A COmparative study with rosuvastatin in subjects with METabolic Syndrome: results of the COMETS study

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Introduction

The metabolic syndrome is a complex constellation of disorders that increase the risk of coronary heart disease (CHD).1–3 The major components of the metabolic syndrome are abdominal obesity, dyslipidaemia, impaired glucose regulation, and hypertension.4 Estimates of the prevalence of the metabolic syndrome vary with the criteria used to define the condition, but are likely to increase in line with worldwide epidemiological trends in obesity and diabetes, together with greater longevity. Changes in lifestyle are fundamental to reducing many of the risk factors associated with the metabolic syndrome,5 but some patients may also require pharmacological intervention for the management of dyslipidaemia, hypertension, and hyperglycaemia.

The atherogenic dyslipidaemia associated with the metabolic syndrome is characterized by low levels of high-density lipoprotein cholesterol (HDL-C) and high levels of triglyceride (TG); in diabetic patients, a preponderance of small low-density lipoprotein (LDL) particles is often seen.6 Many patients may also have raised LDL-C, although this is not part of the diagnostic criteria, and the risk of CHD in patients with the metabolic syndrome is increased irrespective of LDL-C levels.1,4

Statins lower blood cholesterol levels and reduce the risk of cardiovascular events in many patient types and are therefore recommended as first-line agents for lowering LDL-C.4,7 Statins also improve other aspects of the lipid profile, for example, by increasing HDL-C and lowering TG to some extent. Furthermore, statins have ‘pleiotropic’ effects, such as reducing oxidative stress and modulating inflammatory responses,8 and these effects may improve other risk factors associated with the metabolic syndrome.

To date, evidence suggesting that statins can improve lipid levels in patients with the metabolic syndrome has been limited to post hoc subgroup analyses.9–12 Results of the COmparative study with rosuvastatin in subjects with METabolic Syndrome (COMETS, 4522IL/0069), the first large, international, prospective, randomized trial of statin therapy in this patient group, are reported here.

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Methods

Study design

COMETS was a double-blind, double-dummy, randomized, multinational, three-arm, parallel-group study comparing the efficacy of rosvastatin with that of atorvastatin or placebo in patients with the metabolic syndrome. Patients were recruited from 68 primary care and specialist centres in Belgium, Finland, The Netherlands, Norway, Slovakia, the UK, and the USA. Following a 4-week dietary lead-in period, during which they were asked to follow the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) therapeutic lifestyle-change diet, eligible patients were randomized (2:2:1) to receive rosuvastatin 10 mg, atorvastatin 10 mg, or placebo once daily for 6 weeks (Figure 1). The rosuvastatin 10 mg and placebo groups then received rosuvastatin 20 mg and the atorvastatin 10 mg group received atorvastatin 20 mg for a further 6 weeks to assess whether additional benefit was observed by increasing the dose.

Patients

Eligible patients were men and women aged \( \geq 18 \) with the metabolic syndrome as defined by the presence of at least three of the following: abdominal obesity (waist circumference \( > 102 \text{ cm} \) for men and \( > 88 \text{ cm} \) for women); TG \( \geq 1.70 \text{ mmol/L} \) (150 mg/dL); HDL-C \( < 1.04 \text{ mmol/L} \) (40 mg/dL) for men and \( < 1.30 \text{ mmol/L} \) (50 mg/dL) for women; blood pressure \( \geq 130/85 \text{ mmHg} \) or receiving antihypertensive treatment; and fasting blood glucose \( \geq 6.11 \text{ mmol/L} \) (110 mg/dL). Patients with diabetes [fasting glucose \( > 6.94 \text{ mmol/L} \) (125 mg/dL)] were excluded. Patients were also required to have LDL-C \( \geq 3.36 \text{ mmol/L} \) (130 mg/dL) and additional multiple risk factors conferring a 10-year CHD risk score of \( > 10\% \). Other major exclusion criteria included the following: use of lipid-lowering agents within the past 6 months; TG \( > 5.65 \text{ mmol/L} \) (500 mg/dL); LDL-C \( > 6.48 \text{ mmol/L} \) (250 mg/dL); documented history of CHD or other atherosclerotic disease; a history of known familial hypercholesterolaemia; a history of serious or hypersensitivity reactions to other statins; uncontrolled hypocholesterolemia; uncontrolled hypertension; acute liver disease or hepatic dysfunction [hepatic transaminases or bilirubin \( > 1.5 \times \) the upper limit of normal (ULN)]; unexplained serum creatine kinase (CK) \( > 3 \times \) ULN; and use of prohibited concomitant medications.

The study was conducted in accordance with the principles of the Declaration of Helsinki and good clinical practice, with local Ethics Committee approval being obtained at each centre. All patients were fully informed and written consent was obtained.

Assessments

Blood samples were collected at \(-4\) weeks (beginning of the dietary lead-in period), \(-2\) weeks, 0 weeks (randomization), 6 weeks, and 12 weeks. Laboratory samples for lipids, clinical chemistry, and haematology were centrally analysed (Medical Research Laboratories, Highland Heights, KY, USA).

The primary efficacy variable was percentage change from baseline in LDL-C levels after 6 weeks of treatment (rosuvastatin 10 mg vs. atorvastatin 10 mg). Secondary objectives included comparisons of rosuvastatin 10 mg with atorvastatin 10 mg or placebo at 6 weeks and the combined rosuvastatin 10/20 mg and placebo/rosuvastatin 20 mg groups with the atorvastatin 10/20 mg group at 12 weeks in terms of percentage change from baseline in LDL-C; LDL-C goal achievement [1998 and 2003 (post hoc analysis)] European, NCEP ATP III, and LDL-C \( = 2.59 \text{ mmol/L} \) (100 mg/dL), a pre-specified level agreed at the time of study design]; NCEP ATP III non-HDL-C goal achievement for patients with TG \( > 2.26 \text{ mmol/L} \) (200 mg/dL); percentage changes from baseline in total cholesterol (TC), HDL-C, non-HDL-C, TG, lipoprotein ratios, apolipoproteins (Apos), high-sensitivity C-reactive protein (hsCRP), fasting plasma glucose, and insulin resistance using homeostasis model assessment (HOMA). Additional post hoc analyses were performed to compare hsCRP levels in all patients at baseline and 12 weeks and to compare changes in hsCRP levels between treatment groups at 6 and 12 weeks in patients with elevated baseline hsCRP (\( > 2 \text{ mg/L} \) or \( > 3 \text{ mg/L} \)). Safety was assessed from the incidence of adverse events (AEs) and abnormal laboratory data.

Statistical analysis

A total of 133 patients per active treatment group were required for 90% power to detect a clinically significant \( 6\% \) difference at the 5% two-sided level for the primary variable of percentage change from baseline in LDL-C for rosuvastatin vs. atorvastatin at 6 weeks, with an assumed standard deviation of \( 15\% \). Assuming a screen failure rate of \( 60\% \), approximately 940 patients were required to be screened. Assuming a dropout of \( 10\% \) during the randomized treatment period, 150 patients per active treatment arm and 75 patients for the placebo group were required to be randomized.

Efficacy data were evaluated on the basis of the intention-to-treat (ITT) and per-protocol (PP) populations. The ITT population consisted of patients with at least one dose of study medication, a baseline reading, and at least one post-baseline assessment for one or more lipid variables in the randomized treatment period. A misunderstanding by some investigators led to the misrandomization of 42 patients. These patients were allocated a blinded bottle of treatment medication instead of receiving the next available randomization number. This was a genuine error, and as it occurred blind to treatment, it is not felt to have introduced bias into the study. The ITT population was therefore analysed in two ways: the ITT population by randomized treatment was analysed according to the treatment group to which the patients should have been assigned by the randomized schedule and the ITT population by as-allocated treatment was analysed according to the treatment group to which the patients were actually assigned.

The primary result for the primary efficacy variable was ITT population by randomized treatment using the last observation carried forward (LOCF). All efficacy variables were also analysed using LOCF on the ITT population by as-allocated treatment. This approach was chosen as it uses the ITT approach but is deemed more clinically relevant, because it is likely to be more reflective of treatment effects. Results for the primary efficacy variable are presented for the ITT population by randomized and as-allocated treatments. Thereafter, results are presented for all efficacy variables for the ITT population by as-allocated treatment. The PP population excluded misrandomized patients and those with other major violations (inclusion/exclusion criteria not met at screening or randomization) or deviations (non-compliance with treatment, additional cholesterol-lowering drugs, study blind-broken prematurely); patients with violations or deviations were identified before the study was unblinded.

Efficacy endpoints were analysed using analysis of variance (ANOVA). HOMA and hsCRP data were analysed using a non-parametric Kruskal-Wallis test. The percentage of patients...
achieving LDL-C goals was compared by logistic regression analysis. Percentage change from baseline in C-reactive protein for each treatment group was analysed using a Wilcoxon Signed Rank test. hsCRP results are not normally distributed and are highly skewed; the median values were therefore chosen as the most appropriate statistic to summarize these data. On the basis of the actual treatment received, safety data were evaluated for all patients who received at least one dose of study medication.

Figure 2  Patient flow and statistical analysis sets. The two ITT groups did not contain an identical set of patients. Five patients who inadvertently received trial medications different from that required by the allocated patient number were also included in the safety analysis.

Table 1  Patient characteristics (randomized population by as-allocated treatment)

<table>
<thead>
<tr>
<th></th>
<th>RSV 10/20 mg (n = 165)</th>
<th>ATV 10/20 mg (n = 157)</th>
<th>Placebo/RSV 20 mg (n = 79)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean (SD)</td>
<td>58.1 (9.4)</td>
<td>57.3 (9.4)</td>
<td>57.8 (9.0)</td>
</tr>
<tr>
<td>Range</td>
<td>31-80</td>
<td>35-82</td>
<td>40-76</td>
</tr>
<tr>
<td>Gender, men, n (%)</td>
<td>100 (60.6)</td>
<td>106 (67.5)</td>
<td>51 (64.6)</td>
</tr>
<tr>
<td>Race, Caucasian, n (%)</td>
<td>163 (98.8)</td>
<td>154 (98.1)</td>
<td>75 (94.9)</td>
</tr>
<tr>
<td>Body mass index (kg/m²), mean (SD)</td>
<td>30.5 (3.6)</td>
<td>31.1 (3.5)</td>
<td>30.5 (3.9)</td>
</tr>
<tr>
<td>Metabolic syndrome criteria, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal obesitya</td>
<td>150 (90.9)</td>
<td>147 (93.6)</td>
<td>73 (92.4)</td>
</tr>
<tr>
<td>TG ≥1.70 mmol/L (150 mg/dL)</td>
<td>138 (83.6)</td>
<td>131 (83.4)</td>
<td>73 (92.4)</td>
</tr>
<tr>
<td>Low HDL-Cb</td>
<td>84 (50.9)</td>
<td>70 (44.6)</td>
<td>29 (36.7)</td>
</tr>
<tr>
<td>Blood pressure ≥130/85 mmHg</td>
<td>160 (97.0)</td>
<td>154 (98.1)</td>
<td>76 (96.2)</td>
</tr>
<tr>
<td>Fasting glucose 6.11-6.94 mmol/L (110–125 mg/dL)</td>
<td>35 (21.2)</td>
<td>43 (27.4)</td>
<td>18 (22.8)</td>
</tr>
<tr>
<td>NCEP ATP III risk category, c n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>44 (26.7)</td>
<td>45 (28.7)</td>
<td>22 (27.8)</td>
</tr>
<tr>
<td>Medium</td>
<td>119 (72.1)</td>
<td>110 (70.1)</td>
<td>56 (70.9)</td>
</tr>
<tr>
<td>Low</td>
<td>2 (1.2)</td>
<td>2 (1.3)</td>
<td>1 (1.3)</td>
</tr>
</tbody>
</table>

aWaist circumference >102 cm for men and >88 cm for women.
bHDL-C < 1.04 mmol/L (40 mg/dL) for men and <1.30 mmol/L (50 mg/dL) for women.
cNCEP ATP III risk categories: high, CHD or CHD-risk equivalent or 10-year CHD risk >20%; medium, 2+ risk factors and 10-year CHD risk ≤20%; low, 0-1 risk factor.
Results

Patient characteristics

From 1338 patients entering the dietary lead-in period, 401 were randomized into the study and received study medication, and 397 and 318 patients fulfilled the criteria for the ITT and PP populations, respectively (Figure 2).

Discontinuation rates were low [rosuvastatin 10/20 mg, eight patients (4.8%); atorvastatin 10/20 mg, eight patients (5.1%); placebo/rosuvastatin 20 mg, four patients (5.1%)]. The treatment groups were very similar at baseline in terms of demographic and clinical variables (Table 1). Over 80% of patients had abdominal obesity, elevated TG [≥1.70 mmol/L (150 mg/dL)], or hypertension (Table 1). The majority of patients were categorized as medium risk, according to NCEP ATP III guidelines. A total of 10 patients in the rosuvastatin 10/20 mg group, seven patients in the atorvastatin 10/20 mg group, and six patients in the placebo/rosuvastatin 20 mg group fulfilled the criteria for the more stringent 2003 European goal of LDL-C, 2.5 mmol/L (100 mg/dL). Baseline levels of lipoproteins, lipids, ApoA, inflammatory markers, fasting plasma glucose, and insulin resistance were similar among treatment groups (Table 2).

Study medication compliance was high and similar among treatment groups (rosuvastatin 10/20 mg, 96.3%; atorvastatin 10/20 mg, 95.9%; placebo/rosuvastatin 20 mg, 94.6%).

Efficacy

Rosuvastatin was more effective than atorvastatin on the primary endpoint (percentage change from baseline): rosuvastatin 10 mg reduced LDL-C levels from baseline significantly more than atorvastatin 10 mg (41.7 vs. 35.7%, P < 0.001 for the ITT population by randomized treatment) after 6 weeks of treatment. Analysis of the ITT population by as-allocated treatment produced very similar results (reductions of 42.7 and 36.6% for rosuvastatin 10 mg and atorvastatin 10 mg, respectively, P < 0.001) (Figure 3 and Table 3). In addition, rosuvastatin 10 mg reduced LDL-C significantly more than placebo (42.7 vs. 0.3%, P < 0.001; ITT population by as-allocated treatment) (Figure 3 and Table 3). At 12 weeks, significant reductions in LDL-C were observed in the rosuvastatin combined group when compared with the atorvastatin group (48.9 vs. 42.5%, P < 0.001; ITT population by as-allocated treatment) (Figure 3 and Table 3). All further results are presented for the ITT population by as-allocated treatment; however, similar results were obtained in analyses of the ITT population by randomized treatment and the PP population.

Substantially, more patients achieved LDL-C goals in the rosuvastatin group than in the atorvastatin group (Table 4), indicating a clinically relevant effect. For example, the 1998 European LDL-C goal was achieved by

![Figure 3 Percentage change from baseline in LDL-C levels (ITT population by as-allocated treatment). LSM, least-squares mean. *P < 0.001 vs. RSV at the same time point.](image)

<table>
<thead>
<tr>
<th>Lipoprotein/lipid levels (mmol/L), mean (SD)</th>
<th>RSV 10/20 mg (n = 164)</th>
<th>ATV 10/20 mg (n = 155)</th>
<th>Placebo/RSV 20 mg (n = 78)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC</td>
<td>6.48 (0.81)</td>
<td>6.47 (0.79)</td>
<td>6.60 (0.78)</td>
</tr>
<tr>
<td>LDL-C</td>
<td>4.40 (0.70)</td>
<td>4.35 (0.65)</td>
<td>4.42 (0.67)</td>
</tr>
<tr>
<td>HDL-C</td>
<td>1.13 (0.25)</td>
<td>1.16 (0.25)</td>
<td>1.20 (0.25)</td>
</tr>
<tr>
<td>Non-HDL-C</td>
<td>5.35 (0.76)</td>
<td>5.30 (0.76)</td>
<td>5.40 (0.78)</td>
</tr>
<tr>
<td>TG</td>
<td>2.34 (0.79)</td>
<td>2.25 (0.78)</td>
<td>2.42 (0.84)</td>
</tr>
<tr>
<td>Lipoprotein ratio, mean (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TC/HDL-C</td>
<td>5.93 (1.16)</td>
<td>5.78 (1.28)</td>
<td>5.72 (1.21)</td>
</tr>
<tr>
<td>LDL-C/HDL-C</td>
<td>4.02 (0.87)</td>
<td>3.88 (0.90)</td>
<td>3.83 (0.91)</td>
</tr>
<tr>
<td>Non-HDL-C/HDL-C</td>
<td>4.93 (1.16)</td>
<td>4.78 (1.28)</td>
<td>4.72 (1.21)</td>
</tr>
<tr>
<td>Apo levels, mean (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ApoB (mg/dL)</td>
<td>161.6 (25.4)</td>
<td>160.6 (25.6)</td>
<td>164.4 (25.7)</td>
</tr>
<tr>
<td>ApoA-1 (mg/dL)</td>
<td>148.4 (27.1)</td>
<td>151.3 (24.3)</td>
<td>154.0 (22.6)</td>
</tr>
<tr>
<td>ApoA1/ApoB</td>
<td>1.12 (0.23)</td>
<td>1.09 (0.23)</td>
<td>1.09 (0.24)</td>
</tr>
<tr>
<td>HsCRP level (mg/L), median (10th and 90th percentiles)</td>
<td>2.3 (0.9, 8.1)</td>
<td>2.8 (0.7, 8.2)</td>
<td>2.5 (0.7, 8.2)</td>
</tr>
<tr>
<td>Fasting plasma glucose (mmol/L), mean (SD)</td>
<td>5.61 (0.57)</td>
<td>5.60 (0.66)</td>
<td>5.62 (0.70)</td>
</tr>
<tr>
<td>Insulin resistance, median (10th and 90th percentiles)</td>
<td>2.5 (1.4, 5.3)</td>
<td>2.5 (1.3, 5.2)</td>
<td>2.5 (1.1, 5.2)</td>
</tr>
</tbody>
</table>

Non-HDL-C, non-high-density lipoprotein cholesterol.
79% of patients receiving rosuvastatin compared with 71% receiving atorvastatin \( (P < 0.05) \) and 3% receiving placebo at 6 weeks \( (P < 0.001) \) and 90% of rosuvastatin-treated patients compared with 83% of atorvastatin-treated patients at 12 weeks \( (P < 0.05) \). Achievement of 2003 European LDL-C goals was similar to that of 1998 European goals as LDL-C < 3.0 mmol/L \((115 \text{ mg/dL})\) was the relevant goal for most patients. Rosuvastatin enabled the majority of patients with elevated TG to achieve non-HDL-C goals (Table 4).

Percentage improvements in TC, HDL-C, and non-HDL-C from baseline were significantly greater in the rosuvastatin group when compared with the atorvastatin group at 6 and 12 weeks (Table 3). By 12 weeks, HDL-C increased by 10.4% with rosuvastatin when compared with 5.8% with atorvastatin \( (P < 0.01) \). Reductions in TG were similar in the rosuvastatin and atorvastatin groups. Significant improvements in TC/HDL-C, LDL-C/HDL-C, non-HDL-C/HDL-C, ApoB, ApoA-1, and ApoB/ApoA-1 were also observed in the

### Table 3 Percentage change from baseline in lipoprotein, lipid, and lipoprotein ratio levels (ITT population by as-allocated treatment)

<table>
<thead>
<tr>
<th></th>
<th>LSM change from baseline (%) (SE)</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>6 weeks</td>
<td>12 weeks</td>
<td></td>
</tr>
<tr>
<td></td>
<td>RSV 10 mg (n = 164)</td>
<td>Placebo (n = 78)</td>
<td>RSV combined (n = 242)</td>
</tr>
<tr>
<td>TC</td>
<td>-31.9 (0.8)*</td>
<td>-0.7 (1.1)*</td>
<td>-36.8 (0.7)</td>
</tr>
<tr>
<td>LDL-C</td>
<td>-42.7 (1.1)*</td>
<td>+0.3 (1.5)*</td>
<td>-48.9 (0.9)</td>
</tr>
<tr>
<td>HDL-C</td>
<td>+9.5 (1.0)*</td>
<td>+1.1 (1.4)*</td>
<td>+10.4 (1.0)</td>
</tr>
<tr>
<td>Non-HDL-C</td>
<td>-40.6 (1.0)</td>
<td>-0.9 (1.4)*</td>
<td>-46.6 (0.9)</td>
</tr>
<tr>
<td>TG</td>
<td>-19.1 (2.2)</td>
<td>-2.8 (3.1)*</td>
<td>-22.9 (1.8)</td>
</tr>
<tr>
<td>TC/HDL-C</td>
<td>-37.2 (0.9)*</td>
<td>-1.1 (1.3)*</td>
<td>-41.7 (0.9)</td>
</tr>
<tr>
<td>LDL-C/HDL-C</td>
<td>-47.3 (1.1)</td>
<td>-0.8 (1.6)*</td>
<td>-52.7 (1.0)</td>
</tr>
<tr>
<td>Non-HDL-C/HDL-C</td>
<td>-45.0 (1.1)</td>
<td>-1.2 (1.6)*</td>
<td>-50.5 (1.1)</td>
</tr>
<tr>
<td>ApoB</td>
<td>-35.1 (1.0)</td>
<td>-1.0 (1.4)*</td>
<td>-40.8 (0.9)</td>
</tr>
<tr>
<td>ApoA-1</td>
<td>+6.1 (0.9)</td>
<td>+1.2 (1.3)**</td>
<td>+6.5 (0.9)</td>
</tr>
<tr>
<td>ApoB/ApoA-1</td>
<td>-38.2 (1.1)</td>
<td>-0.5 (1.5)*</td>
<td>-43.8 (1.0)</td>
</tr>
</tbody>
</table>

SE, standard error of the mean.
* \( P < 0.001 \) vs. RSV at same time point.
** \( P < 0.01 \) vs. RSV at same time point.

### Table 4 Proportion of patients achieving lipid goals (ITT population by as-allocated treatment)

<table>
<thead>
<tr>
<th>Patients achieving goals, n/total (%)</th>
<th>RSV 10 mg (n = 164)</th>
<th>AT 10 mg (n = 155)</th>
<th>Placebo (n = 78)</th>
<th>RSV combined (n = 242)</th>
<th>AT 10/20 mg (n = 155)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1998 European LDL-C goal(^*)</td>
<td>128/162 (79)</td>
<td>107/151 (71)(^*)</td>
<td>2/78 (3)**</td>
<td>209/232 (90)</td>
<td>120/145 (83)*</td>
</tr>
<tr>
<td>2003 European LDL-C goals(^\dagger)</td>
<td>128/162 (79)</td>
<td>105/151 (70)(^*)</td>
<td>2/78 (3)**</td>
<td>204/232 (88)</td>
<td>118/145 (81)*</td>
</tr>
<tr>
<td>NCEP ATP III LDL-C goals(^\ddagger)</td>
<td>134/162 (83)</td>
<td>109/151 (72)(^*)</td>
<td>8/78 (10)**</td>
<td>211/232 (91)</td>
<td>114/145 (79)**</td>
</tr>
<tr>
<td>LDL-C (&lt; 2.59 \text{ mmol/L (100 mg/dL)})</td>
<td>99/162 (61)</td>
<td>70/151 (46)(^***)</td>
<td>1/78 (1)**</td>
<td>185/232 (80)</td>
<td>85/145 (59)**</td>
</tr>
<tr>
<td>NCEP ATP III non-HDL-C goal in patients with baseline TG (\geq 2.26 \text{ mmol/L (200 mg/dL)})</td>
<td>59/76 (78)</td>
<td>45/67 (67)</td>
<td>0/42</td>
<td>100/115 (87)</td>
<td>52/65 (80)</td>
</tr>
<tr>
<td>NCEP ATP III non-HDL-C goal in patients with TG remaining at (\geq 2.26 \text{ mmol/L (200 mg/dL)}) at 6 and 12 weeks(^\dagger)</td>
<td>20/31 (65)</td>
<td>14/31 (45)</td>
<td>0/30</td>
<td>28/37 (76)</td>
<td>10/19 (53)</td>
</tr>
</tbody>
</table>

\(^*\) LDL-C \(< 3.0 \text{ mmol/L (<115 mg/dL).}^{13}\)
\(^\dagger\) LDL-C \(< 2.5 \text{ or 3.0 mmol/L (<100 or 115 mg/dL})\) depending on risk category.\(^7\)
\(^\ddagger\) LDL-C \(< 2.59, 3.36, \text{ or 4.14 mmol/L (<100, 130, or 160 mg/dL})\) depending on risk category.\(^4\)
\(^\dagger\) NCEP ATP III LDL-C \(< 3.36, 4.14, \text{ or 4.91 mmol/L (<130, 160, or 190 mg/dL})\) depending on risk; no formal statistical analyses were performed.
* \( P < 0.05 \) vs. RSV at same time point.
** \( P < 0.01 \) vs. RSV at same time point.
*** \( P < 0.01 \) vs. RSV at same time point.
rosuvastatin group when compared with the atorvastatin group at 6 and 12 weeks (Table 3).

During the study, median hsCRP decreased in both treatment groups, although data were variable. At 12 weeks, hsCRP levels were significantly reduced when compared with baseline in both groups, with no significant difference between treatments (Table 5). Rosuvastatin and atorvastatin substantially reduced hsCRP levels in patients with hsCRP ≥ 2 mg/L (n = 236) or > 3 mg/L (n = 170) at baseline, with no significant difference between treatments at 6 and 12 weeks (Table 5).

Changes in fasting plasma glucose were small, with no significant difference between treatment groups (Table 6). There was also no significant difference in insulin resistance between the groups (Table 6). The mean glycated haemoglobin (HbA1C) level was 5.7% at baseline; mean HbA1C levels were similar at 6 and 12 weeks and across both treatment groups.

Safety

Both rosuvastatin 10/20 mg and atorvastatin 10/20 mg were well tolerated, with a similar incidence of treatment-emergent AEs (Table 7). After 6 weeks of treatment, the most commonly reported AEs were headache, back pain, and myalgia, whereas after 12 weeks they were myalgia, arthralgia, and back pain. The majority of AEs were of a mild-to-moderate intensity. Three patients experienced non-fatal serious adverse events (SAEs) of dizziness, chondropathy (both atorvastatin 10/20 mg group), and myalgia (rosuvastatin 10/20 mg group), all of which were resolved. There were two deaths during the study owing to cardiovascular events (atorvastatin 10/20 mg group), but these were considered to be unrelated to the treatment by the study investigator. There were no reported cases of rhabdomyolysis or acute renal failure.

Clinically important elevations in alanine aminotransferase (>3× ULN) occurred in one patient (rosuvastatin 10/20 mg). One patient in the atorvastatin 10/20 mg group experienced CK >10× ULN without muscle symptoms. Myalgia was associated with CK >10× ULN in one patient in the rosuvastatin 10/20 mg group, which was indicative of myopathy. No changes in serum creatinine levels were observed during the study. There were no clinically relevant changes in haematology, clinical chemistry, and renal function observed in either treatment arm.

Discussion

COMETS is the first prospectively designed study to evaluate the comparative efficacy of statin treatment in patients with the metabolic syndrome. Treatment for 6 weeks with

<table>
<thead>
<tr>
<th>Table 5</th>
<th>Change from baseline in hsCRP in all patients and in those with hsCRP ≥2 mg/L (n = 236) or &gt;3 mg/L (n = 170) at baseline (ITT population by as-allocated treatment)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median change in hsCRP from baseline (%) (10th and 90th percentiles)</td>
</tr>
<tr>
<td></td>
<td>6 weeks</td>
</tr>
<tr>
<td></td>
<td>RSV 10 mg (n = 164)</td>
</tr>
<tr>
<td></td>
<td>ATV 10 mg (n = 155)</td>
</tr>
<tr>
<td></td>
<td>Placebo (n = 78)</td>
</tr>
<tr>
<td></td>
<td>12 weeks</td>
</tr>
<tr>
<td></td>
<td>RSV combined (n = 242)</td>
</tr>
<tr>
<td></td>
<td>ATV 10/20 mg (n = 155)</td>
</tr>
<tr>
<td>All patients</td>
<td>-18.2 (−64.9, +89.2)</td>
</tr>
<tr>
<td></td>
<td>-16.1 (−70.1, +116.7)</td>
</tr>
<tr>
<td></td>
<td>-6.2 (−55.2, +119.7)</td>
</tr>
<tr>
<td></td>
<td>-28.6* (−67.6, +75.0)</td>
</tr>
<tr>
<td></td>
<td>-27.7* (−68.4, +78.7)</td>
</tr>
<tr>
<td>Patients with</td>
<td>-20.0 (−74.2, +62.5)</td>
</tr>
<tr>
<td>hsCRP ≥ 2 mg/L at baseline</td>
<td>-24.7 (−77.2, +96.9)</td>
</tr>
<tr>
<td></td>
<td>-10.0 (−67.0, +68.9)</td>
</tr>
<tr>
<td></td>
<td>-35.0 (−74.5, +35.8)</td>
</tr>
<tr>
<td></td>
<td>-31.1 (−71.4, +37.4)</td>
</tr>
<tr>
<td>Patients with</td>
<td>-23.7 (−80.6, +37.6)</td>
</tr>
<tr>
<td>hsCRP &gt; 3 mg/L at baseline</td>
<td>-32.2 (−80.4, +78.0)</td>
</tr>
<tr>
<td></td>
<td>-9.9 (−68.3, +49.3)</td>
</tr>
<tr>
<td></td>
<td>-40.7 (−78.3, +27.0)</td>
</tr>
<tr>
<td></td>
<td>-30.1 (−73.4, +37.6)</td>
</tr>
</tbody>
</table>

Note: All patients’ 12-week data; comparisons among treatment groups were not significant at the same time point.

*P < 0.001 vs. baseline.

<table>
<thead>
<tr>
<th>Table 6</th>
<th>Change from baseline in fasting plasma glucose and insulin resistance (ITT population by as-allocated treatment)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Change from baseline (%)</td>
</tr>
<tr>
<td></td>
<td>6 weeks</td>
</tr>
<tr>
<td></td>
<td>RSV 10 mg (n = 164)</td>
</tr>
<tr>
<td></td>
<td>ATV 10 mg (n = 155)</td>
</tr>
<tr>
<td></td>
<td>Placebo (n = 78)</td>
</tr>
<tr>
<td></td>
<td>12 weeks</td>
</tr>
<tr>
<td></td>
<td>RSV combined (n = 242)</td>
</tr>
<tr>
<td></td>
<td>ATV 10/20 mg (n = 155)</td>
</tr>
<tr>
<td>Fasting plasma glucose, LSM (SE)</td>
<td>0.1 (0.7)</td>
</tr>
<tr>
<td>Insulin resistance, median (10th and 90th percentiles)</td>
<td>2.7 (−39, 66)</td>
</tr>
</tbody>
</table>

Comparisons between treatment groups were not significant at the same time point.
Rosuvastatin 10 mg was significantly more beneficial than atorvastatin 10 mg and placebo for lowering LDL-C. The percentage reduction from baseline in LDL-C was also significantly greater in the rosuvastatin group compared with the atorvastatin group after 12 weeks of treatment. Consistent with the greater reductions in LDL-C, more patients in the rosuvastatin group achieved LDL-C goals when compared with the atorvastatin and placebo groups. Improvements in TC, HDL-C, and non-HDL-C were also significantly greater with rosuvastatin than with atorvastatin or placebo, whereas decreases in TG were similar in both active treatment groups. Low HDL-C and raised TG are included in diagnostic criteria for the metabolic syndrome, and in selecting appropriate therapy to treat the complex pattern of lipid abnormalities associated with the metabolic syndrome, it is important to use agents that provide optimal improvements in these variables.

Results of COMETS are consistent with subgroup analyses from other studies of rosuvastatin that included patients with the metabolic syndrome. In a pooled analysis of efficacy trials, rosuvastatin 10 mg improved the lipid profile to a similar extent in hypercholesterolaemic patients with and without the metabolic syndrome. In an analysis of goal achievement in patients with the metabolic syndrome included in the Measuring Effective Reductions in Cholesterol Using Rosuvastatin therapY (MERCURY) I study, treatment with rosuvastatin 10 mg had significant benefits in modifying lipid levels and in achieving goals when compared with atorvastatin 10 mg, simvastatin 20 mg, and pravastatin 40 mg. COMETS is also consistent with data showing that in patients with hypercholesterolaemia, rosuvastatin was significantly more effective than atorvastatin at lowering LDL-C and raising HDL-C. Statin-induced LDL-C reductions have been shown to decrease cardiovascular events by 24–37%, and several large-scale, randomized trials evaluating clinical outcomes of rosuvastatin therapy are ongoing. Further studies are now required to evaluate whether improvements in the lipid profile seen in the present study lead to increased patient survival and reduced morbidity in patients with the metabolic syndrome.

A central role of inflammation at all stages of atherosclerosis is well established, and baseline hsCRP levels are a robust and independent predictor of future cardiovascular events. Furthermore, hsCRP measurement may add clinically important prognostic information concerning future vascular risk in patients with the metabolic syndrome. Statins reduce hsCRP levels, with a greater benefit shown for individuals with elevated hsCRP. Although COMETS did not demonstrate any significant difference between treatments, 28–29% reductions in hsCRP were observed after 12 weeks in all patients, with ~30–40% reductions observed in patients with elevated hsCRP at baseline. Data regarding the effects of rosuvastatin on outcomes in patients with elevated C-reactive protein (≥2 mg/L) levels will be provided by

### Table 7: Treatment-emergent AEs, SAEs, discontinuations due to AEs, and most commonly reported treatment-emergent AEs (events that occurred in three or more patients in any treatment group)

<table>
<thead>
<tr>
<th>Number of patients with AEs, n (%)</th>
<th>Period 1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RSV 10 mg (n = 163)</td>
</tr>
<tr>
<td>Any AE</td>
<td>41 (25.2)</td>
</tr>
<tr>
<td>SAE</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>SAE leading to death</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Discontinuation due to AE</td>
<td>2 (1.2)</td>
</tr>
<tr>
<td>Most commonly reported AE</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>8 (4.9)</td>
</tr>
<tr>
<td>Back pain</td>
<td>3 (1.8)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>3 (1.8)</td>
</tr>
<tr>
<td>Constipation</td>
<td>3 (1.8)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2 (1.2)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Muscular weakness</td>
<td>1 (0.6)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of patients with AEs, n (%)</th>
<th>Period 2a</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RSV 10/20 mg (n = 158)b</td>
</tr>
<tr>
<td>Any AE</td>
<td>35 (22.2)</td>
</tr>
<tr>
<td>SAE</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>SAE leading to death</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Discontinuation due to AE</td>
<td>2 (1.3)</td>
</tr>
<tr>
<td>Most commonly reported AE</td>
<td></td>
</tr>
<tr>
<td>Myalgia</td>
<td>4 (2.5)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>3 (1.9)</td>
</tr>
<tr>
<td>Back pain</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

aTwo non-serious AEs also occurred in two patients who did not receive the correct study medication at the appropriate time in error; one AE occurred in a patient receiving ATV 20 mg in Period 1 and the other AE occurred in a patient receiving RSV 20 mg in Period 2.
b These values include only those patients who received a dose of Period 2 study medication.
Insulin resistance is characteristic of the metabolic syndrome; however, only a small number of studies have investigated the effects of statin therapy on insulin resistance. In COMETS, a small percentage of patients were glucose intolerant, and therefore, it was unlikely that changes in insulin resistance would be observed. Further work is needed to assess the effects of statins on insulin resistance, specifically in patients with glucose intolerance.

Throughout this study, both treatments were well tolerated and the AE profile was consistent with that reported previously for rosuvastatin and atorvastatin. Few SAEs were observed, reflecting previous data indicating that SAEs resulting from statin treatment are rare. As the largest study to date focusing on statin therapy solely in patients with the metabolic syndrome, COMETS supports the good safety profile of rosuvastatin and atorvastatin reported previously by two post hoc subgroup analyses. Further long-term studies in large numbers of patients will give a better indication of the long-term effects of statin treatment in this population.

In conclusion, COMETS has demonstrated that rosuvastatin was significantly more effective than atorvastatin for reducing LDL-C levels, enabling patients to achieve lipid goals and improving other aspects of the atherogenic lipid profile in patients with the metabolic syndrome. These data provide a basis for improving the management of dyslipidaemia and cardiovascular risk in the increasing number of patients requiring treatment for the metabolic syndrome.

Acknowledgements

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Conflict of interest: A.F.H.S. and co-authors would like to disclose their associations with several pharmaceutical companies. A.F.H.S. has received research grant and research funds from AstraZeneca, Pfizer, and Merck. Dr C.M.B. has received research support from AstraZeneca, diadexus, Gene Logic, GlaxoSmithKline, Integrated Therapeutics, Kos, Merck, Novartis, Pfizer, Reliant, Sankyo Pharma, and Schering-Plough; is a consultant for AstraZeneca, Bayer, Merck, Novartis, Pfizer, Reliant, and Schering-Plough; and is a member of the speaker's bureau for AstraZeneca, Bristol Myers-Squibb, Kos, Merck, Novartis, Pfizer, Reliant, Sanofi-Synthelabo, and Schering-Plough. Dr C.S. and Dr J.M. have no financial associations that could pose a conflict of interest in connection with this manuscript. Professor S.T. has received honoraria for lectures given for AstraZeneca, Pfizer, Merck, Schering-Plough, Novartis, Roche, Abbott, and Sanofi-Aventis.

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terolemic patients and in special population groups. Am J Cardiol 2003;91:3C–10C.


