Comparing efficacy and safety of atorvastatin and rosuvastatin in ischemic heart disease patients

**Background:** Statins are very effective in controlling hyperlipidemia, the leading cause of cardiovascular diseases. The most common, worldwide side effect of statins is myopathy. The study aims to compare safety and efficacy of most commonly used statins i.e. atorvastatin and rosuvastatin and effectiveness of CoQ10 in managing statin induced myopathy.

**Materials and Methods:** An investigational study design was adopted using randomized trials at Punjab Institute of Cardiology, Lahore Pakistan from November 2016 - February 2017. A total of 95 male and female patients were enrolled between the age ranges of 40-80 years, using atorvastatin and rosuvastatin. Lipid profile, total cholesterol, serum HDL-C, serum triglycerides, LDL-C and total cholesterol/HDL-C ratio were analysed from blood samples. The effectiveness of CoQ10 was found by the blood CPK levels.

**Results:** The results showed that gender and dose had significant correlation with CPK levels, (p=0.001) and (p>0.001) respectively. Patients using rosuvastatin 20 mg were significantly on high risk to myopathy as compared to atorvastatin 40mg (p=0.023). 20 mg atorvastatin was more prone to induce statin induced myopathy compared to 10 mg (p=0.001). Atorvastatin 20 mg showed higher levels of CPK as compared to rosuvastatin 10 mg (p=0.002). Significant increases in the levels of CPK also found with rosuvastatin 20 mg and atorvastatin 20 mg (p>0.001). Rosuvastatin 20 mg significantly increases the risk of myopathy compared to atorvastatin 10 mg (p<0.001). The effect of rosuvastatin 20 mg was significantly poor than atorvastatin 10 mg (p=0.001). Atorvastatin 10 mg was more efficacious than rosuvastatin 20 mg (p=0.026). The levels of CPK significantly reduced after treatment with CoQ10 (P=0.022).

**Conclusions:** It was concluded that rosuvastatin users were more prone to the risk of myopathy, myalgic symptoms and rise in CPK levels were dose related, and both statins were equally effective. It was further concluded that CoQ10 was quite effective in lowering the levels of CPK and for the reversal of myalgia.

**Keywords:** statin, myalgia, CoQ10, CPK, atorvastatin, rosuvastatin
Goettsch and coworkers investigated the safety of rosuvastatin to evaluate the incidence of myopathy, no significant difference of incidence of myopathy between rosuvastatin and other statin users were found [9].

Ganairy and colleagues evaluated the relationship between the myopathy patterns of hydrophilic rosuvastatin and lipophilic atorvastatin and found that rosuvastatin causes less myopathy manifestations [9]. Fluvastatin myopathy cases were stated the least with least myopathy effect [10].

Backes and colleagues determined the tolerance and effect of every other day dosing (EOD) of rosuvastatin and found that EOD rosuvastatin therapy was effective in most of the patients and was quite useful in patients that are intolerant to once daily dosing of statins [11].

It is investigated that intermittent dosing is very useful in patients with previous history of statin induced myopathy especially with atorvastatin and rosuvastatin [10]. Efficacy of atorvastatin and rosuvastatin was investigated and found that rosuvastatin is more efficacious in reducing LDL-Cholesterol levels in contrast with atorvastatin [12,13].

Baner and colleagues compared the safety, efficacy and cost effectiveness of the most prescribed statins that are atorvastatin, simvastatin, rosuvastatin and pravastatin and found that the most effective statin in reducing total cholesterol and serum lipid patients was considered to be rosuvastatin (10 mg) [14].

Wlodarczyk and colleagues determined the risk over benefit ratio between atorvastatin and rosuvastatin, and found that rosuvastatin was considered to be more efficacious than atorvastatin [15].

Many studies have been done to investigate the safety and efficacy comparison of atorvastatin and rosuvastatin and found that rosuvastatin was found to be more efficacious and well tolerated as compared to atorvastatin and other statins [16-19].

Jones and his fellows compared safety and efficacy of rosuvastatin with simvastatin, atorvastatin and pravastatin at different doses and observed that rosuvastatin at doses 10-80 mg reduces LDL-C levels 8.3% more than atorvastatin while 26% and 18% more than pravastatin and simvastatin respectively. However, the drug tolerability was to be similar across all the treatments [20].

Saku and his colleagues compared the safety and efficacy of atorvastatin rosuvastatin and pitavastatin and found that all the three statins were equally efficacious and safe and the choice of statin to be used totally depends upon the physician [21].

A number of treatments for managing statin induced myopathy are used but CoQ10 supplementation is considered to be final and quite common in almost all patients having cardiovascular diseases [22,23]. Among other treatments, vitamin D supplementation has a significantly important effect in treating statin induced myopathy particularly when vitamin D level was ≤ 20 ng/ml in order to increase statin tolerance [24].

Some statins are safer than others and are preferable for long term therapy [24]. Chio and colleagues predicted the efficacy of CoQ10 along with atorvastatin treatment for hyperlipidemia and found that CoQ10 supplementation not only reduces the myopathy effect but also acts as an anti-obesity agent [23,24].

Study aims to compare safety profile, efficacy of atorvastatin and rosuvastatin and effectiveness of CoQ10 in managing statin induced myopathy.

**Materials and methods**

An investigational study design was adopted using randomized trials at Punjab Institute of Cardiology, Lahore Pakistan from November 2016 - February 2017. A total of 95 patients were enrolled.

For determining safety profile and comparative efficacy of atorvastatin and rosuvastatin both males and females participated between the age ranges of 40-80 years. Patients showing muscle problems or not showing muscle problems whether diabetic or non-diabetic were considered, the most important ischemic heart disease patients were included. For determining efficacy of the treatment with CoQ10 the additional criteria was muscle problems with elevated levels of creatinine phosphor kinase (CPK).

Patients of age less than 40 or greater than 80 were excluded from the study. Moreover, patients having any sort of cancer, periodontal disease; heart failure and migraine were also not considered to be included in the study.

Convenient and random sampling technique was adopted. 50 patients were included for
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**Data collection procedure**

Data was collected from patients visiting the outpatient department of Punjab Institute of Cardiology, Lahore, Pakistan. The patients were divided into two groups, Group A and B. Group A patients were receiving atorvastatin while group B patients were using rosuvastatin at different doses. Patients were further subdivided into three portions. In the first part comparison of the efficacy of the statins was determined in second part safety comparison was determined and in the last portion the efficacy of the treatment recommended for the management of myopathy that is CoQ10 supplementation was determined.

In these groups severity of the symptoms and total cholesterol levels were compared. Furthermore, levels of CK were also measured. The patients showing high levels of CK were given CoQ10 supplementation and its effects were recorded.

1-Randomized trials were conducted in order to compare the efficacy of atorvastatin and rosuvastatin in patients suffering from ischemic heart disease. 50 patients were included and all of them were using these medications for more than one year at different doses (10 mg, 20 mg and 40 mg). Blood samples were collected from the cubital vein of the patient and were analyzed by the pathology department of PIC for lipid profile (triglycerides, total cholesterol, HDL-C, LDL-C, total cholesterol/HDL-C ratio.)

For total cholesterol, serum HDL-C and serum triglycerides Kit method (ADVIA Chemistry systems Siemens) was used. While LDL-C and total cholesterol/HDL-C ratio were calculated by using the following formulas

\[
LDL-C \text{ mg/dL} = \text{Total cholesterol mg/dL} - \text{HDL-C mg/dL} - \left( \frac{\text{Triglycerides}}{5} \right) \text{ mg/dL}
\]

\[
\frac{\text{Total cholesterol}}{\text{HDL-C}} = \frac{\text{Total cholesterol}}{\text{HDL-C}}
\]

2-To determine the safety profile of atorvastatin and rosuvastatin, a randomized trial was conducted. The parameter evaluated for this purpose was CK which is a liver enzyme and is elevated when there is muscle deformation. The patients suffering from myalgia were subjected to perform this test in order to determine the confirmation and severity of myopathy/myalgia. Blood samples of 40 patients were withdrawn from the cubital vein and were analyzed in the pathology department of PIC.

3-To ensure the effectiveness of CoQ10 in managing statin induced myopathy, a randomized trial was conducted. When CK test was performed in order to determine the safety of atorvastatin and rosuvastatin, 5 patients showed elevated levels of CK and were given 100 mg/day CoQ10 supplementation to be used for 30 days. They were recommended to take it after meal. After 30 days their CK levels were again analyzed by withdrawing their blood samples and were compared with the CK levels performed before the therapy.

**Statistical analysis**

All the results were analyzed by using two softwares, SPSS version 21 and Graf pad prism 7. Descriptive statistics (mean, standard deviation, frequency, percentage was applied to summarize the data [24]. Furthermore Graph Pad Prism 7 was used to analyze the results of safety and efficacy comparison of two statins using Independent Sample t Test. Paired t test was used to analyze the effect of CoQ10. *p*>0.05 was taken as statistically significant.

**Results**

- **Safety comparison of atorvastatin and rosuvastatin**

  Association of levels of CPK with gender, age and duration of statin used

  Association of levels of CPK with gender, age and duration of statin used is depicted in TABLE 1. Results showed that males [(mean ± SEM) (142.59 ± 14.195)] showed significantly increased levels of CPK as compared to female [(mean ± SEM) (65.17 ± 7.064)] with *(p=0.007). This shows that males are more prone to myopathy. No significant change was observed in levels of CPK with respect to age and duration of statin used.
Correlation of age, gender, dose and duration with CPK levels

Correlation of age, gender, dose and duration with CPK levels is depicted in Table 2. It was observed that gender showed negative but significant correlation with CPK (Pearson correlation=-0.502) (p=0.001) while dose showed positive significant correlation (Pearson correlation=0.601) (p>0.001). On the other hand duration showed positive correlation and age showed negative correlation with CPK and both were insignificant.

Comparative effect of atorvastatin & rosvastatin on CPK levels

Comparative effect of atorvastatin & rosvastatin on CPK levels in patients with Ischemic Heart Disease is shown in The results revealed that patients using rosvastatin 20mg (mean ± SEM) (139.6 ± 20.16) were significantly on high risk to statin induced myopathy as compared to patients using atorvastatin 40 mg (mean ± SEM) (95.45 ± 6.12) (p=0.023) Figure 1.

Comparison of safety profile of different doses of rosvastatin

The results revealed that the patients taking 20 mg rosvastatin (mean ± SEM) (198.5 ± 24.67) were at higher risk to statin induced myopathy as compared to patients using 10 mg rosvastatin (mean ± SEM) (64.29 ± 8.766) (p>0.001) as shown in Figure 2. Similarly patients taking 20 mg atorvastatin (mean ± SEM) (110 ± 9.34) were more prone to induce statin induced myopathy as compared to patients taking 10mg atorvastatin (mean ± SEM) (61.29 ± 7.609) (p=0.001) (Figure 3).

No significant difference was observed in the levels of CPK in patients using atorvastatin 10 mg with rosvastatin 10 mg.

The results further revealed that patients receiving atorvastatin 20 mg (mean ± SEM) (110 ± 9.34) showed higher levels of CPK as compared to patients using rosvastatin 10 mg(mean ± SEM) (64.29 ± 8.766) (p=0.002) (Figure 4). Significant increases in the levels of CPK also found in patients using rosvastatin 20 mg (mean ± SEM) (198.5 ± 24.67) as compared to atorvastatin 20 mg (mean ± SEM) (110 ± 9.34) (p>0.001) (Figure 5).

Figure 6 shows that rosvastatin 20 mg (mean ± SEM) (198.5 ± 24.67) significantly increases the risk of myopathy as compared to atorvastatin 10 mg (mean ± SEM) (62.71 ± 8.853) with (p>0.001). These results depicted that as the dose increases the incidence of myopathy increases and rosvastatin is responsible to increase CPK level more profoundly as compared to atorvastatin.

Efficacy comparison of atorvastatin & rosvastatin

To determine the efficacy of lipid controlling property of atorvastatin and rosvastatin, patients who were taking these statins for more than 1 year at different doses (10, 20 and 40 mg), five parameters of lipid profile (triglycerides, cholesterol, HDL-C, LDL-C, Tcho/HDL-C ratio) were compared in order to determine that which statin is more efficacious in controlling these parameters. The results showed that no significant difference was observed between the efficacy of atorvastatin on the levels of triglycerides, cholesterol, HDL levels, LDL-C and Tcho/HDL-C ratio.

Figure 7 depicts the levels of Tcho/HDL-C ratio in patients taking atorvastatin and rosvastatin at same doses (20 mg), it was observed that the effect of rosuvastatin 20 mg (mean ± SEM) (4.280 ± 0.2760) was significantly lower than the effect of atorvastatin 20 mg (mean ± SEM) (5.310 ± 0.4448) on the levels of cholesterol (p=0.032). The effect of rosvastatin 20 mg (mean ± SEM) (4.280 ± 0.2760) was significantly poorer than the effect of atorvastatin 10 mg (mean ± SEM) (5.890 ± 0.3828) on the levels of Tcho/HDL-C ratio (p=0.001) (Figure 8).

The effect of atorvastatin 10 mg and atorvastatin 20 mg on the levels of Tcho/HDL-C

| Table 1. Association of CPK levels with gender, age and duration of statin used. |
|-----------------|----------------|------------------|----------------|----------------|
| Variables       | Association of gender and CPK | Association of age and CPK | Association of duration of statin use and CPK |
| Groups          | Male | female | >= 56 | < 56 | >= 5 | < 5 |
| N               | 27   | 12     | 17    | 22   | 12   | 27  |
| Mean            | 149.6 | 65.2 | 121.6 | 116.6 | 121 | 16.1 |
| Standard error mean | 14.2 | 7.1  | 19.1  | 116.6 | 117.8 | 15.3 |
| P value         | 0.007 | 0.592 | 0.351 |
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Table 2. Correlation of age, gender, dose and duration with CPK levels

<table>
<thead>
<tr>
<th>Variables</th>
<th>CPK Pearson Correlation</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>-0.075</td>
<td>0.325</td>
</tr>
<tr>
<td>gender</td>
<td>-0.502**</td>
<td>0.001</td>
</tr>
<tr>
<td>Dose</td>
<td>0.601**</td>
<td>0.000</td>
</tr>
<tr>
<td>duration</td>
<td>0.108</td>
<td>0.257</td>
</tr>
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The effect of rosuvastatin 20 mg was insignificant with the effect of atorvastatin 20 mg on HDL-C and LDL-C, also of atorvastatin 10 mg.

FIGURE 9 shows that atorvastatin 10mg (mean ± SEM) (148.6 ± 18.14) was more efficacious than rosuvastatin 20 mg (mean ± ratio, LDL-C and HDL-C was insignificant.

FIGURE 1. Comparative effect of atorvastatin & rosuvastatin on CPK levels.

FIGURE 2. Comparison of safety profile of different doses of rosuvastatin.

FIGURE 3. Comparison of safety profiles of different doses of atorvastatin.
SEM) (101.5 ± 13.68) when considering the levels of LDL-C (p=0.026).

No significant relation was found with the levels of triglycerides in patients taking both statins at same or different doses.

**Efficacy of CoQ10 in statin induced myopathy**

The effectiveness of CoQ10 was analyzed in 5 patients showing high levels of CPK and taking CoQ10 100 mg/day for 30 days. The results showed that the levels of CPK (mean ± SEM) (122 ± 42.51) significantly reduced after treatment with CoQ10 (P=0.022) (**FIGURE 10**). On the other hand all the patients had normal values of lipid profile expect 1 who was taking 40 mg of atorvastatin but his symptoms were resolved and a reduction in CPK levels were also seen. This showed that CoQ10 is
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FIGURE 7. Comparison of efficacy of atorvastatin & rosuvastatin at same doses on T-Cholesterol/HDL-C ratio.

FIGURE 8. Comparison of efficacy of atorvastatin & rosuvastatin at different doses on T-Cholesterol/HDL-C ratio.

FIGURE 9. Comparison of efficacy of atorvastatin & rosuvastatin at different doses on LDL-C.

FIGURE 10. Effect of CoQ10 in lowering blood CPK levels.
quite effective in reducing CPK and can be a recommended treatment for statin induced myopathy.

**Discussion**

Efficacy and safety of atorvastatin and rosuvastatin has been compared and it was observed that atorvastatin induces significantly higher myalgic effects in females while rosuvastatin induces the same significant effects in males. No data on this fact is available in literature therefore to confirm these findings further research is required.

Variable reports are available on the safety profile of atorvastatin and rosuvastatin. Both the drugs have been reported to be equally safe [20,21]. However rosuvastatin has been reported to be safer as compared to atorvastatin [7,16,18,25,26].

CPK has been reported to be a biochemical marker for the determination of myopathy and the 10 fold increase in levels is an indicator of myopathy [10,16,27,28]. Variable reports have been published regarding the effect of different statin to raise CPK levels. Atorvastatin significantly increased serum CPK levels as compared to rosuvastatin [16,25]. Similar results have been reported in rats [25]. However it has also been reported that atorvastatin and rosuvastatin showed no significant effects to raise CPK levels [15]. In present research neither atorvastatin nor rosuvastatin were able to raise CPK levels 10 times greater than normal, however a significantly increased serum CPK levels were observed due to rosuvastatin as compared to atorvastatin. To confirm these findings more trials are required on greater Asian population.

In present study more than half of patients were having the complaints of myopathy but only a few patients showed elevated levels of CPK. Paul and coworkers has reported that myopathic symptoms can appear in patients who had normal CPK levels. Which concludes that myopathy can also occur with normal levels of CPK or those myalgias may be due to some other reasons [29].

In the present study statin induced myalgia and rise in CPK levels were compared on the bases of doses of atorvastatin and rosuvastatin. The results showed that the atorvastatin 20 mg showed higher levels of CPK as compared to rosuvastatin 10 mg. However, no significant difference was observed in the serum CPK levels of the patient receiving either 10 mg of atorvastatin or 10 mg of rosuvastatin. Various reports have been given on the relationship between atorvastatin and rosuvastatin. Scott and his coworkers reported that the safety profiles of atorvastatin and rosuvastatin were independent of the dose with respect to CPK levels [16]. The similar results have been reported by other researchers [17]. However other studies showed that statin induced myopathy was dose dependent [25,30].

Furthermore it was observed that rise in CPK levels were not duration dependent because a number of patients complain the symptoms of myalgia though their CPK levels were not elevated. Furthermore it was observed that extent of myalgia was duration dependent. No supportive data is available to confirm these results and further research is required to indorse these outcomes.

To compare the efficacy of rosuvastatin and atorvastatin the lipid profile of a number of patients was analysed. Rosuvastatin significantly reduced LDL-C levels along with T.Chol/ HDL-C whereas no significant difference was observed by comparing other parameters of lipid profile. A large number of data is present that tells different reports about the efficacy of both the statins. Saku and his fellows concluded that both the statins have equal efficacy and the choice of statin used purely depends upon the preferability of the doctor [21]. On the other hand most of the data depicts that rosuvastatin is more efficacious as compared to atorvastatin [12,13,15,16,19,20,31]. It was also reported that more rapid reduction in LDL-C levels were seen as the dose of the statin increases [17,20,32].

**Study results are also in line with the previously studies**

The efficacy of CoQ10 in treating statin induced myopathy is still debatable. CoQ10 has been reported to be useful for treating statin induced myopathy [33-35]; however the use of CoQ10 supplementation was unable to reverse the statin induced myopathy [28,36,37]. In present study 5 patients were given CoQ10 and 4 patients showed significant reduction in CPK levels and reversal of myalgic symptoms [38,39].

**Conclusion**

By considering the safety parameters atorvastatin was more prevalent to myalgias as compared to rosuvastatin but the CPK levels
were higher in patients taking rosuvastatin which concludes that the patients taking rosuvastatin were more prone to the risk of myopathy. Myalgic symptoms and rise in CPK levels were also dose related. Efficacy profile showed that both the statins were equally efficacious but the risk of myopathy also increases as the dose increases. So, lower doses of statins are preferable. It was further concluded that CoQ10 was quite effective in lowering the levels of CPK as well as in the reversal of the myalgic symptoms.

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Conflict of interest
Authors have no conflict of interest
REFERENCES


Hassanabad AF. Understanding the Regulation of HMGCR (2013).


Saku K, Zhang B, Noda K. Randomized head-to-head comparison of pitavastatin, atorvastatin, and rosuvastatin for safety and efficacy (quantity and quality of LDL); the PATROL trial. Circ. J. 75(6), 1493-1505 (2011).


Young JM, Florkowski CM, Molyneux SL, et al. Effect of Coenzyme Q10 Supplementation on Simvastatin-Induced...


