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Original Research Article

Is fixed dose combination of rosuvastatin with fenofibrate more effective than high dose Rosuvastatin inpatients with stable coronary artery disease with mixed dyslipidemia? A study

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ABSTRACT

Background: We aimed to compare lipid lowering efficacy and safety of fixed dose combination (FDC) of rosuvastatin and fenofibrate with high dose rosuvastatin (HDR) in patients of stable coronary artery disease (CAD) with mixed dyslipidemia.

Materials and Methods: 165 patients with stable CAD with mixed dyslipidaemia were randomly assigned to HDR group, 40mg per day (n=79) and FDC group; fenofibrate with rosuvastatin, 145 mg and 20 mg per day respectively (n=88). The lipid profile was measured at baseline and at 12 weeks. The safety profile was measured by recording self-reported adverse reactions during follow up visits and by measuring serum levels of transaminases, creatinine phosphokinase (CPK) at 4 weeks. The lipid lowering efficacy was compared by estimating differences in percentage mean change from baseline values of the lipid fractions and percentage of patients achieving target goals between study groups using unpaired t test and X^2test respectively.

Result: The FDC achieved greater reduction compared to HDR in LDL-C, -11.0% 95% C.I. (-17.7% to -4.3%) p<0.001, NHDL-C levels, -10.1% (-16.0% to -4.2%) p<0.001, triglyceride, -18.4% (-32.0% to -4.7%) p<0.0001. The increase in HDL-C was significantly higher in FDC arm, 14.9% (8.3% to 21.4%) p<0.001. The percentage of patients achieving LDL-C and Non HDL-C target goals were higher in FDC arm but difference was statistically not significant. The FDC was tolerated well than HDR regimen.

Conclusion: The combination of moderate dose rosuvastatin and fenofibrate is more effective in reducing atherogenic lipid fractions and increasing the HDL-C level compared to high dose rosuvastatin and had better safety profile.

1. Introduction

Cardio vascular diseases (CVD) are the leading cause of disease burden globally.[1,2] It is a multi factorial in etiology and dyslipidemia is a major risk factor for coronary artery disease (CAD).[3]The low density lipoprotein cholesterol (LDL-C) and non-high density lipoprotein cholesterol (non HDL-C) are atherogenic lipid particles while high density lipoprotein cholesterol (HDL-C) is inversely associated with risk of CVD.[4–6] Elevated levels of atherogenic lipids are the result of combinations of faulty diet, physical inactivity and genetic predispositions. The Statins are potent and safer lipid lowering drugs primarily effective in lowering levels of LDL-C. The incremental reduction in LDL-C

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by doubling the dose of Statins is just about 6% and risk of incident adverse effects increases with increasing dose of Statins.[7] The fenofibrate is more potent than statins in lowering levels of triglycerides and elevating HDL-C.[8–10] The LDL-C is reduced by about 5-20%.[11] Mixed dyslipidemia characterized by elevated LDL-C and triglyceride is the most commonly observed dyslipidemia in patients of CAD. The guidelines recommend high dose statins for primary and secondary prevention in high-risk patients.[12–14] Fenofibrate are recommended if Non-HDL-C goals are not achieved after maximum recommended dose of statins. Post hoc analysis of clinical trials with fenofibrate have revealed significant reduction in CV events in patients with elevated triglycerides at baseline.[13,15]The statin and fenofibrate acts at different targets in lowering lipids thus we hypothesize that combination regimen would be more effective in achieving the lipid target goals than high dose statin in patients with mixed dyslipidemia. There are limited trials comparing safety and efficacy of combination of statins with fenofibrate with high dose statins in patients with mixed dyslipidemia.[16,17] Thus we aimed to compare the lipid lowering efficacy and safety of combination of moderate dose rosuvastatin and fenofibrate with high dose rosuvastatin in patients of stable CAD with mixed dyslipidemia.

2. Materials and Methods

2.1. Set up, study design, patient population and sample size

The patients with established stable CAD with mixed dyslipidemia visiting outdoor services of Cardiology department of tertiary care hospital of Indira Gandhi Medical College (IGMC) Hospital Shimla in HP, India were the target patient population enrolled. The study was prospective randomized open label blinded endpoint parallel arm trial. The sample size was calculated based on assumptions and 179 patients were included in the study (Figure 1).

2.2. Definitions

The stable CAD:[18] was labeled if patients of CAD had any one of the following

1. History of documented myocardial infarction,
2. History of percutaneous coronary intervention (PCI) of more than 3 months duration
3. Coronary artery bypass grafting (CABG) of more than 3 months duration.
4. Angiographic evidence of obstructive CAD.

2.2.1. Mixed dyslipidemia

Patients were labeled to have mixed dyslipidemia if had LDL-C of more than 100 mg/dl, and Triglyceride of >150 mg/dl estimated after more than 10 hours of fasting off lipid lowering drugs for one week.

2.2.2. Inclusion criteria

1. Patients with stable CAD.
2. Patients with Mixed dyslipidemia.
3. Age 30 to 70 years.

2.2.3. Exclusion criteria

The patients were excluded from enrollment if had any one of the following;

1. Scheduled for CABG or PCI,
2. History of PCI/CABG within preceding 3 months,
3. History of hypersensitivity/intolerance for rosuvastatin or to fenofibrate,
4. History of diagnosed hereditary or acquired myopathy
5. Impaired renal function (eGFR<45 ml/minute/1.73m^2,
6. Active liver disease
7. Uncontrolled diabetes mellitus (hemoglobin A1c ≥ 8.5%), or untreated
8. Hypothyroidism or hyperthyroidism
9. Patient judged to be poor compliant for follow up evaluation.
10. The patients not willing to participate.

2.3. Ethical approval & patient enrollment

2.3.1. Ethical approval

The study protocol was approved by IGMC Shimla ethical committee. The trial was registered in ICMR clinical trial registry No.CTRI/2017/01/007633.

2.3.2. Patient enrollment

All consecutive patients of Stable CAD with mixed dyslipidemia were the target population screened for enrollment. Eligible patients consenting to participate after informed consent were enrolled in the study.

2.4. Baseline data collection

The self-reported data of demographics, health behavior, cardio metabolic risk factors, relevant medical history was recorded as per structured data recording format. Following questionnaire-based data recording patients were examined to record anthropometrics, to measure BMI and waist circumference and BP using validated tools and following standard guidelines. Three reading of BP were recorded using mercury sphygmomanometer after 5 minutes of rest at about one-minute intervals and average was used for analysis. The 5 ml of plasma venous blood was drawn after overnight fasting state to measure total cholesterol, Triglyceride, HDL-C in auto analyzer Model Arba Transasia using standard kits, LDL-C was derived using Friedwald formula. Serum SGOT, SGPT, CPK,

creatinine, HbA1c was also measured to assess the safety of the study drugs using standard kits.

2.4.1. Randomization procedure and intervention

The eligible patients volunteering to participate were assigned, to Fixed Dose Combination (FDC) or to high dose statin arms randomly using computer generated random numbers after baseline data collection. The odd numbers were assigned FDC arm and even number were assigned High Dose Rosuvastatin (HDR) arm. In the FDC arm patients were prescribed 20 mg of rosuvastatin and 145 mg of fenofibrate once a day and in high dose statin group was given 40 mg of rosuvastatin once a day. All patients were advised to follow regular exercise and for intake of vegetables and fruits and avoid fast foods and fried foods throughout the study. The addition of other lipid lowering medications was prohibited during the study period. The rest of the treatment was as per discretion of the treating physician.

2.5. Outcomes

1. Primary outcome
   (a) Difference in mean percentage change in baseline levels of LDL-C, Non-HDL-C, Triglycerides and HDL-C between FDC and HDR arm at 12 weeks.
2. Secondary outcomes
   (a) Significance of difference between FDC and HDR arms in;
      i. Percentage of patients achieving LDL-C and Non-HDL-C target goals.
      ii. SBP, DBP, uric acid levels, fasting glucose and HbA1c levels
3. Safety outcomes
   (a) Significance of difference between FDC and HDR arm in
      i. Frequency of adverse symptoms
      ii. Mean levels of serum hepatic transaminases, CPK levels

2.6. Follow up visits for monitoring adverse reactions

Patients were advised to report any time if they experience any adverse symptoms. However regular follow up was scheduled at one month and at 3 months. Patients were withdrawn from the study if they experienced any serious adverse events during the follow-up period, including two fold increase from upper level of reference values in the levels of alanine transaminase and (ALT) and aspartate transaminase (AST) and or increase in creatine phosphokinase (CPK) levels to ≥3 times the upper limit of normal range, associated with muscular symptoms; unexplained CPK elevation 5 or more times the upper limit of normal without muscle symptoms at one month and or fixed drug eruption; or occurrence of serious drug reactions of any kind during follow up visit.

2.7. Outcomes evaluation

The self-reported adverse symptoms and or reactions were recorded unblended. However, the lab personnel measuring lipids and other safety biomarkers were blinded of treatment assignment. To evaluate the efficacy and safety of combination regimen with high dose Rosuvastatin arm the repeat lipids, SGOT, SGPT, CPK, blood glucose and HbA1c levels were measured at the end of 3 months after about 10 hours of fasting state using same auto analyzer and standard kits and following the standard protocol.

2.8. Statistical analyses

The study sample was described as categorical variables were reported as counts and percentages for categorical variables and mean± standard deviation (SD) for normally distributed continuous variables and median and interquartile range at $1^{st}$and 3^{rd} quartile for none normally distributed continuous variables. The distribution of demographics, health behavior, cardio metabolic risk factors and medication history were compared between study arms with chi square test for categorical variables and unpaired t test for continuous variables with normal distribution and Mann Whitney test for not normally distributed variables. The lipid lowering efficacy of HDR and FDC was evaluated by comparing significance of differences in the percentage mean change from baseline levels of LDL-C, HDL-C, Non-HDL-C and triglyceride, using unpaired t test for normally distributed and Mann Whitney test for non-normal distributed continuous variables. The significance of differences in proportion of study population in each treatment arms achieving target goals of LDL-C (<70 mg/dl), Non-HDL-C and HDL-C (<100 mg/dl) were tested using X2 test. As per protocol analysis was done to compare efficacy and safety of the study drugs. Two tailed significances at <0.05 were taken as statistically significant. The data was analyzed using statistical software STATA version 13.

3. Results

3.1. Study population enrollment

Details of patient screening and enrollment are described in patient selection flow chart Figure 1. Out of 291 patients; only 179 patients fulfilled the eligibility criteria, 88 patients were randomly assigned to HDR arm (40mg per day) and 89 patients to FDC arm (fenofibrate 145mg per day with rosuvastatin 20 mg per day). Five patients were withdrawn from study due to adverse drug reactions in HDR arm. Seven patients were lost to follow up four in high dose group and

three in combination group, thus follow up was complete in 95.1% in HDR arm and 96.6% in FDC arm. The follow up period of 3 months was completed by 79 patients in HDR arm and 86 patients in FDC arm and their data was used for analysis.

3.2. Characteristics of the study sample

The detailed description of socio demographics, medical history, health behavior, distribution of CV risk factors are reported in Tables 1 and 2. In brief both the study groups were matched for; demographics, health behavior and CV risk factor distribution and medications. The study sample in both arms was middle age predominantly male population. The majority of the patients had past history of Myocardial infarction in both arms.

3.3. Primary outcome

FDC regimen was significantly more effective in lowering lipid fraction compared to High Dose Rosuvastatin (HDR). Percentage reduction of mean baseline levels of lipid fractions was significant higher for LDL-C, non-HDL-C and TG levels and percentage increase in HDL-C from baseline level of HDL-C was significantly higher for in FDC arm compared to HDR arm. (Figure 2)

Although proportion of patients achieving target goals of LDL-C and non-HDL-C goals were higher in combination arm but was statistically not significant. (Figure 3)

3.4. Effect on cardiometabolic risk factors

The BP, BMI and uric acid decreased significantly in combination arm compared to high dose statin arm. There was no significant difference in HbA1C and fasting blood glucose levels (Table 3).

3.5. Safety outcomes

Adverse effects (AE) were experienced by 44.3% and 27.9% of patients in HDR and FDC arms respectively Figure III. The incidence of myalgia was observed in 34.2% (n-27) patients in the HDR Vs. 23.3% (n-20) patients in FDC arm (p=0.16). No cases of rhabdomyolysis were reported. Anorexia was the significantly higher AEs, in the HDR 44.3% vs. 16.3% (p<0.0001), followed by raised serum CPK level 24.1% vs. 10.5% respectively (p<0.03). Although there was a trend of lower level of SGOT and SGPT in FDC but was statistically not significant (Table 4).

4. Discussion

Mixed dyslipidemia is a common lipid metabolic disorder characterized by elevated levels of both cholesterol and triglycerides.[13] It has diverse underlying mechanisms thus unlikely to be addressed by lipid lowering agent targeting one pathway. The Statins are potent lipid lowering agent

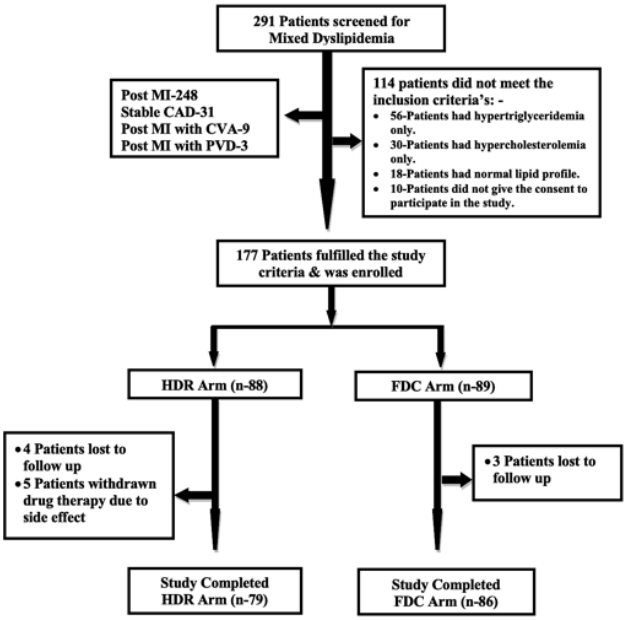

Fig. 1: Flow chart of patient selection and randomization.
Note: FDC: Fixed dose combination, HDR: High dose rosuvastatin.

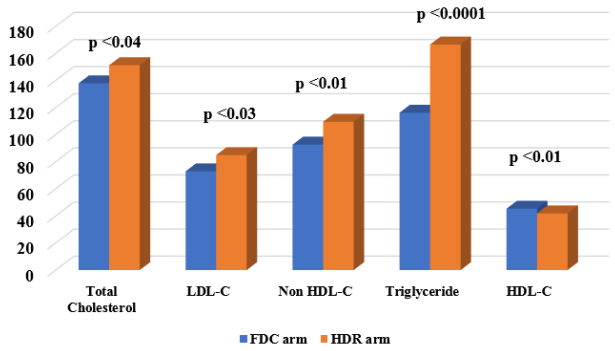

Fig. 2: Mean change in lipid fractions in between the groups.
Note: FDC: Fixed dose combination, HDR: High dose rosuvastatin.

acts by inhibiting intracellular synthesis of cholesterol in hepatocytes resulting in increased expression of surface LDL receptors that enhances uptake of circulating LDL and IDL particles thus lowering the levels of LDL-C primarily.[19] The fibrates enhance the activity of lipoprotein lipase leading to increased hydrolysis of triglycerides and thus decreases level of triglycerides.[20] The mixed dyslipidemia represents an important therapeutic challenge since monotherapy only partially correct the underlying metabolic defects.[21]

The present study was designed to compare the efficacy and safety of high dose rosuvastatin 40 mg with moderate dose rosuvastatin 20 mg and fenofibrate 145 mg on lipid

Table 1: Baseline characteristics of the study population.

Characteristics	HDR (n=79)	FDC (n=86)	2 sided p value
	Socio-Demographic Characteristics		
Age (mean±sd)	57.34 ± 6.94	57.02 ± 8.13	0.86
Gender (Male) %	83.5% (28)	87.2% (75)	0.65
Urban%	35.4% (28)	49.1% (36)	0.49
Literacy%	84.8% (67)	84.9% (73)	0.83
	Medical History		
H/O PCI	11.4% (09)	14% (12)	0.79
H/O CABG	1.3% (01)	7% (06)	0.15
H/O CVA	1.3% (01)	4.7% (04)	0.41
H/O PVD	1.3% (01)	1.2% (01)	0.51
H/O MI	87.3% (69)	79.1% (68)	0.22
H/O Hypertension	27.8% (22)	33.7% (29)	0.51
H/O Diabetes	21.5% (17)	12.8% (11)	0.19
Family H/O CAD	27.8% (22)	24.4% (21)	0.74
	Angina NYHA class		
Class I	72.2% (57)	74.4% (64)	
Class II	26.6% (21)	19.8% (17)	o.32
Class III	1.3% % (01)	5.8% (05)	
Health risk behaviour			
Smoking Status			
Never	19% (15)	14% (12)	
Ex-smoker	67.1% (53)	75.6% (65)	0.14 (trends)
Current	13.9% (11)	10.5% (09)	
	Alcohol Consumption status		
Never	12.7% (10)	09.3% (08)	
Ex	58.2% (46)	64% (55)	0.72
Current	29.1% (23)	26.7% (23)	
	Physical activity status		
Sedentary	46.8% (37)	40.7% (35)	
Moderate	35.4% (28)	44.2% (38)	0.13
Vigorous	17.7% (14)	15.1% (13)	
Intake of Red meat	32.9% (26)	43% (37)	0.23
Intake of Butter & or Ghee	46.8% (37)	45.3% (39)	0.97
Intake of Fast food	58.2% (46)	62.8% (54)	0.06
Intake of fried food	74.7% (59)	60.5% (52)	0.07
	Medication history		
ACE inhibitors/ ARB	68.4%/27.8%	55.9%/34.9%	0.66/0.46
Beta Blockers	93.7% (74)	89.5% (77)	0.4
Calcium Chanel Blockers	11.4% (09)	15.1% (13)	0.63
Nitrates	16.4% (13)	12.8% (11)	0.7
Anti platelets	97.5% (77)	98.8% (85)	0.94
Statins	96.2% (76)	90.7% (78)	0.26
Fenofibrate	7.6% (06)	7% (06)	0.88

Note: - FDC: Fixed dose combination, HDR: High dose rosuvastatin, PCI: Percutaneous Coronary Intervention, CABG: Coronary Artery Bypass Graft, CVA: Cerebrovascular Accident, PVD: Peripheral Vascular Disease, MI: Myocardial infarction, H/O: History Of, CAD: Coronary Artery Disease, NYHA: New York Heart Association, ACE: Angiotensin converting enzyme, ARB: Angiotensin Receptor Blocker.

Table 2: Baseline distribution of anthropometrics, BP and lipid profile, renal function and transaminases

Characteristics	HDR (n=79)	FDC (n=86)	Mean difference (95% C.I.)	P values
Weight	68.55 ± 11.02	68.62 ± 9.51	-0.07(-3.2 – 3.08)	0.96
Height	1.61 ± 0.07	1.62 ± 0.07	-0.01 (-0.03-0.01)	0.29
BMI	26.21±3.6	25.86±3.33	0.034 (-0.72-1.40)	0.52
Waist Circumference	96.05±8.87	96.30±8.65	-0.24(-2.94-2.44)	0.85
Hip Circumference	95.73±7.41	95.79±6.57	-0.06(-2.21-2.08)	0.95
W/H ratio	1.0±0.06	1.0±0.06	-0.001(-0.02-0.01)	0.88
SBP	128.37±18.75	130.41±17.72	-2.04 (-7.64-3.56)	0.47
DBP	82.89±11.14	83.05±9.38	-0.16(-3.31-2.99)	0.92
Total Cholesterol	222.39±47.56	227.66±44.21	-5.27(-19.37-8.83)	0.46
Triglyceride	247.36±102.42	270.03±168.56	-22.66(-66.0-20.67)	0.30
HDL-C	44.75±12.62	41.62±8.25	3.13(-0.11-6.39)	0.05
LDL-C	140.31±38.54	146.44±33.44	-6.12(-17.19-4.94)	0.27
VLDL-C	47.55±20.78	54.50±33.11	-6.94(-15.53-1.63)	0.11
NON-HDL-C	171.91±43.31	184.77±41.0	-6.86(-19.82-6.10)	0.29
Hb	14.17±2.25	14.95±2.22	-0.78{-1.47-(-0.09)}	0.02
Urea	20.87±10.8	18.7±9.73	2.16(-0.98-5.32)	0.17
Creatinine	0.96±0.19	1.75±0.7	-0.78(-2.48-0.9)	0.35
Uric Acid	6.43±1.36	6.8±1.48	-0.36(-0.8-0.07)	0.10
SGOT	31.97±11.68	35.02±17.75	-3.04(-7.71-6.61)	0.19
SGPT	34.92±18.03	38.42±26.83	-3.49(-10.58-3.59)	0.33
Blood Glucose (Fasting)	105.01±18.41	103.72±22.53	1.28(-5.07-7.64)	0.69
HbA1c	6.19±0.71	6.2±0.77	-0.01(-0.24-0.21)	0.88
eGFR	83.94±18.09	87.89±16.81	-3.9 (-9.2-1.45)	0.15

Note: FDC: Fixed dose combination, HDR: High dose rosuvastatin, BMI: Body Mass Index, HDL-C: High Density Lipoprotein Cholesterol, LDL-C: Low Density Lipoprotein Cholesterol, VLDL-C: Very Low-Density Lipoprotein Cholesterol, Non-HDL-C: Non-High Density Lipoprotein Cholesterol, AST: Aspartate Transaminase, ALT: Alanine Transaminase, HbA1c: Glycated Hemoglobin, eGFR: Estimated Glomerular Filtration Rate.

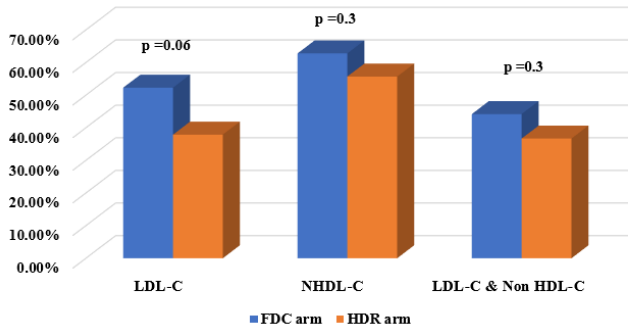

Fig. 3: Percentage of patients achieving lipid target goals in between the groups.
Note: FDC: Fixed dose combination, HDR: High dose rosuvastatin.

lowering efficacy in patients of stable CAD with mixed dyslipidemia. The combination of statin and fenofibrate was more effective in lowering, total cholesterol, LDL-C, Triglyceride and increase in level of HDL-C. The tolerance to combination lipid lowering agents was better than high dose statin. Five patients in high dose statin group had to be withdrawn from the study due to adverse reactions. There was no significant difference in mean levels of markers of liver injury although proportion of patients with elevation in levels of CPK more than three times above the upper level of normal reference value was significantly higher in high dose statin group.

The available evidence from large controlled trials among high-risk patients and patients with established atherosclerotic vascular disease demonstrated the efficacy in reducing the risk of cardiovascular events.[22–27] The benefit is function of extent of LDL-C reduction irrespective of baseline LDL-C levels. LDL-C forms the major atherogenic lipoprotein particle; however, non-HDL-C (VLDL, IDL-C) are also important remaining atherogenic lipoproteins particles especially in patients with mixed dyslipidemia. The post hoc analysis of lipid lowering trials have demonstrated reduction in CV events among patients with elevated triglycerides at baseline in fenofibrate arm at background treatment with high dose statin[13,15] thus substantiating the argument that lowering of non-HDL-C is equally important as is LDL-C in reducing CV events in patients of CAD. The incremental lipid lowering potency of Statins by doubling the dose is by approximately 6%.[7] However addition of fenofibrate lowers the LDL-C by about 5 to 20%.[11] The combination of statin with fenofibrate was also demonstrated to be more effective in reducing the different atherogenic lipids fractions by the other investigators such as Agouridis et al.[28] and Foucher et al.[29]

Table 3: Comparison of lipid lowering efficacy of combination regimen with high dose Rosuvastatin arms

Characteristics	HDR arm (n=79)	FDC arm (n=86)	Difference with 95% C.I.	2 tailed significance
Total Cholesterol	151.30±51.10	137.95±33.15	13.34(0.21-26.48)	0.04
LDL-C	84.94±39.24	72.93±30.92	12.01(1.19-22.83)	0.03
Non HDL-C	109.50±49.33	92.63±33.55	16.86(3.98-29.74)	0.01
Triglyceride	166.53±60.23	116.21±43.55	50.31(34.25-66.38)	0.0001
HDL-C	41.82±9.13	45.32±9.37	-3.49(-6.34 to -0.64)	0.01
Uric acid	5.94±1.13	4.93±1.09	1.01(0.67-1.35)	0.0001
AST	32.7±14.82	30.90±10.80	1.80(-2.15-5.77)	0.36
ALT	34.16±15.56	31.31±13.28	2.85(-1.58-7.29)	0.20
Serum creatinine	0.91±0.17	0.94±0.02	-0.03 (-0.09-0.02)	0.3
Achieved LDL-C target goals (%)	30 (37.9%)	45(52.3%)		0.06
Achieved NHDL-C goals (%)	44 (55.7%)	54(62.8%)		0.32
Achieved LDL-C and Non HDL-C target goals (%)	29 (36.7%)	38(44.2%)		0.32
Mean change in LDL-C (%)	-38.3±24.4%	-49.4±18.9%	11.0(4.3-17.7)	0.02
Mean change in NHDL-C (%)	38.80±22.4%	-48.9±15.8%	10.1(4.2-16.8)	0.001
Mean change in HDL-C Median (I.Q. range) (%)	-6.9% (-13.5 to 6.0)	6.1% (-5.0 to 21.7)	-15(-21.8 to -8.7)	0.001
Mean change in Triglyceride median (I.Q. range) (%)	-29% (-45 to -14)	-54% (-61.0 to -47)	18.5(46-32.3)	0.0001
BMI	25.9±3.5	24.9±3.2	1.0(-0.03 to 2.0)	0.05
HbA1c	6.3±0.6	6.2±0.8	-0.04 (-.018 to 0.28)	0.6
FBS	105.1±18.8	101.8±16.3	3.3(-2.0 to 8.7)	0.22
SBP	124.3±14.6	120.2±13.1	4.1(-0.13 to 8.3)	0.05
DBP	80.8±9.5	75.0±9.2	5.9 (2.9-8.7)	0.001
Uric Acid	5.9±1.1	4.9±1.1	1.0(0.67 - 1.3)	0.001

Note: FDC: Fixed dose combination, HDR: High dose rosuvastatin, HDL-C: High Density Lipoprotein Cholesterol, LDL-C: Low Density Lipoprotein Cholesterol, NHDL-C: Non-High Density Lipoprotein Cholesterol, AST: Aspartate Transaminase, ALT: Alanine Transaminase, HbA1c: Glycated Hemoglobin.

Table 4: Comparison of adverse events between study arms at the end of Follow up

Characteristics	HDR (n=79)	FDC (n=86)	2 sided p values
Myalgia	34.2% (27)	23.3% (20)	0.16
Fatigue	24.1% (19)	27.9% (24)	0.69
Loss of Appetite	44.3% (35)	16.3% (14)	0.0001
Nausea	10.1% (08)	9.3% (08)	0.93
Diarrhoea	7.6% (06)	8.1% (07)	0.87
Raised AST & ALT Level	5.1% (04)	1.2% (01)	0.31
Raised CPK Level	24.1% (19)	10.5% (09)	0.03

Note: FDC: Fixed dose combination, HDR: High dose rosuvastatin, HDL-C: High Density Lipoprotein Cholesterol, LDL-C: Low Density Lipoprotein Cholesterol, NHDL-C: Non-High Density Lipoprotein Cholesterol, AST: Aspartate Transaminase, ALT: Alanine Transaminase, CPK: Creatinine Phosphokinase

Thus, we argue that combination strategy would be more effective and safer in treating mixed dyslipidemia as against the recommended use of maximum dose of Statins and adding fenofibrate only if TG, non-HDL-C targets are not achieved. Future clinical outcome trials are required to compare the efficacy and safety of combination of moderate dose Statins with Fenofibrate with high dose Statins in patients with mixed dyslipidemia.

Interestingly, the mean SBP and DBP of combination arm was significantly lower than HDR arm (120.17±13.11mmHg vs. 124.3±14.65, p<0.05) and (75.02±09.2 mmHg vs. 80.84±9.55mmHg, p<0.0001), respectively. The mechanism(s) of BP lowering effect of fenofibrate is conjectural but could be mediated by decrease in body fat mass (24.9±3.2 vs. 25.9±3.5 p<0.05), decreased oxidative stress leading to improvement in endothelial function and improved insulin sensitivity. The BP lowering effect of fenofibrate was also documented among salt sensitive hypertensives by Gilbert K et al.[30] The mean Uric Acid level was significantly lower in FDC arm compared to HDR (4.93±1.09mg/dL vs. 5.94±1.13mg/dL, p<0.0001), may be an indicator of decrease in oxidative stress. Significant increase in HDL-C level with combination arm may also be contributory factor in reducing oxidative stress as was also observed by other investigators.[31–34] Thus, anti-oxidant and anti-inflammatory effect of fenofibrate could be the some of the underlying mechanisms of favorable effects on cardio metabolic risk factors. There was no significant difference on levels of fasting blood glucose and HbA1c between to study groups however insulin level was no measure to evaluate the effect of studied lipid lowering regimens on insulin sensitivity.

Safety profile of the combination arm was found to be significantly better than high dose arm. No case of rhabdomyolysis or hepatitis with SGOT/SGPT levels more than three times upper reference limit was observed. Decreased appetite was significantly higher in the HDR arm (44.3% vs. 16.3%, p<0.0001) and there was a trend of higher prevalence of myalgia but was statistically insignificant. Proportion of patients with elevated level of CPK was significantly higher in HDR arm (24.1% vs. 10.5%, p<0.03). The similar observations are reported by other investigators.[35–40]

5. Limitations

The symptoms-based reporting of clinical adverse reactions was enquired and recorded by investigator who was not blinded for treatment assigned. Thus, there could be bias in the reported frequencies of adverse reactions. However objective assessment of biomarkers of hepatic and skeletal muscle injury were estimated by lab personals blinded of the treatment assigned.

6. Conclusion

The combination of moderate dose Rosuvastatin and Fenofibrate is more effective in reducing LDL-C, Non-HDL-C and triglyceride and had better tolerance profile than high dose statin in patients of CAD with mixed dyslipidemia. The BMI, Blood pressure and Uric acid levels were decreased significantly in combination regimen. Future clinical outcome trials are warranted to evaluate the superiority of combination regimen with high dose statin in patients of atherosclerotic vascular disease.

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8. Conflict of Interest

None.

References

1. Armitage J. The safety of statins in clinical practice. *Lancet*. 2007;370(9601):1781–90. doi:10.1016/S0140-6736(07)60716-8.
2. Organization WH. World Health Statistics; 2012. Available from: http://www.who.int/gho/publications/world_health_statistics/EN_WHS2012_Full.
3. Reiner Z, Sonicki Z, Tedeschi-Reiner E. Tedeschi-Reiner E. Physicians' perception, knowledge and awareness of cardiovascular risk factors and adherence to prevention guidelines: the PERCRO-DOC survey. *Atherosclerosis*. 2010;13(12):598–603. doi:10.1016/j.atherosclerosis.2010.09.014.
4. Cullen P, Schulte H, Assmann G. Total mortality in middle-aged men is increased at low total and LDL cholesterol concentrations in smokers but not in nonsmokers. *Circulation*. 1997;96(7):2128–36. doi:10.1161/01.cir.96.7.2128.
5. Crouse JR, Raichlen JS, Riley WA. Effect of rosuvastatin on progression of carotid intima-media thickness in low-risk individuals with subclinical atherosclerosis: the METEOR Trial. *JAMA*. 2007;297(12):1344–53. doi:10.1001/jama.297.12.1344.
6. Enas EA, Pazhoor HC, Kuruvila A, Vijayaraghavan K. Intensive Statin Therapy for Indians: Part I Benefits. *Indian Heart J*. 2011;63(3):211–27.
7. McTaggart F, Jones P. Effects of Statins on High-Density Lipoproteins: A Potential Contribution to Cardiovascular Benefit. *Cardiovasc Drugs Ther*. 2008;22(4):321–38. doi:10.1007/s10557-008-6113-z.
8. Knopp RH, Brown WV, Dujovne CA. Effects of fenofibrate on plasma lipoproteins in hypercholesterolemia and combined hyperlipidemia. *Am J Med*. 1987;83(5B):50–9.
9. Kornitzer M, Dramaix M, Vandenbroek MD. Efficacy and tolerance of 200 mg micronised fenofibrate administered over a 6-month period in hyperlipidaemic patients: An open Belgian multicenter study. *Atherosclerosis*. 1994;110:S49–54. doi:10.1016/0021-9150(94)05378-v.
10. Sasaki J, Yamamoto K, Ageta M. Effects of fenofibrate on high-density lipoprotein particle size in patients with hyperlipidemia: A randomized, double-blind, placebo-controlled, multicenter, crossover study. *Clin Ther*. 2002;24(10):1614–26.
11. Brown WV. Potential use of fenofibrate and other fibric acid derivatives in the clinic. *Am J Med*. 1987;83(5B):85–9.
12. 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;106(25):3143–421.

13. Zambon A, Cusi K. The role of fenofibrate in clinical practice. *Diab Vasc Dis Res*. 2007;4(Suppl 3):15–20. doi:10.3132/dvdr.2007.053.
14. Moutzouri E, Kei A, Elisaf MS. Management of dyslipidemias with fibrates, alone and in combination with statins: role of delayed-release fenofibric acid. *Vasc Health Risk Manag*. 2010;6:525–39. doi:10.2147/vhrm.s5593.
15. Mohiuddin SM, Pepine CJ, Kelly MT. Efficacy and safety of ABT-335 (fenofibric acid) in combination with simvastatin in patients with mixed dyslipidemia: A phase 3, randomized, controlled study. *Am Heart J*. 2009;157(1):195–203.
16. Koh KK, Quon MJ, Han SH. Additive beneficial effects of fenofibrate combined with atorvastatin in the treatment of combined hyperlipidemia. *J Am Coll Cardiol*. 2005;45(10):1649–53.
17. Muhlestein JB, May HT, Jensen JR. The reduction of inflammatory biomarkers by statin, fibrate, and combination therapy among diabetic patients with mixed dyslipidemia: the DIACOR (Diabetes and Combined Lipid Therapy Regimen) study. *J Am Coll Cardiol*. 2006;48(2):396–401. doi:10.1016/j.jacc.2006.05.009.
18. Fihn SD, Gardin JM, Abrams J. ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: executive summary: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *Circulation*. 2012;126(25):3097–137.
19. Jones PH, Davidson MH, Stein EA. Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR Trial). *Am J Cardiol*. 2003;92(2):152–60.
20. Sasaki J, Yamamoto K, Ageta M. Effects of fenofibrate on high-density lipoprotein particle size in patients with hyperlipidemia: A randomized, double-blind, placebo-controlled, multicenter, crossover study. *Clin Ther*. 2002;24(10):1614–26.
21. Durrington P. Dyslipidaemia. *Lancet*. 2003;362(9385):717–31. doi:10.1016/S0140-6736(03)14234-1.
22. Report of the Committee of Principal Investigators. WHO Cooperative trial on primary prevention of ischemic heart disease using clofibrate to lower serum cholesterol: mortality follow-up. *Lancet*. 1980;2(8191):379–85.
23. Committee of Principal Investigators. A Co-operative trial on primary prevention of ischemic heart disease using clofibrate. *Br Heart J*. 1978;40(10):1069–118. doi:10.1136/hrt.40.10.1069.
24. The Coronary Drug Project Research Group. Clofibrate and niacin in coronary heart disease. *JAMA*. 1975;231(4):360–81.
25. Trial of Clofibrate in the Treatment of Ischemic Heart Disease. Five year study by a group of physicians of the Newcastle upon Tyne region. *BMJ*. 1971;4:767–75.
26. Ischemic heart disease: a secondary preventive trial using clofibrate. *BMJ*. 1971;4:755–84.
27. Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet*. 2005;366(9493):1267–78. doi:10.1016/S0140-6736(05)67394-1.
28. Agouridis AP, Tsimihodimos V, Filippatos TD. High Doses of Rosuvastatin are Superior to Low Doses of Rosuvastatin Plus Fenofibrate or n-3 Fatty Acids in Mixed Dyslipidemia. *Lipids*. 2011;46(6):521–8. doi:10.1007/s11745-011-3538-0.
29. Foucher C, Aubonnet P, Reichert P, Berli M, Schaeffer A, Vargas CGC, et al. New Fixed-Dose Combinations of Fenofibrate/Simvastatin Therapy Significantly Improve the Lipid Profile of High-Risk Patients with Mixed Dyslipidemia Versus Monotherapies. *Cardiovasc Ther*. 2015;33(6):329–37. doi:10.1111/1755-5922.12148.
30. Gilbert K, Nian H, Yu C. Fenofibrate lowers blood pressure in salt-sensitive but not salt-resistant hypertension. *J Hypertens*. 2013;31(4):820–9.
31. Keating GM, Ormrod D. Micronised fenofibrate. An updated review of its clinical efficacy in the management of dyslipidaemia. *Drugs*. 2002;62(13):1909–44. doi:10.2165/00003495-200262130-00013.
32. Elisaf M. Effects of fibrates on serum metabolic parameters. *Curr Med Res Opin*. 2002;18(5):269–76. doi:10.1185/030079902125000516.
33. Derosa G, Maffioli P, Sahebkar A. Plasma uric acid concentrations are reduced by fenofibrate: A systematic review and meta-analysis of randomized placebo-controlled trials. *Pharmacol Res*. 2015;102:63–70. doi:10.1016/j.phrs.2015.09.012.
34. Kei A, Tellis C, Liberopoulos E. Effect of switch to the highest dose of rosuvastatin versus add-on-statin fenofibrate versus add-on-statin nicotinic acid/laropiprant on oxidative stress markers in patients with mixed dyslipidemia. *Cardiovasc Ther*. 2014;32(4):139–46.
35. Bersot TP. Drug Therapy for Hypercholesterolemia and Dyslipidemia. In: The Pharmacological Basis of therapeutics. 12th edn. New York: McGraw Hill; 2011. p. 877–908.
36. Bergman AJ, Murphy G, Burke J, Zhao JJ, Valesky R, Liu L, et al. Simvastatin does not have a clinically significant pharmacokinetic interaction with fenofibrate in humans. *J Clin Pharmacol*. 2004;44(9):1054–62. doi:10.1177/0091270004268044.
37. Bellosta S, Paoletti R, Corsini A. Safety of statins. Focus on clinical pharmacokinetics and drug interactions. *Circulation*. 2004;109(23 Suppl 1):III50–7. doi:10.1161/01.CIR.0000131519.15067.1f.
38. Law M, Rudnicka AR. Statin safety: A systematic review. *Am J Cardiol*. 2006;97(8A):52C–60. doi:10.1016/j.amjcard.2005.12.010.
39. Neuvonen PJ, Niemi M, Backman JT. Drug interactions with lipid-lowering drugs: Mechanisms and clinical relevance. *Clin Pharmacol Ther*. 2006;80(6):565–81. doi:10.1016/j.clpt.2006.09.003.
40. Schneck DW, Birmingham BK, Zalikowski JA, Mitchell PD, Wang Y, Martin PD. The effect of gemfibrozil on the pharmacokinetics of rosuvastatin. *Clin Pharmacol Ther*. 2004;75(5):455–63. doi:10.1016/j.clpt.2003.12.014..

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