

ORIGINAL ARTICLE

# Treating to target patients with primary hyperlipidaemia: comparison of the effects of ATOrvastatin and ROSuvastatin (the ATOROS study)

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**Key words:** Atorvastatin – Hyperlipidaemia, primary – LDL-cholesterol – Rosuvastatin – Treatment target

## ABSTRACT

**Objectives:** In a 24-week, open-label, randomized, parallel-group study, we compared the efficacy and metabolic effects, beyond low density lipoprotein cholesterol (LDL-C)-lowering, of atorvastatin (ATV) and rosuvastatin (RSV) in cardiovascular disease-free subjects with primary hyperlipidaemia, treated to an LDL-C target (130 mg/dL).

**Methods:** After a 6-week dietary lead-in period, patients were randomized to RSV 10 mg/day ( $n = 60$ ) or ATV 20 mg/day ( $n = 60$ ). After 6 weeks on treatment the dose of the statin was increased (to RSV 20 mg/day or ATV 40 mg/day) if the treatment goal was not achieved. A control group of healthy volunteers ( $n = 60$ ) was also included for the validation of baseline serum and urinary laboratory parameters. The primary outcome was the percentage of patients reaching the LDL-C goal; secondary outcomes were changes in lipid and non-lipid metabolic parameters.

**Results:** A total of 45 patients (75.0%) in the RSV-treated group and 43 (71.7%) in the

ATV-treated group achieved the treatment target at the initial dose. Both regimens were generally well tolerated and there were no withdrawals due to treatment-related serious adverse events. Similar significant reductions in total cholesterol, LDL-C, apolipoprotein (apo) B, triglycerides, apoB/apoA1 ratio, fibrinogen and high-sensitivity C-reactive protein levels were seen. RSV had a significant high density lipoprotein cholesterol (HDL-C)-raising effect and showed a trend towards increasing apoA1 levels. Glycaemic control and renal function parameters were not influenced by statin therapy. ATV, but not RSV, showed a significant hypouricaemic effect.

**Conclusions:** RSV and ATV were equally efficacious in achieving LDL-C treatment goals in patients with primary hyperlipidaemia at the initial dose and following dose titration. RSV seems to have a significantly higher HDL-C-raising effect, while ATV lowers serum uric acid levels.

## Introduction

Statins remain the cornerstone of low-density lipoprotein cholesterol (LDL-C)-lowering therapy<sup>1</sup>. Monotherapy with a statin has proven to be efficacious in achieving LDL-C treatment goals, especially with the advent of 'newer' potent agents, such as atorvastatin (ATV) and more recently rosuvastatin (RSV)<sup>2</sup>. Whether individual statins are different with regard to safety, efficacy and pleiotropic effects remains a matter of debate and continuing investigation.

Most statin-related clinical trials were designed to investigate the superiority or non-inferiority of one treatment regimen over another in terms of reduction in vascular events, safety and/or lipid levels achieved. The present open-label, randomized, parallel-group study compares the metabolic effects of ATV and RSV in cardiovascular disease (CVD)-free subjects with primary hypercholesterolaemia, treated to achieve the same LDL-C target.

## Subjects and methods

Patients referred to the Outpatient Lipid Clinic of the University Hospital of Ioannina, Greece (referral centre for North-Western Greece) were recruited for the study. Men and women with dyslipidaemia were screened for eligibility by medical history, physical examination and clinical laboratory evaluation, including the lipid profile. No participant had symptomatic ischaemic heart disease (IHD) or any other clinically evident vascular disease. The study protocol involved patients at moderate risk, according to the National Cholesterol Education Program (NCEP) classification ( $\geq 2$  risk factors and a 10-year IHD risk of 10–20%) with a LDL-C target of  $< 130$  mg/dL (3.4 mmol/L)<sup>3</sup>. Any lipid lowering medication must have been discontinued for at least 8 weeks prior to enrolment. Patients were assigned to the NCEP diet for 6 weeks and were advised to follow this diet throughout the study. Fasting serum lipid level entry criteria were total cholesterol (TC)  $> 240$  mg/dL (6.2 mmol/L) at weeks  $-4$  and  $-2$ , and triglycerides (TG)  $< 350$  mg/dL (4.0 mmol/L).

The exclusion criteria were:

- (1) Abnormal liver function tests (aminotransferase levels  $> 2$  times the upper limit of normal, and/or history of chronic liver disease, such as cirrhosis or alcohol abuse).
- (2) Impaired renal function (serum creatinine [Cr] levels  $> 1.8$  mg/dL, 159  $\mu$ mol/L).
- (3) Diabetes mellitus (fasting blood glucose  $> 126$  mg/dL [7.0 mmol/L] measured on two

occasions and/or receiving treatment for this condition).

- (4) Raised thyroid-stimulating hormone (TSH) levels (greater than 5.0  $\mu$ U/L).
- (5) Patients with any medical conditions that might preclude successful completion of the study protocol.

Patients taking drugs, such as angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists or calcium channel blockers at a stable dose for at least 8 weeks before entry in the study were considered eligible. Those receiving drugs possibly affecting the laboratory parameters tested (including lipids and serum uric acid levels) were excluded<sup>4</sup>.

After 6 weeks dietary lead-in, eligible patients were randomized to receive either RSV 10 mg or ATV 20 mg for 6 weeks (period II, Figure 1). After completion of this period, subjects were titrated to either RSV 20 mg (if initially on RSV 10 mg) or ATV 40 mg (if initially on ATV 20 mg) if the LDL-C treatment goals were not achieved (period III, Figure 1); this period lasted for 18 weeks.

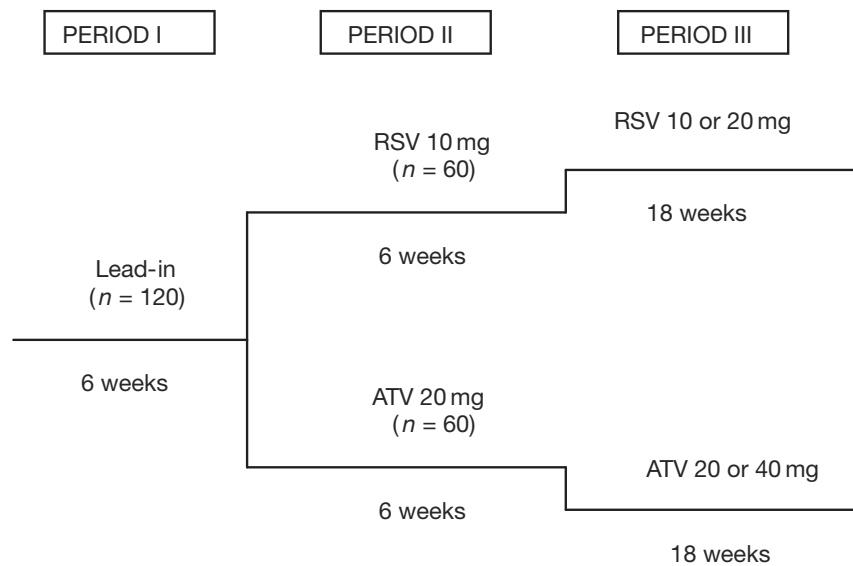
A food record rating score was calculated from 3-day diaries kept by the participants to assess dietary compliance throughout the study. Patients were advised to maintain their usual physical activity. Blood samples were taken after a 14-hour overnight fast for the determination of serum lipids (including apolipoproteins), serum urea, Cr, sodium, glucose, insulin, uric acid, lipids, fibrinogen, high sensitivity C-reactive protein (hsCRP), liver and muscle enzymes at baseline, and at 6 and 24 weeks following treatment initiation. In addition, random urine samples were obtained at 0 and 24 weeks for urinary Cr, total protein, sodium and uric acid determinations.

A control group consisted of 60 subjects selected among volunteers who were evaluated in the Outpatient Lipid Clinic for a Primary Care Family Screening Program conducted during the study period. Eligibility criteria included: no personal history of IHD and no lipid lowering treatment. This group was included to validate baseline serum and urinary laboratory parameters (e.g. protein excretion) prior to any changes potentially induced by statin treatment.

All participants gave their informed consent and the study was approved by the local ethics committee.

## Laboratory determinations

These tests were carried out by automated chemical analysis in the laboratory of the University Hospital of Ioannina using an Olympus AU 600 analyzer (Olympus Diagnostica GmbH, Hamburg, Germany). Specifically, urine and serum samples were analyzed using ion-sensitive electrodes for sodium. A modification of the



**Figure 1.** Study design for the ATOROS study. RSV = rosuvastatin; ATV = atorvastatin

Jaffé-method was used for the determination of Cr levels. The Cr clearance (CrCl) was estimated by the Cockcroft–Gault formula:

$$\text{CrCl} = \frac{[(140 - \text{Age}) \times \text{Body Weight}]}{(72 \times \text{serum Cr})}$$

where lean body weight is in kg, age is in years and serum Cr is in mg/dL<sup>5</sup>. For women, the result is multiplied by a factor of 0.85 to compensate for the lower average muscle mass<sup>5</sup>. Urinary protein was quantitatively determined by a photometric colour test (Olympus Diagnostica GmbH, Hamburg, Germany). The test is linear within a concentration range of 0.01–2.0 g/L. The lowest detectable level was estimated at 0.007 g/L. Proteinuria was estimated by calculating the ratio of total urine protein to urine Cr (in mg/mg, total protein [TPR]/Cr ratio) in a single morning-voided urine specimen<sup>6</sup>. Using this approximation, normal individuals have a ratio of less than 0.2, whereas patients with renal disease can have values between 0.2 and 3.5<sup>6</sup>. The uricase/PAP method (an enzymatic colour test) was used for uric acid determinations. The fractional excretions (FE) of uric acid and sodium were calculated as follows:

$$\text{FE (\%)} = \frac{\text{Urinary (Y)} \times \text{Serum Cr} \times 100}{\text{Serum (Y)} \times \text{Urinary Cr}}$$

where Y equals the concentration of uric acid or sodium.

Glucose was measured by the hexokinase method and serum insulin levels by the AxSYM Insulin assay, which is based on the Microparticle Enzyme Immunoassay technology (Abbott Laboratories, Diagnostic Division, Abbott Park, IL, USA). The HHomeostasis Model Assessment (HOMA) was used as an index of insulin

resistance. The model is known to be nonlinear but can be approximated mathematically:

$$\text{Insulin resistance} = \frac{(\text{Fasting insulin in } \mu\text{U/mL}) \times (\text{Fasting serum glucose in mg/dL}) \times 0.06}{22.5^7}$$

Liver and muscle enzymes were measured using conventional methods. Plasma fibrinogen levels were measured by the Clauss method<sup>4,8</sup>. Serum concentrations of hsCRP were measured by the N High Sensitivity CRP method (Dade Behring Marburg GmbH, Marburg, Germany) based on particle enhanced immunonephelometry. The reference range of this assay is 0.175–55 mg/L<sup>4,8</sup>.

The concentrations of TC, TG, HDL, apolipoproteins (Apo) A-I and B and lipoprotein(a) [Lp(a)] were determined by standardized methods as previously described<sup>8</sup>. LDL-C was calculated using the Friedewald formula.

### Statistical analysis

All parameters were expressed as mean ± standard deviation, except for Lp(a), fibrinogen and hsCRP, which were expressed as median (range). Relationships between variables were assessed by the Pearson's and Spearman correlation coefficients for parametric and non-parametric variables, respectively. A comparison of continuous variables was performed by a paired two-tailed Student's *t*-test for normally distributed variables and Wilcoxon test for non-normally distributed variables. Chi-square tests were used for categorical variables.

To correct for bias, analysis of covariance (ANCOVA) was used to 'remove' the effect of differences in the baseline values of serum lipid parameters (covariate) on

the changes in these parameters ( $\Delta$ TC,  $\Delta$ TG,  $\Delta$ HDL-C, dependent variables) after statin treatment (independent variable). ANCOVA was also performed to assess the effect of statin therapy on serum uric acid levels.

Significance was defined as  $p < 0.05$ . Analyses were performed using the SPSS 11.0 statistical package for Windows (SPSS Inc., 1989–2001, Chicago, IL, USA), and Statistica 6.0 (Statsoft, Inc. 1984–2001, Tulsa, OK, USA).

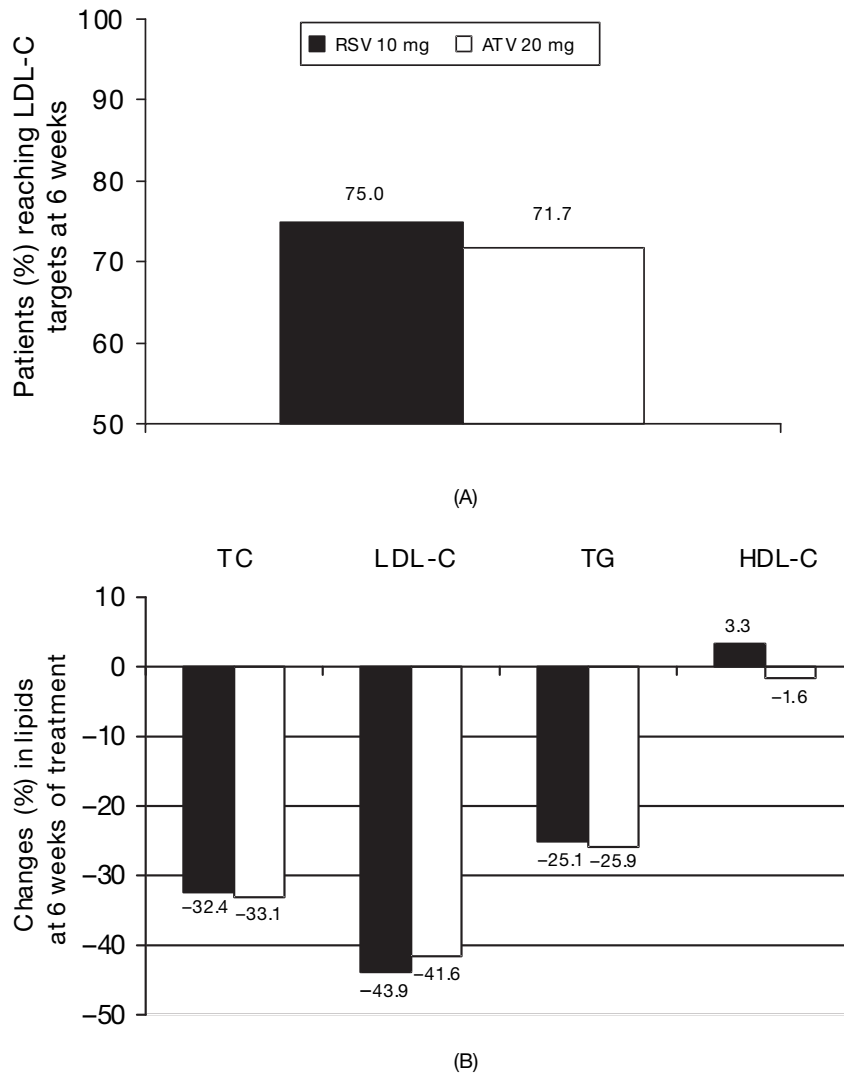
## Results

The demographic data and laboratory characteristics of the population studied are shown in Tables 1 and 2. There were no significant differences in age, sex, body mass index, serum fasting glucose, insulin, HOMA index, serum Cr, estimated CrCl and TPR/Cr ratio

between patient groups at baseline and the control group.

A total of 45 patients (75.0%) in the RSV-treated group and 43 (71.7%) in the ATV-treated group achieved the pre-specified treatment LDL-C target at the initial dose of statin therapy (Figure 2A). At the end of the study the treatment goal was not met in four patients (6.7%) in the RSV group and in five patients (8.3%) in the ATV group. These differences were not significant. The overall mean daily dosage of RSV used was 12.5 mg/day; the ATV daily dose was 25.7 mg/day.

Statin treatment had a beneficial effect on the lipid profile. Significant changes in lipids were produced by the initial dosage regimens (Figure 2B). Dose titration of both statins further improved the lipid profile (Table 1). Specifically, RSV (10/20 mg daily) reduced TC levels by 36.1% (mean value,  $-103$  mg/dL), LDL-C levels by 36.1% (mean value,  $-103$  mg/dL), LDL-C



**Figure 2.** (A) Percentage of patients reaching the LDL-C treatment target of less than 130mg/dL at 6 weeks on treatment with rosuvastatin (RSV,  $n = 60$ ) 10mg/day and atorvastatin (ATV,  $n = 60$ ) 20mg/day. (B) Changes in lipids on the initial dosage of statin therapy. TC = total cholesterol; LDL-C = low density lipoprotein cholesterol; TG = triglycerides; HDL-C = high density lipoprotein cholesterol

by 48.7% (−96 mg/dL) and TG by 29.0% (−46 mg/dL), and increased HDL-C by 5.0% (+2 mg/dL); ATV (20/40 mg/day) reduced TC levels by 36.9% (mean value, −110 mg/dL), LDL-C by 44.6% (−100 mg/dL) and TG levels by 27.8% (−46 mg/dL), and decreased HDL-C levels by 2.1% (−1.0 mg/dL) from baseline (Table 1). After correcting for baseline HDL-C values, the RSV regimen was more efficacious than ATV in raising HDL-C levels (one-way ANCOVA,  $F = 10.45$ ,  $p = 0.002$ ).

Both statins reduced apo B levels (Table 1), but only RSV produced a non-significant increase (by 2.0%) in the apo A1 levels. The apo B/apo A1 ratio was similarly decreased in both groups (−30.1% in the RSV group vs. −29.6% in the ATV group).

No significant changes in Cr, CrCl, fasting glucose, insulin and HOMA index were noted after the completion of the study in both groups of patients (Table 2).

Two patients in both groups (2/60, 3.3%) had dipstick positive proteinuria at the second visit following 6 weeks on treatment, which resolved at the final visit (week 24). No evidence of haematuria was noted in either group of patients. There was no evidence of clinically significant proteinuria evaluated by TPR/Cr ratio in either group (Table 2).

Both statins produced significant reductions in hsCRP and fibrinogen concentrations (Table 2). Notably, in both groups fibrinogen levels were raised

at 6 weeks (median values, 366 vs. 390 mg/dL in the RSV group and 353 vs. 378 mg/dL in the ATV group,  $p < 0.01$  for both comparisons) and dropped at week 24 (RSV: 366 vs. 347 and ATV: 353 vs. 330 mg/dL,  $p < 0.001$  for both comparisons).

Serum uric acid levels were significantly lowered in the ATV-treated patients by 7.5% (mean change: −0.45 mg/dL,  $p < 0.01$ ), but not in the RSV-treated group (Table 2). The uric acid lowering effect of atorvastatin was significantly greater compared to RSV even after correcting for the pre-treatment uric acid levels in the two groups (one-way ANCOVA,  $F = 5.49$ ,  $p = 0.02$ ).

In the ATV-treated group, no correlation was found between 'post-treatment minus baseline' changes ( $\Delta$ ) in serum uric acid ( $\Delta$ UA) levels and changes in serum lipid levels (TC, TG, LDL-C or HDL-C). On further analysis, the 'post-treatment minus baseline' changes in the fractional excretion of uric acid (FEUA) correlated positively with changes in fractional excretion of sodium (FENa) ( $r = 0.32$ ,  $p = 0.04$ ).

A drop in serum uric acid levels (mean change: −0.86 mg/dL) was noted in 42 RSV-treated patients (70.0%). Serum uric acid levels were increased in 14 (23.3%) patients (mean change: 0.53 mg/dL) following RSV treatment, and did not change from baseline in four patients (6.7%). The post-treatment reduction from baseline in  $\Delta$ UA correlated with pre-treatment serum uric acid levels ( $r = 0.53$ ,  $p < 0.001$ ).

**Table 1.** Demographic characteristics and lipid parameters in the ATOROS study population

|                                | Rosuvastatin<br>( $n = 60$ ) |                         | Atorvastatin<br>( $n = 60$ ) |                         | Controls<br>( $n = 60$ ) |
|--------------------------------|------------------------------|-------------------------|------------------------------|-------------------------|--------------------------|
|                                | Baseline                     | Follow-up<br>(24 weeks) | Baseline                     | Follow-up<br>(24 weeks) |                          |
| Age, years                     | 53.5 ± 7.9                   |                         | 53.3 ± 7.7                   |                         | 54.0 ± 8.1               |
| Sex, $n$                       |                              |                         |                              |                         |                          |
| Male                           | 33                           |                         | 35                           |                         | 32                       |
| Female                         | 27                           |                         | 25                           |                         | 28                       |
| BMI, kg/m <sup>2</sup>         | 24.1 ± 3.2                   |                         | 24.0 ± 3.4                   |                         | 23.4 ± 2.9               |
| Current smokers, $n$ (%)       | 14 (23.3)                    |                         | 16 (26.7)                    |                         | 13 (21.7)                |
| Hypertension, $n$ (%)          | 31 (51.7)                    |                         | 30 (50.0)                    |                         | 5 (8.3)                  |
| Family history of CHD, $n$ (%) | 21 (35.0)                    |                         | 19 (31.7)                    |                         | 4 (6.7)                  |
| TC, mg/dL                      | 285 ± 30*                    | 182 ± 32†               | 285 ± 43*                    | 180 ± 27†               | 222 ± 35                 |
| LDL-C, mg/dL                   | 205 ± 42*                    | 105 ± 21†               | 204 ± 40*                    | 113 ± 38†               | 137 ± 26                 |
| TG, mg/dL                      | 159 ± 51*                    | 113 ± 35†               | 157 ± 55*                    | 113 ± 49†               | 124 ± 40                 |
| HDL-C, mg/dL                   | 48 ± 6*                      | 50 ± 6†                 | 48 ± 8*                      | 47 ± 7†                 | 57 ± 11                  |
| Non-HDL-C, mg/dL               | 237 ± 30*                    | 130 ± 25†               | 237 ± 43*                    | 128 ± 22†               | 168 ± 40                 |
| ApoA1, mg/dL                   | 134 ± 21*                    | 137 ± 27                | 133 ± 24*                    | 129 ± 22                | 142 ± 28                 |
| ApoB, mg/dL                    | 185 ± 49*                    | 131 ± 37†               | 184 ± 45*                    | 135 ± 39†               | 121 ± 22                 |
| Lp(a), mg/dL, mean (range)     | 19 (2.4–139)*                | 17 (2.4–114)            | 17 (2.4–146)*                | 17 (2.4–128)            | 12 (2.4–74)              |

\* $p < 0.001$  between patients with primary hyperlipidaemia at baseline and controls

† $p < 0.001$  between baseline and follow-up

Data are shown as mean ± standard deviation, unless otherwise indicated

Conversion factors: to convert TC, LDL-C, non HDL-C and HDL-C levels from mg/dL to mmol/L, multiply by 0.02586. To convert TG levels from mg/dL to mmol/L multiply by 0.01129

BMI = body mass index; TC = total cholesterol; LDL-C = low density lipoprotein cholesterol; TG = triglycerides; HDL-C = high density lipoprotein cholesterol; Apo = apolipoprotein; Lp = lipoprotein

**Table 2.** Serum and urinary metabolic parameters at baseline in patients and controls and after 24 weeks in patients on atorvastatin (20–40 mg/day) or rosuvastatin (10–20 mg/day)

| Variable                        | Rosuvastatin<br>(n = 60) |                         | Atorvastatin<br>(n = 60) |                         | Controls<br>(n = 60) |
|---------------------------------|--------------------------|-------------------------|--------------------------|-------------------------|----------------------|
|                                 | Baseline                 | Follow-up<br>(24 weeks) | Baseline                 | Follow-up<br>(24 weeks) |                      |
| Serum fasting glucose, mg/dL    | 94 ± 10                  | 93 ± 8                  | 94 ± 11                  | 94 ± 10                 | 96 ± 12              |
| Serum insulin, µU/mL            | 9.6 ± 3.7                | 9.5 ± 3.2               | 9.5 ± 4.5                | 9.5 ± 3.8               | 9.8 ± 5.5            |
| HOMA index                      | 2.5 ± 1.1                | 2.5 ± 0.9               | 2.4 ± 1.2                | 2.5 ± 1.0               | 2.5 ± 2.2            |
| hsCRP, mg/L, mean (range)       | 3.1 (0.7–7.2)*           | 1.9 (0.8–3.9)†          | 3.3 (0.8–7.8)*           | 2.1 (0.8–4.0)†          | 2.0 (0.6–4.2)        |
| Fibrinogen, mg/dL, mean (range) | 366 (180–598)*           | 347 (231–501)†          | 353 (236–520)*           | 330 (225–437)†          | 244 (164–367)        |
| Serum uric acid, mg/dL          | 5.1 ± 1.3                | 5.0 ± 1.2               | 5.3 ± 1.1                | 4.9 ± 0.9§              | 4.9 ± 1.4            |
| FEUA, %                         | 4.8 ± 1.9                | 4.8 ± 2.1               | 4.6 ± 1.7                | 4.9 ± 1.5§              | 4.6 ± 2.0            |
| FENa, %                         | 0.5 ± 0.3                | 0.5 ± 0.3               | 0.5 ± 0.3                | 0.7 ± 0.2§              | 0.4 ± 0.2            |
| Serum creatinine, mg/dL         | 0.91 ± 0.12              | 0.89 ± 0.12             | 0.90 ± 0.13              | 0.90 ± 0.13             | 0.93 ± 0.13          |
| CrCl, mL/min                    | 85 ± 26                  | 87 ± 26                 | 85 ± 20                  | 85 ± 21                 | 85 ± 26              |
| Urinary Pr/Cr ratio             | 0.07 ± 0.04              | 0.07 ± 0.05             | 0.07 ± 0.04              | 0.06 ± 0.04             | 0.07 ± 0.05          |

\**p* < 0.01 (Wilcoxon signed-rank test) between patients at baseline and controls

†*p* < 0.001 between baseline and follow-up

§*p* < 0.01 between baseline and follow-up

Data are shown as mean ± standard deviation, unless otherwise indicated

Conversion factors: to convert values for glucose to mmol/L, multiply by 0.05551. To convert values for insulin to pmol/L, multiply by 6.945.

To convert serum uric acid levels from mg/dL to µmol/L multiply by 59.48. To convert values for creatinine to mmol/L, multiply by 88.40

HOMA = homeostasis model assessment; hsCRP = high sensitivity C-reactive protein; FEUA = fractional excretion of uric acid; FENa = fractional excretion of sodium; CrCl = creatinine clearance; Pr = protein

## Safety and tolerability of treatment

Both study treatment regimens were generally well tolerated. All participants completed the study protocol. There were no withdrawals due to treatment-related serious adverse events. Clinically significant elevations in alanine aminotransferase (ALT, values of > 3 times the upper limit of normal on two consecutive occasions) or in creatine kinase (CK) activities (values of > 10 times the upper limit of normal) were not observed during follow up. The occurrence of myalgia (i.e. muscle symptoms reported by the patient with or without CK elevation) was similar in both groups: three patients (5.0%) in the RSV group (two were receiving RSV 10 mg/day and one 20 mg/day) and three patients in the ATV group (one was on ATV 20 mg/day and two on 40 mg/day). One woman treated with RSV 10 mg reported nausea and light-headedness; this resolved over a period of 1 week.

## Discussion

In the present study, statin treatment (RSV 10/20 or ATV 20/40 mg/day) was highly effective in achieving the LDL-C target (130 mg/dL; 3.4 mmol/L) in the majority of patients with primary hyperlipidaemia. Both regimens had favourable effects on lipid parameters, producing similar significant reductions of TC, LDL-C, apo B and TG, as well as of apo B/apo

A1 ratio, which are considered as predictors of vascular risk<sup>9</sup>. Head-to-head comparisons between RSV and ATV in previous studies showed that at equivalent doses RSV was more effective than ATV in reducing LDL-C and achieving LDL-C treatment goals in patients with hypercholesterolaemia, type 2 diabetes mellitus and the metabolic syndrome<sup>2,10–13</sup>. In line with these reports, the LDL-C lowering effect of RSV at the starting dose of 10 mg was greater than that of ATV 20 mg in patients with primary hyperlipidaemia in our study.

ATV had a rather 'neutral' effect on HDL-C, while RSV had a significant HDL-C raising effect and showed a trend towards increasing serum apo A1 levels. Previous studies suggested a possible negative dose-response effect of ATV on HDL-C levels<sup>14</sup>. On the other hand, RSV has been shown to be more effective in improving the LDL-C/HDL-C ratio in patients with CVD and low HDL-C<sup>15</sup>. However, there is evidence that ATV treatment may increase HDL-C, especially in patients with a low pre-treatment HDL-C concentration<sup>16,17</sup>. ATV treatment has also been associated with a favourable effect on the apo A1-containing subpopulation profiles and with an increase in the activity of HDL-C-associated paraoxonase<sup>18,19</sup>. The lack of determination of HDL subpopulation profile and/or paraoxonase activity may represent a study limitation.

Parameters of glycaemic and insulin resistance estimates were not significantly altered by either RSV or ATV. Statin therapy has been reported to improve

insulin resistance and decrease the long-term incidence of diabetes mellitus in treated dyslipidaemic patients<sup>20,21</sup>. However, as shown in this and other studies, short-term treatment with statins (i.e. 24 weeks) in dyslipidaemic patients without evidence of hyperinsulinaemia or insulin resistance did not alter insulin sensitivity<sup>4,8,22</sup>.

No significant variations in renal function parameters (i.e. Cr and calculated CrCl) were observed in either statin group during the study period. Dyslipidaemia is believed to exert deleterious effects on renal function through harmful effects on glomerular mesangial cells and endothelial cells<sup>23–25</sup>. There is evidence of a benefit of statin treatment on renal function modulated by mechanisms other than lipid reduction (i.e. pleiotropic effects)<sup>26,27</sup>. However, not all statins are necessarily beneficial. Concerns about the development of proteinuria (dipstick positive proteinuria defined as a shift from no protein or trace at baseline to ++ or more) have been raised for RSV<sup>28</sup>. Dipstick-positive proteinuria has been described in some patients who received 80 mg/day of rosuvastatin in phase III trials<sup>29</sup>. However, further assessment of the clinical program safety database failed to show that this mild proteinuria was predictive of any acute or progressive change in renal function or that RSV therapy was associated with deteriorating renal function<sup>29,30</sup>. In terms of safety, it appears that a dose of 10–20 mg/day of RSV does not have any impact on kidney function, clinically significant proteinuria or haematuria in patients with primary hyperlipidaemia. Statin effects on renal function are potentially relevant since there is evidence that elevated serum Cr levels, even within the reference range, are independent predictors of IHD adverse outcomes and stroke in high risk patients<sup>31</sup>.

A substantial decrease in hsCRP and fibrinogen levels, which are considered predictors of IHD and severity of atherosclerosis, was also noted following statin treatment. This CRP-lowering effect seems to be shared among statins<sup>4,8,32</sup>. Furthermore, patients who have low CRP levels after statin therapy have better clinical outcomes than those with higher CRP levels, regardless of the resultant level of LDL-C<sup>33</sup>.

A small non-significant increase in plasma fibrinogen levels was seen after 6 weeks of treatment with either RSV 10 mg or ATV 20 mg. There are conflicting results concerning the influence of statins on plasma fibrinogen levels<sup>4,34,35</sup>. Some studies reported a marked increase in fibrinogen levels<sup>36,37</sup>, while others failed to show this change<sup>35</sup>. The heterogeneous nature of patients recruited, the duration of treatment, sampling at a single time point, variations in drug dosage and different assay methods may account, at least in part, for these discrepancies<sup>4,34,35</sup>. A transient increase in fibrinogen levels following statin treatment has been

previously described<sup>34</sup>. The clinical relevance of this effect is questionable. It is possible to speculate that it is related to an inflammatory response associated with changes in plaque structure.

Serum uric acid levels decreased in the ATV-treated group but did not significantly change from baseline after RSV treatment. Although higher serum uric acid concentrations have been identified as predictors of CVD in unselected populations in a number of epidemiological studies, it is unclear whether hyperuricaemia is a true risk factor<sup>38</sup>. Moreover, lowering serum uric acid levels may be associated with reduced vascular morbidity and mortality<sup>39–41</sup>. There is evidence that ATV and simvastatin may exert a serum uric acid-lowering effect<sup>4,40,42</sup>. The significant decrease in serum uric acid levels we observed is comparable with that in previous studies after treatment with ATV<sup>4</sup>. Because the ATV-induced decrease in serum uric acid levels was independent of changes in serum lipids, this effect may not be related to a lipid-lowering effect. The hypouricaemic effect of ATV correlated only with the baseline serum uric acid levels. ATV reduced serum uric acid levels and augmented both FEUA and FENa. Increased urinary secretion of both sodium and uric acid following ATV treatment suggests a decrease in proximal tubular reabsorption rather than a pharmacologically-induced active tubular secretion of urate<sup>4</sup>.

In this small, randomized, open-label study we evaluated the efficacy, safety and tolerability, as well as the non-lipid metabolic effects of ATV and RSV in moderate risk patients with primary hyperlipidaemia treated to LDL-C goals. Differences in variables that were of potential clinical importance were noted after achieving LDL-C targets following dose titration. However, our findings require confirmation in studies with larger patient populations.

## Conclusions

At the start dose of RSV 10 mg and ATV 20 mg and following dose titration, most CVD-free patients with primary hyperlipidaemia achieved the LDL-C target. RSV was equally efficacious to approximately double the dose of ATV. Both statin treatments were safe, well-tolerated and shared an anti-inflammatory potential. RSV seems to have a significantly higher HDL-C-raising effect while ATV produces a significant reduction in serum uric levels.

When RSV and ATV doses are adjusted to achieve similar LDL-C levels there are significant differences in some variables. These differences may be clinically relevant.

## Acknowledgements

**Declaration of interest:** This study was conducted independently; no company or institution supported it financially. Some of the authors have given talks, attended conferences and participated in trials and advisory boards sponsored by AstraZeneca and Pfizer.

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Paper CMRO-3434\_3, *Accepted for publication*: 18 April 2006  
*Published Online*: 11 May 2006  
doi:10.1185/030079906X112462