Original Article

Effect of atorvastatin on lipid and cardiovascular events in patients on maintenance hemodialysis

Azim MAU[a], Rahman MH[b], Salam A[c], Islam SM[d], Waheed S[e]

Abstract

Background: *Cardiovascular disease is the major cause of death in chronic kidney disease patient as well as in patients on hemodialysis. Dyslipidaemia is highly prevalent in patients on maintenance haemodialysis which increases the risk for cardiovascular mortality. This study was designed to evaluate the lipid abnormalities, effect of atorvastatin on lipid profile and cardiovascular events in patients on maintenance hemodialysis.*

Methods: *In this prospective clinical study, 55 end-stage renal disease (ESRD) patients undergoing maintenance hemodialysis participated voluntarily. The study population was divided randomly into group-A (atorvastatin was prescribed) and group-B (without atorvastatin). We compared the lipid status and cardiovascular events of both groups after 6 months.*

Results: *The two groups of patients were well matched in respect to baseline characteristics, history of risk factors and dialysis duration and session. Mean age of study population was about 48 years. Low density lipoprotein (LDL) cholesterol was reduced by 18.79%, total cholesterol was reduced by 9.32% and triglyceride was reduced by 22% in group-A. In group-A, high density lipoprotein (HDL) cholesterol was increased by 6% and it was reduced by 6% in group-B. In this study, myocardial ischemia/infarction on electrocardiogram (ECG) was present 22% in group-A and 14% in group-B at randomization. After 6 months, ischemia/infarction was found 33% in group-A and 25% in group-B. Statistically the ECG findings showed no significant changes after 6 months. In this study, mean ejection fraction (EF %) was 54% in group-A and 51% in group-B at 0 month, after 6 months atorvastatin group failed to show any significant change. In this study, after 6 months of statin therapy there was slight increase of serum glutamic pyruvic transaminase (16.13%) but that was not significant.*

Conclusion: *In this study atorvastatin improved the lipid abnormalities significantly but a significant reduction of cardiovascular events was not achieved.*

Key words*: atorvastatin, cardiovascular events, hemodialysis, lipid profile.*

Author information

a. Muhammed Arshad Ul Azim, Assistant Professor, Department of Nephrology, Shahid Sheikh Abu Naser Specialized Hospital, Khulna, Bangladesh.

b. Md. Habibur Rahman, Professor, Department of Nephrology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh.

c. Abdus Salam, Assistant professor, Department of Neurology, Shahid Sheikh Abu Naser Specialized Hospital, Khulna, Bangladesh.

d. Sayed Mahtabul Islam, Assistant professor, Department of Nephrology, Chittagong Medical College, Chittagong, Bangladesh.

e. Shahryar Waheed, Assistant professor, Department of Nephrology, Sir Salimullah Medical College, Dhaka. Bangladesh.

Address of correspondence: Muhammed Arshad Ul Azim, Assistant professor, Department of Nephrology, Shahid Sheikh Abu Naser Specialized Hospital, Khulna, Bangladesh. Email: arshadulazim@gmail.com

Introduction

Chronic kidney disease (CKD) is a major public health problem. Patients with CKD are at high risk for coronary heart disease (CHD).[1] The incidence of cardiovascular disease (CVD) is high in patients on hemodialysis (HD).[2]

Approximately 50% of patients with end-stage renal disease (ESRD) die from cardiovascular events which indicates that cardiovascular mortality are 30-times higher in dialysis patients.[3] Dyslipidaemia is highly prevalent in patients on maintenance haemodialysis (MHD), which accelerates the progression of atherosclerosis and increases the risk for cardiovascular mortality.[4]

Statin treatment has been proven to reduce the mortality and morbidity in both primary and secondary prevention of CVD.[5,6] The aims of this study were to evaluate the

lipid abnormalities in ESRD patients on MHD and to evaluate the effects of atorvastatin on lipid profile and on cardiovascular events in patients on MHD.

Methods

The present study was a prospective randomized experimental study. The study was carried out on ESRD patients undergoing MHD at the Department of Nephrology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Shahbag, Dhaka, Bangladesh, during period of May 2009 to June 2011.

Total 66 patients with age more than 15 years of either sex, who were on MHD, were included in this study. Patients with serum glutamic pyruvic transaminase (SGPT) more than 3 times upper limit, serious hematological or neoplastic diseases and patient on lipid lowering medication were excluded from the study. Informed consent was obtained from each patient. The study protocol was approved by ethical committee.

Demographic profile, clinical examination and relevant investigation reports of all patients were recorded in pre-designed data collection sheet. The anti-ischaemic and anti-hypertensive medications, if taking, were continued. Fasting lipid profile, electrocardiography (ECG) and echocardiography were done at initiation.

Study population was given serial number from 1 to 66. Starting point (1st sampling unit) being chosen at random by lottery. Then every alternative patient belonged to one group, like group-A and group-B. Group-A was prescribed atorvastatin 10 mg/day. Group-B was not prescribed atorvastatin and follow up was done after 6 months.

At 6 months, four patients died from group-A and five patients died from group-B. One patient was lost due to transfer of dialysis center from group-B and one patient underwent kidney transplantation from group-A. Total 55 patients completed the study. We compared the lipid status and cardiovascular events of both groups after 6 months.

Data analysis and statistical test

Data were processed and analyzed using computer software statistical package for social science (SPSS) version 11.5. The Test statistics used to analyze the data are descriptive statistics, chi square test, Student's t-test. The descriptive statistics are frequency, mean and standard deviation. Continuous data was presented as mean and standard deviation from the mean and was compared using student's t-test. Categorical data was expressed as percentage and evaluated using chi-square test. P value < 0.05 was considered significant.

Results

A total of 55 patients completed the trial, 27 in group-A and 28 in group-B. Basic data of the study subjects was given in Table I. Smoking habit was present 14.8% in group-A and 17.9% in group-B (p 0.760). Diabetes mellitus and was present in 48.1% and 35.7% in group-A and group-B respectively (p 0.350) and as for hypertension these values were 51.9% and 43% respectively (p 0.504).

Table I Basic data of the study subjects (N=55)

Parameters	Group A (n=27)		Group B (n=28)		P value
Age (years)					
Mean±SD	47.59±9.65		48.32±13.55		0.820^{ns}
	No.	(%)	No.	(%)	
Sex					0.074^{ns}
Male	14	(51.9)	21	(75.0)	
Female	13	(48.1)	7	(25.0)	
BMI (kg/m^2)					
Mean±SD	21.55±3.04		20.48±2.65		0.173^{ns}

Chi square/Unpaired Student's't' test

ns = Not significant

The mean duration of dialysis at enrolment was 13.93±9.65 months in a group-A and 14.86±11.97 months in a group-B (p 0.753). The difference of dialysis session between two groups (2 times/week 26%, 50% and 3 times/week 74%, 50% in group-A and group-B respectively) were not statistically significant (p 0.066).

In this study mean (±SD) systolic blood pressure in group-A and group-B, respectively, at 0 month were 155.93±16.47 and 156.07±15.24 mm Hg and at 6 month were 151.11±12.81 and 153.93±13.97 mm Hg. Statistical comparison showed no significant difference either at 0 month or at 6 month.

Level of serum lipids of the study subjects at the beginning was shown in Table II.

Table II Level of serum lipids of the study subjects (n=55)

Level of Serum lipids	At 0 month	
	No.	(%)
Total cholesterol (mg/dl)		
<200	46	(83.6)
200 239	9	(16.4)
≥240	0	
LDL cholesterol (mg/dl)		
<100	14	(25.5)
100 129	36	(65.5)
130 159	5	(9.1)
160 189	0	
≥190	0	
HDL cholesterol (mg/dl)		
<40	31	(56.4)
40 59	24	(43.6)
≥60	0	
Triglyceride (mg/dl)		
<150	28	(50.9)
150 199	12	(21.8)
200 499	15	(27.3)
≥500	0	

Table II shows levels of serum lipids according to the executive summary of the third report of National Cholesterol Education Program (NCEP), serum cholesterol, LDL and HDL level range[7] and the American Heart Association recommendation for blood triglycerides level[8]

At 6 month after giving atorvastatin, total cholesterol level was significantly low (P<0.001) in group-A (162.26±20.96 mg/dl) compared to in group-B (184.75±19.85 mg/dl). Mean (±SD) LDL cholesterol at 0 month in group-A and group-B, respectively, were 108.56±20.26 and 107.89±13.92 mg/dl. However, at 6 month, statistically significant difference (P<0.001) was observed (87.59±16.85 and 110.14±15.60 mg/dl in group-A and group-B, respectively). Mean (±SD) HDL cholesterol at 0 month were 40.78±5.36 and 40.64±5.35 mg/dl in group-A and group-B, respectively. However at 6 month, mean difference between groups (42.63±3.60 mg/dl in group-A, and 37.61±3.26 mg/dl in group-B) was significant (P<0.001).

Mean (±SD) triglyceride in group-A and group-B, respectively at 0 month were 167.85±74.77 and 154.57±50.82 mg/dl and at 6 month were 130.00±66.62 and 164.71±47.26 mg/dl. Mean difference between groups at 0 month was statistically not significant, but at 6 month the difference was statistically significant (P<0.05) (Table III).

Table III Comparison of lipid profile between the two study groups

Parameters	Group A (n=27)	Group B (n=28)	P value
	Mean±SD	Mean±SD	
Total cholesterol (mg/dl)			
At 0 month	179.52±23.57	175.89±20.24	0.543[ns]
At 6 month	162.26±20.96	184.75±19.85	0.0001[***]
Change	17.26±13.59	+8.86±15.68	0.0001[***]
Percent change	9.32	+5.55	
LDL cholesterol (mg/dl)			
At 0 month	108.56±20.26	107.89±13.92	0.888[ns]
At 6 month	87.59±16.85	110.14±15.60	0.0001[***]
Change	20.96±14.27	2.25±18.00	0.0001[***]
Percent change	18.79	+3.61	
HDL cholesterol (mg/dl)			
At 0 month	40.78±5.36	40.64±5.35	0.926[ns]
At 6 month	42.63±3.60	37.61±3.26	0.0001[***]
Change	+1.85±5.02	3.04±4.40	0.0001[***]
Percent change	+5.90	6.63	
Triglyceride (mg/dl)			
At 0 month	167.85±74.77	154.57±50.82	0.443[ns]
At 6 month	130.00±66.62	164.71±47.26	0.030[*]
Change	37.85±31.95	+10.14±18.14	0.0001[***]
Percent change	22.34	+8.58	

Unpaired Student's 't' test
ns = Not significant
* = Significant (P<0.05)
*** = Significant (P<0.001)

ECG finding of the two groups of patients at 0 month and at 6 month showed no statistically significant variation between groups neither at 0 month nor at 6 month (Table IV).

Table IV ECG findings of the study subjects			
ECG finding	Group A (n=27) No. (%)	Group B (n=28) No. (%)	P value
At 0 month			
Normal	18 (66.7)	20 (71.4)	
LVH	3 (11.1)	4 (14.3)	0.730[ns]
Myocardial ischemia/ infarction	6 (22.2)	4 (14.3)	
At 6 month			
Normal	12 (44.4)	12 (42.9)	
LVH	6 (22.2)	9 (32.1)	0.660[ns]
Myocardial ischemia/ infarction	9 (33.3)	7 (25.0)	

Chi square
ns = Not significant

In our study, at 0 month mean (±SD) ejection fraction (EF %) were 54.52±5.51 and 51.57±6.81 in group-A and group-B respectively. At 6 month, mean (±SD) (EF%) were 52.04±9.82 and 50.18±7.72 in group-A and group-B respectively. Mean (±SD) change at 6 month from 0 month was 2.48±6.58% in group-A and 1.39±6.11% in group B; statistically the mean difference between groups was not significant.

Mean (±SD) change of SGPT at 6 month from 0 month were 4.41±6.03 U/L increase in group-A and 2.14±5.61 U/L increase in group-B; the mean difference between groups were not significant (Table **V**).

Table V Status of SGPT in the two study groups			
SGPT (U/L)	Group A (n=27) Mean±SD	Group B (n=28) Mean±SD	P value
At 0 month	28.96±5.79	29.43±8.71	0.817[ns]
At 6 month	33.37±7.92	31.57±10.82	0.486[ns]
Change	+4.41±6.03	+2.14±5.61	0.155 [ns]
Percent change	+16.13	+8.39	

Unpaired Student's 't' test
ns = Not significant

Discussion

In this study, at 6 months the LDL cholesterol level in the group-A was 18.79% lower than baseline level, as compared with a 3.61% increase in the group-B, which was statistically significant. Other study like, Fellstrom B et al,[9] showed, 43% reduction of LDL cholesterol and in the Wanner C et al[10] showed, the median LDL cholesterol level was reduced by 42%. Niepen et al,[11] showed 37% reduction of LDL cholesterol with atorvastatin therapy. So our study result was consistent with those studies.

In our study, at 6 months after atorvastatin in the group-A, there was 9.3% reduction of total cholesterol as compared with group-B where total cholesterol was increased (5.5%).

Fellstrom B et al, [9] showed 26.6% reduction of total cholesterol after rosuvastatin therapy.

In this study, HDL cholesterol was increased 5.9% from baseline (mean ±SD difference 1.85 ± 5.02 mg/dl in the group-A in comparison to 6.63% reduction of HDL cholesterol in group-B. Fellstrom et al, [9] showed, HDL cholesterol level was increased 2.9 % after statin therapy and Niepen et al, [11] showed, mean ± SD difference of HDL cholesterol from baseline after atorvastatin was 2.6 ± 3.6 mg/dl.

In present study, serum triglyceride level was decreased 22.34% in group-A and 8.58% increase in group-B from base line. That means atorvastatin caused significant reduction of triglyceride level in hemodialysis patient. Fellstrom B et al, [9] showed, the triglyceride level was reduced by 16.2% in rosuvastatin group, as compared with an increase of 0.9% in placebo group and Niepen et al,[11] also showed, there was reduction of triglyceride in atorvastatin group.

In this study, atorvastatin did not cause any significant change in ventricular hypertrophy (LVH) on both ECG and Echocardiography. In this study, myocardial ischemia/infarction on ECG was present 22% in group-A and 14% in group-B at randomization. After 6 months, group–A (atorvastatin group) ischemia/infarction was found in 33% where as 25% in non-atorvastatin group. This result also was not significant statistically.

On the other hand on echocardiography ischemia/ infarction at randomization were 25% and 18% in group-A and group-B respectively. After 6 months ischemia/

infarction was 33% in group-A and 18% in group-B. These changes were not statistically significant that means atorvastatin has no effect on cardiovascular events in hemodialysis patients. This may be due to short period of the study. Alam MR et al, [12] showed that the prevalence of coronary artery disease was 16% of hemodialysis patients, aged more than 40 years. That prevalence was consistent with our study. Wanner C et al,[10] showed, that 11% of patients in the atorvastatin group had a nonfatal myocardial infarction, as compared with 12% of those in the Placebo group (p=0.42) and all cardiac events were 33% in atorvastatin group and were 39% in non atorvastatin group which was significant between two groups (p=0.03). Fellstrom B et al,[9] showed in their study, that major cardiovascular events were 9.2/100 patient /yr in rosuvastatin group and were 9.5/100 patient /yr in placebo group. (p=0.59). Our study showed similar result with previous two studies.

In this study, mean ejection fraction (EF %) was 54% in group-A and 51% in group-B at randomization, after 6 months atorvastatin group failed to show any significant change of ejection fraction. Alam et al,[12] showed that heart failure was more in the patients with shorter duration of dialysis. That was not consistent with our study. However heart failure in hemodialysis patients depends on several factors like aneamia, adequate ultrafiltration, medication, myocardial ischemia etc.

Mason NA et al,[13] showed that hemodialysis related chronic inflammatory process plays the central role in accelerated atherosclerosis and cardiovascular mortality and statins play an important role in reducing all cause and cardiovascular mortality besides having an adequate safety profile, making them the first choice treatment of dyslipidemia in dialysis patients. Likewise statins are also known for their ability to reduce inflammatory markers, CRP and LDL cholesterol. For these reason in some studies, statin was used even in very low level of LDL cholesterol to get other pleitrophic effect like mean LDL 77±16.4 mg/dl[11] and 100±35mg/dl .[9] In this study, decrease of cardiovascular events was also expected but was not achieved, may be due to short duration of study period.

In present study, baseline SGPT was similar in both groups and after 6 months there was slight increase of SGPT 16.13% in atorvastatin group as compared with 8.39% in non atorvastatin group. That was not statistically significant. That means atorvastatin did not cause significant increase of SGPT in dialysis patients.

Niepen et al,[11] showed, that SGPT level was increased by 14% in patients with statin therapy which was expected to occur during treatment with statin. Fellstrom B et al,[9] showed that SGPT level was increased >4 times upper limit of normal range in 0.4% of patients in both rosuvastatin and placebo groups. (p=0.75). Wanner C et at,[10] also showed that there was no serious adverse events, specially any hepatic dysfunction.

In conclusion, in this prospective clinical study, after 6 months, a significantly favourable change in lipid profile was found in atorvastatin group but there was no significant difference in cardiovascular events.

Limitations

1. This was a single center study.

2. Study included a small number of patients and study period was shorter, as a longer follow-up could provide more accurate information about cardiovascular effect.

Conflicts of interest: Nothing to declare.

References

1. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: 2002. Evaluation, classification, and stratification. Am J Kidney Dis 2002;39:S1-266.

2. Gowdak, L.H., Arantes RL, de Paula FJ, Krieger EM, De Lima JJ. Under use of American College of Cardiology/American Heart Asso-ciation Guidelines in hemodialysis patients. Ren Fail 2007; 29(5):559-65

3. Foley, R.N., Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. Am J Kidney Dis 1998; 32 [Suppl 3]: S112–S119.

4. Abrass, C.K. Lipid metabolism and renal disease. Contrib Nephro 2006; 151:106-21.

5. 4S: Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: The Scandinavian Survival Study. Lancet 1994; 344: 1383–1389.

6. MRC/ BHF Heart Protection Study Collaborative Group. Randomised placebo-controlled trial of cholesterol-lowering with simvastatin in 20,536 high-risk individuals. Lancet 2002; 360: 7–22.

7. Executive Summary of The 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). JAMA 2001; 285:2486-2497.

8. Morag, N.K., Eran C, Gold B. High blood triglycerides are independent risk factors for stroke. Circulation 2002; 26:6-7.

9. Fellstrom, B., Zannad F, Schmieder R, Holdaas H, Jardine A, Rose H, et al. AURORA Study Group. Rosuvastatin and cardiovascular events in patients undergoing haemodialysis AURORA study. NEJM 2009; 360:1395-407.

10. Wanner, C., Krane V, März W, for the German Diabetes and Dialysis Study Group. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. N Engl J Med 2005; 353:238-248.

11. Niepen, Juiz de Fora. Intermittent doses of statin in hemodialysis patients with spontaneous low LDL cholesterol levels. Arq. Bras. Cardiol 20078.; 90:1-13.

12. Alam MR, Khanam A, Alam KS, Muqueet MA, Islam S, Rashid HU. Prevalence of co-morbidity in hemodialysis patients. Bangladesh Renal Journal 2004; 23:56-60

13. Mason NA, Baillie GR, Satayathum S. HMG-coenzyme a reductase inhibitor use is associated with mortality reduction in hemodialysis patients. Am J Kidney Dis 2005; 45:119-126.