 64 weeks.

‡Median.

§For apoB, apoAI and apoB : apoAI, n's were *E/S* (n = 182) and *E/S+N* (n = 321) in full cohort, *E/S* (n = 24) and *E/S+N* (n = 49) in DM subgroup, *E/S* (n = 82) and *E/S+N* (n = 122) in MS/non-DM subgroup and *E/S* (n = 76) and *E/S+N* (n = 148) in non-DM/non-MetS subgroup at 64 weeks.

¶For hsCRP, n's were *E/S* (n = 187) and *E/S+N* (n = 324) in full cohort, *E/S* (n = 25) and *E/S+N* (n = 47) in DM subgroup, *E/S* (n = 84) and *E/S+N* (n = 123) in MS/non-DM subgroup and *E/S* (n = 77) and *E/S+N* (n = 152) in non-DM/non-MS subgroup at 64 weeks.

‖Geometric mean back-transformed from the log of the value; SI conversion factors: to convert cholesterol to mmol/l, multiply by 0.0259; TG to mmol/l, multiply by 0.0113; apo to g/l, multiply by 0.01; hsCRP to nmol/l, multiply by 9.524.

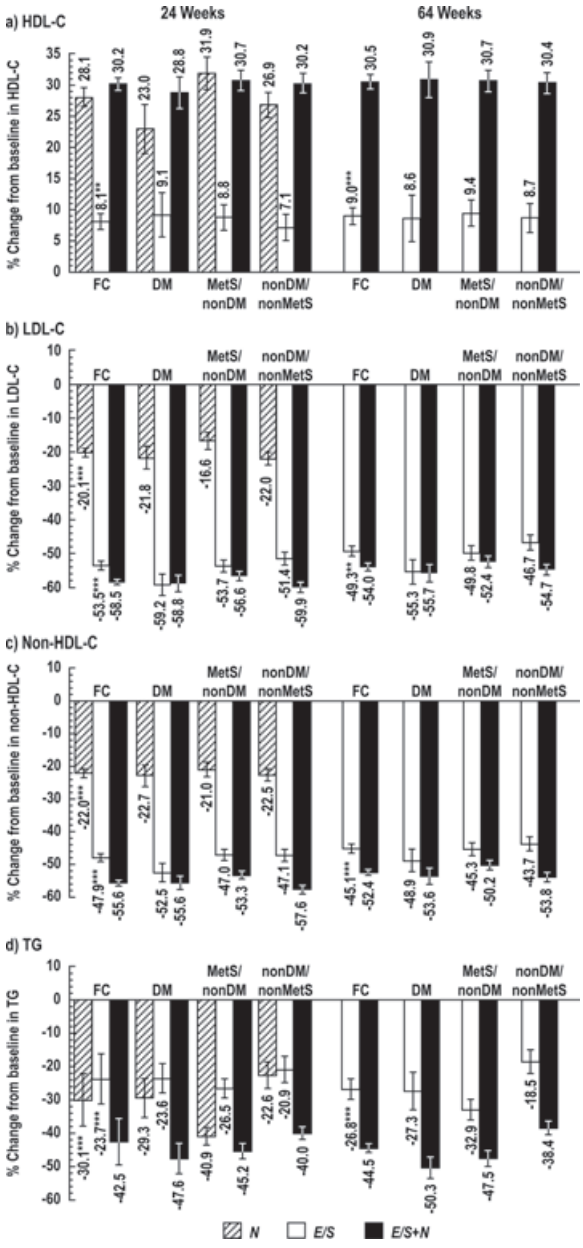

Figure 1. Percentage change from baseline at 24 and 64 weeks in (a) high-density lipoprotein cholesterol (HDL-C), (b) low-density lipoprotein cholesterol (LDL-C), (c) non-HDL-C and (d) triglycerides (TG). $^{**}p < 0.01$, $^{***}p < 0.001$ for *E/S+N* vs. *N* and *E/S* at 24 weeks and *E/S+N* vs. *E/S* at 64 weeks.

E/S+N therapy also improved HDL-C, TG, non-HDL-C, apoB and apoAI to a greater degree than did *E/S* at 64 weeks in all subgroups (figures 1 and 2). At 64 weeks, *E/S+N* was superior to *E/S* in reducing LDL-C levels in MetS/non-DM and non-DM/non-MetS patients, whereas patients with DM had similar LDL-C reduction with either treatment. Changes from baseline in TC were similar among all subgroups (data not shown). *E/S+N* reduced hsCRP levels comparably with *E/S* in MetS and DM patients, and more than *E/S* in those with neither disease. *E/S+N* also improved LDL-C : HDL-C, TC : HDL-C, non-HDL-C : HDL-C and apoB : apoAI ratios

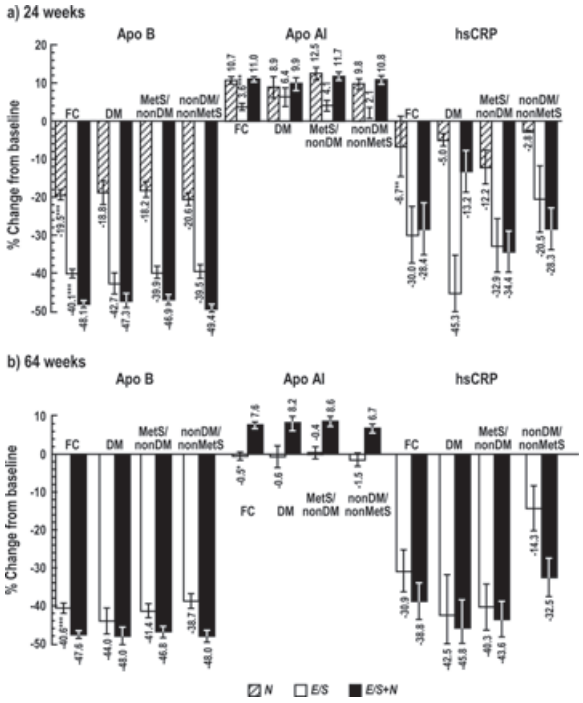

Figure 2. Percentage change from baseline in apolipoprotein B (apoB), apolipoprotein AI (apoAI) and high-sensitivity C-reactive protein (hsCRP) at (a) 24 and (b) 64 weeks. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$ for *E/S+N* vs. *N* and *E/S* at 24 weeks and *E/S+N* vs. *E/S* at 64 weeks.

more than *E/S* in the overall patient population and in each subgroup (figure S1).

Safety

Triple combination *E/S+N* therapy was generally well-tolerated by patients with DM and MetS, and it exhibited a safety profile consistent with that observed for each agent alone in the full study cohort. During 64 weeks, the incidence of clinical adverse events was generally similar for *E/S+N* and *E/S* in the MetS and non-DM/non-MetS subgroups, and was lower in the DM subgroup for *E/S* compared with *E/S+N* (Table 3). Drug-related clinical adverse events leading to discontinuation were higher for *E/S+N* compared with *E/S* treatment in all subgroups, due mainly to *N*-associated flushing (Table 3). Rates of prespecified liver, muscle and gallbladder-related adverse events were relatively low and comparable for both of these treatments in the MetS and non-DM/non-MetS groups, with none occurring in the DM group (Table 3). During 24 weeks, drug-related adverse events and discontinuations were higher for both *E/S+N* and *N* treatments in all subgroups, and attributed to *N*-associated flushing, similarly to the full cohort (Table S1A,B). Discontinuations due to flushing in the full cohort were significantly higher for *E/S+N* vs. *E/S* at 24 weeks (9.9 vs. 0.4%, $p < 0.001$) and comparable to *N* (12.1%). Similarly, the percentage of discontinuations due to flushing with *E/S+N* and *N* was comparable and higher than *E/S* in all subgroups. Muscle and liver adverse events were low and comparable to those

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Table 3. Safety endpoints and adverse events during 64 weeks.

	Full cohort		DM		MetS/non-DM		Non-DM/non-MetS	
	E/S	*E/S+N*	*E/S*	*E/S + N*	*E/S*	*E/S+N*	*E/S*	*E/S+N*
Clinical AEs (%)	n = 272	n = 670	n = 43	n = 101	n = 119	n = 239	n = 108	n = 326
≥1 Adverse event	76.5	82.4	65.1	83.2	79.8	80.3	76.9	83.7
Drug-related†	22.4	56.3	16.3	47.5	23.5	53.1	24.1	61.3
Serious	6.6	5.5	7.0	5.9	4.2	4.2	8.3	6.4
Serious drug-related†	0.4	0	0	0	0.8	0	0	0
Discontinuations	13.2	26.4	14.0	18.8	13.4	23.4	12.0	31.0
Drug-related†	7.0	20.3	7.0	14.9	6.7	15.9	7.4	25.2
Serious	2.9	1.9	4.7	2.0	2 (1.7)	1.7	2.8	2.1
Serious drug-related†	0	0	0	0	0	0	0	0
Deaths	0	0	0	0	0	0	0	0
Prespecified AEs, n (%)	n = 260	n = 605	n = 37	n = 93	n = 116	n = 219	n = 105	n = 291
ALT ≥3× ULN, consecutive	1 (0.4)	2 (0.3)	0	0	1 (0.9)	2 (0.9)	1 (1.0)	0
AST ≥3× ULN, consecutive	2 (0.8)	2 (0.3)	0	0	0	2 (0.9)	1 (1.0)	0
ALT and/or AST ≥3× ULN, consecutive	2 (0.8)	2 (0.3)	0	0	1 (0.9)	2 (0.9)	1 (1.0)	0
CK								
≥10×ULN	2 (0.8)	4 (0.7)	0	0	1 (0.9)	3 (1.4)	1 (1.0)	1 (0.3)
≥10×ULN with muscle symptoms	0	1 (0.2)‡	0	0	0	0	0	1 (0.3)
≥10×ULN with muscle symptoms considered to be drug-related†	0	0	0	0	0	0	0	0
	n = 272	n = 670	n = 43	n = 101	n = 119	n = 239	n = 108	n = 326
Discontinuation due to flushing	2 (0.7)	69 (10.3)*	0	7 (6.9)	1 (0.8)	21 (8.8)	1 (0.9)	40 (12.3)
Gallbladder-related	1 (0.4)	3 (0.4)	0	1 (1.0)	1 (0.8)	2 (0.8)	0	0
Cholecystectomy	1 (0.4)	1 (0.1)	0	1 (1.0)	1 (0.8)	0	0	0
	n = 229	n = 569						
New onset of diabetes¶	‖7 (3.1)	‖28 (4.9)	na	na	‖7 (5.9)	‖22 (9.2)	0	‖6 (1.8)
Initiated use of antidiabetic medications	3 (1.3)	5 (0.9)	na	na	3 (2.5)	4 (1.7)	0	1 (0.3)
Consecutive elevations fasting glucose ≥126 mg/dl	5 (2.2)	25 (4.4)	na	na	5 (4.2)	21 (8.8)	0	4 (1.2)
Diagnosis of type 2 DM	2 (0.9)	6 (1.1)	na	na	2 (1.7)	5 (2.1)	0	1 (0.3)
	n = 43	n = 101						
Worsening of diabetes#	6 (14.0)	15 (14.9)	6 (14.0)	15 (14.9)	na	na	na	na

AE, adverse experience; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatinine kinase; DM, diabetes mellitus; *E/S*, ezetimibe/simvastatin; MetS, metabolic syndrome; *N*, niacin; na, not applicable; ULN, upper limit of normal.

†Determined by the investigator to be possibly, probably or definitely drug related.

‡CK elevation in one patient accompanied by AE of myalgia considered non-drug related, patient recovered.

*$p < 0.001$ for the difference of *E/S+N* vs. *E/S*.

¶Patients who had an AE related to a diagnosis of diabetes, initiated an antidiabetic medication during the study or had two consecutive fasting glucose measurements that increased to ≥126 mg/dl.

‖Two of these patients on *E/S* and 25 on *E/S+N*, 5 on *E/S* and 21 on *E/S+N* in the MetS subgroup and 4 on *E/S+N* in the non-DM/non-MetS subgroup had been diagnosed with new onset of diabetes at 24 weeks [26].

#Clinical AE related to worsening of diabetes (based on MedDRA terms) or a required change in antidiabetic medication (uptitrated existing medication/changed to a new medication or added to existing regimen), 5 patients on *E/S* and 14 on *E/S+N* initiated use/change of antidiabetic medication.

SI unit conversion factors: to convert fasting glucose to mmol/l, multiply by 0.0555.

in the full cohort for all treatments in the MetS and non-DM/non-MetS subgroups, and none occurred in DM patients at 24 weeks.

Consistent with findings in the full study cohort, fasting glucose levels increased above baseline levels during the first 8–12 weeks, then gradually declined over time in all patient subgroups for *N*, *E/S* and *E/S+N* treatments (figure 3). Fasting glucose levels trended higher in both *N*-treatment groups and were highest in DM patients, reaching maximum increments of 24.9 mg/dl for *N* at 12 weeks, 21.2 mg/dl for *E/S+N* at 8 weeks, and 17.5 mg/dl for *E/S* at 4 weeks. By 24 weeks, peak levels of fasting glucose over baseline values had decreased to 12.3 mg/dl for *N*, 12.1 mg/dl for *E/S+N*, and 9.2 mg/dl for *E/S* in DM patients. Levels continued to decline and reached pretreatment levels for *E/S+N* and *E/S* by the end of the study at 64 weeks. This effect did not seem

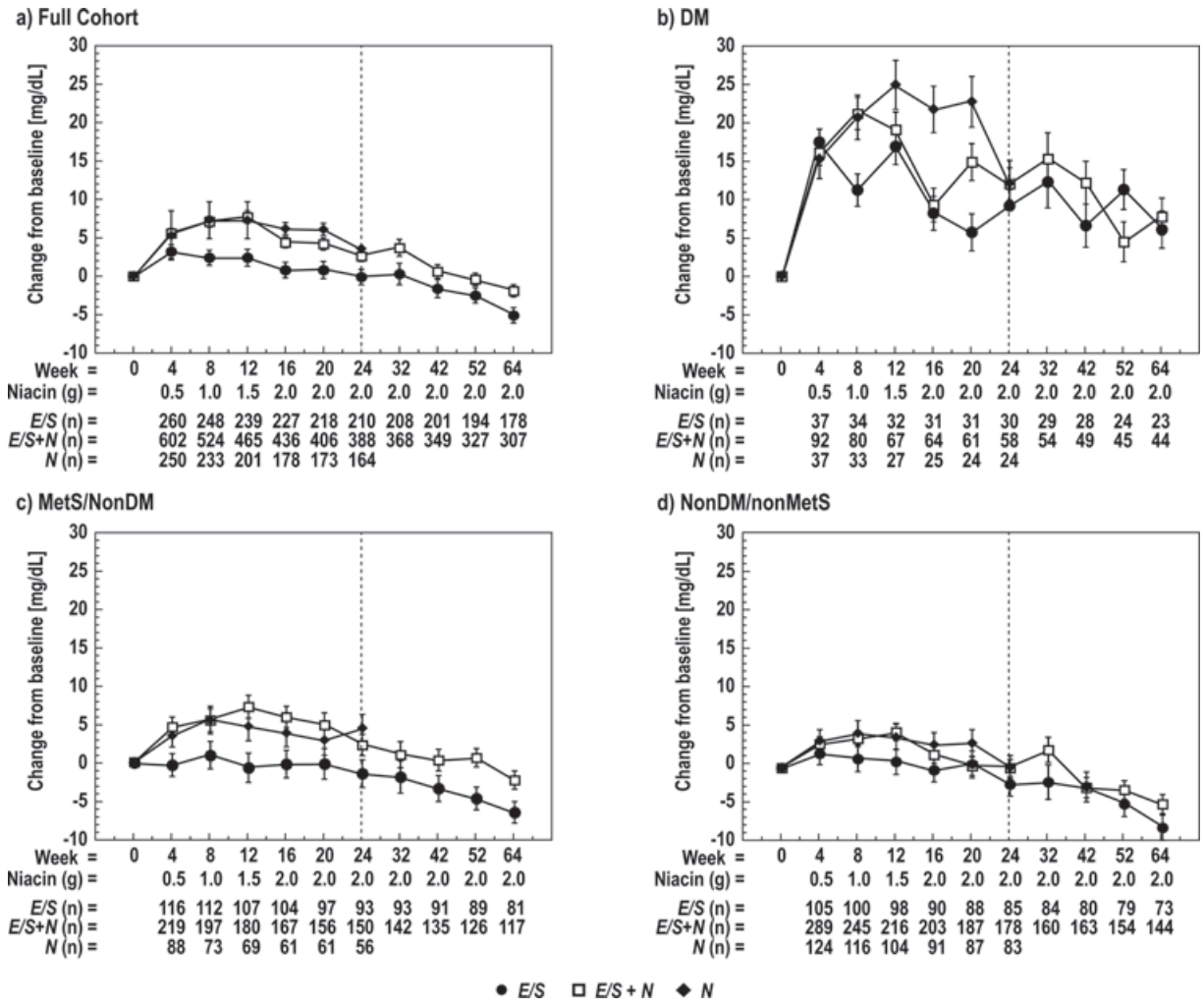

Figure 3. Time and dose effects on fasting glucose in (a) full cohort, (b) diabetes mellitus (DM), (c) metabolic syndrome (MetS) and (d) non-DM/non-MetS patients. Change from baseline in fasting glucose during 64 weeks in modified intent-to-treat population (24-week phase) and primary safety population (24–64 weeks).

to be related to broad increases in antidiabetic medication (Table 3) [28].

Onset of new DM, attributed mainly to two consecutive increases in fasting glucose levels ≥126 mg/dl, occurred more frequently with *E/S+N* than *E/S* treatment, predominantly in the first 6 months of *E/S+N* treatment and most often in patients with MetS [n = 7 (5.9%) for *E/S*, n = 22 (9.2%) for *E/S+N*] compared with those in the non-DM/non-MetS subgroup [0 for *E/S*, n = 6 (1.8%) for *E/S+N*] after 64 weeks of treatment (Table 3). Of these patients, 2 (1.7%) on *E/S* and 21 (8.8%) on *E/S+N* in the MetS/non-DM subgroup, and 4 (1.2%) on *E/S+N* in the non-DM/non-MetS subgroup had been diagnosed with new onset of diabetes at 24 weeks, accounting for most of the cases at 64 weeks (Tables 3 and S1B). The incidence of new-onset DM with *N* [n = 5 (5.1%)] alone at 24 weeks was similar to that of *E/S+N* in MetS/non-DM patients, with none reported in the non-DM/non-MetS subgroup. There were 6 (14.0%) patients in the *E/S* group and 15 (14.9%) in the *E/S+N* treatment group who had a worsening of diabetes at 64 weeks, as recognized by changes in antidiabetic medications.

Increases in uric acid levels at prespecified levels above baseline (>10 mg/dl for males, >9 mg/dl for females) occurred more often with *E/S+N* than *E/S* treatment in patients with DM (9.7 vs. 2.7%), MetS (11.0 vs. 3.4%) or neither DM or MetS (2.4% vs. none) (Table S2). AEs of gout were observed infrequently, with none occurring in DM patients, one on *E/S* (1.0%) and two on *E/S+N* (1.0%) in the MetS group, and two on *E/S* (2.3%) and one on *E/S+N* (0.4%) in the non-DM/non-MetS group. During the first 24 weeks, uric acid increases also occurred more often with both *N* treatments in all patients. No AEs of gout were reported in the first 24 weeks for any treatment.

Discussion

The efficacy and safety of *E/S+N* in patients with DM and MetS was similar to that observed in the overall study population of

hyperlipidaemic patients. Consistent with the complementary lipid-altering effects shown previously in the original full study cohort [26,27], treatment of DM and MetS patients with *E/S+N* substantially improved the overall lipid profile more than *N* and *E/S* after 24 weeks, and more than *E/S* after 64 weeks. The combination was generally well tolerated, aside from *N*-associated flushing in patients with DM and MetS, as in the full study cohort. As might be expected with *N*-based therapy, fasting glucose levels were higher with *N*-based treatments during the first 6 months of therapy, but declined to pretreatment levels by the end of the study. Onset of new DM occurred more often with *N* treatments than *E/S*, mainly in patients with MetS. However, "new DM" was often not sustained over 64 weeks as fasting glucose levels fell, and the rates estimated in this study were clearly augmented by frequent sampling during the peak of glucose levels between 4 and 20 weeks.

The efficacy of *E/S+N* aligns with previous reports showing that *N* and *E*/S therapies can improve the lipid abnormalities associated with dyslipidaemia in patients with DM and MetS. The magnitude of changes in LDL-C, other lipids, and hsCRP observed with *E/S+N* during 24 and 64 weeks in DM and MetS patients was substantially greater than those reported previously for *N* monotherapy and combination therapy in similar patients [14,15,29–32]. Increases in HDL-C levels were also larger than or comparable to those of *N* therapy in these studies. Improvements with *E/S+N* during 24 and 64 weeks were also more efficacious or similar to those reported previously for ezetimibe added to statin therapy and *E/S* combination therapy in populations of DM and MetS patients [20,21], as well as in subgroups of these patients in clinical trials [22–25]. Taken together, these results point to the enhanced benefits of triple combination therapy with *E/S+N* compared with the individual components for the treatment of hyperlipidaemia in patients with DM and MetS.

Although there were no significant treatment interactions by disease subgroup for any efficacy parameter, a few differential trends were noted. LDL-C lowering with *E/S+N* compared with *E/S* alone was consistently greater in MetS patients and those with neither DM nor MetS; however, in DM patients, LDL-C reductions were indistinguishable for *E/S+N* and *E/S* at both 24 and 64 weeks. While the reason for this observation is not known, a similar extent of LDL-C lowering and a slightly greater effect in DM compared with MetS patients have been observed in previous *E/S* (10/20 mg) studies [20–22]. The more pronounced *N*-induced lowering of TG levels observed in MetS patients compared with the full cohort is likely related to the higher baseline levels of TG in the MetS group and the effectiveness of *N* in reducing elevated TG levels [5,33]. Compared with the full cohort and other subgroups, hsCRP reductions were substantially smaller with *E/S+N* than *E/S* treatment in DM patients during 24 weeks, and increased considerably at 64 weeks. The low hsCRP reductions observed at 24 weeks with *E/S+N* in the DM subgroup may indicate a delayed anti-inflammatory response, as seen previously with *N* therapy in MetS and DM patients [15,34,35]. This effect has been attributed to a rebound increase in non-esterified free fatty acids observed several hours after *N* administration that coincides with glucose intolerance, and is consistent with the higher levels of fasting glucose observed during 24 weeks (particularly with *N*), which declined over time in the DM patients [34–36]. Notably, the hsCRP reductions observed at 64 weeks with *E/S* and *E/S+N* are much larger than those seen previously in short-term *E/S* clinical trials, including patients with DM or MetS [17–22,24]. The clinical relevance of changes in hsCRP levels during lipid-lowering therapy is not known. It should also be emphasized that although hsCRP levels are commonly elevated in patients with MetS and DM, as observed in this analysis, some studies have shown that hsCRP may be less predictive of cardiovascular disease risk in these patients compared with those without MetS [37–39].

The safety profile of combined *E/S+N* in DM and MetS patients was similar to that observed in the full study cohort and consistent with prior experience using these agents alone or in combination, including patients with DM and MetS [5,6,13–25,29–32]. Rates of serious AEs were infrequent and generally comparable for all treatments and disease groups. As expected for the 2-g maximum *N* dose, *N*-associated flushing was the main adverse event leading to study discontinuations and drug-related events, and these rates were generally comparable in all disease groups. The potential for hepatotoxicity and myopathy may increase with statin–niacin combination therapy [5,13]; however, there were no statistically significant differences found in muscle and liver AEs in any group and none were observed in DM patients.

In diabetic patients being considered for *N* treatment, the American Diabetes Association has recommended *N* doses of 750–2000 mg/day, although with glucose monitoring, due to concerns of increased blood glucose levels at high doses of *N* therapy [13,40]. Consistent with previous reports for *N* therapy, fasting glucose increased with *E/S+N* during the 16-week dose escalation to 2-g *N*, then declined to pretreatment levels by study end at 64 weeks in all patient groups, with little need for longer-term hypoglycaemic intervention [28]. Increases in fasting glucose levels were largest in DM patients and of similar degree to those observed in previous *N* studies in populations of DM patients [15,31] as well as in subgroups of DM patients in clinical trials [14,29,30].

Another concern with *N* use is a risk for the development of diabetes, particularly in patients with elevated glucose levels, such as those with metabolic syndrome [13]. In this study, new-onset DM occurred at a slightly higher though non-significant rate in the *N*-treatment groups during the first 6 months of therapy, and most often in MetS patients. The majority of these patients were classified as diabetic on the basis of persistently elevated fasting glucose (≥126 mg/dl) and relatively few initiated use of antidiabetic medications. These findings are similar to the low rates of new-onset DM observed previously in patients who were not diabetic at baseline, and who received either *N* monotherapy or combination *N* therapy [14,29,41]. Increased incidence of DM has also been observed with statin therapy [42–46]. In the recent *J*ustification for the *U*se of Statins in *P*rimary Prevention: an *I*ntervention *T*rial *E*valuating

*R*osuvastatin (JUPITER) trial, a significant increase in the incidence of DM was observed with rosuvastatin (20 mg) compared with placebo (3.0 vs. 2.3%, p = 0.01) [46]. A large meta-analysis of 13 statin trials in non-diabetic patients indicated that statin therapy increased the risk of DM development by 9%, although rates varied among trials [47]. While a similarly large database of *N* trials is not available, it is anticipated that additional data regarding the overall effect of *N* on new-onset DM will be provided by ongoing, long-term, clinical studies [48,49].

Elevated uric acid levels are known to occur with *N* therapy [6,7,14,41]. In this study, uric acid levels increased with both *N* therapies in DM and MetS patients compared with *E/S*, but the incidence of gout was very low and not different among treatment groups. *N* should be used with caution in patients predisposed to gout [6] and those with glucose intolerance [14].

In conclusion, the results of this analysis indicate that *N* in combination with *E/S* provides a generally well-tolerated and broad, lipid-altering option for the treatment of hyperlipidaemia in patients with DM and MetS, although glucose monitoring will be required. The glucose changes that diminished over time in these patients, as well as the rates of new-onset DM, liver and muscle AEs, and discontinuations due to flushing are generally consistent with observations in the overall study cohort and prior clinical experience with *E/S* or *N*. It should be noted, however, that these results are limited by the size of the patient subgroups in this analysis and the relatively small number of events that occurred within these groups. Nonetheless, these results concur with previous studies that have shown the long-term benefits of *N* therapy with minimal effects on glucose regulation and safety profiles that were no different than those observed in patients without DM and MetS [14,15,29–32]. Whether this combination of LDL-lowering and HDL-C-raising effects will translate to clinical benefit in dyslipidaemic patients awaits results of clinical outcome trials [48,49]. In this regard, it is worth mentioning that aggressive LDL-C lowering with statin monotherapy and *E*+ statin treatment, combined with intensive blood pressure control, was associated with regression of carotid intima-media thickness in American Indian diabetic patients compared with standard therapies [50,51].

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Conflict of Interest

Dr. Fazio serves as an advisory board member for Merck. Dr. Guyton has received educational and research grants from Merck, Abbott, Genzyme, Amarin Pharma and GlaxoSmithKline, and consulting fees/honoraria from Abbott Laboratories and Merck, and has served as a consultant/advisory board member for Acura/King Pharma. He also holds an equity interest in Eli Lilly & Co and has received CME grant support from Sanofi-Aventis. Drs. Shah, Tershakovec, Tomassini and Mr. Lin are employees of Merck and own stock/stock options.

Drs. Fazio, Guyton, Tershakovec and Tomassini contributed to the conception/design, analysis of data and writing of the manuscript. Dr. Shah and Mr. Lin contributed to the conception/design, data collection, analysis of data and writing of the manuscript. All authors had access to the data and provided final review of the manuscript.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Percentage change from baseline at 24 and 64 weeks in lipid ratios. ***p < 0.001 for *E/S*+*N* vs. *N* and *E/S* at 24 weeks and *E/S* + *N* vs. *E/S* at 64 weeks.

Table S1. Safety endpoints at 24 weeks.

Table S2. Uric acid elevations and gout adverse experiences (AEs) at 24 and 64 weeks.

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References

1. Grundy SM, Cleeman JI, Daniels SR et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute scientific statement. Circulation 2005; **112**: 2735–2752.
2. Smith SC Jr, Allen J, Blair SN et al. AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update: endorsed by the National Heart, Lung, and Blood Institute. Circulation 2006; **113**: 2363–2372.
3. Grundy SM, Cleeman JI, Merz CN et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. Circulation 2004; **110**: 227–239.
4. Brunzell JD, Davidson M, Furberg CD et al. Lipoprotein management in patients with cardiometabolic risk: consensus statement from the American Diabetes Association and the American College of Cardiology Foundation. Diabetes Care 2008; **31**: 811–822.
5. Guyton JR. Niacin in cardiovascular prevention: mechanisms, efficacy, and safety. Curr Opin Lipidol 2007; **18**: 415–420.
6. Niaspan [product insert] 2007. Abbott Laboratories, North Chicago, IL.
7. Brown BG, Zhao XQ, Chait A et al. Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease. N Engl J Med 2001; **345**: 1583–1592.
8. Brown G, Albers JJ, Fisher LD et al. Regression of coronary artery disease as a result of intensive lipid-lowering therapy in men with high levels of apolipoprotein B. N Engl J Med 1990; **323**: 1289–1298.
9. Kane JP, Malloy MJ, Ports TA, Phillips NR, Diehl JC, Havel RJ. Regression of coronary atherosclerosis during treatment of familial hypercholesterolemia with combined drug regimens. JAMA 1990; **264**: 3007–3012.
10. Carlson LA, Rosenhamer G. Reduction of mortality in the Stockholm Ischemic Heart-Disease Secondary Prevention Study by combined treatment with clofibrate and nicotinic acid. Acta Med Scand 1988; **223**: 405–418.

11. Whitney EJ, Krasuski RA, Personius BE et al. A randomized trial of a strategy for increasing high-density lipoprotein cholesterol levels: effects on progression of coronary heart disease and clinical events. Ann Intern Med 2005; **142**: 95–104.
12. Coronary Drug Project Research Group. Clofibrate and niacin in coronary heart disease. JAMA 1975; **231**: 360–381.
13. Guyton JR, Bays HE. Safety considerations with niacin therapy. Am J Cardiol 2007; **99**: 22C–31C.
14. Elam MB, Hunninghake DB, Davis KB et al. Effect of niacin on lipid and lipoprotein levels and glycemic control in patients with diabetes and peripheral arterial disease: the ADMIT study: a randomized trial. JAMA 2000; **284**: 1263–1270.
15. Grundy SM, Vega GL, McGovern ME et al. Efficacy, safety, and tolerability of once-daily niacin for the treatment of dyslipidemia associated with type 2 diabetes: results of the assessment of diabetes control and evaluation of the efficacy of niaspan trial. Arch Intern Med 2002; **162**: 1568–1576.
16. Vytorin [product insert] 2008. Merck/Schering-Plough Pharmaceuticals, North Wales, PA.
17. Bays HE, Ose L, Fraser N et al. A multicenter, randomized, double-blind, placebo-controlled, factorial design study to evaluate the lipid-altering efficacy and safety profile of the ezetimibe/simvastatin tablet compared with ezetimibe and simvastatin monotherapy in patients with primary hypercholesterolemia. Clin Ther 2004; **26**: 1758–1773.
18. Ballantyne CM, Abate N, Yuan Z, King TR, Palmisano J. Dose-comparison study of the combination of ezetimibe and simvastatin (Vytorin) versus atorvastatin in patients with hypercholesterolemia: the Vytorin Versus Atorvastatin (VYVA) study. Am Heart J 2005; **149**: 464–473.
19. Catapano AL, Davidson MH, Ballantyne CM et al. Lipid-altering efficacy of the ezetimibe/simvastatin single tablet versus rosuvastatin in hypercholesterolemic patients. Curr Med Res Opin 2006; **22**: 2041–2053.
20. Robinson JG, Ballantyne CM, Grundy SM et al. Lipid-altering efficacy and safety of ezetimibe/simvastatin versus atorvastatin in patients with hypercholesterolemia and the metabolic syndrome (from the VYMET study). Am J Cardiol 2009; **103**: 1694–1702.
21. Goldberg RB, Guyton JR, Mazzone T et al. Ezetimibe/simvastatin vs atorvastatin in patients with type 2 diabetes mellitus and hypercholesterolemia: the VYTAL study. Mayo Clin Proc 2006; **81**: 1579–1588.
22. Abate N, Catapano AL, Ballantyne CM et al. Effect of ezetimibe/simvastatin versus atorvastatin or rosuvastatin on modifying lipid profiles in patients with diabetes, metabolic syndrome, or neither: results of two subgroup analyses. J Clin Lipidol 2008; **2**: 91–105.
23. Denke M, Pearson T, McBride P, Gazzara RA, Brady WE, Tershakovec AM. Ezetimibe added to ongoing statin therapy improves LDL-C goal attainment and lipid profile in patients with diabetes or metabolic syndrome. Diab Vasc Dis Res 2006; **3**: 93–102.
24. Feldman T, Ose L, Shah A et al. Efficacy and safety of ezetimibe/simvastatin versus simvastatin monotherapy in hypercholesterolemic patients with metabolic syndrome. Metab Syndr Relat Disord 2007; **5**: 13–21.
25. Simons L, Tonkon M, Masana L et al. Effects of ezetimibe added to ongoing statin therapy on the lipid profile of hypercholesterolemic patients with diabetes mellitus or metabolic syndrome. Curr Med Res Opin 2004; **20**: 1437–1445.
26. Guyton JR, Brown BG, Fazio S, Polis A, Tomassini JE, Tershakovec AM. Lipid-altering efficacy and safety of ezetimibe/simvastatin coadministered with extended-release niacin in patients with type IIa or type IIb hyperlipidemia. J Am Coll Cardiol 2008; **51**: 1564–1567.
27. Fazio S, Guyton JR, Polis AB, Adewale AJ, Tomassini JE, Tershakovec AM. Long-term safety and efficacy of triple combination ezetimibe/simvastatin + extended release niacin in hyperlipidemia patients. Am J Cardiol 2009; **105**: 487–494
28. Guyton JR, Fazio S, Adewale AJ et al. New onset diabetes mellitus among patients with type IIa/IIb hyperlipidemia (HL) taking ezetimibe/simvastatin (E/S) +/- niacin (N) in a randomized trial (Abstract). Diabetes 2009; **58**(Suppl. 1): A191.
29. Canner PL, Furberg CD, McGovern ME. Benefits of niacin in patients with versus without the metabolic syndrome and healed myocardial infarction (from the Coronary Drug Project). Am J Cardiol 2006; **97**: 477–479.
30. Canner PL, Furberg CD, Terrin ML, McGovern ME. Benefits of niacin by glycemic status in patients with healed myocardial infarction (from the Coronary Drug Project). Am J Cardiol 2005; **95**: 254–257.
31. Gardner SF, Marx MA, White LM, Granberry MC, Skelton DR, Fonseca VA. Combination of low-dose niacin and pravastatin improves the lipid profile in diabetic patients without compromising glycemic control. Ann Pharmacother J 1997; **31**: 677–682.
32. McGovern ME. Use of nicotinic acid in patients with elevated fasting glucose, diabetes, or metabolic syndrome. Br J Diabetes Vasc Dis 2004; **4**: 78–85.
33. Knopp RH. Clinical profiles of plain versus sustained-release niacin (Niaspan) and the physiologic rationale for nighttime dosing. Am J Cardiol 1998; **82**: 24U–28U.
34. Thoenes M, Oguchi A, Nagamia S et al. The effects of extended-release niacin on carotid intimal media thickness, endothelial function and inflammatory markers in patients with the metabolic syndrome. Int J Clin Pract 2007; **61**: 1942–1948.
35. Westphal S, Borucki K, Taneva E, Makarova R, Luley C. Extended-release niacin raises adiponectin and leptin. Atherosclerosis 2007; **193**: 361–365.
36. Vega GL, Cater NB, Meguro S, Grundy SM. Influence of extended-release nicotinic acid on nonesterified fatty acid flux in the metabolic syndrome with atherogenic dyslipidemia. Am J Cardiol 2005; **95**: 1309–1313.
37. Pischon T, Hu FB, Rexrode KM, Girman CJ, Manson JE, Rimm EB. Inflammation, the metabolic syndrome, and risk of coronary heart disease in women and men. Atherosclerosis 2008; **197**: 392–399.
38. Sattar N, Gaw A, Scherbakova O et al. Metabolic syndrome with and without C-reactive protein as a predictor of coronary heart disease and diabetes in the West of Scotland Coronary Prevention Study. Circulation 2003; **108**: 414–419.
39. Rutter MK, Meigs JB, Sullivan LM, D'Agostino RB, Wilson PWF. C-reactive protein, the metabolic syndrome, and prediction of cardiovascular events in the Framingham Offspring Study. Circulation 2004; **110**: 380–385.
40. Anon. Standards of medical care in diabetes—2009. Diabetes Care 2009; **32**: S13–S61.
41. Zhao XQ, Morse JS, Dowdy AA et al. Safety and tolerability of simvastatin plus niacin in patients with coronary artery disease and low high-density lipoprotein cholesterol (the HDL Atherosclerosis Treatment Study). Am J Cardiol 2004; **93**: 307–312.
42. Collins R, Armitage J, Parish S, Sleight P, Peto R. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. Lancet 2003; **361**: 2005–2016.
43. Sever PS, Dahlof B, Poulter NR et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. Lancet 2003; **361**: 1149–1158.
44. Freeman DJ, Norrie J, Sattar N et al. Pravastatin and the development of diabetes mellitus—evidence for a protective treatment effect in the West of Scotland Coronary Prevention Study. Circulation 2001; **103**: 357–362.
45. Keech A, Colquhoun D, Best J et al. Secondary prevention of cardiovascular events with long-term pravastatin in patients with diabetes or impaired fasting glucose—results from the LIPID trial. Diabetes Care 2003; **26**: 2713–2721.

46. Ridker PM, Danielson E, Fonseca FAH et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. New Eng J Med 2008; **359**: 2195–2207.

47. Sattar N, Preiss D, Murray HM et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. Lancet 2010; **375**: 735–742.

48. University of Oxford. 2007. Treatment of HDL to reduce the incidence of vascular events HPS2-THRIVE. Available from URL: http://www.clinicaltrials.gov/ct2/show/NCT00461630. Accessed 21 August 2009.

49. National Heart Lung, and Blood Institute (NHLBI). 2005. AIM HIGH: niacin plus statin to prevent vascular events. Available from URL: http://www.clinicaltrials.gov/ct2/show/NCT00120289. Accessed 12 August 2009.

50. Fleg JL, Mete M, Howard BV et al. Effect of statins alone versus statins plus ezetimibe on carotid atherosclerosis in type 2 diabetes. J Am Coll Cardiol 2008; **52**: 2198–2205.

51. Howard BV, Roman MJ, Devereux RB et al. Effect of lower targets for blood pressure and LDL cholesterol on atherosclerosis in diabetes—the SANDS randomized trial. JAMA 2008; **299**: 1678–1689.