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COMPARISION OF EFFICACY AND SAFETY OF ROSUVASTATIN 10 MG OD AND ATORVASTATIN 20 MG OD IN HIGH RISK CARDIOVASCULAR DISEASE PATIENTS.

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Abstract: Objective : The objective of this study was to compare safety and efficacy of Rosuvastatin 10 mg OD and Atorvastatin 20 mg OD. **Methods** : Sixty six newly diagnosed patients who are at high risk for cardiovascular disease were enrolled in this open labeled, prospective, non-randomized, parallel group, single centric 8 week study. After baseline assessment, all eligible patients were divided into two groups. One group received Rosuvastatin 10 mg OD and other group received Atorvastatin 20 mg OD and were treated for 8 weeks with two follow up visits. LDL-C, TC, HDL-C, TGs were measured at baseline, 1st follow up (4 weeks) and 2nd follow up (8 weeks). **Results** : In this study, major risk factors identified for cardiovascular disease were Hypertension, Diabetes mellitus, Smoking and History of CHD. The percentage reduction was 43.15% and 37.81% in LDL-C, 24.01% and 19.08% in TC, 24.08% and 15.26% in TGs in Rosuvastatin and Atorvastatin treatment groups, respectively. HDL value was elevated by 22.43% and 13.49% in Rosuvastatin and Atorvastatin treatment group, respectively. **Conclusion** : It was observed that both Rosuvastatin and Atorvastatin showed significant modification in lipid profile in patients at high risk for cardiovascular disease. Rosuvastatin 10 mg OD was found to be more effective and safe in altering LDL-C, Total cholesterol, HDL-C and Triglycerides than Atorvastatin 20 mg OD at 8 weeks. Rosuvastatin therefore seems to be better alternative than Atorvastatin in patients who are at high risk of CVD.

Keywords: Rosuvastatin, Atorvastatin, Cardiovascular disease, High risk

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INTRODUCTION

Cardiovascular disease (also called heart disease) is a class of diseases that involve the heart, the blood vessels (arteries, capillaries, and veins) or both.

Cardiovascular disease refers to any disease that affects the cardiovascular system, principally cardiac disease, vascular diseases of the brain and kidney, and peripheral arterial disease. [1,2]

Cardiovascular diseases are the leading cause of death. In 2008, 30% of all global death is attributed to cardiovascular diseases. It is also estimated that by 2030, over 23 million people will die from cardiovascular diseases annually.[3]

Abnormal levels of lipids (fats) in the blood are risk factors for cardiovascular disease. Rosuvastatin and Atorvastatin both are lipid lowering agents under class- HMG CoA reductase inhibitors. Both are known to be very effective in achievement of Lipid goals in patients with abnormal lipid profile. Till date, different statins have been compared for their safety, efficacy & cost effectiveness in different trials

Strandberg et al (2004), compared rosuvastatin (10 mg) and atorvastatin (10 mg) in patients at high risk for CVD and concluded that greater reduction in LDL-C levels were achieved with a starting dose of rosuvastatin compared with atorvastatin 10 mg and both the treatments were well tolerated.[4] Hirsch et al(2005), compared the cost-effectiveness of rosuvastatin 10 mg and atorvastatin 10 mg in lowering LDL-C and achieving guideline goals after 12 weeks of treatment and concluded that Rosuvastatin has the same acquisition costs as Atorvastatin and is more efficacious than Atorvastatin in lowering LDL-C and treating patients to target LDL-C levels.[5] Jones et al(2003), compared rosuvastatin with atorvastatin, pravastatin, and simvastatin across dose ranges for reduction of low density lipoprotein (LDL) cholesterol and concluded that Rosuvastatin produced significantly better reductions in total cholesterol and similar or significantly better reductions in triglycerides, compared with Atorvastatin, Simvastatin, and Pravastatin.[6] Aszatalos et al(2007), conducted the substudy with STELLAR study and compared the effects of daily doses of rosuvastatin 40 mg with atorvastatin 80 mg for 6-weeks on HDL subpopulations and concluded that both statins, given at their maximal doses, favorably alter the HDL subpopulation profile, but also that Rosuvastatin is significantly more effective in this regard than Atorvastatin.[7] Leiter et al (2007), investigated the efficacy and safety of Rosuvastatin 40 mg and Atorvastatin 80 mg in high-risk patients with hypercholesterolemia in which the primary end point was percentage change in LDL-C levels at 8 weeks and concluded that intensive lipid-lowering therapy with Rosuvastatin 40 mg/day provided greater LDL-C-lowering efficacy than atorvastatin 80 mg/day, enabling more patients to achieve LDL-C goals.[8] Schwartz et al(2004), compared the efficacy and safety of rosuvastatin and atorvastatin in patients with Hypercholesterolemia and a high risk of

Coronary heart disease and concluded that Rosuvastatin was more efficacious than Atorvastatin in modifying lipids in above mentioned patients.[9]

Attempts have been made to compare safety and efficacy of Rosuvastatin and Atorvastatin in hyperlipidemic patients in various parts of the world. But till now, in high risk patients of CVD, such kind of study was not carried out yet. Hence this study "Comparative study of Rosuvastatin and Atorvastatin in high risk patients of CVD" was undertaken at Sanjivani Superspeciality Hospital, Ahmedabad.

MATERIALS AND METHODS

The ethics committee of Sanjivani Superspeciality Hospital, Ahmedabad approved this open labeled, prospective, non-randomized, parallel group, single centric 8 week study. Both male and female patients aged 18 years and above were enrolled in this study. Total 66 patients were enrolled in this study.

After detailed explanation of the study and involved procedures to the patients, a written informed consent was obtained. After that, patients were allocated in two experimental groups. The patients received either 10 mg of Rosuvastatin (Group A) or 20 mg of Atorvastatin (Group B) once daily. Measurement of Lipid profile was done at baseline. The safety assessment was done by measuring adverse reactions [whether detected by the investigator or experienced by patient] at each scheduled visit. Lipid profile was measured at each visit of patient (4 weeks and 8 weeks). Proportion of the patients achieving Lipid goals as defined by NCEP ATP III guidelines was noted. Data was collected in paper case report form and was converted into excel spread sheet. Descriptive data were expressed as number, mean value ± SD and percentage. The categorized values were analyzed using paired and unpaired student t-test by Graph-pad prism software (version-6) and p value<0.05 was considered as statistically significant.

RESULTS

In this study, total 66 patients were enrolled after baseline screening. Among them, 34 patients were in Rosuvastatin group while 32 patients were in Atorvastatin treatment group. There were 19 males and 15 females in Rosuvastatin group as compared to 19 males and 13 females in Atorvastatin treatment group.

The baseline demographic characteristics of patients are shown below in Table 6.1 and Figure 6.1. The mean age was 59.12 ± 7.38 and 57.47 ± 7.84 and the mean BMI was 28.05 ± 3.03 and 28.95 ± 3.04 in Rosuvastatin and Atorvastatin treatment groups, respectively. It was observed that both the treatments groups were no statistically different significantly.

Risk factors responsible for Cardiovascular disease were recorded while screening of the patients and patients were classified according to different risk factors namely, Hypertension, Smoking, Previous History of CHD and Diabetes Mellitus as shown in Table 6.2 and Figure 6.2.

Only 1 risk factor of CVD was associated in 23 and 15 patients of Rosuvastatin and Atorvastatin treatment groups, respectively while 2-4 risk factors for CVD were associated in 11 and 17 patients of Rosuvastatin and Atorvastatin treatment groups, respectively as shown in Table 6.3. Hypertension and Diabetes mellitus were found to be more responsible risk factors of CVD. Maximum number of risk factors recorded was 3 in individual patient.

Efficacy Assessment:

Low Density Cholesterol was extremely statistically significantly (p value <0.0001) reduced to 107.35 ± 8.76 mg/dL and 82.17 ± 8.12 mg/dL at week 4 and week 8, respectively from 144.56 ± 9.07 mg/dL baseline in Rosuvastatin 10 mg OD treatment group whereas it was statistically significantly (p value <0.0001) reduced to 102.47 ± 8.47 and 88.94 ± 8.23 at week 4 and week 8 from 143.03 ± 7.87 baseline in Atorvastatin 20 mg OD treatment group as shown in Table 6.4 and Figure 6.4 (a) and (b).

Total Cholesterol was extremely statistically significantly (p value <0.0001) reduced to 193.94 ± 10.17 mg/dL and 168.97 ± 8.99 mg/dL at week 4 and week 8, respectively from 222.38 ± 10.42 mg/dL baseline in Rosuvastatin 10 mg OD treatment group whereas it was statistically significantly (p value <0.0001) reduced to 188.94 ± 11.62 and 177.78 ± 12.40 at week 4 and week 8 from 219.72 ± 12.15 baseline in Atorvastatin 20 mg OD treatment group as shown in Table 6.4 and Figure 6.4 (a) and (b).

HDL-C was extremely statistically significantly (p value <0.0001) increased to 41.56 ± 4.02 mg/dL and 46.56 ± 3.67 mg/dL at week 4 and week 8, respectively from 38.03 ± 4.09 mg/dL baseline in Rosuvastatin 10 mg OD treatment group whereas it was statistically significantly (p value <0.0001) increased to 40.81 ± 3.46 and 43.06 ± 3.35 at week 4 and week 8 from 37.94 ± 3.83 baseline in Atorvastatin 20 mg OD treatment group as shown in Table 6.4 and Figure 6.4 (a) and (b).

Triglyceride level was extremely statistically significantly (p value <0.0001) reduced to 170.23 ± 16.32 mg/dL and 149.91 ± 16.21 mg/dL at week 4 and week 8, respectively from 197.47 ± 17.44 mg/dL baseline in Rosuvastatin 10 mg OD treatment group whereas it was statistically significantly (p value <0.0001) reduced to 177.00 ± 15.52 and 162.41 ± 16.77 at week 4 and week 8 from 191.66 ± 14.92 baseline in Atorvastatin 20 mg OD treatment group as shown in Table 6.4 and Figure 6.4 (a) and (b).

Statistical analysis was performed to compare the results obtained between groups. All the parameters were extremely statistically significantly (p value<0.05) modified by Rosuvastatin 10 mg OD compared to Atorvastatin 20 mg OD.

As per NCEP ATP III Guidelines, desired lipid goals for high risk CVD patients are below shown in Table 6.6. All patients of Rosuvastatin treatment group reached these goals while in case of Atorvastatin treatment group, LDL-C and HDL-C goal were achieved in 87.50% and 84.37% patients, respectively. TC goal was achieved in all the patients of Atorvastatin treatment group.

Safety Assessment:

Both Rosuvastatin and Atorvastatin were well tolerated with only a few occurrences of mild adverse events. The common adverse events reported in both group were headache, nausea and myalgia as shown in Table 6.7.

DISCUSSION

This open labeled, prospective, non-randomized, parallel group, single centric 8 week study was carried out to assess the efficacy and safety of Rosuvastatin 10 mg OD and Atorvastatin 20 mg OD in achieving lipid goals in patients at high risk for CVD.

The results of present study demonstrated that both Rosuvastatin and Atorvastatin alter lipid profile significantly in patients who are at high risk for cardiovascular disease.

At first follow up visit i.e. 4 weeks from baseline, LDL-C and TC level was lowered more significantly with 20 mg OD dose of Atorvastatin while in case of remaining parameters (HDL and TGs), Rosuvastatin 10 mg OD was better.

However, at the end of study i.e. second follow up visit (8 weeks from baseline), all the lipid profile parameters- LDL-C, TC, HDL-C and TGs were statistically significantly modified in Rosuvastatin 10 mg OD treatment group when compared to Atorvastatin 20 mg OD treatment group.

Strandberg et al compared Rosuvastatin (10 mg) and Atorvastatin (10 mg) in patients at high risk for CVD and concluded that greater reduction in LDL-C levels were achieved with a starting dose of Rosuvastatin compared with Atorvastatin 10 mg and both the treatments were well tolerated. The same kind of pattern was observed in this study.

Aszatalos et al conducted the substudy with STELLAR study and compared the effects of daily doses of Rosuvastatin 40 mg with Atorvastatin 80 mg for 6-weeks on HDL subpopulations and concluded that both statins, given at their maximal doses, favourably alter the HDL subpopulation profile, but also that Rosuvastatin 10 mg OD is significantly more effective in this

regard than Atorvastatin 20 mg OD. In the same way, in our study also, HDL values were significantly modified with Rosuvastatin 10 mg OD than Atorvastatin 20 mg OD.

Risk factors responsible for cardiovascular disease were recorded at the time of baseline screening of the patients. Risk factors like Hypertension, Diabetes mellitus, Smoking and Previous history of coronary heart disease were found to be present in patients. Among those, Hypertension and Diabetes mellitus were more prominent with presence in more number of patients than other risk factors. Also, There were many patients who were having more than one risk factors present.

As per NCEP ATP III guidelines, lipid goals were determined for the patients who participated in this study. These lipid goals were achieved effectively with Rosuvastatin than Atorvastatin. All the patients of Rosuvastatin treatment group achieved all 3 lipid goals whereas only total cholesterol goal was achieved by all patients of Atorvastatin treatment group.

Looking at safety point of view, few occurrences of adverse effects were notified in both treatment groups. Though, Rosuvastatin was proved to be more safe as only one occurrence of adverse effect was seen among 34 patients.

The result of this study suggests that Rosuvastatin seems to be a better alternative than Atorvastatin to achieve lipid goals. However, this is a single centric study of short duration with a small study population so that more evidences are required to get satisfactory results.

CONCLUSION

Rosuvastatin 10 mg OD and Atorvastatin 20 mg OD were efficacious in lipid lowering activity. All patients who were treated with Rosuvastatin 10 mg OD achieved more lipid goals as defined by NCEP ATP III guidelines than Atorvastatin 20 mg OD. Though, Rosuvastatin even at starting dose i.e. 10 mg OD can alter lipid profile effectively compared to Atorvastatin 20 mg OD. Moreover, less occurrences of adverse effects were found with Rosuvastatin 10 mg OD than Atorvastatin 20 mg OD. Thus, Rosuvastatin seems to be better alternative than Atorvastatin in terms of efficacy and safety. However, more evidences are required to obtain satisfactory results as this was single centric study with small study population.

Table 1: Inclusion and exclusion criteria

INCLUSION CRITERIA	• Patients willing to provide informed consent
	• Patients with Hypercholesterolemia ➢ LDL-C level : 130-250 mg/dL ➢ TC level : 200-240 mg/dL
	• History of CHD or other established atherosclerotic disease
EXCLUSION CRITERIA	• Patients not willing/ unable to provide written informed consent form
	• Patients with ➢ known history of hypersensitivity to statins ➢ Uncontrolled diabetes mellitus (DM) or hypertension, unstable CVD (including unstable angina) ➢ Active hepatic disease or hepatic dysfunction ➢ Women who are pregnant or breastfeeding and those taking current treatment with medications -: lipid-modifying agents [eg. fibrates, niacin/nicotinic acid, bile acid sequestrants, other statins, probucol, fish-oils, lipid- modifying dietary supplements]
	• Patients taking medications which are known to interact with statins [eg. Cyclosporine, Warfarin, Digoxin, Iron Salts, Thyroid Hormones, Thiazide, Diuretics, Other statins]

Table No. 2: Demographic characteristics and baseline details of patients

CHARACTERISTIC	ROSUVASTATIN GROUP	ATORVASTATIN GROUP
No. of Patients	34	32
Mean Age in yrs (SD)	59.12(7.38)	57.47(7.84)
SEX		
Male (n)	19	19
Female (n)	15	13
Mean BMI in kg/m^2(SD)	28.5(3.03)	28.95(3.04)

Table No. 3 : Classification of patients according to risk factors

Risk factors for CVD	Rosuvastatin		Atorvastatin	
	No. of patients	% of patients	No. of patients	% of patients
Hypertension	16	35.56	19	38.78
Smoking	8	17.78	9	18.37
Previous History of CHD	6	13.33	7	14.29
Diabetes mellitus	15	33.33	14	28.57

Table No. 4 : Prevalence of risk factors in patients

	Rosuvastatin		Atorvastatin	
	No. of patients	% of patients	No. of patients	% of patients
Only 1 risk factor of CVD present	23	67.65 %	15	46.87 %
2-4 risk factors of CVD present	11	32.35 %	17	53.13 %

Table No. 5 : Change in lipid profile in Rosuvastatin and Atorvastatin Group at week 8

PARA-METER (mg/dL)	ROSUVASTATIN 10 mg OD GROUP			ATORVASTATIN 20 mg OD GROUP		
	Baseline	Week 4	Week 8	Baseline	Week 4	Week 8
LDL-C, Mean(SD)	144.56 (9.07)	107.35 (8.76)	82.17* (8.12)	143.03 (7.87)	102.47 (8.47)	88.94*# (8.23)
TC, Mean(SD)	222.38 (10.42)	193.94 (10.17)	168.97* (8.99)	219.72 (12.15)	188.94 (11.62)	177.78*# (12.40)
HDL, Mean(SD)	38.03 (4.09)	41.56 (4.02)	46.56* (3.67)	37.94 (3.83)	40.81 (3.46)	43.06*# (3.35)
TG, Mean(SD)	197.47 (17.44)	170.23 (16.32)	149.91* (16.21)	191.66 (14.92)	177.00 (15.52)	162.41*# (16.77)

**p* value <0.0001 when week 8 value compared with respective baseline by paired t-test.
#p value <0.05 when week 8 values of Rosuvastatin group compared with week 8 respective values of Atorvastatin group by unpaired t-test.

Table No. 6 : Percentage change in lipid profile in Rosuvastatin and Atorvastatin treatment group at week 8

PARAMETER	Percentage change in lipid profile			
	Rosuvastatin 10 mg OD		Atorvastatin 20 mg OD	
	Week 4	Week 8	Week 4	Week 8
LDL-C	25.74	43.15	28.35	37.81
TC	12.79	24.01	14	19.08
HDL-C	9.16	22.43	7.56	13.49
TG	13.79	24.08	7.64	15.26

Table No. 7 : Proportion of enrolled patients achieving lipid goal as per NCEP ATP III guideline

PARAMETER	GOAL (mg/dL)	No. of Patients achieving Goal (%)	
		ROSUVASTATIN (N=34)	ATORVASTATIN (N=32)
LDL-C	<100	34(100)	28(87.5)
HDL	>40	34(100)	27(84.37)
TC	<200	34(100)	32(100)

Table No. 8 : Occurrence of adverse effects

Adverse Effect	Rosuvastatin (N=34)	Atorvastatin (N=32)
Myalgia (Muscle pain)	0	3
Nausea	0	1
Headache	1	1

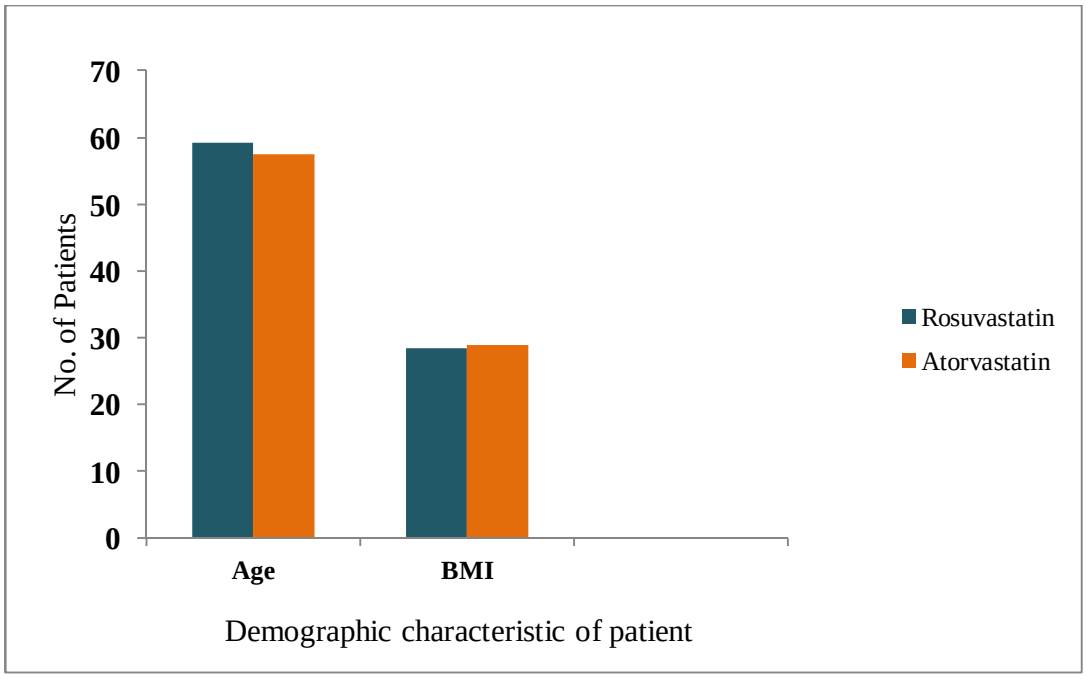


Fig. 1: Demographic characteristics and baseline details of patients

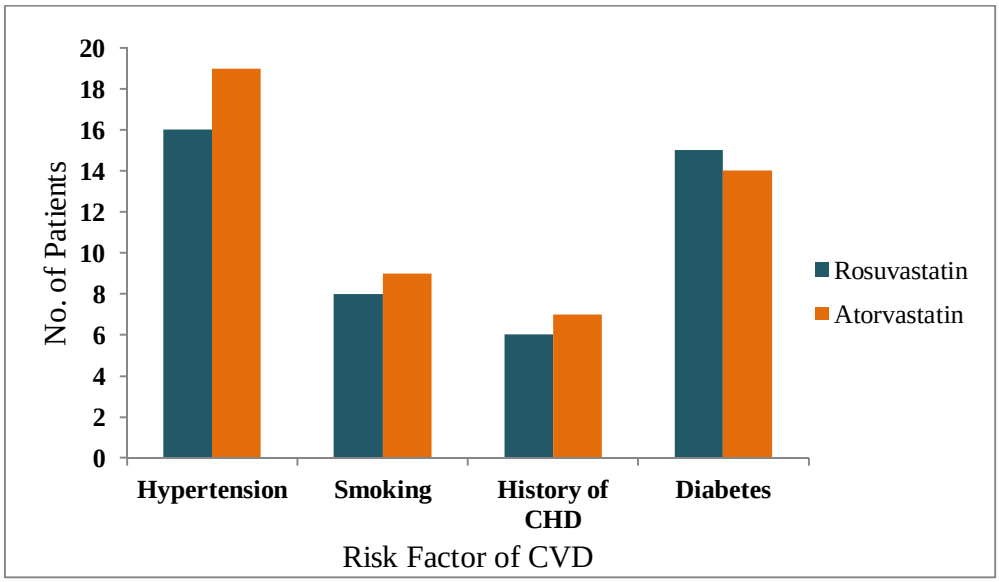
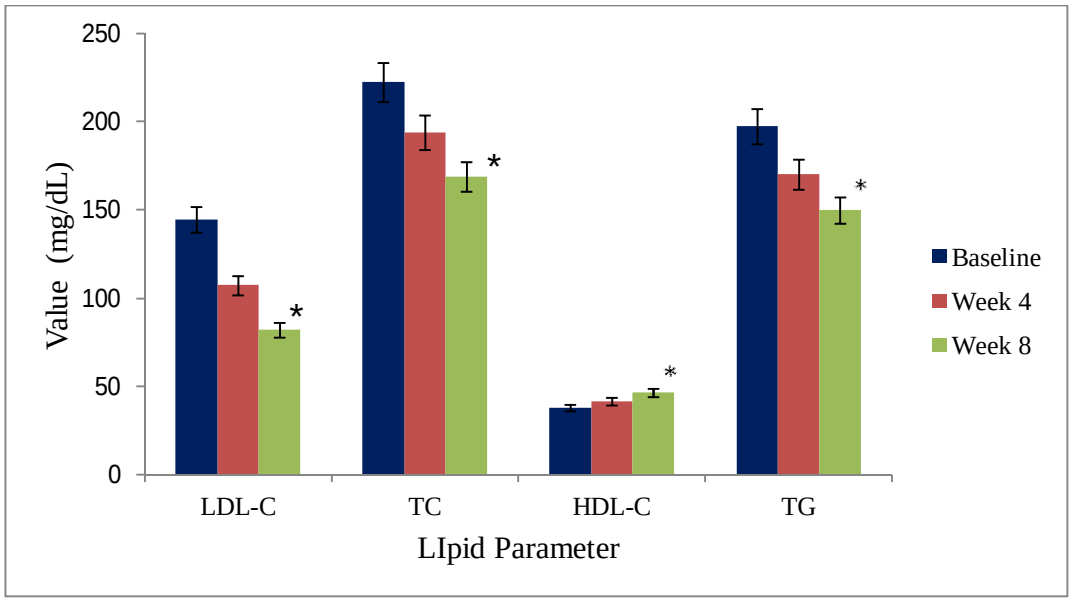
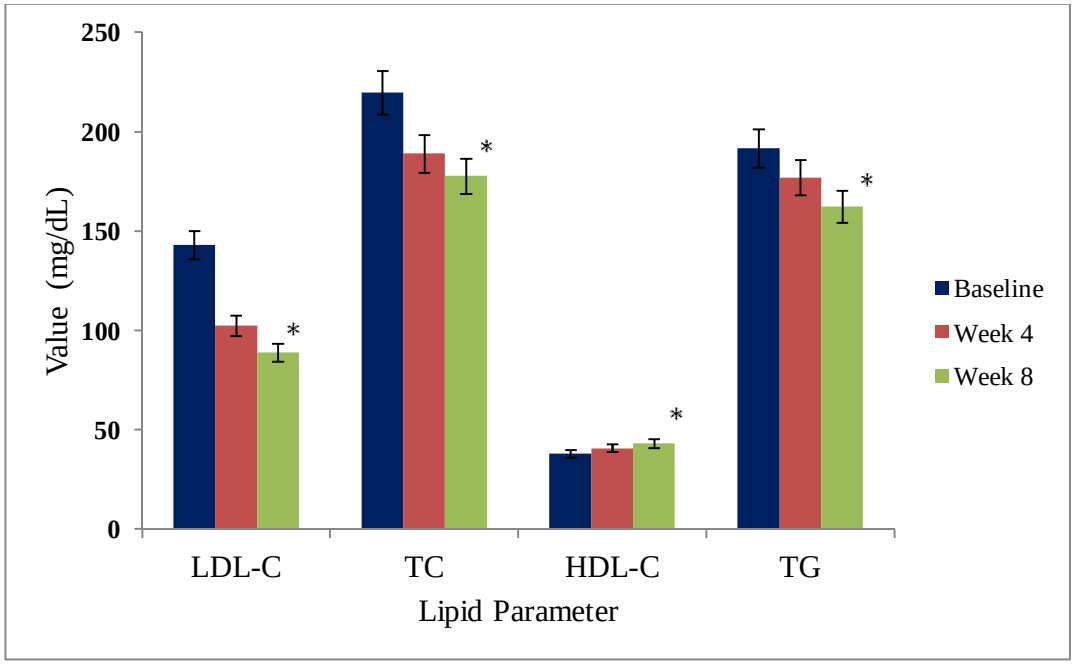


Fig. 2: Classification of patients according to risk factors



***p* value <0.0001 when week 8 value compared with respective baseline by paired t-test.**

Fig. 3 (a): Change in lipid profile in Rosuvastatin 10 mg OD treatment group at week 8



***p* value <0.0001 when week 8 value compared with respective baseline by paired t-test.**

Fig. 3 (b): Change in lipid profile in Atorvastatin 20 mg OD treatment group at week 8

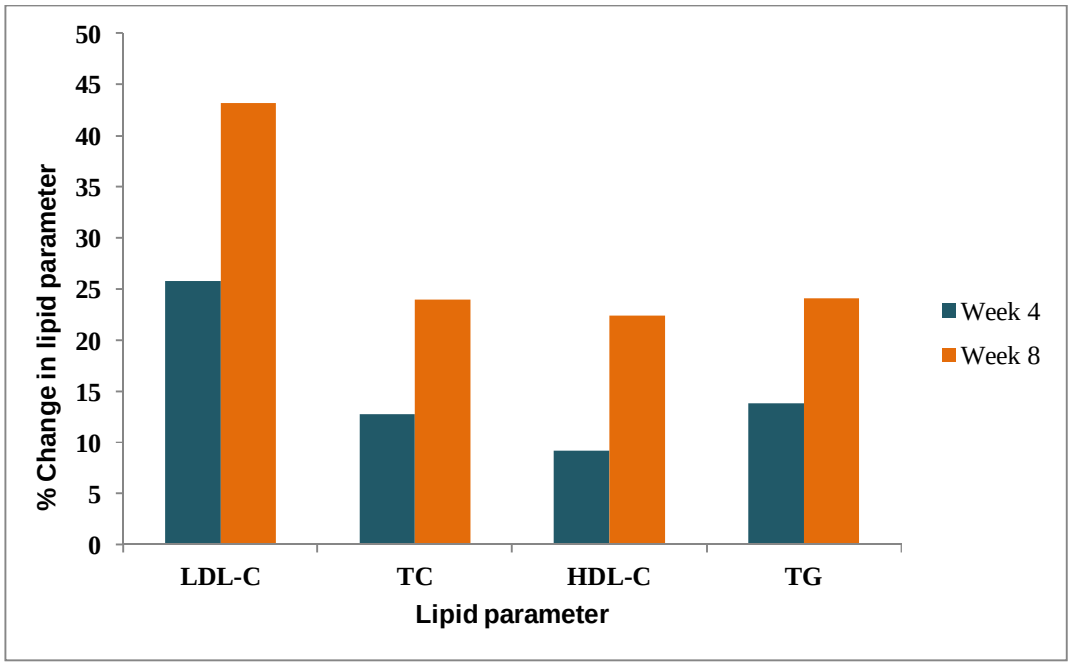


Fig. 4 (a): Percentage change in lipid profile in Rosuvastatin 10 mg OD treatment group at week 8

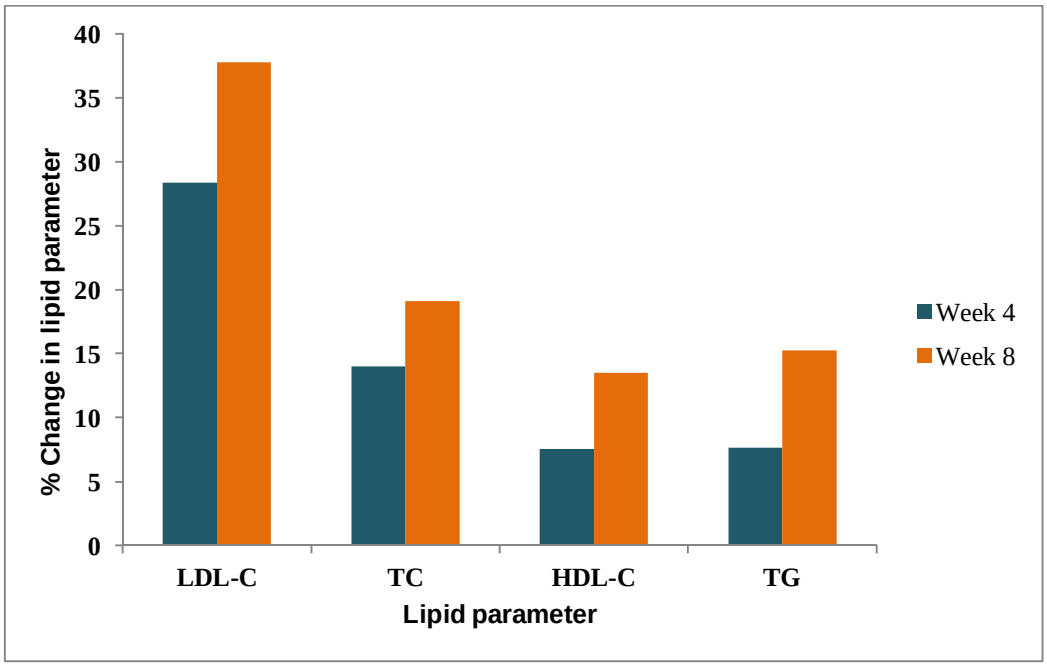


Fig. 4 (b): Percentage change in lipid profile in Atorvastatin 20 mg OD treatment group at week 8

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