Efficacy of Rosuvastatin in Achieving Target HDL, LDL, Triglycerides and Total Cholesterol Levels in Type 2 Diabetes Mellitus (T2DM) with Newly Diagnosed Dyslipidaemia: An Open Label, Nonrandomised, Non-Interventional and Observational Study in India

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Abstract
Asian Indians with dyslipidaemia should be treated as aggressively as if they had a CHD risk equivalent—similar to the treatment of patients with diabetes or heart disease.

Objective: To evaluate efficacy of Rosuvastatin in achieving target HDL, LDL, triglycerides and total cholesterol levels in type 2 diabetes mellitus (T2DM) patients with newly diagnosed dyslipidaemia, but without known coronary artery disease.

Methods: The study was an open label, nonrandomised, non-interventional, observational study in India involving T2DM patients who require statin therapy to control dyslipidaemia. Data were collected at baseline, interim (8 weeks) and subsequently at 16 weeks of Rosuvastatin (10 and 20 mg) therapy. Efficacy of the treatment was assessed by evaluating whether subjects reached target LDL and total cholesterol levels according to NCEP ATP III guidelines.

Results: Four thousand three hundred and sixty-nine patients completed the study. Out of 4369, 1115 (25.52%) have achieved a target LDL level of < 100 mg/dL and 2930 (67.06%) falls under HDL level of 40-60 mg/dL. The mean change in HDL levels was 5.56 mg/dL in females and 4.59 mg/dL in males. Overall 63.95% of patients had achieved the total cholesterol target and 50.06% achieved triglyceride target. The adverse events reported were generally mild.

Conclusion: On the basis of the above results, it can be concluded that Rosuvastatin safely and beneficially alters the entire spectrum of lipoproteins in Indian patients.

Background
Diabetes mellitus is a very commonly occurring metabolic disorder affecting approximately 285 million individuals aged between 20 -79 years worldwide. This accounts for 6.4% of the global population. It is projected to increase to 438 million by 2030, which should be 7.7% of the global population. A 69% increase in numbers of adults with diabetes in developing countries and a 20% increase in developed countries, is projected for 2030. 87 million of them are expected to be from India as against current prevalence of 50.8 million.¹ Diabetes is associated with increased oxidative stress due to hyperglycaemia.² The oxidative damage plays a role in development of micro and macro vascular complications leading to significant morbidity and mortality.³ There
is a growing evidence to show that hyperglycaemia and dyslipidaemia are associated with excess of cardiovascular risk\(^1\) while dyslipidaemia is a major risk factor for macrovascular complications in patients with type 2 diabetes mellitus (T2DM),\(^5,6\) affecting almost 50% of this population.\(^7\) During the past three decades prevalence of diabetes mellitus, hypertension, and dyslipidaemia has been increased markedly in India.\(^8,9\) Diabetic patients tend to have a higher concentration of low density lipoprotein cholesterol (LDL-C) which is a major risk factor for CVD.\(^5\) Approximately 80% of deaths in diabetic patients are attributable to CVD and Asian Indians have higher risk of heart attacks than whites, which in turn is highly correlated with diabetic dyslipidaemia.\(^10, 11\) Lowering LDL level is the first priority in treating diabetic dyslipidaemia.\(^12-14\) Therefore, aggressive lipid treatment goals have been recommended for patients with T2DM.\(^12-15\)

Statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) are the first drug of choice treating elevated LDL-C levels. Current evidence and guidelines mandate the aggressive treatment achieving lipid goals in most patients with diabetes.\(^16\) During the last 20 years evidence has accumulated showing dramatic reduction in cardiovascular risk using statins to lower levels of LDL-C.\(^17\) Rosuvastatin is a synthetic statin that possesses a greater number of binding interactions with HMG-CoA reductase and has a high affinity for the active site of the enzyme. Rosuvastatin is relatively hydrophilic and is selectively taken up by, and active in, hepatic cells.\(^18\) Rosuvastatin has the longest terminal half-life among statins and is only minimally metabolized by the cytochrome P450 (CYP 450) enzyme system, with no significant involvement of the 3A4 enzyme.\(^19\) Clinically significant drug interactions are absent between Rosuvastatin and other drugs known to inhibit CYP 450 enzymes.\(^19,20\) Rhabdomyolysis has been seen with all statins and is observed rarely across the full dose range.\(^21\) There were a few criticisms over safety of Rosuvastatin.\(^21\) However, there have been no cases to date of fatal rhabdomyolysis, directly or indirectly related to the rosuvastatin drug, on a background of over 5 million prescriptions.\(^21\) Rosuvastatin has an excellent benefit-risk profile compared with the other marketed statins, having better efficacy in lowering LDL cholesterol and raising HDL cholesterol and a safety profile comparable to those of the other marketed statins.\(^22\)

Conventional risk factors explain only half of variance in CVD; In Indian scenario, the conventional risk factors are important but cannot fully explain this excess risk. For these reasons, NCEP ATP III goes on with\(^23\) identifying elevated LDL cholesterol as the primary target of cholesterol-lowering therapy. As a result, the primary goals of therapy and the cutpoints for initiating treatment are stated in terms of LDL. For these reasons, Asian Indians with dyslipidaemia should be treated as aggressively as if they had a CHD risk equivalent–similar to the treatment of patients with diabetes or heart disease.

The present study was conducted to evaluate efficacy of Rosuvastatin in achieving target HDL, LDL, triglycerides and total cholesterol levels in T2DM patients with newly diagnosed dyslipidaemia, but without known coronary artery disease.

### Methods

The study was an open label, nonrandomised, non-interventional, observational study in India involving T2DM patients who require statin therapy to control dyslipidaemia. Data were collected at baseline, interim (8 weeks) and subsequently at 16 weeks of Rosuvastatin (10 and 20 mg) therapy.

A total of 5005 patients were recruited at tertiary centres by 1,500 participating physicians. The inclusion criteria were: men and women aged ≥ 18 years of age with newly diagnosed dyslipidaemia and a known history of T2DM; patients were required to have LDL levels of > 140 mg/dL, HDL levels of < 40 mg/dL and total cholesterol levels of > 200 mg/dL at the time of enrolment. Patients with following criteria were excluded: history of coronary artery disease, statin therapy, alcohol or drug abuse within the last five years, and malignancy; current active liver disease; unexplained increase in serum creatine kinase levels; uncontrolled hypothyroidism; initiation of hormone replacement therapy or oral contraceptives within 3 months of enrolment; pregnant or breastfeeding women; refusal to sign informed consent forms.

Efficacy of the treatment was assessed by evaluating

### Table 1: Demographic characteristics of patients

<table>
<thead>
<tr>
<th>Age</th>
<th>BMI (kg/m²)</th>
<th>Height</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Min</td>
<td>20</td>
<td>12.86</td>
<td>1.4</td>
</tr>
<tr>
<td>Max</td>
<td>88</td>
<td>47.38</td>
<td>2</td>
</tr>
</tbody>
</table>

**Mean (SD)** 52.18 (9.73) 25.91 (3.75) 1.64 (0.09) 69.61 (10.08)
whether subjects reached target LDL and total cholesterol levels according to NCEP ATP III guidelines. Safety of Rosuvastatin in T2DM patients with dyslipidaemia was assessed by monitoring the frequency and type of adverse events (AEs) and serious adverse events (SAEs) occurring in subjects. This study has been conducted in accordance with the Good Clinical Practice guidelines. This study was approved by an Independent Ethics Committee, Clinicom. Informed consent was taken from all participating subjects.

### Statistical Methods

Statistical testing was done using appropriate statistical tests. Demographic characteristics and results of lipid profile tests were summarised with descriptive statistics, including mean and standard deviation (SD) for continuous variables, and frequency and percentages for categorical variables. t-Test was used to check the difference between two doses and p≤0.05 was considered to be significant. The data from all participating doctors were pooled for analysis. After accounting for dropouts and exclusions, the evaluable patients were analysed for demographic features, indications for Rosuvastatin
Results

Out of the 5005 recruited, 4369 patients, 2976 males (68.12%) and 1393 females, (31.88%), completed the study. Patients were available at the 3rd visit at 16 weeks for the completion of treatment. The dropout rate was 12.7%. Mean age of the patient population during the recruitment was 52.18 years (± 9.73). Mean weight was 69.61 (± 10.08) kg, mean height was 1.64 (± 0.09) meters, and mean BMI was 25.91 (± 3.75) kg/m² (Table 1).

Lipid profile characteristics for difference between baseline to visit 3 (16 week) (n=4369)

Mean Change in Low-density lipoprotein Cholesterol Level after treatment for 16 weeks

Out of 4369, 1115 (25.52%) have achieved a target LDL level of < 100 mg/dL and 1559 (35.68%) were in the ‘near optimal range’ of 100-129 mg/dL of LDL. In the optimal target of < 100 mg/dL of LDL, the mean change was 45.94 (± 38.19) mg/dL in females and 44.17 (± 38.58) mg/dL in males (Table 2). In the ‘near optimal’ category of 100-129 mg/dL of LDL, the mean change for females was 38.53 (± 35.36) mg/dL, and for males was 57.15 (± 54.02) mg/dL. Interestingly, in the ‘very high’ category of > 190 mg/dL of LDL, in which only 2.7% of the population falls, there was an increase of 114.89 (± 282.06) mg/dL of LDL cholesterol in females but no increase was noted in male. This increase in LDL (although in only 2.7% of the study population) seems to be against the normal observation (Table 2). Since the trial has not been conducted in a clinical trial setting, but in a real world scenario, this increase might be because of compliance issues or other co-morbid conditions, which are inherent to observational trials.

Table 5: Mean change in triglyceride level after treatment for 16 weeks

<table>
<thead>
<tr>
<th>Triglyceride level*</th>
<th>Frequency (%)</th>
<th>TG Levels in mg/dl (at 16 weeks)</th>
<th>% Change in TG Levels</th>
<th>TG Levels in mg/dl (at 16 weeks)</th>
<th>% Change in TG Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>Female</td>
<td>Target Achievement</td>
<td></td>
<td>Male</td>
<td></td>
</tr>
<tr>
<td>&lt;150</td>
<td>2187 (50.06%)</td>
<td>-56.13 (66.29)</td>
<td>-32.2%</td>
<td>-63.31 (94.79)</td>
<td>-34.4%</td>
</tr>
<tr>
<td>150-199</td>
<td>1706 (39.05%)</td>
<td>-42.57 (55.38)</td>
<td>-20.3%</td>
<td>-39.56 (55.04)</td>
<td>-19.1%</td>
</tr>
<tr>
<td>200-499</td>
<td>471 (10.78%)</td>
<td>-57.14 (86.09)</td>
<td>-19.0%</td>
<td>-52.70 (84.23)</td>
<td>-17.5%</td>
</tr>
<tr>
<td>≥500</td>
<td>5 (0.11%)</td>
<td>-53.18 (67.63)</td>
<td>-9.41%</td>
<td>395.37 (780.46)</td>
<td>84.6%</td>
</tr>
<tr>
<td>Target Achievement</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>687 (15.72%)</td>
<td></td>
<td></td>
<td>1500 (34.33%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>706 (16.16%)</td>
<td></td>
<td></td>
<td>1476 (33.78%)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>2187 (50.06%)</td>
<td></td>
<td></td>
<td>2182 (49.94%)</td>
<td></td>
</tr>
</tbody>
</table>

TG: triglyceride; *NCEP ATP III Guidelines

Table 6: Comparison between doses: Rosuvastatin 10 mg and 20 mg

<table>
<thead>
<tr>
<th>Variable</th>
<th>N</th>
<th>Mean (mg/dl)</th>
<th>Std. Dev.</th>
<th>95% CI</th>
<th>t-value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 mg</td>
<td>3984</td>
<td>121.97</td>
<td>43.003</td>
<td>(120.63, 123.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20 mg</td>
<td>385</td>
<td>126.64</td>
<td>57.108</td>
<td>(120.92, 132.36)</td>
<td>-1.56</td>
<td>0.1188</td>
</tr>
<tr>
<td>Diff (1-2)</td>
<td></td>
<td>-4.672</td>
<td>44.423</td>
<td>(-9.32, -0.024)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDL-C</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 mg</td>
<td>3984</td>
<td>47.63</td>
<td>18.193</td>
<td>(47.065, 48.195)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20 mg</td>
<td>385</td>
<td>47.063</td>
<td>11.716</td>
<td>(45.889, 48.237)</td>
<td>0.86</td>
<td>0.3924</td>
</tr>
<tr>
<td>Diff (1-2)</td>
<td></td>
<td>0.5675</td>
<td>17.719</td>
<td>(-1.287, 2.4215)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 mg</td>
<td>3984</td>
<td>190.75</td>
<td>44.548</td>
<td>(189.36, 192.13)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20 mg</td>
<td>385</td>
<td>197.65</td>
<td>55.335</td>
<td>(192.1, 203.19)</td>
<td>-2.37</td>
<td>0.0180</td>
</tr>
<tr>
<td>Diff (1-2)</td>
<td></td>
<td>-6.9</td>
<td>45.599</td>
<td>(-11.67, -2.129)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TG</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 mg</td>
<td>3984</td>
<td>152.34</td>
<td>52.703</td>
<td>(150.7, 153.97)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20 mg</td>
<td>385</td>
<td>158.7</td>
<td>52.665</td>
<td>(153.42, 163.97)</td>
<td>-2.26</td>
<td>0.0238</td>
</tr>
<tr>
<td>Diff (1-2)</td>
<td></td>
<td>-6.36</td>
<td>52.699</td>
<td>(-11.87, -0.846)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein; TC: Total Cholesterol; TG: triglyceride

and efficacy of the two prescribed doses in controlling dyslipidaemia in diabetic subjects.
males. The HDL levels were below 40 mg/dL in 21.4% and above 60 mg/dL in 11.54% of patient population. Interestingly, in < 40 frequency, there was a decrease in the HDL levels both in males and females (Table 3).

**Mean change in total cholesterol level after treatment for 16 weeks**

In < 200 mg/dL category, 2794 (63.95%) of patients had achieved the target. The mean change was 51.20 (± 46.26) mg/dL in females and 56.10 (± 71.35) mg/dL in males. Overall, 1097 (25.11%) patients achieved the category of ‘borderline high’ (200-239 mg/dL range). Only 478 (10.94%) patients achieved ‘high’ category TC (> 240 mg/dL) (Table 4).

**Mean change in triglyceride level after treatment for 16 weeks**

In < 150 mg/dL category, 2187 (50.06%) patients population have achieved target. The mean change was 56.13 (± 66.29) mg/dL in females and 63.31 (± 94.79) mg/dL in males. Overall, 39.05% of the patient population achieved ‘borderline high’ (150-199 mg/dL) category. Only 471 (10.78%) patients achieved ‘high’ category of triglyceride (200-499 mg/dL). A few patients (0.11%) achieved ‘very high’ category (>500 mg/dL) (Table 5). The reason could be same as mentioned for the increase in LDL.

There was no statistical significance between two doses (10 mg and 20 mg) of Rosuvastatin (Table 6) changing the LDL-C and HDL-C levels from baseline. However, there was a statistically significant difference between Rosuvastatin 10 mg and 20 mg when it came to lowering of total cholesterol and triglycerides. Rosuvastatin 20 mg had a greater effect on lowering total cholesterol as well as triglyceride, compared to 10 mg. Overall, the adverse events reported were generally mild. The most common AEs were pain (262), pharyngitis (219), myalgia (175), and headache (131) which were reported by 6%, 5%, 4%, and 3%, respectively. There were no deaths reported during the study.

**Discussion**

The study results were consistent with those of the individual studies, confirming that Rosuvastatin is safe and efficient in lowering LDL-C.

The degree of LDL reduction is important to achieve the treatment goals suggested by guidelines. The NCEP III recommends a goal of less than 100 mg/dL for patients at high risk for coronary heart disease. In the present study 61.20% of patients achieved the target of LDL-C according to the NCEP ATP III guidelines. Among the most potent statins, Rosuvastatin is capable of getting the majority of patients to their LDL cholesterol goals. According to NCEP III recommendations amendments, the aggressive treatment should lower the LDL-C levels below 1.81 mmol/L (70 mg/dL), benefiting patients with high-risk coronary artery disease. Use of one of the more potent statins can serve the purpose, especially Rosuvastatin or Atorvastatin. The range of 40 - 60 mg/dL is designated as optimum HDL–C as per ATP III guidelines. Rosuvastatin produces favourable effects on HDL cholesterol, which is an independent marker of cardiovascular risk. In the present study, 67.06% of the total patient population achieved the HDL-C range of 40-60 mg/dL after 16 weeks of Rosuvastatin treatment. In Statin Therapies for Elevated Lipid Levels compared across doses to Rosuvastatin [STELLAR] study, HDL cholesterol increased by 8% to 11% and triglyceride reductions ranged from 22% to 34% with Rosuvastatin.

In the present study, HDL cholesterol increased by 10.8% in males and 13.42% in females.

A study compared Atorvastatin and Rosuvastatin in reducing LDL cholesterol in hypercholesterolaemia (HHF): 623 patients were randomised to 20 mg/day of atorvastatin (n = 187) or Rosuvastatin (n = 436) with forced titration at 6-week intervals to 80 mg/day. At week 18, Rosuvastatin therapy produced a greater reduction in LDL cholesterol (−57.9% vs. −50.4%; p _ 0.001) and a greater increase in HDL cholesterol (12.4% vs. 2.9%) than atorvastatin. At 12 weeks, 83% of patients achieved NCEP ATP III LDL cholesterol goals, which were maintained during 2 to 4 years. At 4 years, LDL cholesterol was reduced by 54% and HDL cholesterol increased by 13%. In present study, at 16 weeks of treatment, 2187 (50.06%) patients population have achieved target triglyceride levels (< 150 mg/dL), according to ATP III category. The mechanism of Rosuvastatin to increasing HDL cholesterol is unclear. However, it is believed that Rosuvastatin dose-dependently can increase plasma HDL cholesterol and apolipoprotein-I concentrations in the metabolic syndrome. This could relate to the reduction in plasma triglycerides with remodeling of HDL particles and reduction in apolipoprotein-I fractional catabolism. Rosuvastatin produces an increase in HDL cholesterol in the range of 4 to 6 mg/dL and to be responsible for an additional cardiovascular risk reduction in the range of 8% to 6%. There was no significant difference in mean percentage change in LDL-C levels between the Rosuvastatin 10 mg and 20 mg. Rosuvastatin, at its lowest dose (5 mg/day) can lower LDL-C by an average of 1.8 mmol/L and reduces the risk of ischaemic heart disease (IHD) events by about 60% and stroke by 17%. Even better results are expected after treatment at the commonly used dose of 10 mg/day. From the study ‘To Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden’ [ASTEROID], after 24 months, 349...
patients had evaluable serial IVUS examinations. Very high-intensity statin therapy using Rosuvastatin 40 mg/day achieved an average LDL-C of 60.8 mg/dL and increased HDL-C by 14.7%, resulting in significant regression of atherosclerosis for all pre-specified IVUS measures of disease burden.\textsuperscript{30} Rosuvastatin decreased mean LDL cholesterol, total cholesterol, non-high-density lipoprotein (non-HDL) cholesterol, apolipoprotein B, and lipid ratios from baseline to a significantly greater extent than atorvastatin at both weeks 8 and 16 (p < 0.001 vs. atorvastatin).\textsuperscript{31} Reducing the risk of CVD in atherosclerotic renal artery stenosis (RAS) patients, Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) trial used a medical treatment intervention that included tight control of blood pressure, treatment of dyslipidaemia and diabetes. According to the adult treatment panel III, RAS is considered a coronary artery disease equivalent in terms of cardiovascular risk. Thus, lowering low-density lipoprotein cholesterol to at least < 100 mg/dL is the goal of therapy, with some suggesting a target LDL-C of < 70 mg/dL.\textsuperscript{32}

Although statin therapy decreases LDL cholesterol levels and the risk of CHD, it has a considerable short-term effect on health care budgets.\textsuperscript{18} Rosuvastatin was demonstrated to be the most cost-effective statin.\textsuperscript{33} The ‘Use of Rosuvastatin versus Atorvastatin in Type 2 diabetes mellitus’ (URANUS) study compared Rosuvastatin with Atorvastatin for the reduction of low-density lipoprotein cholesterol (LDL-C) in patients with T2DM. At the starting dose and following dose titration, Rosuvastatin was significantly more effective than atorvastatin at reducing LDL-C and achieving European LDL-C goals in patients with T2DM.\textsuperscript{34} In present study, overall, trial treatment was well tolerated. The percentages of patients who reported AEs during randomised treatment were similar to the previous trials.\textsuperscript{35} There were no deaths or SAEs reported during the treatment with Rosuvastatin. These higher potency statins appear to be safe, even when used at higher dose. The incidence of myopathy and rhabdomyolysis, as documented in long-term clinical trials, is < 0.1% and < 0.01%, respectively.\textsuperscript{36} Concerns have been raised about increased risk of cancer in Lipid-lowering trials,\textsuperscript{37,38} but in the diabetes sub-population, no increase in any type of incident cancer was observed in relation to statin treatment. The decrease in LDL-C levels with statins has consistently decreased the occurrence of cardiovascular events in a broad range of patients.\textsuperscript{39}

We must admit that this research have some limitations. First of all the study duration is relatively short i.e. only 16 weeks, because of which we could not study any CV events, since it generally requires at least 52 weeks of follow up from baseline. Secondly, subjects were recommended to undergo only lipid profile tests, but not NMR lipoprotein and HbA1c level tests, since these are not routinely recommended in Indian clinical world setting. Given the large number of patients, it was economically not viable to support additional laboratory tests which are not a part of routine tests in India. However, we would like to consider these points and conduct follow up studies to supplement the current findings.

**Conclusion**

On the basis of the above results, it can be concluded that Rosuvastatin safely and beneficially alters the entire spectrum of lipoproteins in Indian patients. Results of previous randomised trials have shown that interventions able to lower LDL cholesterol concentrations (NCEP ATP III) can significantly reduce the incidence of coronary heart disease and other major vascular events in a wide range of individuals.\textsuperscript{40}

**References**


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31. Betteridge DJ, Gibson JM, Sanger PG. Comparison of Effectiveness of Rosuvastatin versus Atorvastatin on the Achievement of Combined Low-density lipoprotein (<2 mg/L) and Low-Density Lipoprotein Cholesterol (<70 mg/dl) Targets in Patients With Type 2 Diabetes Mellitus (from the ANDROMEDA Study). Am J Cardiol 2007;100:1245–48.


