Available online at http://jddtonline.info

RESEARCH ARTICLE

A COMPARATIVE STUDY OF ROSUVASTATIN AND FENOFIBRATE AS MONOTHERAPY IN DYSLIPIDEMIA AND NCEP ATP III GOALS

***Kumar Raj[1],** Rai Jaswant[2], Goel Ashok Kumar[3]

[1]Associate Professor, Deptt. of Pharmacology, GGS Medical College, (a constituent college of Baba Farid University of Health Sciences), Faridkot-India

[2]Professor And Head, Deptt. of Pharmacology, Govt. Medical College, Amritsar- India

[3]Associate Professor, Deptt. of Pharmacology, Govt. Medical College, Amritsar- India

**Corresponding Author's Email: anurajkumar76@gmail.com*

ABSTRACT:

Background: Dyslipidemia is the commonest cause of the cardiovascular diseases and increases mortality worldwide. It leads to disturbance in the range of Total Cholesterol, LDL-C, VLDL and HDL-C in the plasma of dyslipidemic patients. Most of the studies relating to the effectiveness of Rosuvastatin and Fenofibrate have been conducted in the western countries and scant attention has been paid to examine the effectiveness of these drugs on the people of South Asian countries. The present study is an effort to focus on the effectiveness of these drugs on the people of Majha region of Punjab, India.

Aim: To see the effects of both drugs as monotherapy on the various parameters of lipid profile and goals achieved according to NCEP-ATP III guidelines in North Indian population.

Material and Methods: This was a randomized, open label, parallel study conducted to assess the effect of rosuvastatin 10 mg and fenofibrate 160 mg daily for 12 weeks in newly diagnosed dyslipidemic patients (n=60). Patients were evaluated at day 0 and at 6 and 12 weeks.

*Results:*At 6 weeks there were falls for Total cholesterol by 20.41% vs. 15.64% ($p< 0.001$, both), triglycerides 16.21% vs. 19.85% ($p< 0.001$, both) and LDL-C 27.47% vs. 21.43% ($p< 0.001$, both) respectively with rosuvastatin and fenofibrate from baseline. And at 12 weeks plasma levels continued to fall for Total cholesterol by 35.79% vs. 25.60% ($p< 0.001$, both), triglycerides 29.30% vs. 39.92% ($p< 0.001$, both), LDL-C 47.82% vs. 34.67% ($p< 0.001$, both), and there was rise of HDL-C levels by 18.75% vs. 30.53% ($p< 0.001$, both) respectively with rosuvastatin and fenofibrate. Both the agents achieved desired goals of NCEP-ATP III for Total Cholesterol, Triglyceride, LDL, HDL and also treat the metabolic syndrome (by 39.22% and 42.66% respectively) patients.

*Conclusion:*Rosuvastatin and Fenofibratemonotherapy in patients with dyslipidemia effectively improved the Lipid profile as both these agents have had achieved the desired goal to treat the components of metabolic syndrome and other NCEP-ATP III targets.

Key words: Dyslipidemia, Metabolic syndrome, NCEP-ATP III goals, Fenofibrate and Rosuvastatin.

INTRODUCTION:

Dyslipidemia is the commonest cause of the blood vessel diseases and it leads to narrowing of lumen of arteries due to the sedimentation of lipid in their walls.[1,2] Dyslipidemia occurs due to disturbance in the range of Total Cholesterol, LDL-C, VLDL, TGs and HDL-C.[1] The incidence of this phenomenon is seen rising all over the world thereby increasing the morbidity and mortality due to cardiovascular diseases.[1,2] NCEP-ATP III expert panel has set a goal to treat the dyslipidemic patients to minimize the risk who develop serious cardiovascular complications.[3]These goals can be achieved by proper treatment with lipid lowering drugs and improving the life style of the patients (NCEP-ATP III, 2002).[3] A number of drugs e.g. statins, fenofibrate, niacin, ezetamibe, bile sequestrants etc. are used to treat this disorder.[2]

The statins and fenofibrate have been widely studied and found least toxic, according to the studies conducted in the western countries.[1,2] Few studies have been made in India and this study has been made keeping in view the people of North India especially the Punjabis of Majha-region because their socio-economic background and standard of living is quite different from the people of Western countries.[4]

The present study is meant to see the effects of the Rosuvastatin (newer statins) and Fenofibrate (as Superbioavailable tablet formulation) as monotherapy on the various parameters of lipid profile and goals achieved according to NCEP-ATP III guidelines.

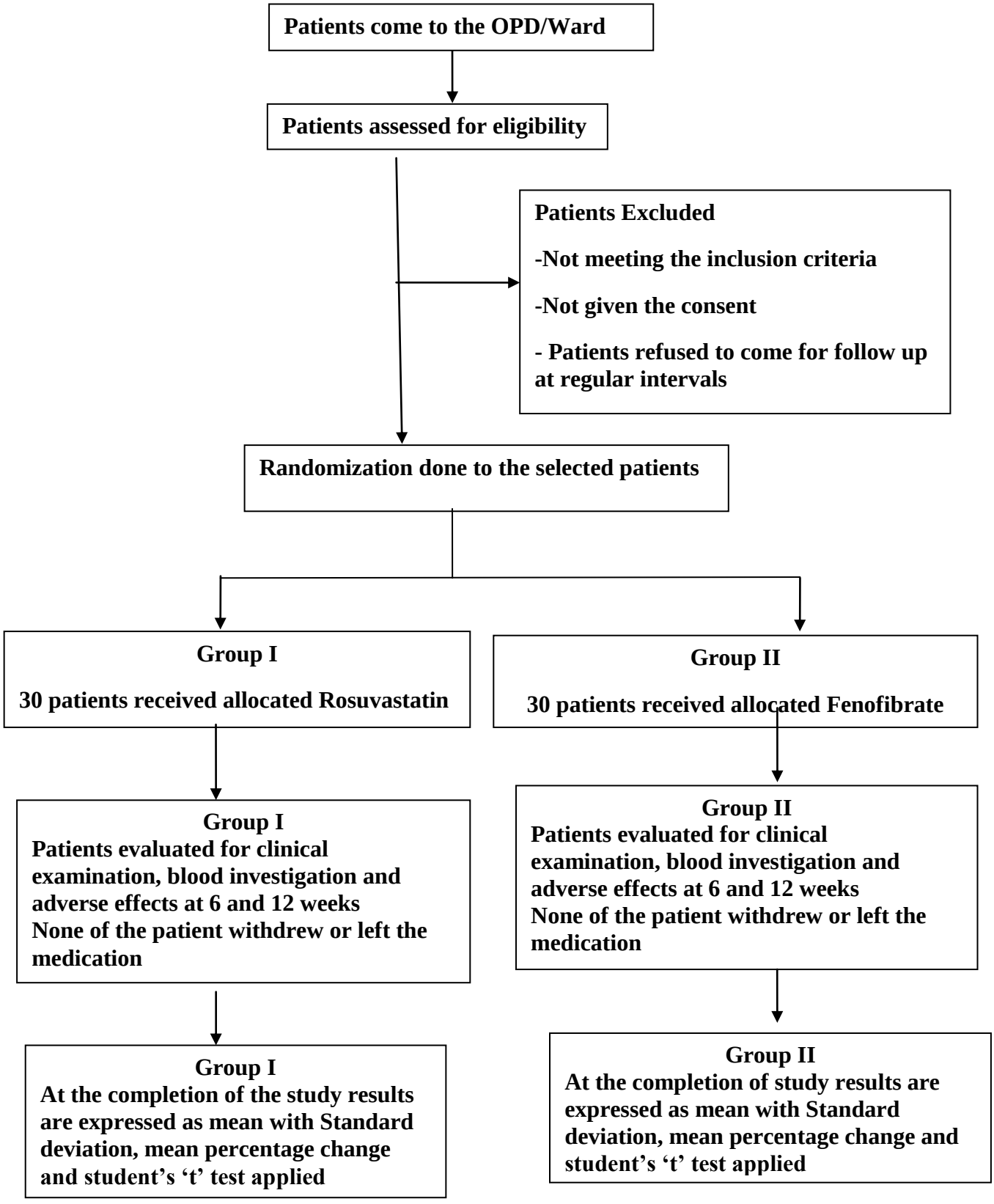
METHODOLOGY:

This is a randomized, open-label, parallel study, conducted to assess the effects of Rosuvastatin (10 mg) and Fenofibrate (160 mg) as monotherapy daily for 12 weeks, 60 patients (30 in each group) of newly diagnosed dyslipidemic patients, aged 30-70 years, were selected visiting the OPD/ Wards of Department of Medicine, Govt. Medical College, Amritsar. This study has already been approved by the Institutional Ethical Committee. Patient's written consent was taken before the commencement of the study. Both the study drugs have been allocated among the patients randomly. The randomization has been achieved by using a Random Number Table.[5]Patients were evaluated at day 0, then at 6 and 12 weeks for clinical examination, lipid profile and other parameters (Flowchart- I).

Patients having hepatic, renal and thyroid disorder, Triglyceride > 600 mg/dl, already taking medication (like

hypolipidemics, oral contraceptive pills, corticosteroids), pregnant and lactating ladies and patients who were sensitive to the study drugs were excluded from the study.

Flowchart -I



Statistical Analyses: The data were expressed as mean ± standard deviation (SD) and mean percentage change. Treatment effects were tested with a paired student's 't' test for data.

 ISSN: 2250-1177 CODEN (USA): JDDTAO

RESULTS:

Baseline characteristics (Table I) and baseline levels of different parameters (Table II) of the group I and group II were compared at the start of therapy. The difference in both the groups was statistically insignificant (p>0.05) at baseline (0 day). Monotherapy of Rosuvastatin and Fenofibrate in group I and group II showed significant changes of Total Cholesterol, triglycerides, LDL-C and HDL-C at 6 weeks and 12 weeks (Table III).

In the category of Group I, CAD or CHD equivalent patients[3] had shown more fall in the levels of LDL-C, and TC:HDL ratio as compared to total mean percentage fall in the group at 12 weeks, while less fall was noted in levels of LDL:HDL ratio (Table III and Table IV). While in group II, CAD or CHD equivalent patients had resulted in more fall in the levels of TGs and TC:HDL ratio as compared to total mean percentage fall, while slightly less fall was noted in the levels of LDL-C and LDL:HDL ratio (Table III and Table IV) as compared to total mean percentage in the group.

Table I: Baseline Characteristics

Variables	Group I	Group II
Mean Age (years)	57.13	51.9
Gender Male Female	 10 20	 17 13
Waist circumference (cm) Male Female	 102.8 93.8	 98.82 102.38
Diabetic	2	6
Hypertensive	21	21
CAD	11	11
Post menopausal	17	5
Alcoholic	6	8

Table II: Baseline Parameters values

Parameters	Group I	Group II	p-value
T. Cholesterol (mg/dl)	241.62 ± 30.67	231.6 ± 41.09	p>0.05
TGs (mg/dl)	239.90 ± 70.48	259.67 ± 28.62	p>0.05
LDL-C (mg/dl)	154.61 ± 22.65	143.67 ± 27.93	p>0.05
HDL-C (mg/dl)	36.80 ± 2.70	36.13 ± 1.48	p>0.05
*value in mean ±S.D			

Table III: Mean percentage change in the parameters at 6 weeks and 12 weeks

	Group I		Group II	
Parameters	6 weeks	12 weeks	6 weeks	12 weeks
T. Cholesterol	-20.41% (p<0.001)	-35.79% (p<0.001)	-15.64% (p<0.001)	-25.60% (p<0.001)
TGs	-16.21% (p<0.001)	-29.30% (p<0.001)	-19.85% (p<0.001)	-39.92% (p<0.001)
LDL-C	-27.47% (p<0.001)	- 47.82% (p<0.001)	-21.43% (p<0.001)	-34.67% (p<0.001)
HDL-C	+7.69% (p<0.001)	+18.75 (p<0.001)	+13.10% (p<0.001)	+30.53% (p<0.001)
TC:HDL ratio	-23.20% (p<0.001)	- 43.61% (p<0.001)	-25.42% (p<0.001)	-35.41% (p<0.001)
LDL:HDL ratio	-32.93% (p<0.001)	-91.94% (p<0.001)	-30.47% (p<0.001)	-49.87% (p<0.001)

 ISSN: 2250-1177 CODEN (USA): JDDTAO

Table IV: Mean percentage change in the parameters in CAD patients		
Parameters	**Group I**	**Group II**
T. Cholesterol	-38.10% (p<0.001)	-24.84% (p<0.001)
TGs	-30.47% (p<0.001)	-43.91% (p<0.001)
LDL-C	-52.11% (0.001)	-32.37% (p<0.001)
HDL-C	+21.32% (p<0.001)	+29.83% (p<0.001)
TC:HDL ratio	-49.03% (p<0.001)	-41.89% (p<0.001)
LDL:HDL ratio	-60.64% (p<0.001)	-47.82% (p<0.001)

According to NCEP- ATP III criteria (NCEP- ATP III, 2002), Group I and Group II achieved desired purpose for Total cholesterol (by 100% vs 93.33%), LDL-C (by 90% vs. 76.67%), TGs (by 26.67% vs 53.33%) and HDL-C (by 40% vs. 60%) (Table V).

Among metabolic syndrome patients, both the groups achieved the set target for the components of metabolic syndrome (39.22% vs 41.66%), Triglycerides (52.94% vs. 57.14%), HDL-C (29.41% vs. 71.14%). The waist circumference also reduced by 12.50% in group II but not in group I (Table V).

DISCUSSION

Group I

Rosuvastatin 10 mg per day in group I resulted in statistically significant fall in levels of serum TC, TGs, and LDL-C at 12 weeks (Table III). TC and LDL-C fall is slightly less as reported by CORALL study (33.2% and 45.9%, and 37.1% and 50.6% at both 6 weeks and 12 weeks) [6] while TGs level falls at 6 weeks (Table III) is slightly less, but at 12 weeks is more as revealed by CORALL study (18.8% and 23.7% respectively).[6]

HDL-C level rises by 7.69% and 18.75% at 6 weeks and 12 weeks [Table III] which are less as stated by Jayaram et al (+13.8 % at 6 weeks),[7] but more as reported by Shepherd et al (+8 % at 12 weeks).[8]

Table V: Goals achieved according to NCEP-ATP III criteria		
Parameters	Group I	Group II
T. Cholesterol	100%	93.33%
TGs	26.67%	53.33%
LDL-C	90%	76.67%
HDL-C	40%	60%
Metabolic syndrome	39.22%	41.66%
TGs*	52.94%	57.14%
HDL-C*	29.41%	71.14%
WC*	Insignificant	12.50%
**Target levels achieved in Metabolic syndrome patients according to NCEP-ATP III Criteria [TGs (< 150 mg/dl), HDL (M>40 mg/dl & F >50 mg/dl), *WC (Waist Circumference) (M<102 cm & F <88 cm)]*		

Lipid ratios like TC:HDL and LDL:HDL [Table III] fall is more as published by Jayaram S et al, (39.8% and 47.42% at 6 weeks)[7] and CORALL study (37.2% and 50.3% at 12 weeks).[6]

In CAD or CHD equivalent patients (NCEP-ATP III, 2002) Rosuvastatin results in significant fall in the levels of LDL-C, and TC:HDL ratio as compared to total mean percentage fall, while less fall is noted in levels of and LDL:HDL ratio [Table IV].

Rosuvastatin effectively achieves NCEP-ATP III goals for TC, TGs, LDL-C, HDL-C and also treats the components of metabolic syndrome [Table V].

The LDL-C goal (Table V) achieved is slightly more as stated by PULSAR study (68.8%)[9] and Park JS et al (87.64%).[10] While the Triglycerides goal (Table V) achieved is markedly less as recorded by PULSAR study (62.1%).[9]

Group II

Fenofibrate 160 mg per day resulted in statistically significant fall in levels of serum TC, TGs and LDL-C at both 6 and 12 weeks (Table III). The fall continued to show in the levels of TC and LDL-C as compared to TGs as accounted by McKenney et al, (11.2%, 9.1% and 28.1% respectively),[11] whereas at 12 weeks these levels falls (Table III) are more as reported byBairaktari ET et al, (16%, 26% and 18% respectively).[12]

TC and LDL-C fall levels at 6 weeks and 12 weeks is more as reported by McKenney et al (11.2% and 9.1% at 6 weeks)[11] and Jones PH et al (12.6% and 5.3% at 12 weeks).[13]

TGs level falls is markedly less at 6 weeks as reported by McKenney et al, 2005 (28.1%) while more fall at 12 weeks as reported by Jones PH et al, 2010 (31.9%).[13]

HDL-C level raised by Fenofibrate (Table III) are more as declared by McKenney et al (+11.8% at 6 weeks),[11] and Steinmetz A et al, 1996 (+41.4% at 12 weeks).[14]

Lipid ratio of TC:HDL (Table III) is slightly less fall while fall in LDL:HDL ratio (Table III) is more as stated by Steinmetz A et al, (34.94% and 31.31% respectively) at 12 weeks.[14]

In CAD or CHD equivalent patients Fenofibrate results in more fall in the level of TC: HDL ratio [Table III] as compared to total mean percentage fall, while less fall is noted in the levels of LDL-C and LDL:HDL ratio [Table III].

Fenofibrate also successfully achieves NCEP-ATP III goals for TC, TGs, LDL-C, HDL-C and also treats the components of metabolic syndrome [Table IV]. Till date no study has so far been done to see the effects of lipid lowering agents on the goals achieved according to NCEP-ATP III criterion that is a must for the patients who have CAD or CHD equivalent patients for better therapy to prevent the serious complications of cardiovascular diseases (CVDs).

Comparison of effectiveness of Rosuvastatin and Fenofibrate

On comparing Rosuvastatin and Fenofibrate, it was found that Rosuvastatin is more effective in lowering TC, LDL-C and Lipid ratios (Table III). Rosuvastatin also results in more goals achievements for these parameters according to NCEP-ATP III criteria [Table V]. Thus Rosuvastatin is effective in a patient who has dyslipidemia with higher TC and LDL-C levels.While Fenofibrate resulted in significant decrease in TGs and raised HDL-C level as compared to Rosuvastatin [Table IV]. It also resulted in more goals achievements of NCEP-ATP III for TGs, HDL-C and Metabolic syndrome [Table V].

It has been seen that both the drugs significantly achieved the set goals as per NCEP-ATP III for dyslipidemic patients. But their effects are variable on the different parameters of lipid profile. In Indian patients, there is higher incidence of hypertriglyceridaemia and lower levels of HDL-C,[4] thus Fenofibrate is the drug of choice in these dyslipidemic patients.

Clinical assessment and blood tests of the study's patients had not shown any serious adverse effects during the trial, indicated that these drugs were well tolerated by those patients and none of the patients were withdrawn during it. Mild side- effects were seen like myalgia (10% vs 5%) and headache (6.66% vs 3.33%) in Rosuvastatin and Fenofibrate respectively. Fenofibrate also led to nausea (6.66%) and constipation (3.33%).

It has been observed that most of the people had concomitant other diseases like hypertension, coronary disease and diabetes mellitus and thus it becomesnecessary to treat these diseases along with dyslipidemia simultaneously otherwise high risk of developing cardiovascular complications is always there. Therefore, it is mandatory to treat the dyslipidemia at priority basis with the lipid lowering agents (statins or Fenofibrate).

There is also a need to confirm the result on the basis of larger trial so that we could better treat the dyslipidemic patients according to India's socio-cultural scenario.

In conclusion, monotherapy of Rosuvastatin and Fenofibrate in patients with dyslipidemia effectively improves the Lipid profile levels as both these agents had achieved the desired goal to treat the components of metabolic syndrome and other NCEP –ATP III targets as well.

ACKNOWLEDGMENTS:

Expert statistical support was provided by Dr. Gansham Mishra, Ph.D, Lecturer in statistics, Deptt. of SPM, GGS Medical College, Faridkot.

Declaration:

Funding: None

Competing interests: None

REFERENCES

1. Brunzell JD, Failor RA. Diagnosis and Treatment of dyslipidemia. In: Dale DC, Federman DD. ACP MEDICINE. 3rded. New York: WebMD Inc; 2007. P. 729-747.
2. Talbert RL. Dyslipidemia. In: Diprio JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM ed. Pharmacotherapy- A Pathophysiological Approach. 8thed. New York: McGraw-Hill; 2008. P. 365-388.
3. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panal III). Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on detection, Evalution, and Treatment of High Blood Cholesterol in adults (Adult Treatment Panal III) final report. Circulation, 2002,106, 3143-3421.
4. Bhopal Raj, Unwin N, White M, et al. Heterogeneity of coronary heart disease risk factors in Indian, Pakistani, Bangladeshi, and European origin populations: cross sectional study. Biomed Journal, 1999, 319, 215-220.
5. Rao C R, Mitra S K, Matthai A. Formulae and Tables for statistical work. Calcutta, India: Statistical Publishing Society; 1966. P. 193
6. Wolffenbuttel BHR, Franken AAM, Vincent HH. Cholesterol-lowering effects of rosuvastatin compared with atorvastatin in patients with type 2 diabetes- CORALL study. Journal of Internal Medicine, 2005, 257, 531-539.
7. Jayaram S, Jain MM, Naikawdi AA, Gawde A, Desai A. Comparative Evaluation of the Efficacy, Safety and Tolerability of Rosuvastatin 10 mg with Atorvastatin 10 mg in Adult patients with hypercholesterolaemia: The First Indian Study. Journal of The American Medical Association, 2004,102, 48-52
8. Shepherd J, Packard C, Littlejohn Ill TW, Walker J, Stein EA. Lipid-modifying effects of rosuvastatin in postmenopausal women with hypercholesterolemia who are receiving hormone replacement therapy. Current Medical Research Opinion, 2004, 20 (10), 1571-1578.
9. Clearfield MB, Amerena J, Bassand JP, Garcia HRH, Miller SS, Sosef FFM, et al. Comparsion of the efficacy and safety of rosuvastatin 10 mg and atorvastatin 20 mg in high-risk patients with hypercholesterolemia- Prospective study to evaluate the Use of Low doses of the statins Atorvastatin and Rosuvastatin (PULSAR). BioMedCentral [serial on the internet], Dec. 2006 [Trials 2006 Dec 21], 7:35. Available from http;//trialsjournal.com/content/7/1/35.
10. Park JS, Kim YJ, Choi JY, Kim YN, Hong TJ, Kim DS, Kim KY, et al. Comparative Study of Low Dose of Rosuvasatin and Atorvastatin on Lipid and Glycemic Control in Patients with Metabolic syndrome and Hypercholestrolemia. The Korean Journal of Internal Medicine, March 2010, 25 (1), 27-35
11. McKenney J, Jones M, Abby S. Safety and efficacy of colesevelam hydrochloride in combination with fenofibrate for the treatment of mixed hyperlipidemia. Current Medical Research Opinion, 2005, 21 (9), 1403-1412.
12. Bairaktari ET, Tzallas CS, Tsimihodimos VK et al. comparison of the efficacy and safety of atorvastatin and micronized fenofibrate in the treatment of mixed hyperlipiodemia. Journal of Cardiovascular Risk, 1996, 6, 113-116.
13. Jones PH, Cusi Kenneth, Davidson MH, Kelly MT, Setz CM, Thakker K, et al. Efficacy and Safety of Fenofibric Acid Co-Administered with Low- or Moderate-Dose Statin in Patients with Mixed Dyslipidemia and Type 2 Diabetes Mellitus. American Journal of Cardiovascular Drugs, 2010, 10 (2), 73-84.
14. Steinmetz A, Schwartz T, Hehnke U, Kaffarnik H. Multicenter Comparison of Micronized Fenofibrate and Simvastatin in Patients with Primary Type IIA or IIB Hyperlipoproteinemia. Journal of Cardiovascular Pharmacology, April 1996, 27 (4), 563-570.

 ISSN: 2250-1177 CODEN (USA): JDDTAO