

## A Comparative Study to Evaluate Efficacy and Safety of Daily Dosing versus Alternate-Day Atorvastatin Therapy in Patients with Dyslipidemia

Allen J. Rodrigues<sup>1</sup>, Syed S. Farookh<sup>1</sup>, Laxminarayana Kamath<sup>1</sup>, Raveendra K.R<sup>2</sup>

<sup>1</sup>Department of Pharmacology, Bangalore Medical College and Research Institute, Bangalore - India

<sup>2</sup>Department of Medicine, Bangalore Medical College and Research Institute, Bangalore - India

### Abstract

Dyslipidemia is a well-recognized risk factor for the development of diseases associated with atherosclerosis, including coronary artery disease and stroke. Statins are the first choice hypolipidemic drug which are the most effective and best tolerated agents for treating dyslipidemia. Atorvastatin confers an HMG-CoA reductase inhibition up to 20-30 hours which makes it even effective on the next day. The present study is randomized open labeled study done at Victoria Hospital - Bangalore to compare efficacy and safety of daily dosing versus alternate-day atorvastatin therapy in patients with dyslipidemia. A total of 86 patients with dyslipidemia were randomized into 2 groups. Group A received 10 mg of atorvastatin daily (DS) and group B received 10 mg of atorvastatin on alternate day (AS) for six weeks. Among the 86 patients included in the study, mean age of the participants in the AS group was  $53.12 \pm 10.32$  whereas that in the DS group was  $52.26 \pm 11.13$ . LDL-C decreased by 25.3% versus 22.4% (CI 0.95, P = 0.35) on daily and alternate-day dosing, respectively. Also 12.5% versus 15% (CI 0.95, P= 0.83) improvement was seen with HDL-C. Both dosage regimens provided reductions in total cholesterol (20.7% versus 20.2%) and triglyceride (20.7% versus 21.2%). There was no statistically significant difference in reduction in lipid parameters between two groups. Adverse effects were found less occurred in alternate day therapy than daily therapy. Gastrointestinal disturbances and myalgia were most commonly reported in both groups. Hence this study concludes alternate-day atorvastatin is as effective as daily atorvastatin in dyslipidemia.

**Keywords:** Dyslipidemia, LDL cholesterol, Alternate day atorvastatin

### Introduction

Dyslipidemia is a well-known prominent risk factor for the development of cardiovascular and cerebrovascular diseases. Worldwide and in India cardiovascular diseases (CVD) are one of the leading cause of death.<sup>1,2</sup> The present prevalence of dyslipidemia among adults was 39% globally and 30% in India.<sup>3-6</sup> Elevated plasma Low-density Lipoprotein-

Cholesterol (LDL-C) levels being a major modifiable risk factor for atherosclerosis, presents an important point for intervention in primary prevention of CVD.<sup>1,2,19,20</sup>

American Association of Cardiology/ American Heart Association (AAC/AHA) both recommend statins as the first choice hypolipidemic drug which are the most

Corresponding author: Syed Salman Farookh. Department of Pharmacology, Bangalore Medical College and Research Institute. Email: [ssfarookh@gmail.com](mailto:ssfarookh@gmail.com)

Received: 20 January 2021. Revised: 7 April 2021. Published: 8 August 2021

effective and best tolerated agents for treating dyslipidemia.<sup>7</sup> The long-lasting active metabolites of atorvastatin confer an HMG-CoA reductase inhibition up to 20-30 hours<sup>8</sup> which reduces LDL-C and TC for a duration of 48 to 72 hours.<sup>9</sup> Thus, effective results are still obtained with non-daily use.<sup>10</sup>

Despite many beneficial effects of statins, patients of lower socio-economic status may discontinue long term statin therapy due to its prohibitive costs. Though statins are well-tolerated, few adverse effects like myalgia, muscle cramps and weakness were witnessed in 10% of the patients making it difficult to continue on a daily basis.<sup>1</sup> Thus, alternate-day dosing may solve the problem of statin underutilization with equal efficacy. In view of the limited comparative studies between the two regimes, the present study was undertaken to compare the efficacy and safety of daily versus alternate day atorvastatin on reduction of lipid parameters in treatment naïve patients of dyslipidemia.

## Methods

### *Study Design*

This prospective, randomized, open labeled, and comparative study was conducted in Department of Medicine, Bangalore Medical College and Research Institute. Eligible 86 patients entered a 6-week treatment period. Sample size was calculated using Epitools online sample size calculator with 5% level of significance at 80% power considering difference between the two means as 9.21 and variance of 210. By substituting above values, the sample size was 39 for each group, but it was decided to include 43 per group considering dropouts and for better evaluation.

Patients were randomized (1:1) to receive either atorvastatin 10 mg/day orally at night or atorvastatin 10 mg alternate-day orally

at night for 6 weeks. Both the groups were advised to follow low fat diet. The study was conducted in accordance with ICH-GCP and the study protocol was approved by the Institutional Ethics Committee (No. BMC/PGs/159/2015-16).

### *Study Population*

We screened 118 patients for eligibility and enrolled 86 treatment naïve patients ( $\geq 18$  years old) of dyslipidemia in low to moderate risk group (LDL  $< 160$ mg/dL) according to NCEP ATP III (National Cholesterol Education Program Adult Treatment Panel III) guidelines who satisfied the inclusion and exclusion criteria.

### *Inclusion and Exclusion Criteria*

Patients with dyslipidemia who met following criteria were included:

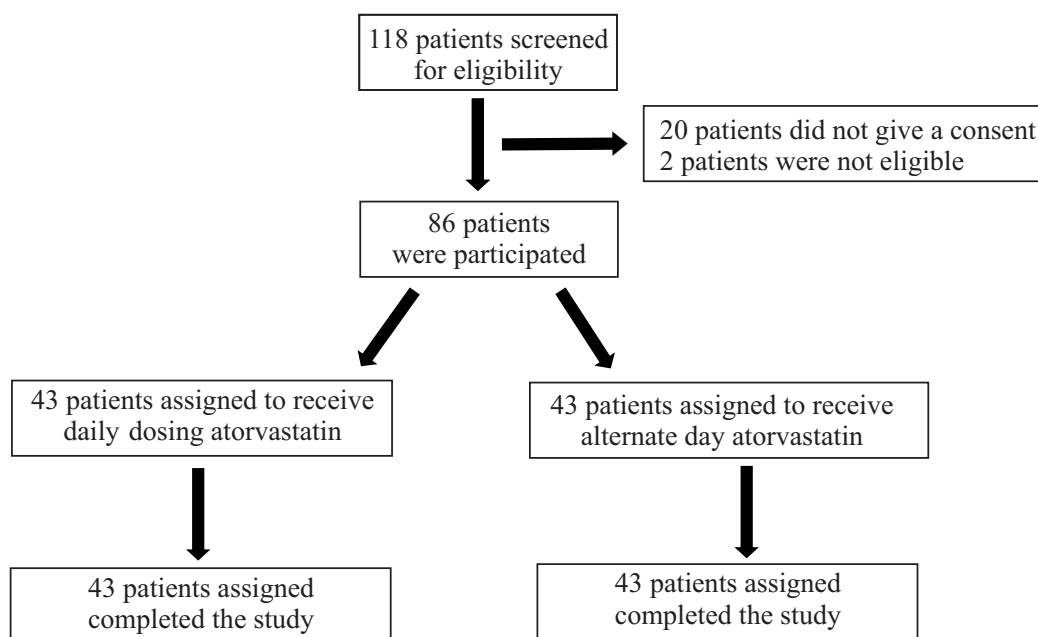
1. Naïve patients of dyslipidemia in low to moderate risk group as diagnosed by NCEP ATP III guidelines<sup>7</sup>
2. Patients aged  $> 18$  years
3. Informed consent was obtained from all subjects involved in the study

Exclusion criteria were patients with:

1. History of myocardial infarction, angina, and stroke.
2. Framingham's CHD risk score  $> 20$
3. Uncontrolled diabetes and hypertension ( $\geq 160/100$  mm Hg)
4. Had very high lipid profile according to NCEP III guidelines
5. Pregnancy and lactating conditions
6. Coexisting medications which aggravate statin myopathy
7. Unwilling to give informed consent

### *Study Assessments*

Before starting the study, all patients underwent an initial screening assessment that included demographic characteristics, medical history, concomitant medications



**Figure 1. Study Flow Diagram**

and detailed physical/clinical evaluation. At the baseline and week 6, we evaluated the following parameters: LDL-C and other lipid markers such as High-density of Lipoprotein (HDL-C), triglycerides, and total cholesterol (TC). Safety assessments included incidence and severity of adverse events were reported.

#### *Statistical Analyses*

Results were analyzed using IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp. All continuous variables were presented as mean  $\pm$  SD, if they were normally distributed. Data were tested for normal distribution using the Shapiro–Wilk test. Categorical variables were described with absolute and relative (percentage) frequencies. Comparisons between the 2 individual groups were performed using the Mann Whitney U test, unpaired ‘t’ test and Pearson Chi-square test for continuous and categorical variables, respectively. Wilcoxon sign rank test was used to compare before and after comparison. All tests were two-sided and a probability value of  $p < 0.05$  was considered statistically significant.

#### **Results and Discussion**

We screened 118 patients for eligibility and recruited 86 patients. Thus, 43 patients were randomized to receive alternate day dosing of atorvastatin (AS) and the remaining 43 were allocated to the daily dosing (DS) group. The participant flow diagram is shown in Figure 1.

This study was undertaken to compare the safety and efficacy of daily dosing versus alternate-day atorvastatin therapy in treatment of naïve patients with dyslipidemia. The present study emphasizes the possibility of using atorvastatin every other day, due to its potency and long half-life. When adopting a long-interval dosing regimen it is crucial to have knowledge about the pharmacokinetics of statins mainly plasma half-life of the medication needs to be considered. Among the statins, atorvastatin with long-lasting active metabolite which confer an HMG-CoA reductase inhibition up to 20-30 hours.<sup>8</sup> Hence reduces LDL-C and TC for 48 to 72 hours.<sup>9</sup> Thus, these make atorvastatin as a good choice for an alternate-day regimen.<sup>10</sup>

**Table 1. Baseline Socio-Demographic Characteristics**

Variable		AS Group (N= 43)	DS Group (N= 43)	Significance
Age	Mean ± SD	53.12 ± 10.32	52.26 ± 11.13	0.782
Sex (Male)	Frequency (%)	23 (53.50%)	25 (58.10%)	0.666
Kuppuswamy's SES	Mean (SD)	7.68 ± 8.16	7.72 ± 8.53	0.365
Diabetes	Frequency (%)	13 (30.2%)	14 (32.60%)	0.817
Hypertension	Frequency (%)	4 (9.3%)	1 (9.30%)	0.999

\* Significance value is based on unpaired 't' test for continuous variables and Pearson's Chi square test for categorical variables across both groups

**Table 2. Baseline Lipid Parameters**

Variable	AS Group (N= 43) Mean ± SD	DS Group (N= 43) Mean ± SD	Significance
Total Cholesterol	257.12 ± 25.03	260.56 ± 32.29	0.762
LDL	174.63 ± 27.71	170.56 ± 24.55	0.484
HDL	34.72 ± 4.68	35.14 ± 4.84	0.736
Triglycerides	203.86 ± 34.66	213.35 ± 55.57	0.859

\* Significance value is based on Mann Whitney U test as Shapiro Wilk test of Normality revealed a non-normal distribution of all variables across both groups

**Table 3. Mean Reduction in Lipid Parameters after 6 weeks of Atorvastatin Therapy**

Parameters	AS Group (Mean ± SD) mg/dL after 6 weeks	DS group Mean ± SD) mg/dL after 6 weeks	P- Value*	AS Group (mg/dL)		DS Group (mg/dL)	
				Mean diff from baseline	P-Value **	Mean diff from baseline	P-Value **
Total Cholesterol	205.00 ± 30.54	206.00 ± 22.28	0.551	-52.12	<0.001	-54.56	<0.001
LDL	133.74 ± 26.44	127.21 ± 21.35	0.352	-40.89	<0.001	-43.45	<0.001
HDL	40.16 ± 4.61	40.37 ± 5.40	0.832	+5.44	<0.001	+5.23	<0.001
Triglycerides	160.09 ± 34.02	169.05 ± 42.12	0.325	-43.77	<0.001	-44.30	<0.001

\* P- value is based on Mann Whitney – U test

\*\*P- Value is based on Wilcoxon signed ranks test

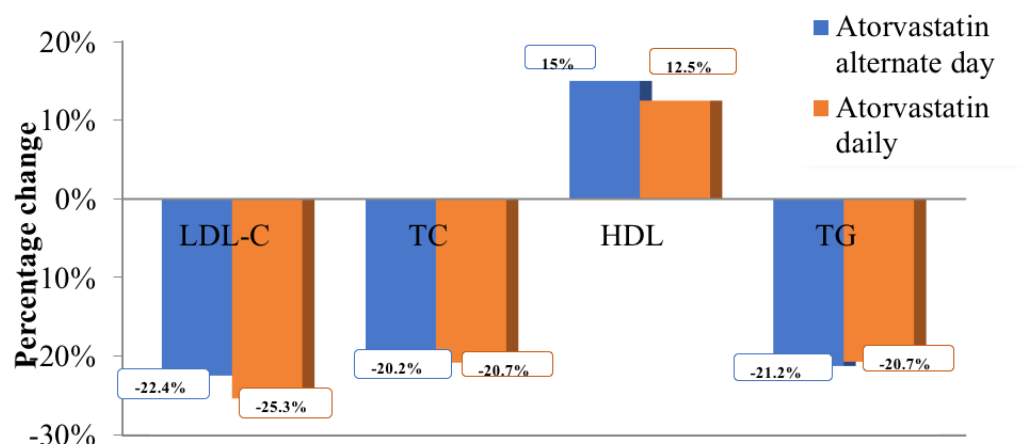
Patients who participated in the present study had optimal to borderline elevations in lipid parameters without any CHD risk equivalents and were within the range of therapy where drug therapy was optional or which required mild interventional drug therapy according to NCEP ATP III guidelines.<sup>7</sup>

The baseline demographic characteristics

between both groups and various lipid parameters such as TC, LDL, HDL and triglycerides in both AS and DS group are shown in Table 1 and Table 2.

*Efficacy*

*Effect of alternate day and daily dosing of*



**Figure 2. Mean Percentage Change in Lipid Parameters from Baseline to 6th week**

*atorvastatin on reduction of various lipid parameters from baseline to 6th week*

When comparing the values of lipid parameters at week 6 with the baseline, it showed statistically significant reduction in the values of TC, LDL and triglycerides in both alternate-day and daily dosing. There was also a significant increase in the HDL values in both the groups. In the AS group, mean total cholesterol reduced by 52.12 mg/dL and 54.56 mg/dL reduction in the DS group. With regards to the LDL cholesterol values, there was a mean reduction of 40.89 mg/dL and 43.45 mg/dL in the AS and DS groups respectively. Similarly, there was mean reduction of serum triglycerides in both the groups -43.77 mg/dL and - 44.30 mg/dL respectively in AS and DS groups. However, there was an increase in mean HDL in both the groups. It increased by 5.44 mg/dL in the AS group and by 5.23 mg/dL in the DS group. The test that was used was Wilcoxon signed ranks test. However, mean of lipid parameters shown no difference in between the 2 groups at 6th week with Mann Whitney – U test. (Table 3)

In the present study, alternate day dosing provided percentage reductions of LDL-C by 22% which was comparable to 25% reduction with daily dosing regimen. Similar reductions were seen in previous studies done by Ferrer-

Garcia et al, Pramanik et al and Matalka et al.<sup>11-13</sup> In contrast to our study, Ghia et al, Pattanaik S et al and Hajdibabaie et al concluded alternate-day regimen of statin was inferior to daily regime.<sup>9,14,15</sup> LDL is the major atherogenic lipoprotein and has long been identified by NCEP as the primary target of cholesterol-lowering therapy.<sup>7</sup> There is considerable evidence that lowering LDL-C reduces the risk of both cardiovascular events and mortality. Hence there needs to be a concrete conclusion regarding the reduction of LDL-C with two dosage regimen with a meta-analysis. (Figure 2)

The reduction in TC was 20.23% and 20.76% in alternate versus daily therapy, which is in congruence with studies conducted by Ferrer Garcia et al, Pramanik et al, Hadjibabaie et al, Bijay et al, Aghasadeghi et al and Jafari M et al.<sup>1-12,15-17,22</sup> Interestingly, Matalka et al found out that 21% reduction in alternate day vs 28% in daily regimen at the end of 6 weeks which is not significant. However, on follow up till 12 weeks revealed that the reduction was 27% vs 31% in alternate vs daily regimen respectively stating both the regimen are comparable and which is significant.<sup>13</sup>

Whereas triglycerides reduced by 21.18% vs 20.65% in alternate and daily therapy respectively which is in congruence with

**Table 4. Incidence of Adverse Events**

<b>Incidence of Adverse Events</b>	<b>Atorvastatin 10mg Alternate day</b>	<b>Atorvastatin 10mg Daily</b>
Total (%)	5 (11.62)	9 (20.93)
<b>Musculoskeletal System</b>		
Myalgia	1	3
<b>Central Nervous System</b>		
Dizziness	-	1
Headache	1	2
<b>Gastrointestinal System</b>		
Nausea/Vomiting	-	1
Dyspepsia	2	1
Flatulence	1	1

previous studies at 6 weeks.<sup>11,13</sup> Early multivariate analyses generally did not identify serum triglycerides as an independent risk factor for CHD. Lipoprotein metabolism is integrally linked, and elevations of serum triglycerides can be confounded by significant correlations with total, LDL, and HDL-C levels.

Also, in terms of HDL-C, it increased by 15% in alternate-day and 12.5% in daily dosing after 6 weeks. Some researchers have documented results similar to the present study.<sup>11,18</sup> Bijay et al found an increase in 35.3% and 37.8% in alternate-day and daily therapy respectively.<sup>16</sup> However, on the contrary, Ghia et al showed an 0.86% increase in alternate day and 12.9% increase in daily therapy.<sup>9</sup> Surprisingly, Matalka et al found an increase in 4% in alternate-day atorvastatin group and decrease in 2% in daily therapy group at 6 weeks but both were comparable at the end of 12 weeks.<sup>13</sup> Strong epidemiological evidence links low levels of serum HDL-C to increased CHD morbidity and mortality. Clinical trials provide suggestive evidence that raising HDL-C cholesterol levels will reduce risk for CHD.<sup>7</sup> However, it remains uncertain whether raising HDL-cholesterol

level is independent of other changes in lipid and/or non-lipid risk factors will reduce risk for CHD.

No serious adverse events were reported during treatment in both groups. Out of 43 patients, nine experienced adverse events in the group receiving atorvastatin 10 mg daily vis-a-vis five adverse events in the group receiving alternate day therapy (Table 4). Headache, myalgia, dyspepsia, dizziness etc., were the reported adverse events. These adverse events were mild in intensity.

We encountered mild adverse effects in both the groups [alternate-day (11%) versus daily dosing therapy (20%)] which is similar to Ghia et al and Matalka et al. Gastrointestinal disturbances were the most common adverse effects seen in both the groups however myalgia is common with daily therapy. Overall, the frequency of adverse effects were less with alternate-day therapy than daily dosing therapy.

Our study has some limitations. Patients were recruited from a single tertiary care hospital but a multicenter study with a larger sample size would be the ideal setting. We



didn't follow up the subjects after 6 weeks as it could deprive patients from standard of care as per treatment guidelines. Further long term, double blind, randomized control trials are required to accurately evaluate these effects.

### Conclusion

Alternate day atorvastatin therapy was found to be as efficacious as that of daily atorvastatin therapy for treating mild to moderate dyslipidemia. Also, the side effects are less reported with alternate day atorvastatin therapy when compared to daily therapy and thus is more cost effective taking into consideration the reduction in expenditure that is offered with comparable treatment outcomes.

### Acknowledgement

The authors thank all the study participants, research assistants and the faculty from the Department of Medicine, Bangalore Medical College and Research Institute, Bengaluru, for their immense support in conducting the project work. All authors have made a substantial contribution to drafting the article or reviewing it. All authors have given final approval of this version of the article to be published.

### Funding

None

### Conflict of Interest

None

### References

1. Bersot PT. *Drug Therapy for Hypercholesterolemia and Dyslipidemia*. In: Goodman and Gilman's "The Pharmacological basis of Therapeutics In: Brunton LL, 12th ed. New York. McGraw-Hil; 2010. p. 884–91.
2. Park K. *Epidemiology of chronic non-communicable diseases and conditions*. In: Park's Textbook of Preventive and Social Medicine, In: Park K. 23rd ed. Jabalpur: Bhanot; 2009. p. 365–72.
3. National cardiovascular disease database (online)(cited 2015 June 11): available from [http://www.searo.who.int/india/topics/cardiovascular\\_diseases/NCD\\_Resources\\_National\\_CVD\\_database-final\\_report.pdf?ua=1](http://www.searo.who.int/india/topics/cardiovascular_diseases/NCD_Resources_National_CVD_database-final_report.pdf?ua=1).
4. Gupta S, Gupta R, Deedwania P, Bhansali A, Maheshwari A, Gupta A, et al. Cholesterol lipoproteins and prevalence of dyslipidemias in urban Asian Indians: A cross sectional study. *Indian Heart Journal*. 2014 May;66(3):280–8.
5. Gupta R, Rao RS, Misra A, Sharma SK. Recent trends in epidemiology of dyslipidemias in India. *Indian Heart Journal*. 2017 May - Jun;69(3):382-92.
6. Joshi SR, Anjana RM, Deepa M, Pradeepa R, Bhansali A, Dhandania VK, et al. Prevalence of Dyslipidemia in Urban and Rural India: The ICMR–INDIAB Study. Goel K, editor. *PLoS ONE*. 2014 May 9;9(5):e96808.
7. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation*. 2002 Dec 17;106(25):3143–421.
8. Stern RH, Yang BB, Hounslow NJ, MacMahon M, Abel RB, Olson SC. Pharmacodynamics and pharmacokinetic-pharmacodynamic relationships of atorvastatin, an HMG-CoA reductase inhibitor. *Journal of Clinical Pharmacology*. 2000;40:616–23.
9. Ghia CJ, Panda AS, Khobragade LR, Jha

- RK, Rambhad GS. Alternate Day versus Once Daily Atorvastatin for Primary Prevention of (CHD) in Naïve Patients of Dyslipidemia. *Journal of Clinical and Diagnostic Research*. 2014 Mar;8(3):27-31.
10. Awad K, Mikhailidis DP, Toth PP, Jones SR, Moriarty P, Lip GYH, et al. Efficacy and Safety of Alternate-Day Versus Daily Dosing of Statins: a Systematic Review and Meta-Analysis. *Cardiovascular Drugs and Therapy*. 2017 Aug;31(4):419-31.
  11. Ferrer-García JC, Pérez-Silvestre J, Martínez-Mir I, Herrera-Ballester A. Alternate-day dosing of atorvastatin: effects in treating type 2 diabetic patients with dyslipidaemia. *Acta Diabetologica*. 2006 Nov;43(3):75-8.
  12. Pramanik S, Das AK, Chakrabarty M, Bandyopadhyay SK, Ghosh M, Dalai CK. Efficacy of alternate-day versus everyday dosing of atorvastatin. *Indian Journal of Pharmacology*. 2012 May;44(3):362-5.
  13. Matalka MS, Ravnan MC, Deedwania PC. Is alternate daily dose of atorvastatin effective in treating patients with hyperlipidemia? The Alternate Day Versus Daily Dosing of Atorvastatin Study (ADDAS). *American Heart Journal*. 2002 Oct;144(4):674-7.
  14. Pattanaik S, Malhotra S, Sharma YP, Pandhi P. Comparison of alternate-day atorvastatin treatment to daily treatment in maintaining LDL-cholesterol targets in patients with variable coronary risk profile. *Journal of Cardiovascular Pharmacology*. 2012 May;59(5):479-84.
  15. Hadjibabaie M, Gholami K, Khalili H, Khoei SH, Nakhjavani M, Rayati K, et al. Comparative efficacy and safety of atorvastatin, simvastatin and lovastatin in the management of dyslipidemic Type 2 diabetic patients. *Therapy*. 2006 Nov;3(6):759-64.
  16. Bijay K, Agarwal PK, Pranjal P, Meghwani MK. Dose alternate day dosing of statin suffice? (A comparative study of O.D to A/D dosing of atorvastatin on hypercholesterolemia). *Journal of Advance Researches in Biological Sciences*. 2013;5(1):23-4.
  17. Aghasadeghi K, Zare D. Efficacy of alternate day dosing of atorvastatin. *Central European Journal of Medicine*. 2008 Apr 10;3(2):163.
  18. Keleş T, Akar Bayram N, Kayhan T, Canbay A, Sahin D, Durmaz T, et al. The comparison of the effects of standard 20 mg atorvastatin daily and 20 mg atorvastatin every other day on serum LDL-cholesterol and high sensitive C-reactive protein levels. *The Anatolian Journal of Cardiology*. 2008 Dec;8(6):407-12.
  19. Rader DJ et al. *Disorders of lipoprotein metabolism*. In: Lango D, Kasper DL, James JI, Fauci AS, Hauser SL, Loscalzo J. editors. In: Harrison's principles of internal medicine. 18th ed. New York: McGraw-Hill; 2012. p. 3145-61.
  20. Jacques Genest, Peter Libby. *Lipoprotein Disorders and Cardiovascular Disease*. In: Braunwald's heart disease, A textbook of cardiovascular medicine. 9th ed. Philadelphia: Elsevier saunders; p. 975-94.
  21. Malloy MJ, Kane JP. *Agents used in dyslipidemia*. In: In:Katzung BG, Trevor AJ editors Basic and Clinical pharmacology. 13th ed. New Delhi: McGraw Hill education private limited; 2012. p. 602-17.
  22. Jafari M, Ebrahimi R, Ahmadi-Kashani M, Balian H, Bashir M. Efficacy of Alternate-Day Dosing Versus Daily Dosing of Atorvastatin. *Journal of Cardiovascular Pharmacology and Therapeutics*. 2003 Jun;8(2):123-6