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Effect of atorvastatin and rosuvastatin on 25-hydroxy vitamin d levels in newly diagnosed South Indian dyslipidemic subjects: A randomized, open-label, single center study

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Abstract---Background: Statins are one of the mainstay treatment modality for the people suffering from dyslipidemia. Statins reduce the cholesterol bio-synthesis by ß-hydroxy-ß-methyl glutaryl Co-A (HMG-CoA) reductase inhibition which is rate-limiting enzyme. It also affects the Vit-D levels as metabolism of cholecalciferol and cholesterol are interrelated. Objectives: Effect of atorvastatin/ rosuvastatin on 25-hydroxy Vitamin-D (25OHD) concentrations among subjects with newly diagnosed dyslipidemia. Materials and Methods: Prospective randomized, open-label, parallel group study. Lipid and 25OHD levels are measured at baseline and end of 6 months after statin treatment. One group received atorvastatin and another study group received rosuvastatin for 6 months. Results: Mean 25OHD concentrations are

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32.0±4.7, 31.7±4.8 and 32.9±4.9 in the control, atorvastatin and rosuvastatin groups respectively. Both atorvastatin and rosuvastatin groups, except TGs, all the lipid parameters and 25OHD has showed significant difference (<0.001) from baseline to end-line repeated parameters. All the study participants were well tolerated and no one discontinued the drug due to drug-related adverse reactions. Conclusion: Participants with atorvastatin treated group showed significant reduction in 25OHD concentrations. In addition, 25OHD concentrations are dependent on statin efficacy.

***Keywords*---**Dyslipidemia, Statins, HMG-CoA reductase inhibitors, Atorvastatin, Rosuvastatin, 25-OHD concentration, Vitamin-D levels.

Introduction

Cardiovascular diseases are one of the leading causes of morbidity and mortality in developing countries like India which accounts about 26% of death according to the World health organization (WHO) census.(1) INTERHEART study reported that high prevalence of coronary artery diseases (CAD) with patients aged >20 years. The prevalence in rural (4%) and urban (10%) areas in 1960 which has been doubled in rural and 6-times rise in urban areas in 2000.(2) To treat CAD, Indian physicians are prescribing different generic formulations of statins as one of the goal of the treatment which can lowers the lipid levels in the blood. Increased frequency of statins prescribing has been seen in recent times.(3)

Statins inhibits the enzyme ß-hydroxy-ß-methyl glutaryl Co-A (HMG-CoA) reductase which plays a rate limiting step for the synthesis of cholesterol. Each drug molecule shows its own pharmacokinetics, safety, metabolic properties and inter-individual variability. Atorvastatin, Simvastatin, Fluvastatin, Lovastatin and Pitavastatin which are lipophilic in nature. Hence, these drugs are underwent first pass metabolism in the liver thus oral bioavailability was reduced significantly. Rosuvastatin and Pravastatin are hydrophobic which may overcome the above situation and shows the better oral bioavailability as compared to the lipophilic drugs.(4)

Cytochrome P450 (CYP-P450) iso-enzymes like CYPA4 metabolizes Atorvastatin and Simvastation etc. where as Rosuvastatin and Pravastatin are not significantly metabolized by the CYPP450 system. CYP3A4 aromatic hydroxylation metabolizes the Atorvastatin in the liver, the resultant metabolites shows inhibition of HMG-CoA reductase which produces hypolipidemic effect.(5) Although statins exhibits beneficial pharmacological effects to control the hyperlipidemia in the blood, other side these drugs known to affect important endogenous metabolites such as ubiquinone in the body which results to cause statin induced myopathy.(6) Apart from statin induced myopathy statins may decrease the Vitamin-D concentrations in the blood because cholesterol and cholecalciferol are formed through a common pathway which was inhibited by the statins. Drug treatment with statins may decrease the vitamin-D synthesis leading to fall in Vit-D levels in the blood.(7) Cardiometabolic outcomes and cardiovascular events are positively correlated with Vitamin-D status which was decreased and reported by the

various clinical studies.(8) The reported vitamin-D insufficiency is associated with statin-induced myopathy.(9)

The prevalence of CHD is much higher in the Indian scenario and more patients are receiving the statins for the underlying cause and 25hydroxyVitamin-D (25OHD) deficiency is commonly reported in India. So it is very important to measure and asses the 25OHD status in patients taking the statins. The present study was undertaken to asses the effect of 6 month Atorvastatin versus Rosuvastatin treatment on 25OHD concentrations in newly diagnosed dyslipidemia subjects and to assess the 25OHD on statin efficacy to control the dyslipidemia.

Materials and Methods

This is a prospective, open label, randomized study carried out in the Department of Pharmacology in collaboration with General Medicine and Cardiology departments at Maharaja Institute of Medical Sciences, Vijayanagaram, Andhra Pradesh, India. Healthy subjects with either gender aged between 40-60 years were selected and recruited. Subjects with hepatic disorders, diabetes, disorders of kidney, abnormal thyroid functions and history of cardiac manifestations were excluded from the study.(10) All the participants who are willing to participate were selected and informed consent was obtained from then before commencement of the study. The present study was approved by the Ethics committee and all necessary permissions were obtained from institutional review boards.

Study groups

After recruiting the study participants, lipid parameters which include total cholesterol, high-density cholesterol, low-density cholesterol and triglycerides as well as 25OHD concentrations were measured at the time of screening. Adult treatment panel (HTP-III) guidelines were used for risk assessment for dyslipidemia. Based on the assessment, patients were further screened and categorized into different groups. Based on guidelines, a total of 110 subjects not required statin therapy. Among them, a total of 35 participants were selected and moved to the control group by using computer generated random numbers method. Baseline 25OHD concentrations were estimated from participants to differentiate any seasonal change or anything else.

Interventional groups

A total of 70 participants have significant dyslipidemia and required statin therapy based on ACT-III guidelines. One group (Group-1, n=35) received atorvastatin 10mgday for 6 months and another group (Group-2, n=35) received the rosuvastatin 5mg/day for 6 months.(11) Computer generated allocation sequence method was used to randomize in to interventional groups. Generation of allocation sequence and participant's allocation was performed by statistician. The reason for choosing the atorvastatin and rosuvastatin was, as these are the commonly using statins at the study center as well as in India although these drugs have different pharmacological properties.(12,13) To asses the current and

past health status and medical history was obtained by a qualified medical physician who is not involved in the study.

Biochemical Parameters

Venous blood sample was collected from the study participants after an overnight fasting of 12 hours. Same reagents, instruments and technician was involved to estimate the biochemical parameters to prevent the bias. All the instruments used in the study was periodically calibrated as per standard operating procedure. Every time fresh samples were used for estimating fasting blood sugar, SGPT and CR. Lipid parameters which includes TC, HDL-C, LDL-C, VLDL-C and TG were estimated at baseline and at the end of study by using enzymatic method. 25OHD concentrations were estimated by using ELISA method at baseline and end of the study.(14)

Anthropometry and Body composition

Electronic digital scale was used to measure the weight of the participants. Leicester height meter was used to measure the height and BMI was computed by using formulae. Total body fat composition was measured by using lunar DPX-PRO densitometer.(15)

Follow-up visits

To assess the drug effectiveness and drug toxicity, participants were clinically examined during their monthly follow-up visits and SGPT levels were measured at every 3 months. Tablet strips were dispensed once in a month and participants were advised to come every month follow-up visit to assess the clinical response, safety and dispensed next month medicines. Treatment related adverse drug reactions were recorded during their routine follow-up visits. Patient compliance was checked by asked to bring the empty tablet strips physically during every month follow-up visit.(16)

Statistical Analysis

Descriptive data was shown as percentages, mean with standard deviation and median with inter-quartile range. SPSS software was used for data analysis. To test normality of data kolnogorov-Smirnov teat was used and this test was carried out before inferential statistics. Paired t-test was used to test the change before and after the intervention. Treatment of statin effect on 25OHD and vice verse was compared within and between the groups.(17) 2 sided equality t-test was used for calculation of sample size. Based on the previous studies, we kept power 80% and alpha error 5% and dropout rate (10%), the calculated sample size was 30 in each group.

Results

A total of 240 subjects were screened, out of these 160 subjects were excludes due to diabetes hepatic, renal and thyroid disorders as well as cardiac comorbidities. Consort flow diagram was showed in Flowchart 1. Out of 160

subjects 110 subjects not required statin treatment based on ACT-III guidelines and 35 of 110 was taken as controls. 70 participants required statins and randomized to 35 in each study group. Lost to follow-up was reported as 4, 5 and 4 in control group, atorvastatin group and rosuvastatin group respectively. Majority of lost to follow-up was due to rejection of consent form (n=9) followed by relocation to other place (n=3) and unable to tolerate the treatment initially (n=1). Finally control group (n=31), atorvastatin group (n=30) and rosuvastatin group (n=31) has completed the entire study period and analyzed statistically.

A total of 92 participants were completed entire study, among these 31 participants from control group, 30 from atorvastatin group and 31 from rosuvastatin group. Baseline demographic details are showed in Table 1. Mean age among study groups were fall between 44-46 years with the range of 35-60. Higher proportions of individuals are male gender. Greater then 90% of study participants was overweight and 5% were Obese among study groups. Mean 25OHD concentrations are 32.0±4.7, 31.7±4.8 and 32.9±4.9 in the control, atorvastatin and rosuvastatin groups respectively. All the lipid parameters in the atorvastatin group have showed significant difference from control group. In the rosuvastatin group, except HDL-C remaining all lipid parameters have showed significant difference as compared to control group.

A total of 30-50% of study participants among study groups had history of smoking and drinking alcohol. Study participants were taking concomitant drugs such as ACE inhibitors/ARBs, diuretics and antiplatelet drugs etc. (Table 1). A total of 51 participants from all the groups taking other medications for their long-term illness such as diabetes, hypertension etc.

Comparison of baseline and end-line concentrations of 25OHD and lipids among study groups are showed in Table 2. Control group not showed the any significant difference in 25OHD and lipid parameters before and after the treatment. In the atorvastatin group, except TGs, all the lipid parameters and 25OHD has showed significant difference (<0.001) from baseline to end-line repeated parameters. A total of -4.67 mean difference of 25OHD concentration was decreased with SD of 0.20 and this was statistically significant (<0.001).

In the rosuvastatin group, all lipid parameters except TGs has showed significant difference from the baseline to end-line repeated parameters. 25OHD concentration was slightly increased (absolute change 0.60) from baseline which was not significant (P=0.194). Table 3 showing the absolute difference from baseline among study groups. The difference of 25OHD levels from baseline in atorvastatin group was towards negative side while in the rosuvastatin group slight positive side (P<0.0001). All lipid parameters has showed significant difference from baseline among study groups.

Correlation between 25OHD concentrations and difference in lipid levels among study groups are showed in Table 4. Correlation of 25OHD concentrations on lipid parameters were assessed, LDL-C has showed positive correlation with 25OHD concentrations in the atorvastatin group. Rosuvastatin group did not show any significance correlation with any lipid parameters. Hence, absolute

change of LDL-C concentrations from baseline were depends on 25OHD concentrations.

Treatment related adverse drug reactions among study groups are showed in Table 5. All the study participants were well tolerated and no one discontinued the drug due to drug-related adverse reactions. The most frequent adverse events in the rosuvastatin group were edema and dizziness. Myalgia was reported by 2 participants in the atorvastatin group. All adverse effects are mild and most of them were seen after 2 weeks of starting the treatment, no action has been taken and all are resolved spontaneously. Rhabdomyolysis has been seen in one patient with Rosuvastatin group.

Discussion

Vitamin-D synthesis was inhibited by statins by depleting the substrate needed for the Vit-D biosysnthesis. In addition to this, statins increase the catabolism of Vit-D. However, most of the published studies showed that either no change or increased 25OHD concentrations were reported after treatment with statins.(18) Previous studies published by Demir C.C et al., Anagnostis P et al., and Thabit A et al., reported no change in 25OHD concentrations after treatment with Atorvastatin, Rosuvastatin or Simvastatin.(17,19,20) In contrast to the above studies, Yavuz B et al., and Ertugrul D.T et al., conducted different studies and concluded that serum concentrations of 25OHD were improved after treatment with Rosuvastatin.(21,22) In addition, Sathyapalan T et al and Perez-Castrillon J.L et al. reported a significant increase in 25OHD concentrations after atorvastatin treatment.(23,24) The contradictory results published by the previous studies might be due to higher Vitamin-D dietary intake or Vit-D absorption are the possible explanations in patients taking statins. Descamps O.S et al., and van Himbergen T.M et al., reported that statins accelerate the cholesterol absorption which is absolute contradictory mechanism which was originally shown by statins.(25,26)

Long-term treatment with statins prevent the cholesterol synthesis (statin related) may up-regulate the membrane transporters which might be responsible for the increase absorption of cholesterol.(26) Hui D.Y et al., reported that scavenger receptor B-1 (SRB1) is the main membrane receptor responsible for the absorption of cholesterol in the intestine. Same membrane receptors are shared the intestinal absorption of Vitamin-D which was confirmed.(27)

Membrane transporters such as SR-B1, CD6 and NPC1L1 of intestinal explants of mouse were introduced via transfection, these significantly enhance the uptake of 25OHD and introduction of SR-B1, CD36, NPC1L1 inhibitors significantly reduced the 25 OHD uptake respectively.(28) Along with standard statin therapy, drugs which reduce the cholesterol absorption such as Ezetimibe were added, a fall in 25OHD concentration was observed.(29) However, statin related improved intestinal absorption increase the 25OHD concentrations in people who are taking high vitamin-D intake through their diet. Population in the present study is not taking or negligible dietary vitamin-D which shows less 25OHD concentrations.(30) In addition, we used low or less frequent doses of statins which are different from already published studies. Radhakrishnan A et al.,

conducted a cross-sectional study and reported that lower concentrations of 25OHD were seen with statin therapy.(18)

In the present study, TC and LDL-C concentrations significantly reduced with Atorvastatin treatment group but not with Rosuvastatin group. Peroz-Castrillon J.L et al., conducted a study and reported the similar observations showed that atorvastatin effective action was seen with plasma 25OHD concentration greater than 30nmolL.(24) Atorvastatin is metabolized by CYP3A4 to its active metabolites. 1, 25 (OH)2D is a potent enzyme inducer of CYP3A4 which accelerate the metabolism of atorvastatin and decrease the plasma concentration. In contrast to atorvastatin, rosuvastatin is not metabolized by CYP3A4, so 25OHD concentrations are not or less likely influenced.(31)

The main strength of the present study is recruited the newly diagnosed dyslipidemic participants and carried out the study to measure the effect of statins on Vit-D status. To the best of our knowledge, very limited studies have been published so far in India. Limitations which include open label study design, used less doses of statins with limited time frame. Future studies are warranted with frequent doses of statins, double blind cross-over study with large sample size. Hence, results give reliable and valid conclusions for this important contradictory issue.

Conclusions

Statins treatment either for coronary artery disease or dyslipidemia showed causal metabolic relationship with 25OHD concentrations which decrease the concentrations of 25OHD in the present study. The intensity of relationship is much stronger if people are taking less or no dietary Vit-D consumption. A careful monitoring of 25OHD concentrations should be required who are taking atorvastatin for reducing lipid levels. However, people who are taking atorvastatin, simultaneously either they have to take high dietary intake or Vit-D supplements to overcome the situation of low 25OHD concentration related adverse affects.

Table 1: Baseline demographic details among study groups

Parameter	Controls	Atorvastatin	Rosuvastatin
n	31	30	31
Age in years	44.2±10.8	45.8±11.0 (0.568)	46.2±11.4 (0.481)
Gender, n			
Male:Female	20:11	20:10	18:13
BMI, kg/m^2	24.4±4.8	25.7±5.1 (0.309)	25.9±5.3 (0.247)
Body fat percentage	26.2±6.4	27.1±6.8 (0.596)	27.7±7.0 (0.382)
25OHD, ng/mL	32.0±4.7	31.7±4.8 (0.806)	32.9±4.9 (0.463)
Lipid parameters			
TC, mg/dl	170.2±16.7	255.2±20.5 (0.001)	259.5±22.2 (0.001)
LDL-C, mg/dl	105.2±18.2	157.0±22.4 (0.001)	160.1±22.6 (0.001)

TG, mg/dl	124.0±15.2	182.7±15.8 (0.001)	185.5±16.2 (0.001)
HDL-C, mg/dl	45.1±3.5	43.1±2.6 (0.014)	44.1±2.7 (0.212)
LDL-C to HDL-C ratio	2.3±0.4	3.7±0.6 (0.001)	3.6±0.6 (0.001)
History of smoking, n			
Yes:No	14:17	12:18	11:20
History of alcohol consumption, n (%)			
Yes:No	15:16	13:17	15:16
Concomitant medications, n (%)			
ACEIs/ARBs	8 (25.8)	17 (56.7)	18 (58.1)
Diuretics	7 (22.6)	11 (36.7)	10 (32.3)
Antiplatelet drugs	3 (9.7)	16 (53.3)	18 (58.1)
ß-blockers	8 (25.8)	15 (50.0)	16 (51.6)
Others	10 (32.3)	20 (66.7)	21 (67.7)

P- values in the parenthesis was compared with control group. Unpaired t-test was used to compare the control and test group. BMI=Body mass index; 25OHD= 25-hydroxy-Vitamin-D; TC= Total cholesterol; LDL-C= Low-density lipoprotein cholesterol; TG= Triglycerides; HDL-C= High-density lipoprotein cholesterol; ACEI= Angiotensin converting enzyme inhibitors; ARB= Angiotensin receptor blockers.

Table 2: Comparison of baseline and endline concentrations of 25OHD and lipids among study groups

Variable	Baseline	End-line	P-value	Absolute change from baseline
Controls				
n	31	31		
25OHD, ng/mL	32.0±4.7	32.2±4.7	0.454	0.17±0.07
TC, mg/dl	170.2±16.7	169.4±16.2	0.178	-0.78±0.50
LDL-C, mg/dl	105.2±18.2	103.9±19.5	0.067	-1.28±1.30
TG, mg/dl	124.0±15.2	123.0±15.0	0.066	-1.03±0.17
HDL-C, mg/dl	45.1±3.5	45.4±4.0	0.448	0.30±0.43
LDL-C to HDL-C ratio	2.3±0.4	2.3±0.5	0.495	-0.03±0.08
Atorvastatin group				
n	30	30		
25OHD, ng/mL	31.7±4.8	27.0±4.6	0.001	-4.67±0.20
TC, mg/dl	255.2±20.5	230.3±17.9	0.001	-24.98±2.67
LDL-C, mg/dl	157.0±22.4	122.7±18.9	0.001	-34.27±3.47
TG, mg/dl	182.7±15.8	180.6±150	0.092	-2.11±0.77
HDL-C, mg/dl	43.1±2.6	41.8±2.5	0.001	-1.30±0.11

LDL-C to HDL-C ratio	3.7±0.6	3.0±0.5	0.001	-0.70±0.03
Rosuvastatin group				
n	31	31		
25OHD, ng/mL	32.9±4.9	33.5±5.1	0.194	0.60±0.25
TC, mg/dl	259.5±22.2	221.9±18.0	0.001	-37.65±4.17
LDL-C, mg/dl	160.1±22.6	120.7±16.2	0.001	-39.39±6.38
TG, mg/dl	185.5±16.2	184.8±160	0.742	-0.61±0.19
HDL-C, mg/dl	44.1±2.7	42.0±2.3	0.001	-2.10±0.43
LDL-C to HDL-C ratio	3.6±0.6	2.9±0.4	0.001	-0.76±0.16

P-values were compared before and after the treatment among study groups. Paired t-test was used to compare the difference from baseline to endline treatment. 25OHD= 25-hydroxy-Vitamin-D; TC= Total cholesterol; LDL-C= Low-density lipoprotein cholesterol; TG= Triglycerides; HDL-C= High-density lipoprotein cholesterol.

Table 3: Comparison of absolute change from baseline among study groups

Variable	Absolute change from baseline		P-value
	Atorvastatin group	Rosuvastatin group	
n	30	31	
25OHD, ng/mL	-4.67±0.20	0.60±0.25	0.0001
TC, mg/dl	-24.98±2.67	-37.65±4.17	0.0001
LDL-C, mg/dl	-34.27±3.47	-39.39±6.38	0.0003
TG, mg/dl	-2.11±0.77	-0.61±0.19	0.0001
HDL-C, mg/dl	-1.30±0.11	-2.10±0.43	0.0001
LDL-C to HDL-C ratio	-0.70±0.03	-0.76±0.16	0.0480

Un-paired t-test was used to compare the absolute difference from baseline among study groups. 25OHD= 25-hydroxy-Vitamin-D; TC= Total cholesterol; LDL-C= Low-density lipoprotein cholesterol; TG= Triglycerides; HDL-C= High-density lipoprotein cholesterol.

Table 4: Correlation between 25OHD concentrations and difference in lipid levels among study groups

Group	Independent variable	Difference from baseline (Correlation coefficient)			
		TC	LDL-C	HDL-C	LDL-C to HDL-C ratio
Control	25OHD	0.245	0.264	0.134	0.045
Atorvastatin		0.517*	0.596*	0.054	0.213
Rosuvastatin		0.064	0.154	0.256	0.154

*Statistically significant; Pearson correlation test was performed to calculate correlation coefficient values. 25OHD= 25-hydroxy-Vitamin-D; TC= Total

cholesterol; LDL-C= Low-density lipoprotein cholesterol; TG= Triglycerides; HDL-C= High-density lipoprotein cholesterol.

Table 5: Treatment related adverse drug reactions among study groups

	Control (n=31)	Atorvastatin (n=30)	Rosuvastatin (n=31)
Any adverse events	4 (12.9)	8 (26.7)	14 (45.2)
Serious adverse events	0 (0.0)	2 (6.7)	1 (3.2)
Drug related adverse events	0 (0.0)	4 (13.3)	0 (0.0)
Adverse events which caused discontinuation of the study	0 (0.0)	0 (0.0)	0 (0.0)

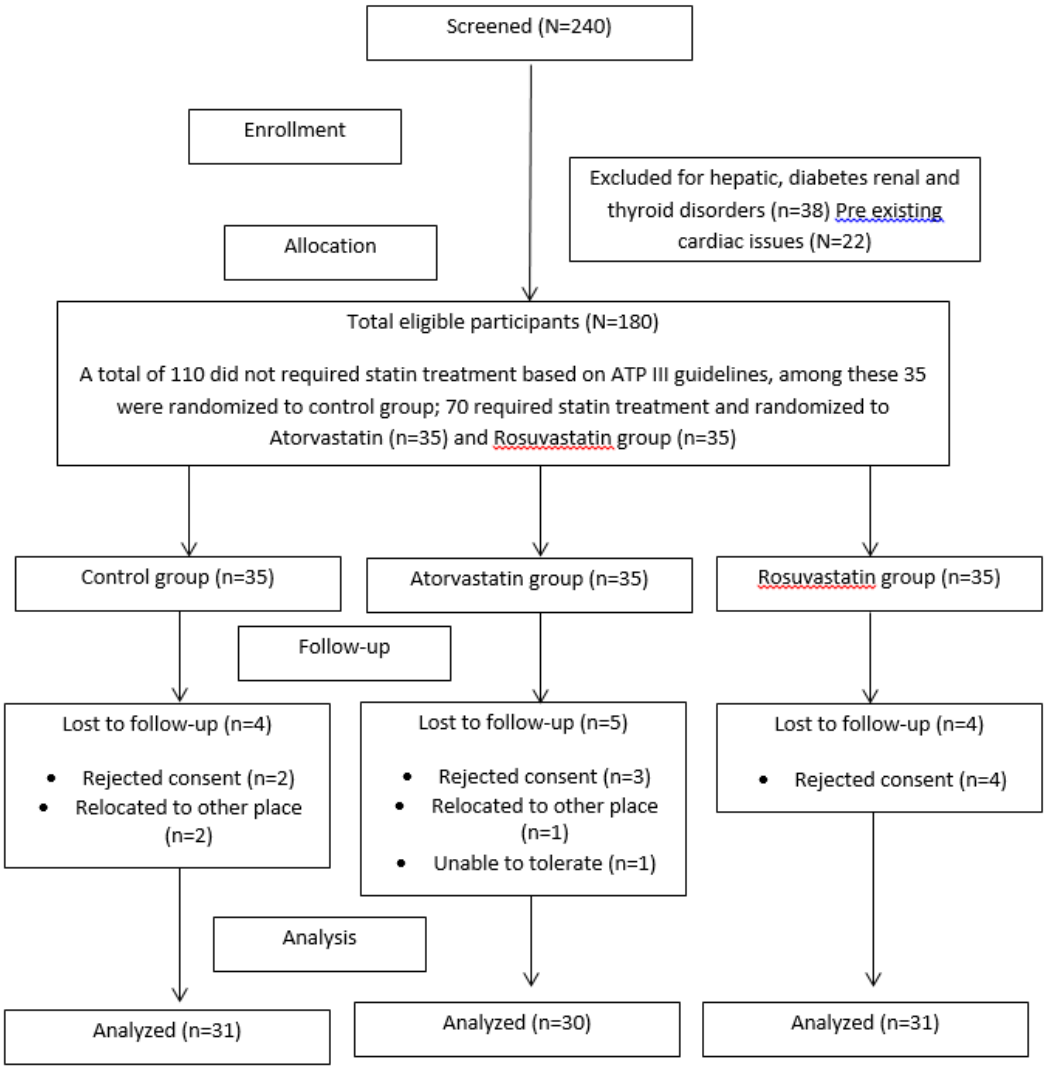

Figure 1: Consort flow diagram

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Conflict of Interest

All authors are declared no conflict of interest

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