Effects of Rosuvastatin and Atorvastatin on LDL and HDL Particle Concentrations in Patients With Metabolic Syndrome

A randomized, double-blind, controlled study

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OBJECTIVE — The purpose of this study was to examine the effects of statin therapy on lipoprotein particle concentrations in patients with the metabolic syndrome. Changes in lipoprotein particle concentration may predict the risk of coronary heart disease more accurately than lipoprotein cholesterol levels.

RESEARCH DESIGN AND METHODS — Patients with dyslipidemia and the metabolic syndrome ($n = 318$) were randomly assigned in a double-blind study comparing 10 mg rosuvastatin (RSV), 10 mg atorvastatin, or placebo daily for 6 weeks. From weeks 6 to 12, patients in the RSV and placebo groups received 20 mg RSV, whereas the ATV group increased their dose to 20 mg daily. Lipoprotein particle concentrations were measured by nuclear magnetic resonance spectroscopy, LDL cholesterol was measured by β-quantification, and other lipoproteins were measured by standard methods at baseline, 6 weeks, and 12 weeks. Lipoprotein levels were compared by analysis of covariance.

RESULTS — Statins reduced LDL particle concentration less than LDL cholesterol (−30 to −38 vs. −38 to −51%). Reductions were greater with RSV than with ATV ($P < 0.05$ for LDL particle concentration and $P < 0.001$ for LDL cholesterol). Most patients attained LDL cholesterol <2.59 mmol/l (100 mg/dl) at 12 weeks (80% with RSV and 59% with ATV; $P = 0.003$), but only 27% of patients receiving RSV and 19% receiving ATV attained the goal of LDL particle concentration <1,000 nmol/l ($P = 0.07$).

CONCLUSIONS — In patients with the metabolic syndrome, statin-induced changes in LDL cholesterol do not accurately reflect changes in LDL particle concentration. Consequently, despite attainment of LDL cholesterol goals, these patients may retain considerable residual coronary heart disease risk.

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Although LDL cholesterol reduction serves as a cornerstone of prevention of coronary disease (1), the coronary heart disease (CHD) risk may be better predicted by measures of atherogenic particles, such as non–HDL cholesterol (2), apolipoprotein B (apoB) (3), or LDL particle concentration (4–6).

Patients with the metabolic syndrome may have relatively normal LDL cholesterol when LDL particle concentration is elevated because these patients have a preponderance of small, cholesterol-poor LDL particles (7). Thus, LDL cholesterol may underestimate risk in patients with the metabolic syndrome (2,8). Likewise, in men with CHD, low HDL cholesterol (≤1.04 mmol/l [40 mg/dl]), and often many other characteristics of the metabolic syndrome, new CHD events were correlated with high LDL particle concentration but not LDL cholesterol, and a low HDL particle concentration was more strongly inversely correlated with CHD events than was HDL cholesterol (5).

This exploratory analysis of the Comparative Study with Rosuvastatin in Subjects with Metabolic Syndrome (COMETS, 4522IL/0069) (9) compares the effects of rosuvastatin (RSV) and atorvastatin (ATV) on lipoprotein particle concentrations and cholesterol levels in patients with the metabolic syndrome. We sought to determine the efficacy of statin therapy in achieving LDL cholesterol targets set by the National Cholesterol Education Program Adult Treatment Panel III (ATP III) and the corresponding numbers of patients who achieved LDL particle concentration targets below the 50th percentile (<1,300 nmol/l) and below the 20th percentile (<1,000 nmol/l) based on values established by the Multi-Ethnic Study of Atherosclerosis (MESA) (10).

RESEARCH DESIGN AND METHODS

The study population included men and women, aged ≥18 years, with the metabolic syndrome as defined by ATP III criteria (1) (Table 1). Other inclusion criteria included LDL cholesterol 3.36–6.48 mmol/l (130–250 mg/dl) and a 10-year CHD risk score >10%. Exclusion criteria included triglycerides ≥5.65 mmol/l (500 mg/dl), use of lipid-lowering therapy within 6 months, CHD or other atherosclerotic disease, diabetes, and liver dysfunction.

The study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice. Study procedures were approved by ethics committees, and all patients provided informed, written consent.

Patients were randomly assigned at 56 clinical centers in Europe and the U.S. into a double-blind, double-dummy, parallel-group study (9). After a 4-week dietary lead-in period, patients were randomly assigned (2:2:1) to 10 mg/day RSV (RSV10), 10 mg/day ATV (ATV10), or

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Table 1—*Demographic and clinical characteristics of the study population*

	10/20 mg RSV	10/20 mg ATV	Placebo/20 mg RSV
n	136	119	63
Age (years)	58.6 ± 9.3	58.2 ± 9.7	58.5 ± 9.0
Male sex	87 (64.0)	78 (65.5)	43 (68.3)
Caucasian race	134 (98.5)	116 (97.5)	60 (95.2)
BMI (kg/m^2)	30.5 ± 3.8	31.0 ± 3.5	30.4 ± 4.0
Metabolic syndrome criteria			
Abdominal obesity*	123 (90.4)	116 (97.5)	57 (90.5)
Triglycerides ≥1.70 mmol/l (150 mg/dl)	110 (80.9)	81 (68.1)	52 (82.5)
Low HDL cholesterol†	73 (53.7)	54 (45.4)	24 (38.1)
Blood pressure ≥130/85 mmHg	128 (94.1)	113 (95.0)	60 (95.2)
Fasting glucose 6.11–6.94 mmol/l	33 (24.3)	29 (24.4)	14 (22.2)

Data are means ± SD or *n* (%). *Waist circumference >102 cm for men and >88 cm for women. †HDL cholesterol <1.04 mmol/l (40 mg/dl) for men and <1.30 mmol/l (50 mg/dl) for women.

placebo for 6 weeks. After the 6-week treatment period, patients treated with RSV10 or placebo received 20 mg/day RSV (RSV20), and patients previously treated with ATV10 received 20 mg/day ATV (ATV20) for another 6 weeks.

Fasting blood samples were collected at baseline and at 6 and 12 weeks. Lipoprotein particle concentrations were measured by automated nuclear magnetic resonance spectroscopy (LipoScience, Raleigh, NC) (10). Lipids and lipoproteins were measured at a central laboratory certified for lipid analysis by the Standardization Program of the Centers for Disease Control and Prevention and the National Heart, Lung, and Blood Institute (Medical Research Laboratories International, Zaventum, Belgium, and Highland Heights, KY). β-Quantification was performed to provide the most accurate measure of LDL cholesterol in the presence of high triglyceride levels. Plasma samples were overlaid with normal saline and ultracentrifuged (105,000*g*) for 18 to 22 h at 10°C; centrifuge tubes were sliced to separate the top (density <1.006; VLDL) and bottom (density >1.006; LDL and HDL cholesterol) fractions. The cholesterol contents of the bottom fraction and whole plasma were measured using an automated analyzer (Hitachi 747). For determination of HDL cholesterol, plasma was treated with Mn^{2+} and heparin to precipitate chylomicrons, VLDL, and LDL cholesterol. After centrifugation, the HDL cholesterol content of the supernatant was measured in an automated analyzer. VLDL cholesterol was calculated as total cholesterol from whole plasma minus (LDL + HDL cholesterol) from the bottom ultracentrifugation fraction. LDL cholesterol was calculated as (LDL + HDL cholesterol) from the bottom ultracentrifugation fraction minus HDL cholesterol from the precipitation assay. Non-HDL cholesterol was calculated as total cholesterol from whole plasma minus HDL cholesterol from the precipitation assay. Triglycerides were measured using the automatic analyzer, and apolipoproteins were measured by immunonephelometry.

Statistical analysis

Data from the per-protocol patient population were used for this exploratory analysis because a complete laboratory dataset was required for each patient. Statistical significance of least-squares differences among treatment groups was determined with an ANCOVA model that included controls for treatment, study center, and baseline value. The statistical significance of differences in goal attainment was determined by the χ^2 test.

RESULTS — The first patient was enrolled into the study on 16 May 2002, and the last patient completed the study on 30 September 2003. The population included 318 patients at baseline, of whom 136 were randomly assigned to RSV10, 119 to ATV10, and 63 to placebo. At week 6, the per-protocol population included 278 patients (RSV10, $n = 122$; ATV10, $n = 101$; and placebo, $n = 55$); at the end of the study (12 weeks); data for 257 patients were available for analysis (RSV20, $n = 166$, and ATV20, $n = 91$). Baseline lipid and lipoprotein parameters were well balanced among patients in the three treatment arms (Table 2).

Effects on LDL and VLDL

Compared with placebo, both RSV10 and ATV10 significantly ($P < 0.001$) reduced LDL cholesterol, LDL particle concentration, apoB, and non-HDL cholesterol (Fig. 1) after 6 weeks of treatment. RSV was more effective than ATV in reducing LDL cholesterol ($P < 0.001$), LDL particle concentration ($P < 0.05$), and non-HDL cholesterol ($P < 0.01$) after 6 and 12 weeks. With either statin, percent reductions in LDL particle concentration were smaller than reductions in LDL cholesterol. This difference was apparent at 6 weeks (34 vs. 45% for RSV10 and 30 vs. 38% for ATV10) and became more pronounced after 12 weeks (38 vs. 50% for RSV20 and 33 vs. 44% for ATV20). Reductions in LDL cholesterol, LDL particle concentration, non-HDL cholesterol, and apoB did not differ substantially among

Table 2—*Baseline lipoprotein levels*

Parameter	Rosuvastatin	Atorvastatin	Placebo
n	122	101	55
HDL-C (mmol/l)	1.1 ± 0.2	1.2 ± 0.2	1.2 ± 0.2
HDL-P (μmol/l)	28 ± 6	29 ± 6	31 ± 6
ApoA-I (mg/dl)	146 ± 26	151 ± 25	152 ± 21
LDL-C (mmol/l)	4.3 ± 0.6	4.4 ± 0.6	4.4 ± 0.7
Non-HDL-C (mmol/l)	5.3 ± 0.7	5.3 ± 0.8	5.4 ± 0.8
Total cholesterol (mmol/l)	6.4 ± 0.7	6.5 ± 0.8	6.6 ± 0.8
LDL-P (nmol/l)	1,962 ± 383	1,869 ± 367	2,018 ± 440
ApoB (mg/dl)	160 ± 24	161 ± 26	164 ± 28
VLDL-P (nmol/l)	109 ± 35	104 ± 37	105 ± 34
Triglycerides (mmol/l)	2.3 ± 0.8	2.1 ± 0.7	2.5 ± 0.9
C-reactive protein (mg/l)	2.2	2.9	2.6

Data are means ± SD or median. HDL-C, HDL cholesterol; HDL-P, HDL particle concentration; LDL-C, LDL cholesterol; LDL-P, LDL particle concentration; non-HDL-C, non-HDL cholesterol; VLDL-P, VLDL particle concentration.

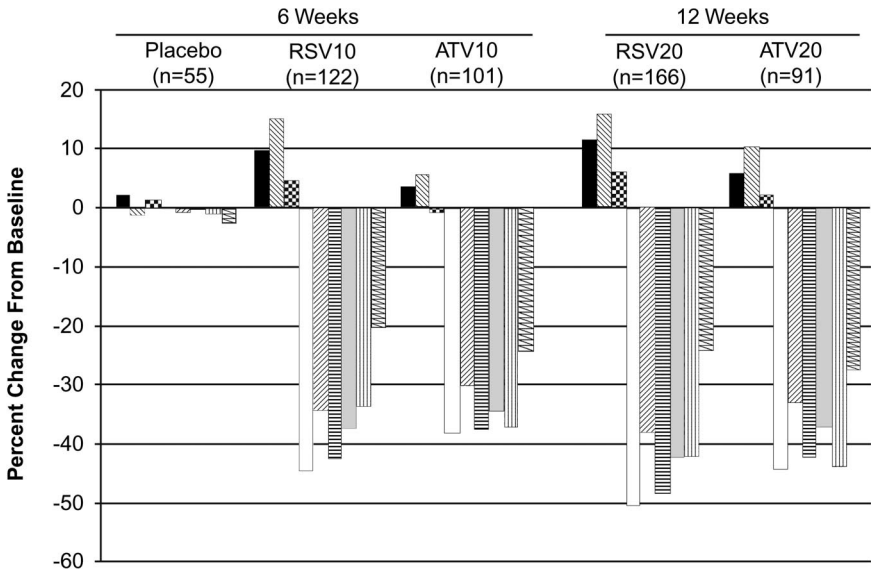

Figure 1—*Least-squares mean percentage change from baseline in lipids and lipoproteins by treatment group.* ▩, *apoA-I;* ▨, *apoB;* ■, *HDL cholesterol;* ▧, *HDL particle concentration;* □, *LDL cholesterol;* ▨, *LDL particle concentration;* ▤, *non–HDL cholesterol;* ▧, *triglycerides;* ▥, *VLDL particle concentration.*

patients with higher or lower baseline serum triglycerides (Table 3).

Compared with placebo, RSV10 and ATV10 significantly ($P < 0.001$) reduced VLDL particle concentration and serum triglycerides by 6 weeks (Fig. 1). The two statins were similarly effective in reducing VLDL particle concentration and serum triglycerides at weeks 6 and 12.

Effects on HDL

Compared with placebo, RSV10 increased HDL particle concentration (15%) and HDL cholesterol (10%) significantly ($P < 0.001$) (Fig. 1). Although ATV10 also significantly increased HDL particle concentration (6%, $P = 0.013$ vs. placebo), it was not more effective than placebo in increasing HDL cholesterol (4%, $P = 0.45$). RSV was significantly more effective than ATV in increasing HDL particle concentration and HDL cholesterol after 6 and 12 weeks ($P \leq 0.002$). Neither statin showed a statistically significant effect on apoA-I compared with placebo; however, increases in apoA-I were significantly greater with RSV than with ATV at 6 ($P = 0.001$) and 12 weeks ($P = 0.02$) (Fig. 1). In patients with high baseline triglyceride levels, HDL cholesterol, HDL particle concentration, and apoA-I increases with ATV20 appeared higher (4–19%) than in those with low baseline triglycerides (1–5%) (Table 3). HDL cholesterol, HDL particle concentration, and apoA-I increases with RSV20 were numerically greater than those with ATV20 regardless of baseline triglyceride levels.

Goal attainment

Most patients achieved LDL cholesterol <2.59 mmol/l (<100 mg/dl), but a significantly higher proportion of patients assigned to RSV achieved this goal ($P < 0.01$ at 6 weeks and $P < 0.0001$ at 12 weeks vs. ATV) (Table 4). Patients assigned to RSV were also more likely to

Table 3—*Baseline lipoprotein levels and percent change from baseline by triglyceride subgroup*

	Baseline triglyceride <2.26 mmol/l					Baseline triglyceride ≥2.26 mmol/l				
	Week 6			Week 12		Week 6			Week 12	
Parameter	RSV10	ATV10	Placebo	RSV20	ATV20	RSV10	ATV10	Placebo	RSV20	ATV20
n	66	64	22	80	58	56	37	33	86	33
HDL-C (mmol/l)	1.1	1.2	1.3			1.1	1.1	1.1		
% change	7*	3	−1	9§	3	12†§	4	4	14	11
HDL-P (μmol/l)	28	29	32			29	29	30		
% change	12*	8	2	15§	5	14	13	6	21	19
ApoA-I (mg/dl)	149	148	152			158	156	154		
% change	4	0.02	3	6‖	1	5§	−2	1	6	4
LDL-C (mmol/l)	165	168	162			171	176	173		
% change	−47‡§	−39‡	−3	−52‖	−46	−43‡‖	−37‡	2	−49§	−42
Non-HDL-C (mmol/l)	5.0	5.0	4.8			5.6	5.8	5.7		
% change	−44‡‖	−37‡	−2	−49‖	−43	−43‡‖	−37‡	1	−48‖	−42
LDL-P (nmol/l)	1,812	1,736	1,691			2,140	2,100	2,236		
% change	−33‡	−29‡	−1	−37	−32	−37‡‖	−30‡	−2	−40	−35
ApoB (mg/dl)	152	153	146			169	175	176		
% change	−38‡	−33‡	1	−43‖	−37	−37‡	−35‡	−1	−42	−37
VLDL-P (nmol/l)	95	89	86			126	130	117		
% change	−39‡	−40‡	−5	−42	−44	−29‡	−33‡	−4	−40	−40
Triglycerides (mmol/l)¶	1.8	1.7	1.7			3.0	2.9	3.0		
% change	−15*	−22†	1	−18	−24	−30‡	−26†	−7	−30	−31

*$P < 0.05$ vs. placebo. †$P < 0.01$ vs. placebo. ‡$P < 0.001$ vs. placebo. §$P < 0.01$ vs. ATV. ‖$P < 0.05$ vs. ATV. ¶A triglyceride concentration of 2.26 mmol/l corresponds to 200 mg/dl. HDL-C, HDL cholesterol; HDL-P, HDL particle concentration; LDL-C, LDL cholesterol; LDL-P, LDL particle concentration; non-HDL-C, non-HDL cholesterol; VLDL-P, VLDL particle concentration.

Table 4—*Number and percentage of patients achieving LDL particle and LDL cholesterol goals*

	Baseline	6 weeks	12 weeks
LDL-P <1,000 nmol/l			
Rosuvastatin	0	30/122 (25)	45/166 (27)
Atorvastatin	0	12/101 (12)	17/91 (19)
Placebo	0	1/55 (2)	—
LDL-P <1,300 nmol/l			
Rosuvastatin	4/122 (3)	70/122 (57)	115/166 (69)
Atorvastatin	3/101 (3)	60/101 (59)	50/91 (55)
Placebo	3/55 (5)	1/55 (2)	—
LDL cholesterol <2.59 mmol/l			
Rosuvastatin	0	99/162 (61)	185/232 (80)
Atorvastatin	0	70/151 (46)	85/145 (59)
Placebo	0	1/78 (1)	—

Data are *n* (%). LDL particle concentration (LDL-P) <1,000 nmol/l corresponds to the 20th percentile and <1,300 nmol/l to the 50th percentile of values from the MESA study (10).

reach LDL particle concentration <1,300 nmol/l at 12 weeks ($P = 0.02$ vs. ATV) and LDL particle concentration <1,000 nmol/l at 6 weeks ($P = 0.02$ vs. ATV). The percentage of patients who attained LDL particle concentration <1,300 nmol/l was similar to that achieving LDL cholesterol <2.59 mmol/l (<100 mg/dl), but fewer patients reached LDL particle concentration <1,000 nmol/l.

CONCLUSIONS — In patients with the metabolic syndrome, statins reduced atherogenic lipoproteins, and reductions generally were higher with RSV than with ATV. RSV increased HDL cholesterol, and both statins increased HDL particle concentration compared with placebo. Increases in HDL cholesterol, HDL particle concentration, and apoA-I were greater with RSV than with ATV ($P < 0.001$ for all vs. ATV10; $P < 0.01$ for HDL cholesterol and HDL particle concentration, and $P < 0.05$ for apoA-I vs. ATV20). A higher proportion of patients assigned to RSV achieved LDL cholesterol <2.59 mmol/l (<100 mg/dl); however, even with RSV20, only 27% of these patients with the metabolic syndrome reached comparably low LDL particle concentration levels of <1,000 nmol/l.

In this population, the magnitude of LDL particle concentration reduction with statins was smaller than that of LDL cholesterol reduction, suggesting that LDL cholesterol may underestimate residual CHD risk in patients with the metabolic syndrome. In contrast, in a dyslipidemic population not selected to have the metabolic syndrome, modest statin-induced reductions in LDL cholesterol (28%) and LDL particle concentration (24%) by pravastatin were more concordant (11). These observations support the possibility that LDL particle goals, assessed by nuclear magnetic resonance or apoB measurement, may offer an advantage over LDL cholesterol goals (2,12), particularly in patients with the metabolic syndrome.

Although the statin effect on LDL particle concentration was attenuated in comparison with the effect on LDL cholesterol, the fractional HDL particle concentration response was higher than that of HDL cholesterol. ApoA-I levels were only modestly increased (4–6% by RSV and −1 to 2% by ATV), consistent with the known heterogeneity of HDL particles with regard to apoA-I and lipid content (13). Thus, the observed treatment effects could reflect an increase in relatively cholesterol-depleted HDL particles. Whether this cholesterol depletion is due to higher cholesterol ester transfer protein–mediated reverse cholesterol transport activity or to reduced cholesterol uptake from the periphery is uncertain. A recent report described the apparent dysfunction of HDL in patients with the metabolic syndrome (14); thus, any mechanistic hypothesis would not necessarily apply to other patient groups. Restoring HDL function may be particularly valuable in these patients, but the utility of statins for this purpose remains to be established.

Strengths of this analysis include the randomized, blinded, and placebo-controlled design and the increasing clinical relevance of the patient population studied. Several possible limitations should be noted. First, the 12-week assessments did not include a placebo comparator. However, the objective nature of the measurements and the small magnitude of changes observed with placebo in the first 6-week period suggest that changes by 12 weeks can be attributed to statin therapy. Second, patients in the RSV20 group included both those treated previously with RSV10 and those given placebo previously, possibly leading to heterogeneity in clinical response. Third, the study population was almost entirely Caucasian (392 of 401; 98%); thus, the findings may not apply to other racial and ethnic groups. Finally, in view of the exploratory nature of this post hoc analysis, results should be interpreted cautiously.

The paradigm that the concentration of atherogenic particles is a more important determinant of cardiovascular risk than conventional lipid measures such as LDL cholesterol (3,15) implies that measurements such as LDL particle concentration or apoB may move toward the center of future risk assessment. In nearly all prospective studies, LDL particle concentration or apoB has been a stronger predictor of cardiovascular outcomes than LDL cholesterol. A recent analysis of the Framingham Offspring Study showed that LDL particle concentration was approximately twice as strongly related to CVD incidence as was LDL cholesterol (6). In individuals whose LDL cholesterol and LDL particle concentration were discordant, which was defined as having above-median LDL cholesterol and below-median LDL particle concentration (or vice versa), CVD event risk was associated more closely with LDL particle concentration than with LDL cholesterol (6).

Our analysis confirmed that, at equal doses, RSV was more effective than ATV for treating dyslipidemia in patients with the metabolic syndrome. For both statins, the percent reduction in LDL particle concentration was smaller than that in LDL cholesterol, whereas, conversely, HDL particle concentration increases were greater than HDL cholesterol increases. These findings suggest the possibility that treating patients with the metabolic syndrome to targets based on LDL particle concentration rather than on LDL cholesterol may provide a more reliable approach to reducing residual CHD risk, but this remains to be established. The American Diabetes Association/American College of Cardiology Foundation consensus conference report recently

suggested more aggressive lipoprotein goals for patients with the greatest cardiometabolic risk (2). This proposal is supported by our observation in patients with the metabolic syndrome that LDL particle concentration remains elevated in many patients who achieve LDL cholesterol goals. Further study will be needed to determine whether more stringent statin monotherapy or combination treatment, with the goal of further reducing LDL particle concentration, will translate into better outcomes in patients with the metabolic syndrome.

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