

# EFFICACY AND SAFETY OF ROSUVASTATIN COMPARED TO SIMVASTATIN IN CORONARY ARTERY DISEASE

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## ABSTRACT

**Background:** Coronary artery disease is the leading cause of morbidity and mortality worldwide. Hyperlipidemia is a major risk factor for it. This trial was conducted to compare the efficacy and safety of rosuvastatin and simvastatin in patients with coronary artery disease.

**Material & Methods:** This study was conducted at Pharmacology Department, Gomal Medical College, D.I.Khan from May 1, 2008 to December 31, 2008. Patients with history of coronary artery disease were randomized to receive Rosuvastatin 5mg or Simvastatin 20mg for six weeks. Primary end point was number of patients achieving National Cholesterol Education Program Adult Treatment Panel (NCEP ATP III) target LDL-C < 100mg/dl, while secondary end points were reduction of LDL-Cholesterol, Total Cholesterol and increase in HDL-Cholesterol and safety profile of the two drugs.

**Results:** Eighty patients were randomized into two groups. Rosuvastatin Group consisted of 23(57.5%) males and 17(42.5%) females while Simvastatin Group 22(55%) males and 18(45%) females. Mean age was  $55.35 \pm 9.7$  and  $55.7 \pm 8.6$  years respectively. Primary end point was achieved in significantly higher number of patients in Rosuvastatin Group 30(75%) as compared to Simvastatin 17(42.5%),  $p=0.003$ . Significantly greater reduction in LDL-C from baseline occurred in Rosuvastatin group  $78.2 \pm 6.14$  mg/dl (44.3%) as compared to  $66.8 \pm 9.9$  mg/dl(37.7%) in Simvastatin,  $p<0.001$ . Total cholesterol was significantly reduced in Rosuvastatin group  $98.5 \pm 8.8$ mg/dl (38.6%) as compared to  $78.4 \pm 7.8$ mg/dl (30.4%) in Simvastatin,  $p<0.001$ . Increase in HDL-C was significantly greater in Rosuvastatin  $4.4 \pm 0.87$  mg/dl(11.5%) as compared to  $2.45 \pm 0.55$ mg/dl(6.5%) in Simvastatin,  $p=0.009$ . Both treatments were well tolerated with no serious adverse effects.

**Conclusion:** Rosuvastatin is more efficacious in modifying lipid profile and has comparable safety and adverse event profile to Simvastatin.

**Key words:** Rosuvastatin, Coronary Artery Disease, Cholesterol, LDL Cholesterol, HDL Cholesterol.

## INTRODUCTION

Coronary artery disease (CAD) is the leading cause of morbidity and mortality world wide.<sup>1</sup> It is also the leading cause of death of adult population of Pakistan.<sup>2</sup> Hyperlipidemia is a major risk factor for the development of CAD.<sup>3</sup> The risk of CAD increases by 2-4 fold by increase in level of LDL-C (Low Density Lipoprotein Cholesterol).<sup>4</sup> The direct relationship between CAD and serum lipids has led to the development of strategies aimed in reducing LDL-C resulting in significant reduction in morbidity and mortality.<sup>5</sup> 4S trail showed 42% reduction in mortality by reducing LDL-C by 35%.<sup>6</sup>

Statins are the diverse class of drugs that lower cholesterol levels in patients with and without at risk of CAD by inhibiting the enzyme 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA reductase),

which is rate limiting enzyme of cholesterol synthesis.<sup>7</sup> Results of various trails have shown that Statins are the most efficacious drugs in primary and secondary prevention of CAD by reducing LDL-C levels but residual morbidity and mortality is still on the higher side.<sup>8</sup>

Despite the guidelines and availability of the lipid lowering therapy many patients fail to reach the desired goals, depriving the remaining from the beneficial effects of statin therapy.<sup>9</sup> This treatment gap has considerable clinical and economical implications in terms of preventing cardiovascular events and increased costs to health care plans.<sup>10</sup>

More recent studies have shown that cardiovascular end points are further reduced with even more lower level of LDL-C suggesting for the de-

velopment of more effective form of lipid lowering therapy.<sup>11</sup> Clinical trails have shown that Rosuvastatin provides the greatest LDL-C reduction as compared to other Statins.<sup>12,13</sup> But no such data is available in our part of country so we conducted this study to compare the efficacy and safety of Rosuvastatin with Simvastatin in achieving National Cholesterol Education Program Adult Treatment Panel (NCEP ATP III)<sup>11</sup> target LDL-C level in patient with CAD.

## MATERIAL AND METHODS

This study was conducted at Pharmacology Department, Gomal Medical College, Dera Ismail Khan from 1<sup>st</sup> May 2008 to 31<sup>st</sup> December 2008. A total of 80 patients between 18-70 years of age with history of CAD who had their LDL-C >160 mg/dl were randomized to receive Rosuvastatin 5mg and Simvastatin 20 mg for six weeks. Patients with history of hypersensitivity to Statins, pregnancy, breast feeding, use of oral contraceptive pills (OCP's), impaired renal and liver functions, uncontrolled diabetes, uncontrolled hypertension and unstable angina were excluded from the study. Demographic variables of the study population were recorded on preformed proforma. All the patients were advised to continue lipid lowering diet during the course of study. LDL-C, TC(Total Cholesterol), HDL-C (High Density Lipoprotein Cholesterol), Creatine kinase (CK), Alanine aminotransferase (ALT) ,Urea, Creatinine were carried out in all the patients at week 0 and then at the end of study at week 6. The primary endpoint

of the study was achievement of NCEP ATP III target LDL-C <100mg/dl in both the groups. Secondary end points were the change of LDL-C, HDL-C and TC from baseline between the two groups and the safety of two treatment drugs evaluated through clinical assessment of adverse events and elevation of ALT >3 times upper limit normal (ULN) and CK >10 times ULN.

All data was analyzed using SPSS 11 for windows. Categorical variables were expressed as frequencies and percentages while continuous variables were expressed as Mean  $\pm$  SD. Comparative analysis between the two groups were done using Chi-Square ( $\chi^2$ ) and student 't' test where appropriate. A p value of <0.05 was taken as significant.

## RESULTS

A total of 80 patients were randomized to receive Rosuvastatin 5mg and Simvastatin 20mg for six weeks. There were 40 patients in each group. Mean age of patients was  $55.35 \pm 9.7$  years in Rosuvastatin group and  $55.7 \pm 8.6$  years in Simvastatin group. There were 23 (57.5%) males and 17(42.5%) females in Rosuvastatin group, while Simvastatin group consisted of 22(55%) males and 18(45%) females. (Table 1)

Hypertension was present in 30(75%) patients in Rosuvastatin group patients and 29(72.5%) patients in Simvastatin group. There were 17(42.4%) patients suffering from Angina Pectoris in Rosuvastatin group and 20(50%) patients in Simvastatin group. (Table 1)

**Table 1: Demographic variables of the patients.**

Variable		Rosuvastatin Group n=40	Simvastatin Group n=40
Age (years)	Mean	55.35 $\pm$ 8.6	55.7 $\pm$ 8.6
Males		23(57.5%)	22(55%)
Females		17(42.5%)	18(45%)
Diabetes		23(57.5%)	27(67.5%)
Hypertension		30(75%)	29(72.5%)
Smoking		16(40%)	18(45%)
Angina pectoris		17(42.5%)	20(50%)
MI		8(20%)	9(22.5%)
CABG		4(10%)	3(7.5%)
PCI		11(27.5%)	8(20%)

**Abbreviations:** Myocardial Infarction = MI; Coronary Artery Bypass Grafting = CABG; Percutaneous Coronary Intervention = PCI.

**Table 2: Change from baseline in LDL-C and Total Cholesterol after six weeks of treatment.**

Lipids	Rosuvastatin Group n=40			Simvastatin Group n=40			P value*
	Mean at	Mean change from base line		Mean at	Mean change from base line		
	Base line	week 6		Base line	week 6		
LDL-C (mg/dl)	176.35±11.2	98.2±8.95	78.18±6.14	177.2±11.2	110.4±15.7	66.8±9.9	< 0.0001
TC (mg/dl)	254.8±20.64	156.4±14.6	98.5±8.8	258.5±19.4	180±17.38	78.4±7.8	< 0.0001
HDL-C (mg/dl)	38.25±4.6	42.65±4.65	4.4±0.87	37.45±4.36	39.9±4.52	2.45±0.55	0.009

**Abbreviations:** Low Density Lipoprotein Cholesterol = LDL-C, Total Cholesterol = TC, High Density Lipoprotein Cholesterol = HDL-C.

\* For percentage change from baseline with Rosuvastatin Group versus Simvastatin Group at 6 weeks

**Table 3: Number of patients with Side effects.**

Variable	Rosuvastatin Group n=40	Simvastatin Group n=40
<b>Myalgia</b>	3(7.5%)	2(5%)
<b>Abdominal pain</b>	2(5%)	2(5%)
<b>ALT</b> 1-2 times ULN	1(2.5%)	1(2.5%)
<b>CK</b> 1-2 times ULN	2(5%)	1(2.5%)

**Abbreviations:** Alanine aminotransferase = ALT, Creatine kinase = CK

Rosuvastatin group had significantly greater reduction in mean LDL-C ,44.3% (from 176.35±11.2 mg/dl to 98.2±8.95 mg/dl) as compared to Simvastatin group, 37.7% (from 177.2±11.2 mg/dl to 110.4 ±15.7 mg/dl), p<0.001, Table 2.

Significantly greater number of patients achieved NCEP ATP III target goal of LDL-C after six weeks of therapy in Rosuvastatin group 30 (75%) as compared to Simvastatin group 17(42.5%) ,P = 0.003, Figure 1.

Total Cholesterol was reduced significantly in Rosuvastatin group, 38.6% (from 254.8 ±20.6 mg/dl to 156.4 ±14.6 mg/dl) as compared to Simvastatin group, 30.4% (from 258.5±19.4 mg/dl to 180±17.4 mg/dl), p<0.0001, Table 2.

Increase in HDL-C was significantly greater in Rosuvastatin group, 11.5% (from 38.25±4.6 mg/dl to 42.65±4.65.19mg/dl) as compared to Simvastatin group, 6.5%(from 37.45±4.4 mg/dl to 39.9±4.5mg/dl), p=0.009.

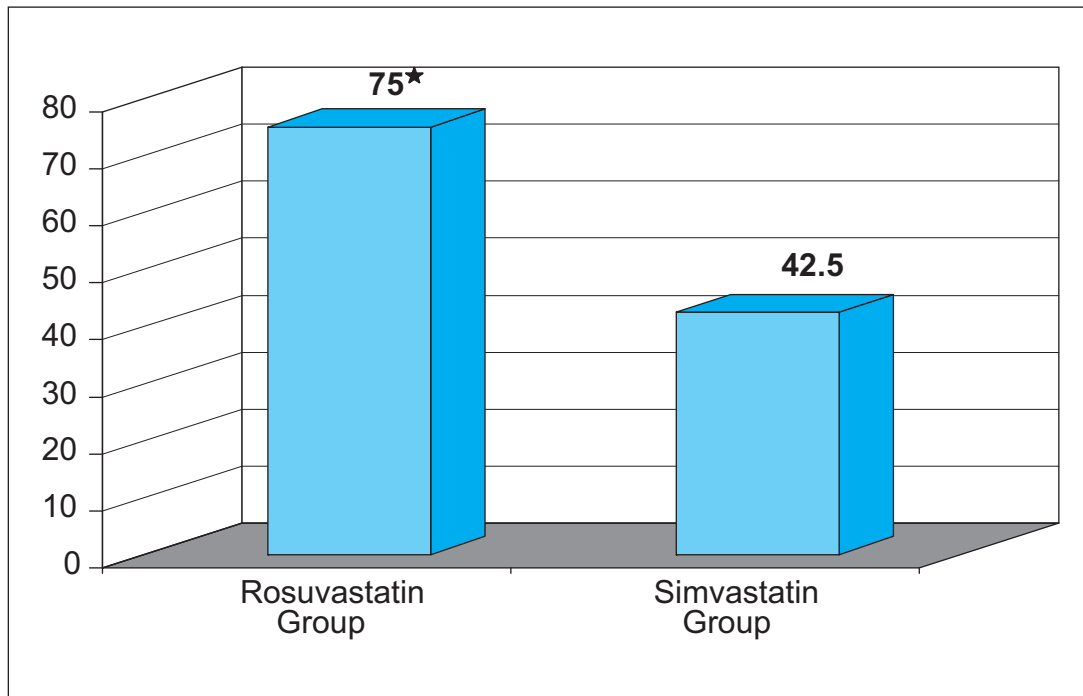
Both treatments were well tolerated and the overall frequency and type of adverse events were

similar in two groups. Myalgia was the most frequent reported adverse event in both the groups. There was only 1(2.5%) patient from both the groups with ALT within 1-2 times ULN; while CK was raised to 1- 2 times ULN in 2(5%) patients in Rosuvastatin group and 1(2.5%) patient in Simvastatin group, Table 3, with no patients having ALT >3 times ULN or CK > 10 times ULN. No serious side effects were reported in both the groups.

## DISCUSSION

Elevated LDL-C is important contributing factor for development of atherosclerosis and is recognized as the major risk factor for CAD, as a result LDL-C is the key therapeutic target for the prevention of CAD, with Statin as the first line treatment.<sup>11</sup>

In this randomized trial comparing the efficacy and safety of Rosuvastatin with Simvastatin showed that Rosuvastatin has greater efficacy in achieving NCEP ATP III LDL-C level as compared to Simvastatin over six weeks of treatment in patients with CAD.



\* p = 0.003 versus Simvastatin Group

Fig. 1: Percentage of patients achieving ATP III LDL Cholesterol after six weeks of treatment.

In our study, at six weeks, mean LDL-C decreased by 44.3% in Rosuvastatin group as compared to 37.7% in Simvastatin group. Brown et al<sup>12</sup> reported 39.1% decrease in LDL-C in Rosuvastatin group as compared to 34.6% in Simvastatin group. Meta-analysis by Law and colleagues<sup>14</sup> showed 38% reduction in LDL-C in Rosuvastatin group as compared to 32% in Simvastatin group which is similar to our results. DISCOVERY-Beta<sup>15</sup> study reported a decrease of 38.79% in LDL-C in Rosuvastatin group as compared to 32.03% in Simvastatin group.

Achievement of LDL-C targets in high risk patients have been a challenging objective in clinical practice.<sup>15</sup> The significantly greater decrease in LDL-C with Rosuvastatin as compared to Simvastatin in our study enabled more patients in the Rosuvastatin group to achieve NCEP ATP III target LDL-C, 30 (75%) in Rosuvastatin group vs 17(42.5%) in Simvastatin group, p=0.003. Our results are similar with other trials. In MERCURY II<sup>16</sup> trial target LDL-C was achieved in 82% patients with Rosuvastatin as compared to 33% with Simvastatin. MERCURY I<sup>17</sup> trial reported 80% patients in Rosuvastatin group achieving target LDL-C as compared to 54% in Simvastatin group. Achieving the target LDL-C has been associated with improved cardiovascular outcomes.<sup>5</sup> In this regard Rosuvastatin therapy may prove valuable

in high risk patients unable to achieve lipid goals with other Statins.

In addition to reducing LDL cholesterol, improvement in other components of lipid profile may be beneficial in reducing risk in patients with CAD.<sup>11</sup>

In our study, Rosuvastatin showed a statistically significant decrease in TC, 38.6% as compared to 30.4% in Simvastatin. This decrease in TC is similar to reported by other studies. In MERCURY II trial<sup>16</sup>, 37% decrease in TC is reported with Rosuvastatin as compared to 24.1% with Simvastatin. Edwards and Moore<sup>18</sup> in their Meta-analysis reported 30% reduction in TC in Rosuvastatin group as compared to 21% in Simvastatin group. Brown et al<sup>12</sup> reported 28% decrease in TC in Rosuvastatin as compared to 23% in Simvastatin group.

After 6 weeks of treatment HDL-C increased by 11.5% in Rosuvastatin group as compared to the Simvastatin group 6.5%. This increase is similar to reported by other studies. Edwards and Moore<sup>18</sup> in their Meta analysis reported 9% increase in HDL with Rosuvastatin as compared to 8% with Simvastatin. McTaggart and Jones<sup>19</sup> in their review reported 8.5% rise in HDL-C in Rosuvastatin as compared to 6.4% in Simvastatin group. A very modest rise in HDL-C is reported in DISCOVERY-

Beta<sup>18</sup> study both with Rosuvastatin (0.66%) and Simvastatin (2.26%). This modest rise in HDL-C in DISCOVERY trial can be due to higher levels of HDL-C at baseline in these patients.

In our study, Rosuvastatin was well tolerated with safety profile similar to Simvastatin, with no occurrence of serious adverse side effects. These findings are similar to those reported by other studies.<sup>17, 20, 21</sup>

In this study, Rosuvastatin 5mg showed greater lipid modifying efficacy and goal attainment with a safety profile similar to that of Simvastatin 20mg.

## CONCLUSION

Rosuvastatin, the newer third generation statin is more efficacious in modifying lipid profile and has comparable safety and adverse event profile to Simvastatin.

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