Efficacy and Safety of Different Dosage of Rosuvastatin in Bangladeshi Patients: A Multi-Center Real-World Study

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Abstract

Background: Dyslipidemia is a major cause of disease burden in both the developed and developing world as a risk factor for ischemic heart disease and stroke. The effectiveness of rosuvastatin in Bangladesh has not been adequately studied. Therefore, this study was conducted to understand the efficacy and safety of rosuvastatin in real-world practice in Bangladesh.

Methods: This was a single-arm; non-intervention, multi-center, real-world study conducted in clinical practice settings in Bangladesh. Adult patients with dyslipidemia diagnosed by the treating physician and prescribed rosuvastatin (5 mg, 10 mg or 20 mg) were enrolled. The patients were treated over a 12 week period, with the primary objectives of assessing the percentage change from baseline in serum lipid profile, and assessing the proportion of patients reaching the Low-Density Lipoprotein Cholesterol (LDL-C) target goal of <100 mg/dL after 12 weeks of therapy.

Results: 280 patients were enrolled, with mean age 51.56 years, mean Body Mass Index (BMI) 26.43 kg/m2, mean baseline LDL-C 155.35 mg/dL. Mean Total Cholesterol (TC), LDL-C and Triglyceride (TG) levels decreased significantly. Overall, the mean LDL-C levels declined by 32.1% (49.9 mg/dL) from baseline to end-of-study, while the mean TC levels declined by 24.8% (58.8 mg/dL) and the mean HDL-C level increased by 16.71% (5.7 mg/dL). The proportion of patients that attained the LDL-C goal (LDL-C <100 mg/dL) in 5 mg, 10 mg and 20 mg dosage group was 24%, 49.21% and 65.71% respectively. On logistic regression analysis, higher BMI and use of clopidogrel reduced the odds of attaining LDL-C goal. Overall, 10.4% of all patients reported an Adverse Event (AE) at the end of the study. Most AEs were reported in the ‘muscle’ (6.5%) and ‘GI’ categories (6.8%).

Conclusion: This study demonstrates that all dosage form of rosuvastatin was effective in lowering TG and raising HDL-C in addition to lowering its primary target LDL-C in real-world conditions in Bangladesh. High dosage of rosuvastatin has no significant safety risk in Bangladeshi patients.

Keywords: Rosuvastatin; Dyslipidemia; Cardiovascular disease

Introduction

Dyslipidemia is a key risk factor for ischemic heart disease and stroke, making it a major cause of disease burden across the world. In 2008, the global prevalence of dyslipidemia, defined as total cholesterol ≥ 5.0 mmol/L was 37% in adult men and 40% in adult women. Dyslipidemia is estimated to contribute to one third of ischemic heart disease, and estimated to cause 2.6 million deaths and 29.7 million disability adjusted life year’s globally [1].

Dyslipidemia is a major public health issue in Bangladesh. With a population of over 164 million people, Bangladesh is the 8th most populous nation in the world [2]. The prevalence of dyslipidemia in urban regions of Bangladesh approaches that seen in developed countries. A systematic review and meta-analysis reported that the prevalence of dyslipidemia in Bangladesh was 41.5% in urban regions and 34.4% overall [3]. The prevalence of Cardiovascular Disease (CVD) in urban areas of Bangladesh is 8%, and has been increasing by ~0.12% per year from the 1970s until the 2010s [4]. CVDs along with their associated risk factors contribute to 13.4% of DALYs in Bangladesh [3].
Statins are the mainstay of pharmacotherapy to lower lipid levels [5,6]. Statins competitively inhibit HMG-CoA reductase (3-hydroxy-3-methyl-glutaryl-coenzyme A reductase), thereby reducing cholesterol synthesis in the liver. This induces increased hepatic Low Density Lipoprotein (LDL) receptor expression, which results in increased uptake of LDL-Cholesterol (LDL-C) from the blood, and therefore a reduced concentration of circulating LDL-C and other apo B-containing lipoproteins. Statins have demonstrated the ability to reduce LDL-C levels by 30% to over 50%; and their safety has been well-established [5,6]. Statins have also demonstrated a reduction in major cardiovascular events. The cholesterol treatment trialsists collaborators meta-analysis of data from 90,056 individuals in 14 randomized trials of Statins showed that a 1 mmol/L reduction in LDL-C corresponded to a 20% reduction in major cardiovascular events, and a 12% reduction in all-cause mortality [7].

Rosuvastatin is a selective, reversible competitive inhibitor of HMG-CoA reductase with high affinity for HMG-CoA reductase - the affinity of rosuvastatin is 4 times greater than the affinity of HMG-CoA for the enzyme. Key advantages of rosuvastatin include low extrahepatic tissue penetration, low potential for CYP3A4 interactions and potent LDL-C lowering capacity [8].

Rosuvastatin’s efficacy and safety have been well-established. In the stellar study (Comparison of the efficacy and safety of rosuvastatin vs. atorvastatin, simvastatin, and pravastatin across doses) rosuvastatin was significantly superior to other Statin comparators. Rosuvastatin 10 mg to 80 mg reduced LDL-C by a mean of 8.2% more than atorvastatin 10 mg to 80 mg, 26% more than pravastatin 10 mg to 40 mg, and 12% to 18% more than simvastatin 10 mg to 80 mg, at 6 weeks [9]. These results were replicated in the real-world DISCOVERY (Direct Statin Comparison of LDL-C Values: An Evaluation of Rosuvastatin therapy) studies. A meta-analysis of 5 studies participating in the DISCOVERY program showed that rosuvastatin was more effective than comparator Statins at lowering LDL-C levels and enabling patients to achieve 2003 European LDL-C goals at recommended start doses [10]. Pooled safety data from the Phase II/III trials, as well the post-marketing experience have demonstrated that rosuvastatin, when used at 10 mg to 40 mg daily, is well-tolerated and has a safety profile that is comparable to the other available Statins [8].

Regional efficacy and safety data are important in this context. Certain Asian populations may be more responsive to specific Statins, and there are safety concerns due to the potentially higher blood levels of Statins in Asian patients [6,11,12]. However, data pertaining to the use of rosuvastatin in Bangladesh are scarce, and are limited to small RCTs or studies of prescription patterns [13-16]. Given the paucity of Bangladesh-specific data, this study was conducted to understand the efficacy and safety of rosuvastatin prescribed to patients with dyslipidemia in real-world practice in Bangladesh.

**Methods**

**Overall design and eligibility criteria**

This was an open-labeled single-arm; non-interventional multicentric real-world study conducted in clinical practice settings in 26 centers in Bangladesh. The study recruited adult men and women with dyslipidemia diagnosed by the treating physician based on the ACC/AHA 2013 guidelines [17]. Patients with clinical Atherosclerotic Cardiovascular Disease (ASCVD), or LDL-C ≥ 190 mg/dL, or with diabetes and LDL-C 70 mg/dL to 189 mg/dL without clinical ASCVD (in patients aged 40-75 years), or those considered by their physician to potentially benefit from Statin treatment based on their ASCVD risk, were screened for the study. The patients were prescribed rosuvastatin as part of their standard of care treatment for dyslipidemia. Patients already receive Statin treatment for more than 4 weeks; those with a history of Statin-induced myopathy or serious hypersensitivity reaction to Statins; with a history of malignancy; with known active liver disease; or women who were pregnant, breastfeeding or of child-bearing potential and not using a reliable form of contraception; were excluded from the study.

**Study visits**

The study involved 3 visits over a 12-week treatment period. At the baseline visit (V1), patients were prescribed rosuvastatin 5, 10 or 20 mg per day as per the physician’s decision. At the second study visit at 6 weeks (V2), the rosuvastatin dose was increased, if needed, to a maximum of 40 mg per day at the physician’s discretion, based on the lipid control (LDL-C) achieved and patient characteristics. The final study visit (V3) was conducted at 12 weeks. Serum lipid profile (serum Total Cholesterol [TC], LDL-C, High Density Lipoprotein Cholesterol [HDL-C], and Triglyceride [TG]) was conducted prior to each visit. Other laboratory investigations included serum transaminases and serum Creatine Phosphokinase (CPK).

**Permitted treatments**

During the study period, concomitant treatments for comorbidities were continued as per the physician’s discretion. Erythromycin, fluconazole, ketoconazole, and itraconazole; lipid-modifying drugs, such as niacin; and certain Immunosuppressant’s, such as cyclosporine; were prohibited during the study period. The physician was permitted to initiate any other treatment during the course of the study if it was felt necessary or beneficial for the patient.

**Efficacy and safety endpoints**

The primary study objectives were to assess the percentage change from baseline in serum lipid profile (change in TC, HDL-C, TG, and LDL-C) after 12 weeks of therapy, and to assess the proportion of patients reaching the LDL-C target goal of <100 mg/dL after 12 weeks of therapy in different dosage of Rosuvastatin. The key safety objectives were to monitor and record Adverse Events (AEs) including, but not limited to, liver enzyme change, kidney function and muscle toxicity.

**Ethics and consent**

Independent ethics committee approval was obtained from Bangladesh Medical Research Council. Informed consent was obtained from all patients after providing them a detailed explanation of the study including the risks and benefits.

**Statistical analysis**

A descriptive analysis was conducted for the baseline and demographic characteristics. Change in lipid profile over time was analyzed with repeated measures Analysis Of Variance (ANOVA) followed by Tukey’s test for post-hoc pairwise comparison if repeated measures ANOVA returned p<0.05. Comparisons of LDL-C goal attainment across rosuvastatin dose groups were conducted using the chi-square test. A univariate analysis was conducted for identifying predictors for LDL-C goal attainment at V3 by testing for the following factors: Gender, Body Mass Index (BMI), blood pressure, smoking, comorbidities, and concomitant medications. All the factors found significant in the univariate analysis, along with age, were then entered together into a logistic regression analysis. Overall model
quality was fair with Nagelkerke’s R² value of 0.4279 (indicating that about 43% of the variability was accounted for by the variables selected). The power of the model’s predicted values to discriminate between positive and negative cases, as quantified by the area under curve, was 0.843 indicating high discriminating power. The cases that attain LDL-C goal were correctly predicted to the extent of 77.91% by the model.

**Results**

**Baseline and demographics**

A total of 280 patients were enrolled who completed the study. The mean age was 51.56 years and mean BMI was 26.43 kg/m². The mean Blood Pressure (BP) was 142 mmHg systolic and 88.1 mmHg diastolic. In terms of lipid profile, the mean LDL-C level was 155.35 mg/dL and mean total cholesterol was 237.00 mg/dL. Table 1 shows the baseline and demographics data for the study sample.

**Efficacy**

After 12 weeks of Rosuvastatin therapy, mean TC, LDL-C and TG levels decreased significantly, while HDL-C levels increased significantly, from baseline to week 6 (‘V1-V2’ in the Table 2), as well as from week 6 to week 12 (‘V2-V3’ in the Table 2). Overall, the mean LDL-C levels declined by 32.1% (49.9 mg/dL) from baseline to end-of-study (see ‘V1-V3’ in the Table 2), while the mean TC levels declined by 24.8% (58.8 mg/dL). For all 4 parameters, the changes in the initial 6 weeks of treatment were larger than the changes in the later 6 weeks (Figure 1). Table 2 shows the change over time in the serum lipid profile parameters.

The proportion of patients that attained the LDL-C goal (LDL-C <100 mg/dL) was 8.57% (95% CI 5.29-11.85%) at 6 weeks, and 41.43% (95% CI 35.66-47.20%) at 12 weeks. Table 3 shows the LDL-C goal attainment at 12 weeks separately by the baseline rosuvastatin dose groups. There was a significant difference across groups, with the highest proportion (65.7%) in the 20 mg group and the lowest (24.0%) in the 5 mg group (Figure 2).

On regression analysis, the following parameters were significantly associated with 12-week LDL-C goal attainment on univariate analysis- low BMI; low systolic BP; low diastolic BP; less frequent angina, Diabetes Mellitus (DM) and smoking; less frequent use of beta blockers and clopidogrel; and more frequent use of angiotensin converting enzyme inhibitors. All these variables, along with age, were entered into a multivariate logistic regression analysis (Table 4). LDL-C goal attainment was independently predicted by BMI, baseline rosuvastatin dose level and clopidogrel use. Higher BMI and use of clopidogrel reduced the odds of attaining LDL-C goal, whereas higher rosuvastatin dose increased the odds of attaining LDL-C goal.

### Table 1: Baseline and demographics data.

<table>
<thead>
<tr>
<th>Valid N</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>278 51.56 ± 9.78</td>
</tr>
<tr>
<td>BMI</td>
<td>253 26.43 ± 3.61</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>272 142.02 ± 19.08</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>272 88.10 ± 10.82</td>
</tr>
<tr>
<td>TC</td>
<td>280 237.00 ± 45.70</td>
</tr>
<tr>
<td>LDL-C</td>
<td>280 155.35 ± 36.03</td>
</tr>
<tr>
<td>HDL-C</td>
<td>280 34.09 ± 8.86</td>
</tr>
<tr>
<td>TG</td>
<td>280 246.28 ± 92.37</td>
</tr>
<tr>
<td>SGPT</td>
<td>280 34.78 ± 17.23</td>
</tr>
<tr>
<td>CPK</td>
<td>280 95.49 ± 85.17</td>
</tr>
</tbody>
</table>

BMI: Body Mass Index; BP: Blood Pressure; CPK: Creatine Phosphokinase; HDL-C: High Density Lipoprotein Cholesterol; LDL-C: Low Density Lipoprotein Cholesterol; SGPT: Serum Glutamic-Pyruvic Transaminase; TC: Total Cholesterol; TG: Triglyceride

### Table 2: Change over time in serum lipid profile.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean difference V1 - V2 (% change from baseline)</th>
<th>P value</th>
<th>Mean difference V1 - V3 (% change from baseline)</th>
<th>P value</th>
<th>Mean difference V2 - V3 (% change from Visit 2)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC</td>
<td>39.1 (16.50)</td>
<td>&lt;0.001</td>
<td>58.80 (24.81%)</td>
<td>&lt;0.001</td>
<td>19.69 (9.95%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL-C</td>
<td>-32.97 (21.22%)</td>
<td>&lt;0.001</td>
<td>-49.94 (32.14%)</td>
<td>&lt;0.001</td>
<td>16.97 (13.86%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL-C</td>
<td>-3.39 (1.99%)</td>
<td>&lt;0.001</td>
<td>-5.70 (1.67%)</td>
<td>&lt;0.001</td>
<td>2.36 (1.61%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TG</td>
<td>51.02 (20.72%)</td>
<td>&lt;0.001</td>
<td>71.87 (29.18%)</td>
<td>&lt;0.001</td>
<td>20.86 (10.68%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

HDL-C: High Density Lipoprotein Cholesterol; LDL-C: Low Density Lipoprotein Cholesterol; TC: Total Cholesterol; TG: Triglyceride; V: Visit
Safety

Overall, Study drug was well tolerated. No patient had withdrawn from the study due to adverse events. Total 10.36% of all patients reported an AE at the end of the study. Most AEs were reported in the 'muscle' (6.79%) and 'Gastrointestinal (GI)' categories (1.43%) (Table 5).

AEs were numerically more frequent in the rosuvastatin 20 mg dose group compared to the other doses. For 5, 10 and 20 mg dose groups, the AE frequency was 35.5%, 22.9% and 40.0% respectively at visit 2, and 7.6%, 5.1% and 0% respectively at visit 3. The frequency of AEs decreased from 6 weeks to 12 weeks.

Table 6 shows the change over time in median SGPT and CPK values. Although statistically significant, the changes in SGPT and CPK levels were not clinically relevant. During the study, elevated CPK levels (>2 times ULN i.e. >400 U/L) were noted in 3 subjects, 1 subject and 1 subject respectively at baseline, 6 weeks and 12 weeks. One subject had a high value at baseline and maintained it throughout the study period. Elevated SGPT levels (>3 times ULN i.e. >120 U/L) were noted in 1 subject throughout the study.

Discussion

To the best knowledge of the authors, this is the first published real-world study on the effectiveness of rosuvastatin in Bangladesh. The study involved a reasonably large sample of 280 patients, and was conducted in clinical practice settings.

Most patients in our study were treated with rosuvastatin 10 mg or lower doses, with only 35 patients (12.5%) receiving the 20 mg dose. This is consistent with the data seen in other real-world studies in the Asian population, where 5 mg and 10 mg doses are used more frequently than higher doses.
VOYAGER meta-analysis of RCTs, among patients with a baseline LDL-C ≥ 130 mg/dL, the mean proportion of patients meeting their LDL-C goal ranged from 38.0% to 90.1% with rosuvastatin doses 5 mg to 20 mg, and showed a similar dose-response relationship [25].

In terms of factors associated with meeting LDL-C goals, using the higher doses of rosuvastatin (10 mg and 20 mg) was significantly more likely to result in goal attainment compared to the lower dose (5 mg). A high BMI was associated with a lower likelihood of meeting LDL-C goals, which is consistent with previous studies that have identified lifestyle issues and cardiovascular risk factors as relevant risk factors for non-attainment of LDL-C goals [24,26]. It is interesting that use of clopidogrel was associated with lower odds of meeting LDL-C goals in our study; perhaps, this finding may be explained by clopidogrel use being a marker for more severe disease in these patients. Notably, this association persisted in the adjusted analysis.

The safety data were reassuring with muscle and GI-related AEs being the most frequently reported events. The proportion of patients with any adverse event decreased over time, and there was no clinically significant change in the SGPT or CPK levels over time. This is consistent with the findings form a recent real-world study in Bangladesh, which reported that patients with clinical atherosclerotic cardiovascular disease receiving rosuvastatin experienced lesser muscle pain, fatigue, cramp/spasticity and weakness, compared to those receiving atorvastatin [14]. The favorable risk-benefit profile may explain why rosuvastatin is currently the 2nd most commonly prescribed statin in Bangladesh [16].

There were a few limitations with our study. This was conducted as a real-world study in clinical practice settings, therefore detailed information regarding screen failures, and detailed AE information was not captured. Additionally, this was a relatively short study; whilst 12 weeks were sufficient to demonstrate the benefit of rosuvastatin, a longer treatment period may have helped to better understand the change in effect size and persistence of effect over time. Despite these limitations, we believe the study fulfilled the purpose of assessing the effectiveness of rosuvastatin in treating dyslipidemia in real-world conditions in Bangladesh.

Future studies on rosuvastatin in Bangladesh could be conducted with longer treatment duration to examine the maintenance of effect and long-term safety, and could attempt to examine the dose-response relationship and factors associated with response in further detail.

**Conclusion**

Our study demonstrates that all dosage form of rosuvastatin was effective in lowering TG and raising HDL-C in addition to lowering its primary target LDL-C in Bangladesh. High dosage of rosuvastatin has no significant safety risk in Bangladeshi patients. Effect of rosuvastatin along with adverse events was found to be more pronounced in the initial weeks than the subsequent period. Future studies on rosuvastin in Bangladesh could be conducted with longer treatment duration to examine the maintenance of effect and long-term safety, and could attempt to examine the dose-response relationship and factors associated with response in further detail.

**Conflict of Interests**

This is to certify that the Investigators do not have any matters which might give rise to a real or perceived conflict of interest. There is no existence of any personal interest, pressure of biasness and involvement with any organization which can mislead during the study procedure. The study was conducted by Cardiology Study group which was supported by the unconditional unrestricted educational grant from Beximco Pharmaceuticals Ltd.

**Annexure**


**References**

1. World Health Organization.
2. The World Bank.


