

Rosuvastatin Alone or With Extended-Release Niacin: A New Therapeutic Option for Patients With Combined Hyperlipidemia

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Combination therapy with a statin and niacin may provide optimal therapy for patients with combined hyperlipidemia and low levels of high-density lipoprotein (HDL) cholesterol. The authors assessed the efficacy and safety of rosuvastatin monotherapy, extended-release (ER) niacin monotherapy, or rosuvastatin and ER niacin combined therapy in patients with atherogenic dyslipidemia. In a 24-week, open-label, multicenter trial, men and women aged 18 years with fasting levels of total cholesterol 200 mg/dL, HDL cholesterol 45 mg/dL, triglycerides 200-800 mg/dL, and apolipoprotein B 110 mg/dL were randomly assigned to one of four treatment groups: rosuvastatin 10-40 mg, ER niacin 0.5-2 g, rosuvastatin 40 mg plus ER niacin 0.5-1 g, or rosuvastatin 10 mg plus ER niacin 0.5-2 g. Daily doses of rosuvastatin 40 mg monotherapy reduced low-density lipoprotein (LDL) cholesterol and non-HDL cholesterol levels significantly more than did either ER niacin 2 g monotherapy or rosuvastatin 10 mg combined with ER niacin 2 g. Addition of ER niacin 1 g to rosuvastatin 40 mg did not further reduce total or non-HDL cholesterol. Triglyceride reductions were similar among the four treatment groups. ER niacin mono- and combined therapy produced significantly greater rises in HDL cholesterol and apolipoprotein A-1 than did rosuvastatin monotherapy. Rosuvastatin monotherapy was better tolerated than ER niacin taken either alone or with rosuvastatin. In this study, rosuvastatin very effectively improved the three major lipoprotein-lipid abnormalities of combined hyperlipidemia.

In well controlled clinical trials, a new generation statin, rosuvastatin (Crestor; AstraZeneca, Wilmington, DE), has produced striking dose-dependent reductions in plasma levels of the most atherogenic lipoprotein particles, particularly low-density lipoproteins (LDLs).^[1-3] Results of these and other trials have shown that rosuvastatin can significantly reduce levels of triglycerides, total cholesterol, and apolipoprotein B, and increase levels of high-density lipoprotein (HDL) cholesterol and its major carrier protein, apolipoprotein A-1, to a greater degree than have earlier statins.^[2-5]

Nicotinic acid (niacin), the most effective medication for increasing HDL cholesterol, has broadly improved all the major elements of the lipid profile, and has been shown to reduce occurrence of atherosclerotic complications and all-cause mortality in multiple clinical trials.^[6-12] Extended-release (ER) niacin also has produced beneficial effects on plasma lipid levels in a safe, effective, long-term fashion.^[9-11] Niacin preparations have also improved lipoprotein subclass distribution, decreasing the more atherogenic, small, dense LDL particles and enhancing the cardioprotective, large HDL particles.^[10,13]

Studies with earlier statins have demonstrated that statin-niacin combinations produced improvements in multiple lipid parameters^[14,15] to a significantly greater degree than statins alone.^[16-19] With the growing recognition and likely increased prevalence of atherogenic dyslipidemia, the lipid pattern commonly associated with metabolic syndrome, physicians must broaden their approach to modification of plasma lipids beyond just lowering LDL cholesterol. Adult Treatment Panel (ATP) III guidelines^[20] now include non-HDL cholesterol (total cholesterol minus HDL cholesterol) as a secondary therapeutic target, with goal levels of 30 mg/dL above those for LDL cholesterol. Because combination therapies generally improve lipoprotein regulation, we performed a randomized, controlled clinical trial to assess and compare the efficacy and safety of rosuvastatin, ER niacin (Niaspan; KOS Pharmaceuticals, Miami, FL), and two different dosage combinations in patients with combined hyperlipidemia and low HDL cholesterol levels.

This 24-week, randomized, open-label trial (Trial Number: 4522IL/0029) was conducted at 39 participating centers in the United States.^[21] Eligible patients were randomized at a 2:3:3:3 ratio to rosuvastatin alone, ER niacin alone, or one of two dosage combinations, beginning with nightly doses of 10 mg rosuvastatin and 0.5 g ER niacin.

Patients were randomized using an 18-week drug escalation period, followed by a 6-week period of maintenance dosing, respectively, to one of four treatment plans: rosuvastatin 40 mg nightly about 3 hours after dinner; ER niacin 2 g taken with water at bedtime after a low-fat snack; rosuvastatin 40 mg and ER niacin 1 g taken in like fashion; and rosuvastatin 10 mg and ER niacin 2 g nightly. Dosage escalation proceeded to these levels in patients whose LDL cholesterol levels remained 50 mg/dL.

Men or women aged 18 years with combined dyslipidemia were enrolled for a 6-week lead-in period during which they were instructed to discontinue all lipid-modifying medications, dietary supplements, and food additives, and to adhere to the American Heart Association Step I diet (). Entry criteria included dietary adherence and fasting levels of total cholesterol 200 mg/dL,

triglycerides 200 mg/dL and 800 mg/dL, apolipoprotein B 110 mg/dL, and HDL cholesterol <45 mg/dL. Patients with active arterial disease within the prior 3 months, with major organ dysfunction, or taking other medications that posed potential study concerns were excluded. Other demographic characteristics of the subjects are shown in .

Table I. Demographic Characteristics of Randomized Patients

Medscape®		www.medscape.com			
CHARACTERISTIC	ROSUVASTATIN 40 MG (N=46)	ER NIACIN 2 G (N=72)	ROSUVASTATIN 40 MG + ER NIACIN 1 G (N=72)	ROSUVASTATIN 10 MG + ER NIACIN 2 G (N=80)	
Age (yr) (mean ± SD)	58.6±10.6	55.5±9.8	55.8±10.5	54.2±11.8	
Men (n [%])	32 (70)	52 (72)	55 (76)	55 (69)	
White (n [%])	42 (91)	71 (99)	69 (96)	77 (96)	
Body mass index (mean ± SD)	30.2±4.4	29.8±4.4	31.4±5.2	30.2±4.8	
Diabetes mellitus (n [%])	8 (17)	9 (13)	9 (13)	14 (18)	
ER=extended-release. Reproduced with permission from Excerpta Medica, Inc. from <i>Am J Cardiol.</i> 2003;91:1304–1310. ²¹					
Source: Prev Cardiol © 2004 Le Jacq Communications, Inc.					

Table I. Demographic Characteristics of Randomized Patients

Medscape®		www.medscape.com			
CHARACTERISTIC	ROSUVASTATIN 40 MG (N=46)	ER NIACIN 2 G (N=72)	ROSUVASTATIN 40 MG + ER NIACIN 1 G (N=72)	ROSUVASTATIN 10 MG + ER NIACIN 2 G (N=80)	
Age (yr) (mean ± SD)	58.6±10.6	55.5±9.8	55.8±10.5	54.2±11.8	
Men (n [%])	32 (70)	52 (72)	55 (76)	55 (69)	
White (n [%])	42 (91)	71 (99)	69 (96)	77 (96)	
Body mass index (mean ± SD)	30.2±4.4	29.8±4.4	31.4±5.2	30.2±4.8	
Diabetes mellitus (n [%])	8 (17)	9 (13)	9 (13)	14 (18)	
ER=extended-release. Reproduced with permission from Excerpta Medica, Inc. from <i>Am J Cardiol.</i> 2003;91:1304–1310. ²¹					
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The primary efficacy end point was the percent change in fasting plasma LDL cholesterol levels at 24 weeks. Secondary end points included 24-week percent changes in fasting plasma levels of total cholesterol, non-HDL cholesterol, triglycerides, very-low-density lipoprotein (VLDL) cholesterol, apolipoprotein B, HDL cholesterol, apolipoprotein A-1, and lipoprotein(a) (Lp[a]).

Blood samples were obtained after a 12-hour fast, and all laboratory analyses were carried out at a certified central laboratory with appropriate Centers for Disease Control-National Heart, Lung, and Blood Institute standardization and utilizing methods as described.^[21] Safety was assessed by evaluation of reported adverse events, clinical laboratory values, and clinical and electrocardiographic results.

For all end points, percent changes from baseline were determined by analysis of variance at Week 24, performed and compared separately between the rosuvastatin monotherapy group and each remaining treatment group.^[21]

The per-protocol population comprised all patients who adhered to the medication schedule, and to dietary and other protocol requirements. The safety population included all patients who received 1 dose of trial medication.^[21]

The treatment groups were well matched demographically (). A total of 270 patients (of 774 recruited) were randomized as follows: rosuvastatin monotherapy (n=46), ER niacin monotherapy (n=72), rosuvastatin 40 mg/ER niacin 1 g (n=72), and rosuvastatin 10 mg/ER niacin 2 g (n=80) ().

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CHARACTERISTIC	ROSUVASTATIN 40 MG (N=46)	ER NIACIN 2 G (N=72)	ROSUVASTATIN 40 MG + ER NIACIN 1 G (N=72)	ROSUVASTATIN 10 MG + ER NIACIN 2 G (N=80)	
Age (yr) (mean ± SD)	58.6±10.6	55.5±9.8	55.8±10.5	54.2±11.8	
Men (n [%])	32 (70)	52 (72)	55 (76)	55 (69)	
White (n [%])	42 (91)	71 (99)	69 (96)	77 (96)	
Body mass index (mean ± SD)	30.2±4.4	29.8±4.4	31.4±5.2	30.2±4.8	
Diabetes mellitus (n [%])	8 (17)	9 (13)	9 (13)	14 (18)	

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Table II. Percent Change in Lipid Measures From Baseline at 24 Weeks (Intention-to-Treat Population)*

LIPID MEASURE	ROSUVASTATIN 40 MG	ER NIACIN 2 G	ROSUVASTATIN 40 MG + ER NIACIN 1 G	ROSUVASTATIN 10 MG + ER NIACIN 2 G
LDL cholesterol				
n	46	70	71	78
Baseline (mg/dL) (mean ± SD)	146±56	145±47	145±41	145±37
LSM change (% ± SE)	-48±4	-0.1±3**	-42±3	-36±3†
Non-HDL cholesterol				
n	46	70	71	78
Baseline (mg/dL) (mean ± SD)	227±53	222±50	225±47	225±45
LSM change (% ± SE)	-49±3	-11±2**	-47±2	-38±2†
Total cholesterol				
n	46	70	71	78
Baseline (mg/dL) (mean ± SD)	262±55	257±51	262±48	263±44
LSM change (% ± SE)	-41±2	-7±2**	-38±2	-29±2**
Triglycerides				
n	46	70	71	78
Baseline (mg/dL) (mean ± SD)	383±119	364±121	370±133	380±122
Baseline (mg/dL) (median)	365	343	330	341
LSM change (% ± SE)	-33±5	-21±4	-39±4	-34±4
Median change (%)	-42	-26	-46	-41
VLDL cholesterol				
n	44	68	64	73
Baseline (mg/dL) (mean ± SD)	89±33	80±37	81±35	83±41
LSM change (% ± SE)	-51±6	-22±5**	-47±5	-38±5
Apolipoprotein B				
n	46	69	71	78
Baseline (mg/dL) (mean ± SD)	173±40	171±36	168±30	169±35
LSM change (% ± SE)	-42±3	-9±2**	-42±2	-34±2††
HDL cholesterol				
n	46	70	71	78
Baseline (mg/dL) (mean ± SD)	35±5	36±6	37±5	37±6
LSM change (% ± SE)	11±3	12±2	17±2	24±2**
Apolipoprotein A-I				
n	46	69	71	78
Baseline (mg/dL) (mean ± SD)	130±19	129±20	133±19	133±21
LSM change (% ± SE)	5±2	7±2	6±2	11±2††
Lipoprotein(a)				
n	45	68	69	75
Baseline (mg/dL) (mean ± SD)	23±21	25±23	25±28	30±27
Baseline (mg/dL) (median)	14	15	11	22
LSM change (% ± SE)	7±6	-20±5**	-18±5†	-20±5**
Median change (%)	6	-23	-13	-22

LDL=low-density lipoprotein; LSM=least-squares mean; HDL=high-density lipoprotein; VLDL=very-low-density lipoprotein; †baseline levels are reported as mean values for all measures, except for triglycerides and lipoprotein(a), for which both mean and median baseline values are reported, change values correspond to the LSM (or median) percentage change from baseline at Week 24, and analysis of variance was conducted on Week 24 data using the last observation carried forward from the intention-to-treat population; ** $p<0.001$; † $p<0.01$; †† $p<0.017$ (all treatment comparisons vs. rosuvastatin 40 mg)

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After exclusions, the per-protocol population consisted of 31, 21, 35, and 36 patients in the rosuvastatin, ER niacin, rosuvastatin 40 mg/ER niacin 1 g, and rosuvastatin 10 mg/ER niacin 2 g groups, respectively.^[21] Noncompliance with trial medication was the most common reason for exclusion of patient data from analysis.

A total of 54 patients withdrew from randomized treatment: three (8%) in the rosuvastatin monotherapy group, 19 (43%) in the ER niacin monotherapy group, 12 (32%) in the rosuvastatin 40 mg plus ER niacin 1 g group, and 20 (36%) in the rosuvastatin 10 mg plus ER niacin 2 g group. The occurrence of adverse events and withdrawal of informed consent accounted for most patient withdrawals.

As shown in , rosuvastatin 40 mg monotherapy produced the greatest decrease in LDL cholesterol (-48% at 24 weeks); ER niacin 1 g, when added to this regimen, did not further the reduction (-42%). ER niacin 2 g alone had no detectable effect on LDL cholesterol level (-0.1%; $p < 0.001$ between monotherapy groups). Rosuvastatin 10 mg combined with ER niacin 2 g reduced LDL cholesterol levels to a significantly lesser degree than did rosuvastatin 40 mg monotherapy (-36% vs. -48%; $p = 0.007$). Thus ER niacin did not augment the LDL cholesterol-lowering effect of rosuvastatin.

Table II. Percent Change in Lipid Measures From Baseline at 24 Weeks (Intention-to-Treat Population)*

LIPID MEASURE	ROSUVASTATIN 40 MG	ER NIACIN 2 G	ROSUVASTATIN 40 MG + ER NIACIN 1 G	ROSUVASTATIN 10 MG + ER NIACIN 2 G
LDL cholesterol				
n	46	70	71	78
Baseline (mg/dL) (mean ± SD)	146±56	145±47	145±41	145±37
LSM change (% ± SE)	-48±4	-0.1±3**	-42±3	-36±3†
Non-HDL cholesterol				
n	46	70	71	78
Baseline (mg/dL) (mean ± SD)	227±53	222±50	225±47	225±45
LSM change (% ± SE)	-49±3	-11±2**	-47±2	-38±2†
Total cholesterol				
n	46	70	71	78
Baseline (mg/dL) (mean ± SD)	262±55	257±51	262±48	263±44
LSM change (% ± SE)	-41±2	-7±2**	-38±2	-29±2**
Triglycerides				
n	46	70	71	78
Baseline (mg/dL) (mean ± SD)	383±119	364±121	370±133	380±122
Baseline (mg/dL) (median)	365	343	330	341
LSM change (% ± SE)	-33±5	-21±4	-39±4	-34±4
Median change (%)	-42	-26	-46	-41
VLDL cholesterol				
n	44	68	64	73
Baseline (mg/dL) (mean ± SD)	89±33	80±37	81±35	83±41
LSM change (% ± SE)	-51±6	-22±5**	-47±5	-38±5
Apolipoprotein B				
n	46	69	71	78
Baseline (mg/dL) (mean ± SD)	173±40	171±36	168±30	169±35
LSM change (% ± SE)	-42±3	-9±2**	-42±2	-34±2††
HDL cholesterol				
n	46	70	71	78
Baseline (mg/dL) (mean ± SD)	35±5	36±6	37±5	37±6
LSM change (% ± SE)	11±3	12±2	17±2	24±2**
Apolipoprotein A-I				
n	46	69	71	78
Baseline (mg/dL) (mean ± SD)	130±19	129±20	133±19	133±21
LSM change (% ± SE)	5±2	7±2	6±2	11±2††
Lipoprotein(a)				
n	45	68	69	75
Baseline (mg/dL) (mean ± SD)	23±21	25±23	25±28	30±27
Baseline (mg/dL) (median)	14	15	11	22
LSM change (% ± SE)	7±6	-20±5**	-18±5†	-20±5**
Median change (%)	6	-23	-13	-22

LDL=low-density lipoprotein; LSM=least-squares mean; HDL=high-density lipoprotein; VLDL=very-low-density lipoprotein; †baseline levels are reported as mean values for all measures, except for triglycerides and lipoprotein(a), for which both mean and median baseline values are reported, change values correspond to the LSM (or median) percentage change from baseline at Week 24, and analysis of variance was conducted on Week 24 data using the last observation carried forward from the intention-to-treat population; ** $p<0.001$; † $p<0.01$; †† $p<0.017$ (all treatment comparisons vs. rosuvastatin 40 mg)

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Rosuvastatin monotherapy clearly produced significantly greater reductions in total cholesterol, non-HDL cholesterol, VLDL cholesterol, and apolipoprotein B than did ER niacin. Both monotherapy groups increased plasma HDL cholesterol and decreased triglyceride levels similarly. Although rosuvastatin 40 mg lowered the levels of total cholesterol, non-HDL cholesterol, and apolipoprotein B more effectively than did the combination rosuvastatin 10 mg/ER niacin 2 g, the latter combination produced significantly greater increases in HDL cholesterol and apolipoprotein A-1 than did rosuvastatin 40 mg alone. Significant reductions in Lp(a) were found only in the three treatment groups that included ER niacin.

Reported occurrence of treatment-related adverse events was lower in the group receiving rosuvastatin monotherapy than in any of the three groups of patients receiving ER niacin. Seventy-four percent of patients receiving rosuvastatin monotherapy, 90% of those receiving ER niacin monotherapy, and 85% of those receiving both medications experienced adverse treatment-related events. Pain, diarrhea, pharyngitis, and myalgia were the most common events found in patients receiving rosuvastatin alone, compared with flushing, pruritus, rash, paresthesia, and pharyngitis in those receiving ER niacin alone.

Patient withdrawal in the three groups receiving ER niacin was most commonly due to the drug's vasodilatory effects, especially flushing, rash, and pruritus. One patient receiving combination therapy withdrew because of myalgia.

No serious adverse events that were considered treatment-related were reported in any patients participating in this trial, and the overall occurrence of serious adverse events in any treatment group was low (<5%). A serious adverse event is defined as any event that occurs from any cause during a clinical trial period or within 30 days after the last dose of the trial drug(s) that is fatal, life-threatening, requires or prolongs hospitalization, or results in disability or incapacity. No clinically significant increases in levels of hepatic transaminases or creatine kinase were observed in any patient, except for a transient marked elevation in creatine kinase in an asymptomatic patient receiving ER niacin alone that was deemed treatment-related.

The metabolic syndrome is increasingly found in a substantial and rising proportion of the US population and is associated with increased risk of cardiovascular disease events (acute coronary syndromes, myocardial infarction, stroke, aortic aneurysm, and peripheral arterial obstruction including claudication of the truncal extremities). This constellation of variable combinations of mixed dyslipidemia, glucose intolerance/overt type 2 diabetes mellitus, obesity, and hypertension is a common metabolic abnormality with resistance to insulin-mediated glucose transport and multiple lipid abnormalities. Mixed dyslipidemia, which is fundamental to this syndrome, is usually characterized by combined hyperlipidemia with low HDL cholesterol levels (<45 mg/dL), elevated plasma triglycerides, and either unremarkable or elevated levels of LDL cholesterol. The LDL particles are qualitatively poor, with increased concentrations of small, dense LDL subclass sizes, and HDL particles that are also small and likely reflect impaired lipolysis of triglyceride-rich lipoproteins.

The statin drugs exert their greatest effects on lowering LDL cholesterol levels, with lesser impact on reducing plasma triglycerides and raising levels of HDL cholesterol. Rosuvastatin is a new, recently US Food and Drug Administration-approved statin that is more potent than any other approved statin in lowering LDL cholesterol levels,^[5] but this medication also has robust effects on both raising HDL cholesterol levels and lowering levels of non-HDL cholesterol and circulating triglycerides.^[4]

The use of drug combinations for plasma lipid regulation and for stabilization and/or regression of atherosclerosis is likely to be additive, complementary, and synergistic.^[7,9,12] Reviews of the recent literature indicate that combinations of niacin, including brand-specific ER niacin, with other hyperlipidemic drugs, particularly statins, impart improved lipid regulation over other therapies.^[9,11,12,22] Striking reductions as high as 80% in clinical events have been demonstrated with niacin combination therapy.^[7,8,23]

Niacin is the most potent agent for raising HDL cholesterol levels. Niacin also has good efficacy for lowering plasma triglycerides and modestly reducing LDL cholesterol levels. Additional effects of niacin included shifting LDL cholesterol particle size and density to larger, more buoyant particles that are likely less atherogenic, and modifying smaller HDL particles to become larger and likely reflect improvement in reverse cholesterol transport.^[12,13] These qualitative benefits on lipoprotein particle size are not detectable in the standard lipid profile.^[24]

In the present trial, medication dosages were selected based on established efficacies of the individual agents at the uppermost and lower ends of the dose range for each drug. Combinations were tailored to evaluate and compare the effects of rosuvastatin and ER niacin utilized alone and in combination. A combination consisting of the highest doses of each agent (rosuvastatin 40 mg/ER niacin 2 g) was not tested here because concomitant use of elevated doses would obviate a chief objective of combination therapy, which is to utilize reduced drug doses and strive to achieve complementary therapeutic benefit.

Rosuvastatin produced pronounced reductions of LDL cholesterol, non-HDL cholesterol, and triglyceride levels, and elevated HDL cholesterol levels. The highest dose of rosuvastatin monotherapy was equivalent in effect to the highest dose of ER niacin in

modifying levels of plasma triglycerides, HDL cholesterol, and apolipoprotein A-1. The addition of a higher dose of ER niacin to a lower dose of rosuvastatin amplified the elevations of HDL cholesterol and apolipoprotein A-1 levels above those found with either drug alone. ER niacin, but not rosuvastatin, lowered Lp(a) levels.

ER niacin 2 g did not, by itself, reduce LDL cholesterol levels from baseline, and the addition of ER niacin 1 g to rosuvastatin 40 mg did not reduce LDL levels to a greater degree than did rosuvastatin monotherapy. The surprising findings that ER niacin monotherapy had no significant effect on LDL cholesterol levels and no augmentation of the LDL-lowering effect of rosuvastatin appear consistent with the results of some previous trials. In the first published placebo-controlled trial of ER niacin, Morgan et al.^[25] showed that 1-and 2-g doses of this drug reduced LDL cholesterol levels by just 6% and 15%, respectively, in patients with primary hypercholesterolemia. Similar later trials produced comparable results. In a 17-week trial of patients with mixed dyslipidemias, ER niacin had no effect on LDL cholesterol levels at either 1.5- or 2-g doses.^[26]

The National Cholesterol Education Program ATP III recommends reduction in non-HDL cholesterol levels as a secondary target of therapy in patients with elevated triglycerides (≥ 200 mg/dL).^[20] In the present trial, rosuvastatin monotherapy reduced non-HDL cholesterol (total cholesterol minus HDL cholesterol) levels to a greater degree than did any other treatment.

Patients receiving rosuvastatin monotherapy had a much lower incidence of treatment-related adverse events and associated study withdrawals than did patients who received ER niacin alone or as part of combination therapy. As expected, the usual discomforting symptoms secondary to the vasodilatory actions of ER niacin were experienced by patients in the three groups receiving ER niacin, and probably accounted for their decreased treatment adherence and increased withdrawals. The latter symptoms largely stem from the pharmacologic properties of niacin, but continue to pose a challenge for physicians and patients. Slow upward dose titration with concomitant use of aspirin as needed, careful patient instruction, dosing with food, and avoidance of its use with hot beverages, spices, and alcohol can help to ameliorate these symptoms in the majority of patients that require niacin therapy.

Statin-niacin combination therapies can effectively help to address the combination of lipoprotein abnormalities present in patients with combined (mixed) atherogenic dyslipidemias. The results of the present trial provide continuing evidence that rosuvastatin used either alone or in combination with ER niacin markedly improves the complex lipoprotein abnormalities present in these patients.

The potent effects of rosuvastatin on all three hallmarks of combined hyperlipidemia (high plasma LDL cholesterol and triglyceride levels, and low HDL cholesterol level) render it ideal for management of this common lipid abnormality associated with the metabolic syndrome and premature cardiovascular disease events. These beneficial effects may be augmented by concomitant use of niacin to optimize plasma levels of HDL cholesterol and apolipoprotein A-1, and to reduce Lp(a) levels. However, the often distressing vasodilatory effects associated with niacin monotherapy or combination therapy necessitate careful patient instruction and encouragement along with careful and gradual dose titration to maintain treatment adherence.

References

1. Olssen AG, Pears J, McKellar J, et al. Effect of rosuvastatin on low-density lipoprotein cholesterol in patients with hypercholesterolemia. *Am J Cardiol.* 2001;88:504-508.
2. Brown WV, Bays HE, Hassman DR, et al. Efficacy and safety of rosuvastatin compared with pravastatin and simvastatin in patients with hypercholesterolemia: a randomized, double-blind, 52-week trial. *Am Heart J.* 2002;144:1036-1043.
3. Davidson M, Ma P, Stein EA, et al. Comparison of effects on low-density lipoprotein cholesterol and high-density lipoprotein cholesterol with rosuvastatin versus atorvastatin in patients with type IIa or type IIb hypercholesterolemia. *Am J Cardiol.* 2002;89:268-275.
4. Olsson AG, McTaggart F, Raza A. Rosuvastatin: a highly effective new HMG-CoA reductase inhibitor. *Cardiovasc Drug Rev.* 2002;20(4):303-328.
5. Jones PH, Davidson MH, Stein EA, et al. STELLAR Study Group. Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR Trial). *Am J Cardiol.* 2003;92(2):152-160.
6. Canner PL, Berge KG, Wenger NK, et al. Fifteen year mortality in Coronary Drug Project patients: long-term benefit of niacin. *J Am Coll Cardiol.* 1986;8:1245-1255.
7. Malloy MJ, Kane JP, Kunitake ST, et al. Complementarity of colestipol, niacin, and lovastatin in treatment of severe familial

hypercholesterolemia. *Ann Intern Med.* 1987;107:616-623.

8. Brown BG, 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. Capuzzi DM, Morgan JM, Brusco OA, et al. Niacin dosing: relationship to benefits and adverse effects. *Curr Atheroscler Rep.* 2000;2:64-71.
10. Brown GB, 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(22):1583-1592.
11. Malik S, Kashyap ML. Niacin, lipids, and heart disease. *Curr Cardiol Rep.* 2003;5(6):470-476.
12. Miller M. Niacin as a component of combination therapy for dyslipidemia. *Mayo Clin Proc.* 2003;78:735-742.
13. Morgan JM, Capuzzi DM, Baksh RI, et al. Effects of extended-release niacin on lipoprotein subclass distribution. *Am J Cardiol.* 2003;91:1432-1436.
14. Duvall WL, Blazing MA, Saxena S, et al. Targeting cardiovascular risk associated with both low density and high density lipoproteins using statin-niacin combination therapy. *J Cardiovasc Risk.* 2002;9(6):339-347.
15. Kashyap ML, McGovern ME, Berra K, et al. Long-term safety and efficacy of a once-daily niacin/lovastatin formulation for patients with dyslipidemia. *Am J Cardiol.* 2002;89:672-678.
16. Davignon J, Roederer G, Montigny M, et al. Comparative efficacy and safety of pravastatin, nicotinic acid, and the two combined in patients with hypercholesterolemia. *Am J Cardiol.* 1994;73:339-345.
17. Jacobson TA, Chin MM, Fromell GJ, et al. Fluvastatin with and without niacin for hypercholesterolemia. *Am J Cardiol.* 1994;74:149-154.
18. Vacek JL, Dittmeier G, Chiarelli T, et al. Comparison of lovastatin (20 mg) and nicotinic acid (1.2 g) with either drug alone for type II hyperlipoproteinemia. *Am J Cardiol.* 1995;76:182-186.
19. Bays HE, Dujovne CA, McGovern ME, et al. Comparison of once-daily, niacin extended-release/lovastatin with standard doses of atorvastatin and simvastatin (the Advicor Versus Other Cholesterol-Modulating Agents Trial Evaluation [ADVOCATE]). *Am J Cardiol.* 2003;91(6):667-672.
20. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA.* 2001;285:2486-2497.
21. Capuzzi DM, Morgan JM, Weiss RJ, et al. Beneficial effects of rosuvastatin alone and in combination with extended-release niacin in patients with a combined hyperlipidemia and low high-density lipoprotein cholesterol levels. *Am J Cardiol.* 2003;91:1304-1310.
22. Knopp RH. Evaluating niacin in its various forms. *Am J Cardiol.* 2000;86(suppl):51L-56L.
23. Carlson LA, Rosenhammer G. Reduction of mortality in the Stockholm Ischaemic Heart Disease Secondary Prevention Trial by combined treatment with clofibrate and nicotinic acid. *Acta Med Scand.* 1988;223:405-418.
24. Van J, Van JT, Chan E, et al. Extended-release niacin treatment of the atherogenic lipid profile and lipoprotein(a) in diabetes. *Metabolism.* 2002;51:1120-1127.
25. Morgan JM, Capuzzi DM, Guyton JR, et al. Treatment effects of Niaspan, a controlled-release niacin, in patients with hypercholesterolemia: a placebo-controlled trial. *J Cardiovasc Pharmacol Ther.* 1996;1:195-202.
26. Guyton JR, Blazing MA, Hagar J, et al. Extended-release niacin vs. gemfibrozil for the treatment of low levels of high-density lipoprotein cholesterol. *Arch Intern Med.* 2000;160:1177-1184.

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