Dose-Dependent Effect of Rosuvastatin on Very-Low Density Lipoprotein- Apolipoprotein C-III Kinetics in the Metabolic Syndrome

Running title: Rosuvastatin and VLDL apoC-III kinetics

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Word count: 3315 words

Number of Tables: 2

Number of Figures: 1
Abstract

Objective Dysregulated apolipoprotein (apo) C-III metabolism may account for hypertriglyceridemia and increased cardiovascular risk in the metabolic syndrome. This study investigated the dose-dependent effect of rosuvastatin on very-low density lipoprotein (VLDL) apoC-III transport in men with the metabolic syndrome.

Research Design and Methods Twelve men with the metabolic syndrome were studied in a randomized, double-blind, cross-over trial of 5-week intervention periods with placebo, 10mg rosuvastatin or 40mg rosuvastatin, with 2-week placebo wash-outs between each period. VLDL apoC-III kinetics were examined using a stable isotope method and compartmental modeling at the end of each intervention period.

Results Compared with placebo, there was a significant dose-dependent reduction with rosuvastatin in plasma triglyceride and VLDL apoC-III concentrations. Rosuvastatin significantly (p<0.05) increased VLDL apoC-III fractional catabolic rate (FCR) and decreased its production rate, with a significant (p<0.05) dose-related effect. With 40mg rosuvastatin, changes in VLDL apoC-III concentration were positively associated with changes in VLDL apoC-III FCR and inversely associated with VLDL apoC-III PR (p<0.05). Changes in VLDL apoC-III concentration and PR were positively correlated with changes in VLDL apoB concentration and PR, and inversely correlated with VLDL apoB FCR (p<0.05). Similar associations were observed with 10mg rosuvastatin but were either less or not statistically significant.
Conclusions In this study, rosuvastatin decreased the production and increased the catabolism of VLDL apoC-III, a mechanism that accounted for the significant reduction in VLDL apoC-III and triglyceride concentrations. This has implications for the management of cardiometabolic risk in obese subjects with the metabolic syndrome.

Clinical Trial Registration Information: http://www.clinicaltrials.gov/ NCT00240305
Hypertriglyceridemia, a key feature of the metabolic syndrome, is associated with increased risk of cardiovascular disease (CVD) (1). It is the most consistent lipid disorder in subjects with obesity and type 2 diabetes mellitus. Hypertriglyceridemia is primarily related to dysregulated triglyceride-rich lipoproteins (TRL) metabolism, including overproduction of very-low-density lipoprotein (VLDL) particles and delayed catabolism of TRL and their remnants (2). These abnormalities are a collective consequence of insulin resistance and increased lipid substrate availability in the liver, as well as depressed activities of lipoprotein lipase (LPL) and hepatic clearance receptors (3).

ApoC-III is an 8.8 kD glycoprotein synthesized by the liver and intestines. ApoC-III is highly associated with hypertriglyceridemia and is a powerful independent predictor of CVD risk (4). In the circulation, apoC-III is associated with TRL and high-density lipoprotein (HDL), exchanging rapidly between these particles (5). In normolipidemic subjects the majority of plasma apoC-III is bound to HDL, while in hypertriglyceridemic subjects the majority is bound to TRL (4). ApoC-III inhibits LPL activity and TRL remnant uptake by hepatic lipoprotein receptors (4). Elevated plasma apoC-III concentrations, and specifically its accumulation in TRL and their remnants, is causally related to hypertriglyceridemia in the metabolic syndrome (6). Furthermore, insulin resistance is associated with elevated plasma apoC-III concentrations (7). Hence, interventions that target apoC-III metabolism are clinically important.

Statins decrease de novo cholesterol synthesis, thereby up-regulating LDL receptor activity. This enhances the uptake of both hepatic and intestinal derived TRLs, thereby decreasing their concentrations in the circulation (8). Animal studies suggest that statins decrease apoC-III hepatic mRNA expression and plasma concentrations via the peroxisome proliferator-activated receptors (PPAR)-α pathway (9,10). However, their effect on apoC-III metabolism in vivo is not known.
Rosuvastatin is a highly efficacious statin, recently shown to decrease the progression of atherosclerosis in high risk subjects (11). In a dose-range between 10 and 40mg, rosuvastatin significantly reduce plasma LDL cholesterol and triglyceride, and increase HDL cholesterol concentrations in the metabolic syndrome (12). We recently reported that rosuvastatin dose-dependently increased TRLs and decreased LpA-I fractional catabolic rates, consistent with parallel reduction in plasma triglycerides and increase in HDL cholesterol concentrations (13,14). The triglyceride-lowering effect of rosuvastatin may, in part, be regulated by the reduction of plasma apoC-III concentrations (13). However, the precise mechanism of action of this agent on VLDL-apoC-III kinetics in metabolic syndrome subjects has not been examined.

In the present study, we investigated the dose-related effect of rosuvastatin on VLDL apoC-III transport in the metabolic syndrome. We hypothesized that a higher dose of rosuvastatin would reduce VLDL apoC-III concentration by a mechanism that primarily involves decreasing the production of apoC-III. We also explored the dose-dependent effect of rosuvastatin on other markers of TRL metabolism including apoB-48 and apoA-V.

**Research Design and Methods**

**Subjects**

Twelve Caucasian men with the metabolic syndrome by the NCEP ATP III definition (15) were recruited. Upper limits for HDL cholesterol ≤1.2mmol/L, LDL cholesterol ≤6mmol/L, triglycerides ≤4.5mmol/L were stipulated to exclude subjects with genetic hyperlipidemia including familial hypercholesterolemia and familial hypertriglyceridemia, and other secondary causes of severe dyslipidemia. Subjects with diabetes mellitus (fasting glucose >7mmol/l),
cardiovascular disease, renal dysfunction (macroproteinuria and/or serum creatinine >150μmol/l), apoE2/E2 genotype, hypothyroidism, abnormal liver or muscle enzymes, alcohol consumption >30g alcohol/day and use of lipid modifying agents were excluded. All were non-smokers and were consuming ad libitum, weight maintenance diets. Participants provided informed written consent, and the study was approved by the Ethics Committee of Royal Perth Hospital.

**Study design and clinical protocols**

This was a randomized, double-blind, three-way cross-over trial. Eligible patients entered a four-week run-in diet-stabilizing period, at the end of which they were randomized to a five-week intervention period of either rosuvastatin 40mg, rosuvastatin 10mg or placebo. Rosuvastatin was provided by AstraZeneca Pty. Ltd, London, UK. Advice was given to continue isocaloric diets and maintain physical activity constant. Compliance with study medication was assessed by tablet count.

All subjects were admitted to the metabolic ward in the morning after a minimum of 12-hour fast. They were studied semi-recumbent and allowed water only for the initial 10 hours of the study. Venous blood was collected for biochemical measurements. Body weight and height were measured and arterial blood pressure recorded using a Dinamap1846 SX/P monitor (Critikon, Tampa, FL). Dietary intake was assessed using 24-hour dietary diaries and DIET 4 Nutrient Calculation Software (Xyris Software, Qld, Australia).

A single bolus of D3-leucine (5mg/kg) was administered intravenously into an antecubital vein via a Teflon cannula. Blood samples were taken at baseline and at 5, 10, 20, 30, 40 minutes, and 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8 and 10 hours after isotope injection. Additional blood samples were
collected in the morning on the four following days (24, 48, 72 and 96 hours) after a minimum 12-hour fast. All the procedures were repeated at the end of each treatment period.

**Biochemical analyses**

Laboratory methods for measurements of lipids, lipoproteins and other biochemical analytes have been previously detailed (13,14). Insulin resistance was calculated using a homeostasis model assessment (HOMA) score. VLDL apoC-III were determined by electro-immunodiffusion using a Hydragel LP CIII Electro-immunodiffusion kit (Sebia, France); inter-assay CVs were <5.0% (5). Plasma apoB-48 concentrations were measured by a sandwich enzyme immunoassay (ELISA) using anti-human apoB-48 monoclonal antibodies (inter-assay CV<5%). Plasma apoA-V concentration was determined using a dual-antibody sandwich enzyme-linked immunosorbent assay (Linco Diagnostic Services).

**Isolation of VLDL apoC-III**

The methods for the isolation of lipoproteins and apoC-III have been previously described (5). In brief, 3ml of plasma was used for isolation of 1ml VLDL (<1.006kg/L) fraction by sequential ultracentrifugation at 40,000 rpm in a Ti 50.4 rotor (Optima LE-80K, Beckman Coulter, Australia). The VLDL samples were then prepared for isoelectric focusing (IEF) gel electrophoresis. VLDL (200µl) from each time point was delipidated and reconstituted in 50µl IEF sample buffer (8M urea; 0.001% w/v bromphenol blue). ApoC-III was isolated by preparative isoelectric focusing (IEF) gel electrophoresis (8M urea; 7.5% acrylamide; 1.5% ampholytes pH 4-6; 16 hours; 200V; 4°C). Gels were electro-blotted onto polyvinylidene fluoride (PVDF)
membranes (Immobilon, Millipore, USA) at 700mA for 1 hour using a Hoefer TE 42 transfer unit (Amersham Biosciences, Australia) and stained with Coomassie Brilliant Blue R 250 (5).

**Measurement of D₃-leucine enrichment in apoC-III₁**

IEF resolves apoC-III into three isoforms, apoC-III₀, apoC-III₁ and apoC-III₂. ApoC-III₁ was investigated in this study because of its greater concentration in plasma, and observations from previous studies that the kinetics of apoC-III isoforms was similar (16). All references to apoC-III kinetics will correspond to the kinetics of apoC-III₁. The apoCIII₁ protein bands were excised from the PVDF and hydrolyzed in 200μl 6M HCl overnight at 110°C in pyrolysis-cleaned half-dram vials. Samples are dried at 110°C and derivatized using a modified oxazolinone method. The oxazolinone derivatives are analyzed by negative ion chemical ionization gas chromatography-mass spectrometry (GCMS). The isotopic enrichment is determined as the tracer to tracee ratio (TTR) of monitored selected ions at mass to charge (m/z) ratio of 212/209. The average coefficient of variation of apoC-III tracer measurement, including processes associated with isolation of apoC-III from plasma through to the measurement of isotopic enrichment, is 5.4% (5).

**Kinetic Analyses**

A model of VLDL apoC-III metabolism was developed using the SAAM II program (SAAM Institute, Seattle) (Figure 1 (17)). The model consists of a four-compartment subsystem (compartments 1-4) that describes plasma leucine kinetics. This subsystem is connected to two intrahepatic delay compartments (compartments 5-6) that account for the time required for the assembly, synthesis and secretion of apoC-III into plasma. The kinetics of VLDL apoC-III is
described by a plasma compartment (compartment 7) and an extravascular exchange compartment (compartment 8). The time for delay compartment 5 (mean ± SEM: 0.52 ± 0.04 hours) was shorter than compartment 6 (1.98 ± 0.25 hours), however, this did not impact on estimates of VLDL apoC-III fractional catabolic rate (FCR), nor was there any effect of treatment on delay times. FCR of VLDL apoC-III, equivalent to the irreversible loss from compartment 7, was estimated after fitting the model to the VLDL apoC-III tracer data. The production rate (PR), the transport rate of apoC-III through the VLDL pool, was calculated as the product of FCR and pool size, which equals the plasma concentration multiplied by plasma volume; plasma volume was estimated as 4.5% of body weight with adjustment made to account for decrease in relative plasma volume with body weights in the obese range.

**Statistical analyses**

Skewed variables were logarithmically transformed where appropriate. Data at the end of the three treatment periods were compared using a mixed-effect model (SAS Proc Mixed; SAS Institute, USA), which also tested for carry-over, treatment sequence and time-dependent effects. There were no significant carry-over, treatment sequence or time-dependent effects. A mixed effect model was also used to examine the dose-related effect of rosuvastatin on study variables. The p-values are reported, with statistical significance set at the 5% level. Statistical associations between changes in variables were also examined on both doses of rosuvastatin using simple, stepwise and multiple linear regression methods.

**Results**

The clinical and biochemical characteristics of the 12 subjects were reported previously (13,14). They were centrally-obese, insulin resistant and dyslipidemic. There were no significant
treatment effects on body weight, blood pressure, insulin, glucose, fatty acids and HOMA score. Both rosuvastatin 10mg and 40mg were well tolerated. There were no significant changes in liver and muscle enzymes or serum creatinine, and no subjects developed dip-stick positive proteinuria. Mean daily dietary intake was: energy (10245 ± 575kJ), total fat (90.9 ± 6.3g), total carbohydrate (256 ± 15g), protein (123 ± 7g), cholesterol (385 ± 46mg) and alcohol (6.5 ± 2.9g) and did not differ significantly between treatment phases.

Table 1 gives the plasma concentrations of lipids, lipoproteins and apolipoproteins on placebo, rosuvastatin 10mg and rosuvastatin 40mg. Compared with placebo, rosuvastatin significantly decreased plasma cholesterol, triglycerides, LDL cholesterol, apoB and apoC-III concentrations and the apoB/apoA-I and lathosterol:cholesterol ratios with a significant increase in HDL cholesterol concentration and campesterol:cholesterol ratio. These changes were greater with 40mg than 10mg of rosuvastatin, with a statistically significant dose-dependent effect.

Table 2 gives the plasma concentrations and kinetics of VLDL apoC-III on placebo and on 10mg and 40mg rosuvastatin. Compared with placebo, rosuvastatin decreased VLDL apoC-III concentration (R10 -22%, R40 -45%) and production rate (R10 -15%, R40 -25%) and increased VLDL apoC-III FCR (R10 +17%, R40 +36%). There was a statistically significant dose-dependent effect of rosuvastatin on VLDL apoC-III concentration, FCR and PR (Table 1). Rosuvastatin dose-dependently lowered plasma apoB-48 (P 4.46±0.25 R10 4.12±0.31 R40 3.54±0.19, p-value_{dose}=0.002). There was no significant effect of rosuvastatin on apoA-V concentration (P 132±28 R10 155±34 R40 103±17, p-value_{dose}=0.107).

With 40mg rosuvastatin, the reduction in VLDL apoC-III concentration was significantly associated with an increase in VLDL apoC-III FCR (r=-0.710, p=0.01) and a fall in VLDL apoC-III PR (r=0.939, p<0.01). The changes in VLDL apoC-III PR and FCR were independent determinants of change in VLDL apoC-III concentration (adjusted r²=98%, p<0.01). With 10mg
rosuvastatin, the decrease in VLDL apoC-III concentration was significantly associated with the reduction in VLDL apoC-III PR (r=0.752, p<0.01). The fall in VLDL apoC-III concentration was associated with the increase in VLDL apoC-III FCR but this failed to reach statistical significance (r=-0.511, p=0.08). The changes in VLDL apoC-III PR and FCR were independent determinants of change in VLDL apoC-III concentration (adjusted $r^2=97\%$, p<0.01).

Given the role of apoC-III in regulating TRL metabolism, associations between VLDL apoC-III and VLDL apoB kinetic parameters were explored. Both VLDL apoC-III and VLDL apoB kinetic parameters were derived from the same subjects. The dose-dependent effect of rosuvastatin on apoB-containing lipoproteins in these subjects was reported earlier (13). Changes in VLDL apoC-III concentration were significantly associated with changes in VLDL apoB concentration (r=0.901, p<0.01), FCR (r=-0.791, p=0.002) and PR (r=0.642, p=0.024). Similar associations were observed between plasma total apoC-III concentration and the corresponding VLDL apoB FCR. Changes in VLDL apoC-III PR was significantly associated with changes in VLDL apoB concentration (r=0.934, p<0.01), FCR (r=-0.897, p<0.01) and PR (r=0.639, p=0.025). The above associations between VLDL apoC-III and VLDL apoB kinetic parameters were also seen with rosuvastatin 10mg but were not as significant.

Additional analysis revealed that changes in plasma triglycerides were associated with changes in VLDL apoC-III concentration, FCR and PR (r=0.958, p<0.01, r=-0.653, p=0.021 and r=0.932, p<0.01, respectively), VLDL apoB concentration, FCR and PR (r=0.879, p<0.01, r=-0.860, p<0.01 and r=0.570, p=0.053, respectively) and plasma apoB-48 concentration (r=0.586, p=0.045). In a stepwise regression model that included plasma apoB-48 and VLDL apoB concentrations, VLDL apoC-III concentration was an independent predictor of changes in plasma triglycerides (adjusted $r^2=93\%$, p<0.01). Furthermore, changes in VLDL apoC-III FCR and PR
were independent determinants for changes in plasma triglyceride concentrations in a stepwise regression model that included VLDL apoB FCR and PR (adjusted $r^2=94\%$, $p<0.01$).

Discussion

We provide new information on the dose-ranging effect of rosuvastatin, a potent HMG-CoA (or 3-hydroxy-3-methyl-glutaryl-CoA) reductase inhibitor, on VLDL apoC-III metabolism in subjects with the metabolic syndrome. We demonstrated that rosuvastatin dose-dependently decreased VLDL apoC-III concentrations by increasing the FCR and decreasing the PR of VLDL apoC-III. These results add further to our work on the dose-dependent effect of rosuvastatin on apoB-containing lipoproteins and HDL particle kinetics in the same subjects (13,14).

Hypertriglyceridemia in insulin resistant states, including the metabolic syndrome results from overproduction and reduced catabolism of TRL and their remnants. These kinetic aberrations may be related to altered VLDL apoC-III metabolism. Previous studies demonstrated that overproduction of VLDL apoC-III explained the higher VLDL apoC-III concentration in these subjects (17). The increased VLDL apoC-III concentration and production rate were associated with elevated VLDL triglycerides, oversecretion of VLDL apoB and reduced VLDL apoB catabolism (17,18). Statins have been shown to effectively reduce plasma and VLDL apoC-III concentrations (4). The effect of statin therapy on VLDL apoC-III transport, however, has not been examined. We extend these reports by examining the dose-related effect of rosuvastatin on VLDL apoC-III kinetics in the metabolic syndrome using a three-way crossover study design.

Consistent with larger clinical trials, rosuvastatin dose-dependently reduced plasma triglyceride concentrations in subjects with the metabolic syndrome (12). The reduction in plasma triglyceride concentrations was chiefly explained by the decrease in VLDL apoC-III concentrations. This is consistent with previous observations that reduced apoC-III in TRL
enhances LPL-mediated lipolysis and receptor-mediated clearance of TRL, thereby lowering plasma triglyceride levels (4).

We demonstrated, for the first time, that rosvastatin dose-dependently increased VLDL apoC-III fractional catabolism and reduced VLDL apoC-III production. Both VLDL apoC-III FCR and PR were independent determinants of VLDL apoC-III concentration. The increase in VLDL apoC-III FCR may be explained, in part, by direct removal of VLDL apoC-III from circulation and/or its redistribution to other lipoproteins, specifically HDL. The redistribution of apoC-III from VLDL to HDL during LPL-mediated hydrolysis of VLDL triglycerides, and its subsequent transfer back to triglyceride-rich particles is well established (19). The precise mechanism of action of rosvastatin on VLDL apoC-III PR is unclear. Statins has been shown to activate the PPAR-α pathway via inhibition of rho-signaling, thereby, repressing apoC-III mRNA expression and reducing apoC-III synthesis in human HepG2 hepatoma cells (9). To date, no studies have examined the effect of statins on apoC-III synthesis in humans. Further analysis of total plasma apoC-III kinetics in the same subjects showed that rosvastatin reduced total plasma apoC-III concentration by dose-dependently increasing total plasma apoC-III FCR, with no significant changes to total plasma apoC-III PR (total plasma apoC-III PR is synonymous with the amount of apoC-III secreted into plasma by both the liver and intestine) (unpublished data). We propose that the reduction in VLDL apoC-III PR may be a function of altered distribution of apoC-III between VLDL and HDL particles with rosvastatin treatment, rather than an effect on apoC-III gene expression and hence, hepatic or intestinal apoC-III synthesis.

The reduction in CETP mass and activity with rosvastatin may also contribute to an altered distribution of apoC-III between VLDL and HDL particles and hence, changes to its
kinetics, by favoring the formation of smaller VLDL and larger HDL species (20) with different thermodynamic stability and composition.

The reduction in VLDL apoC-III production with rosuvastatin was associated with the decrease in VLDL apoB concentration and PR, and increase in VLDL apoB FCR. The precise reason for a potential coupling of VLDL apoC-III and VLDL apoB metabolism remains unclear, but is consistent with the role of apoC-III as a regulator of apoB transport. Sundaram et al demonstrated that overexpression and hence oversecretion of apoC-III stimulated apoB synthesis, VLDL assembly and secretion in McARH7777 cells (21). Although rosuvastatin significantly reduced VLDL apoC-III PR, there was no impact on VLDL apoB PR (13), suggesting an uncoupling of this association. This observation further reinforces that the persistent state of insulin resistance in metabolic syndrome subjects is a powerful promoter of apoB secretion (3).

ApoA-V may regulate triglyceride metabolism, including VLDL assembly, LPL activity and VLDL receptor binding (22). However, the association between apoA-V and plasma triglycerides remains contentious (22). To date, no studies have examined the effect of statin therapy on apoA-V levels. Rosuvastatin, while significantly reducing plasma triglycerides, did not alter apoA-V concentrations in our study. This may be explained, in part, by recent evidence suggesting that the primary metabolic role of apoA-V is intracellular rather than extracellular (23). Consistent with this notion, apoA-V was shown to reduce the lipidation of VLDL without altering apoB secretion (23). Future studies employing VLDL triglyceride kinetics, coupled with cellular studies are warranted to better understand the role of apoA-V in vivo.

Our study was restricted to men, and we did not study type 2 diabetic subjects. Our findings may apply to women, type 2 diabetes patients and subjects of different ethnicity, although this requires further investigation. Measurements of lipases in post-heparin plasma may
have corroborated our findings. The effects of rosuvastatin on apoC-II, a co-factor for LPL should also be examined. ApoC-III displays non-competitive inhibitory properties against apoC-II, indicating the opposing regulatory effects of these two apolipoproteins on TRL metabolism (24). The ratio of apoC-III to apoC-II may therefore, be a crucial factor in the regulation of triglyceride hydrolysis.

In conclusion, elevated plasma triglycerides are powerful predictors of CVD in the metabolic syndrome. ApoC-III may account for this association. Rosuvastatin effectively reduces plasma triglycerides by improving VLDL apoC-III transport in subjects with the metabolic syndrome. Our findings further suggest that these subjects may derive incremental benefit from higher-dose rosuvastatin therapy (12). Future studies should explore whether lifestyle changes and other pharmacotherapies can further reduce apoC-III concentrations against the background of rosuvastatin in the metabolic syndrome.

Acknowledgements

This study was funded by research grants from the National Heart Foundation of Australia and the Raine Medical Research Foundation. We are grateful to Dr. V. Burke for statistical advice. EMMO is a Research Fellow of the National Heart Foundation of Australia (PF 07P 3263). PHRB and DS are research fellows of the National Health and Medical Research Council and PHRB is supported, in part by the National Institutes of Health (NIH/NIBIB P41 EB-001975). DCC is supported by an NHMRC Career Development Award.
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Figure 1: Compartment model describing apoC-III tracer kinetics

Leucine tracer is injected into plasma, compartment 2, and distributes to extravascular compartments, 1, 3 and 4. Compartments 1-4 are required to describe leucine tracer kinetics observed in plasma. Compartment 1 is connected to two intracellular delay compartments (compartment 5 and 6) that account for the assembly, synthesis and secretion of apoC-III. Compartment 7 describes the kinetics of VLDL apoC-III and compartment 8 is an extravascular exchange compartment.
Table 1: Lipid, lipoprotein and apolipoprotein concentrations on placebo, rosuvastatin 10mg and rosuvastatin 40mg

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Placebo (P)</th>
<th>Rosuvastatin 10 mg (R10)</th>
<th>Rosuvastatin 40 mg (R40)</th>
<th>Group Difference (p-value)</th>
<th>Dose-effect (p-value)</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>P vs. R10</td>
<td>P vs. R40</td>
</tr>
<tr>
<td>Total Cholesterol (mmol/L)</td>
<td>5.52 ± 0.25</td>
<td>3.64 ± 0.16</td>
<td>3.20 ± 0.13</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
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<tr>
<td>Triglycerides (mmol/L)</td>
<td>2.47 ± 0.32</td>
<td>1.88 ± 0.21</td>
<td>1.44 ± 0.13</td>
<td>0.027</td>
<td>&lt;0.001</td>
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<td>LDL cholesterol (mmol/L)</td>
<td>3.50 ± 0.22</td>
<td>1.78 ± 0.12</td>
<td>1.51 ± 0.10</td>
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<td>HDL cholesterol (mmol/L)</td>
<td>0.94 ± 0.04</td>
<td>0.98 ± 0.05</td>
<td>1.03 ± 0.04</td>
<td>0.227</td>
<td>0.011</td>
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<td>Apolipoprotein B (g/L)</td>
<td>1.19 ± 0.05</td>
<td>0.74 ± 0.03</td>
<td>0.65 ± 0.03</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
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<tr>
<td>Apolipoprotein A-I (g/L)</td>
<td>1.22 ± 0.04</td>
<td>1.27 ± 0.04</td>
<td>1.25 ± 0.03</td>
<td>0.090</td>
<td>0.086</td>
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<td>ApoB/ApoA-I ratio</td>
<td>0.98 ± 0.02</td>
<td>0.58 ± 0.02</td>
<td>0.51 ± 0.03</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Apolipoprotein C-III (mg/L)</td>
<td>139 ± 9.85</td>
<td>122 ± 8.98</td>
<td>107 ± 4.55</td>
<td>0.045</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lathosterol (µmol/L)</td>
<td>24.0 ± 2.64</td>
<td>6.33 ± 0.80</td>
<td>3.42 ± 0.35</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
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<td>Lathosterol:Cholesterol Ratio</td>
<td>4.36 ± 0.42</td>
<td>1.73 ± 0.19</td>
<td>1.08 ± 0.11</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
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<td>Campesterol (µmol/L)</td>
<td>11.8 ± 1.73</td>
<td>9.84 ± 1.36</td>
<td>10.1 ± 1.30</td>
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<td>Campesterol:Cholesterol Ratio</td>
<td>2.11 ± 0.28</td>
<td>2.74 ± 0.38</td>
<td>3.12 ± 0.36</td>
<td>&lt;0.001</td>
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Data presented as mean ± SEM
Table 2: Concentrations, fractional catabolic rates and production rates for VLDL apoC-III during placebo, rosvastatin 10mg (R10) and rosvastatin 40mg (R40) treatments

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Placebo (P)</th>
<th>Rosuvastatin 10 mg (R10)</th>
<th>Rosuvastatin 40 mg (R40)</th>
<th>P vs. R10</th>
<th>P vs. R40</th>
<th>R10 vs. R40</th>
<th>Dose-effect (p-value)</th>
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<tbody>
<tr>
<td>Concentration (mg/L)</td>
<td>84.6 ± 12.0</td>
<td>64.1 ± 8.9</td>
<td>46.4 ± 4.5</td>
<td>0.041</td>
<td>&lt;0.001</td>
<td>0.036</td>
<td>&lt;0.001</td>
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<td>Fractional Catabolic Rate (pools/day)</td>
<td>0.96 ± 0.06</td>
<td>1.09 ± 0.07</td>
<td>1.28 ± 0.06</td>
<td>0.027</td>
<td>&lt;0.001</td>
<td>0.002</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Production Rate (mg/kg/day)</td>
<td>2.86 ± 0.42</td>
<td>2.42 ± 0.29</td>
<td>2.14 ± 0.19</td>
<td>0.145</td>
<td>0.018</td>
<td>0.298</td>
<td>0.029</td>
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</tbody>
</table>

Data presented as mean ± SEM