Research Article

# Comparative Study of Atorvastatin plus Fenofibrate versus Atorvastatin alone for its safety and efficacy in Hyperlipidemic patients

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## ABSTRACT

The aim of this study is to compare the efficacy and safety of combination containing Atorvastatin plus Fenofibrate (ATO + FENO) and to determine whether combination of Fenofibrate had clinically significant benefit over Atorvastatin alone (ATO) in patients with Hyperlipidemia. This is a single centric, open labelled, prospective study, involving 50 Hyperlipidemic patients of 18 years and older. Data of only Hyperlipidemic patients with Low Density Lipoprotein (LDL –C) ≥ 140 - < 250 mg/dl, High Density Lipoprotein (HDL-C) < 40 - > 60 mg/dl, Total Cholesterol (TC): 200-240 mg/dl and Triglyceride (TG): ≥ 165- < 400 mg/dl and who were prescribed either Atorvastatin 10 mg and Atorvastatin plus Fenofibrate 160 mg were included in the study. Efficacy end points included the change in LDL-C, HDL-C, TC and TG at week 12 and the safety of the treatment was also evaluated based on adverse events. Total of 50 patients were enrolled in the study but 1 patient lost follow up in ATO Group and 2 patients in ATO + FENO Group. Therefore 24 patients in ATO and 23 patients in ATO + FENO group completed study. A statistically significant reduction in LDL-C, TG and TC was seen in both the groups (Atorvastatin 10 mg and Atorvastatin plus Fenofibrate 160 mg). Similarly a statistically significant increase in HDL-C levels was observed in both the groups. ATO + FENO treatment showed a statistically significant reduction in TG at week 12 as compared to ATO alone. Decrease in LDL-C, TC, and TG were 24.86%, 24.81%, and 30.13% respectively and increasing HDL-C 42.37% in ATO + FENO group while the reduction was 21.1%, 21.31%, and 22.84% respectively and increasing HDL-C 38.2% in ATO alone group. The most common adverse events were headache, myalgia and nausea. ATO + FENO treatment showed a greater reduction in lipid parameters as compared to ATO alone (percentage change). Both treatments were well tolerated with similar incidence of adverse events. Study demonstrated that combination treatment was more effective than Atorvastatin alone in reducing LDL-C, Total Cholesterol and Triglyceride. It was also better in increasing HDL-C as compared to Atorvastatin. Statin in combination of fenofibrate may have lesser adverse effects. Thus Combination therapy seems to be a better treatment in patients having Hyperlipidemia.

**Key words:** Adverse effects, Atorvastatin, Fenofibrate, Hyperlipidemia.

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## INTRODUCTION

High serum cholesterol and elevated low-density lipoprotein (LDL) cholesterol are important risk factors for coronary heart disease. Many patients on statin therapy have initial or recurrent coronary heart disease events despite reductions in LDL cholesterol.[1] Interestingly, fibrate therapy, which significantly decreases triglycerides and increases high-density lipoprotein (HDL) cholesterol without reducing LDL cholesterol, is associated with significant decreases in coronary events.[2] Moreover, combined therapy with statins and fibrates is more effective in controlling atherogenic dyslipidaemia in patients with combined Hyperlipidemia than the administration of either drug alone.[3] Of concern is the fact that the combination of statins and fibrates is more

likely to be accompanied by severe myopathy.[4] This limitation is not observed with fenofibrate, and no significant side effects have been reported with combined statin and fenofibrate treatment.[3–5] Coronary heart disease frequently is associated with insulin resistance and metabolic disorders, such as obesity and combined Hyperlipidemia. Endothelial dysfunction associated with cardiovascular diseases may contribute to insulin resistance.[6] The effects of statins on insulin resistance are controversial.[7,8] Peroxisome proliferators activated receptor-alpha activators improve insulin sensitivity in rodents.[9] The impact of atorvastatin and fenofibrate therapies on endothelial homeostasis and insulin resistance may differ because the mechanisms underlying the biological actions of these drugs are distinct. Therefore, we investigated whether combined therapy has additive beneficial effects greater than atorvastatin or fenofibrate alone in patients with combined Hyperlipidemia.

## MATERIALS AND METHODS

The ethics committee of HCG Multispecialty Hospital, Ahmedabad approved this observational, open label, prospective, randomized and single centric Study. Both male and female patient's ≥18 of age included in this study. Total 50 patients were enrolled in this study as per inclusion and exclusion criteria as shown in table 1 and table 2.

After detailed explanation of the study and involved procedures to the patients, a written informed consent was obtained and patients were allocated in two experimental groups with the time frame of 12 weeks. The patients received either 10 mg of atorvastatin alone (Group ATO) or 10 mg of atorvastatin in combination with 160 mg of fenofibrate (Group ATO + FENO) once daily. Measurement of biochemical characteristics and lipid profile at baseline was done. Safety report card was given to patients to note the adverse reactions if any during study period. The safety evaluation in this study included monitoring of 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 week, 8 week and 12 week). The outcome of the patients, LDL-C, TC, TG, and HDL-C were also noted. Data was collected in paper Case Report Form and was converted into Excel spreadsheet. Descriptive data was expressed as the mean value ± SD, number and percentage. The categorized values were analysed using paired and unpaired student t-test by Graph-pad prism software (version-6) and $p$ value <0.0001 was considered as statistically significant.

## RESULTS

A total 50 patients who met selection criteria were enrolled in the study. Among them, 1 from Group-

**Table 1: Inclusion criteria**

| | | |
|---|---|---|
| 1 | : | LDL-C : ≥140 - <250 mg/dl |
| 2 | : | TG : ≥165- <400 mg/dl |
| 3 | | TC : 200 - 240 mg/dl |
| 4 | : | Those who have given their written consent for the study |
| 5 | : | Subjects willing to adhere to protocol and study requirements during the entire study duration |
| 6 | : | Subjects having no abnormalities in general physical examination |

**Table 2: Exclusion criteria**

| | | |
|---|---|---|
| 1 | : | A History of Hypersensitivity to Statins and Fibrates |
| 2 | : | Pregnant or Lactating Mothers |
| 3 | : | Subjects with hypertension, Type-1 & Type-2 Diabetes mellitus |
| 4 | : | Subjects who are incapable of giving informed consent for the study |
| 5 | : | Patients having Renal Disease having serum Creatinine > 1.5 mg/dL |
| 6 | : | Subjects with any other clinical condition which, in the opinion of the Investigator, might interfere with administration of investigative drugs and evaluation of the study objectives |
| 7 | : | Recent on-going inter current infection. |
| 8 | : | Subjects on other combinational therapies for treatment of hyperlipidemia |
| 9 | : | Subjects with known history of substance abuse (drug or alcohol dependency) |
| 10 | : | Patients with hepatic dysfunction |
| 11 | : | Patients with any other serious concurrent illness |

**Table 3: Enrollment of the patients in both treatment groups**

| | ATORVASTATIN (group-ATO) (N) | ATORVASASTIN+FENOFIBRATE (group- ATO+FENO) (N) |
|---|---|---|
| **Patients enrolled in study** | 25 | 25 |
| **Patients dropped out** | 1 | 2 |
| **Patients completed the study** | 24 | 23 |

**Table 4: Demographic data and other baseline characteristics**

| Characteristic | ATORVASTATIN (group-ATO) (n=25) | ATORVASASTIN+FENOFIBRATE (group- ATO+FENO) (n=25) |
|---|---|---|
| **Age (Yr)(Mean ± SD)** | 54.52 ± 15.24 | 65.76 ± 10.19 |
| **Male (N)** | 17 | 15 |
| **Female (N)** | 08 | 10 |
| **BMI (Kg/m$^2$)(Mean ± SD)** | 25.30 ± 4.36 | 25.77 ± 4.70 |
| **LDL-C** | 206.04 ± 28.39 | 206.32 ± 28.52 |
| **Triglycerides** | 205.78 ± 30.93 | 205.44 ± 44.19 |
| **Total Cholesterol** | 245.16 ± 21.93 | 245.6 ± 23.80 |
| **HDL-C** | 31.08 ± 3.82 | 31.26 ± 3.27 |

**Table 5: Laboratory parameters at baseline**

| Characteristic | ATO (Mean ± SD) (N=25) | ATO+FENO (Mean ± SD) (N=25) |
|---|---|---|
| **Hb (g %)** | 12.57 ± 0.41 | 12.52 ± 0.46 |
| **Total RBC (millions/cmm)** | 4.53 ± 0.32 | 4.51 ± 0.38 |
| **Total WBC (/cmm)** | 7978.75 ± 754.12 | 7884.67 ± 831.23 |
| **Platelets count (lack/cmm)** | 2.94 ± 0.32 | 2.93 ± 0.37 |
| **S.G.P.T (U/L)** | 32.86 ± 2.24 | 32.26 ± 3.06 |
| **S.G.O.T(U/L)** | 52.26 ± 1.12 | 52.96 ± 1.24 |
| **Mean MSSBP** | 124 ± 6.26 | 124.24 ± 4.20 |
| **Mean MSDBP** | 94.66 ± 4.44 | 94.86 ± 6.66 |
| **S. creatinine (mg/dL)** | 0.97 ± 0.08 | 0.96 ± 0.05 |
| **S. potassium (mEq/L)** | 4.44 ± 0.24 | 4.39 ± 0.24 |
| **S. sodium (mEq/L)** | 140.19 ± 1.33 | 139.87 ± 1.36 |

A and 2 from Group ATO + FENO were dropped out because of loss of follow up. Therefore, total 47 patients, 24 from group-A and 23 patients from group-A+F completed study as shown in Table 3.

Demographic data and other baseline characteristics like age, body mass index, LDL-C, TC, TG HDL-C shown in Table 4 were collated. There were no statistically significant differences in general demographic data and other baseline characteristics in both the treatment groups at baseline.

Various biochemical parameters of patients in both the treatment group at baseline are shown in Table 5 were noted. There were no statistically significant differences in biochemical parameters like haemoglobin, total RBC, total WBC, platelet count, total cholesterol, low density lipoprotein, serum creatinine and serum potassium when compared both the treatment groups. Though statistically significant difference was found in serum glutamic pyruvic transaminase, serum glutamic oxaloacetic transaminase, high density lipoprotein and serum sodium.

### *Treatment Efficacy Assessment*

Patients in ATO (Group-I) showed reduction in LDL-C from 206.97 ± 27.55 at baseline to 101.2 ± 6.12 at 12 week,HDL-C from 29 ± 3.22 at baseline to 40.95 ± 1.83 at 12 week, TGs from 205.98 ± 30.81 at baseline to 142.45 ± 2.88 at 12 week and TC from 245.96 ± 21.92 at baseline to 193.54 ± 5.91 at 12 week.

While in ATO + FENO (Group-II) showed Reduction in LDL-C from 206.32 ± 28.52 at baseline to 96.13 ± 3.18 at 12 week, HDL-C from 29.08 ± 3.26 at baseline to 43.73 ± 3.13 at 12 week, TGs from 205.88 ± 30.34 at baseline to 135.6 ± 2.83 at 12 week and TC from 245.6

**Table 6(a): Change in Lipid parameters in Group-ATO at various follow-up**

| Parameters (mg/dl) | Group-ATO (mean ± SD) ATORVASTATIN (10 mg) | | | | |
|---|---|---|---|---|---|
| | Baseline | Visit-1 | Visit-2 | Visit-3 | % Reduction |
| LDL-C | 206.97 ± 27.55 | 200.32 ± 29.36 | 150.8 ± 7.27 | 101.2 ± 6.12* | 21.1 |
| TC | 245.96 ± 21.92 | 240.04 ± 21.96 | 223.56 ±14.17 | 193.54 ± 5.91* | 21.31 |
| TG | 205.98 ± 30.81 | 199.76 ± 30.32 | 173 ± 6.43 | 142.45 ± 2.88* | 22.84 |
| HDL-C | 29 ± 3.22 | 31.72 ± 2.47 | 35.52 ± 2.84 | 40.95 ± 1.83* | 38.2 |

* p value < 0.0001 when all follow up value compared with their respective baseline value, paired t-test

**Table 6(b): Change in Lipid Parameters in Group-ATO+FENO at various follow-up**

| Parameters (mg/dl) | Group ATO+FENO (mean ± SD) ATO (10 mg) + FENO (160 mg) | | | | |
|---|---|---|---|---|---|
| | Baseline | Visit-1 | Visit-2 | Visit-3 | % Reduction |
| LDL-C | 206.32 ± 28.52 | 196.92 ± 26.58 | 128.4 ± 8.68 | 96.13 ± 3.18*# | 24.86 |
| TG | 205.88 ± 30.34 | 192.28 ± 31.04 | 157.44 ± 5.44 | 135.6 ± 2.83*# | 30.13 |
| TC | 245.6 ± 20.79 | 236.44 ± 21.55 | 208.28 ±6.17 | 184.65 ±4.85*# | 24.81 |
| HDL-C | 29.08 ± 3.26 | 33.24 ± 2.37 | 37.72 ± 2.20 | 43.73 ± 3.13*£ | 42.37 |

* p value < 0.0001 when all follow up value compared with their respective baseline value, paired t-test; # p value <0.0001 ( at week 12 compared to week 12),unpaired t-test; £ p value =0.0005 ( at week 12 compared to week 12),unpaired t-test.
LDL=Low Density Lipoprotein, HDL-C=High Density Lipoprotein Cholesterol, TC= Total Cholesterol, TG=Triglyceride..

**Table 7: Adverse reactions related to different treatment**

| Adverse reactions | ATO | | ATO+FENO | |
|---|---|---|---|---|
| | Occurrence (N) | % of the study population | Occurrence (N) | % of the study population |
| Headache | 1 | 4.1 | 1 | 4.3 |
| Myalgia | 2 | 8.3 | 2 | 8.6 |
| Nausea | 1 | 4.1 | 1 | 4.3 |

± 20.79 at baseline to 184.65 ± 4.85 at 12 week. Mean reductions in trough LDL-C, HDL-C, TG and TC from baseline were statistically significantly with ATO + FENO compared with ATO treated group ($p<0.0001$)

So, above all reported data ATO + FENO showed a better reduction in all other lipid parameter as compared to ATO alone at week 12.

The percentage decrease in lipid parameters like LDL-C, TC and TG were 21.1%, 21.31% and 22.84% respectively in ATO group as compared to 24.86%, 24.81% and 30.13% respectively in ATO + FENO group. The increase in HDL-Clevel was 42.37% in ATO + FENO group as compared to 38.2% in ATO group. These data indicate that combination therapy is able to reduce the lipid parameter to a greater extent as compared to Atorvastatin alone.

### *Treatment Safety Assessment*

No patients were withdrawn from the study because of serious adverse effects.The adverse effect profiles reported by the patients through the safety card which was given to them. Elevations in gastrointestinal upset, nausea, and headache were mainly transient and resolved spontaneously after patients finished the study. So, we can say that present treatment therapy is safe & well tolerated.

Both treatments were well tolerated with only a few incidences of mild adverse events. The common adverse events reported in both group were headache, nausea and myalgia as shown in Table 7.

## DISCUSSION

The study reported here addresses the efficacy and tolerability of the combination therapy in patients with hyperlipidaemia, defined as elevated LDL-C (>130 mg/dL) and elevated TG (≥150 and ≤500 mg/dL) independent of HDL-C levels. The 160-mg dose of fenofibrate plus 10 mg of Atorvastatin in the combination therapy and 10 mg dose of Atorvastatin as monotherapy were used in this study. One of the objectives was to evaluate whether the combination would confer the same or better lipid lowering than atorvastatin monotherapy. It is reported that, atorvastatin and fenofibrate therapy alone changed the lipoprotein profiles[11] in Hyperlipidemic patients, so it may possible that they have additional benefits with combined fibrate/statin therapy.

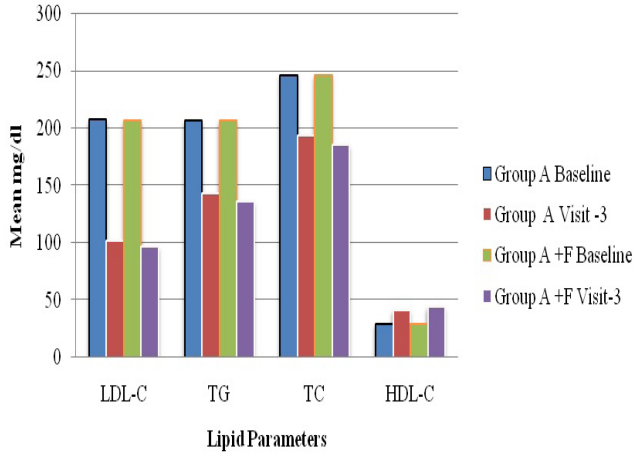


**Figure 1: Change in Lipid Profile at Baseline and at 12 week**

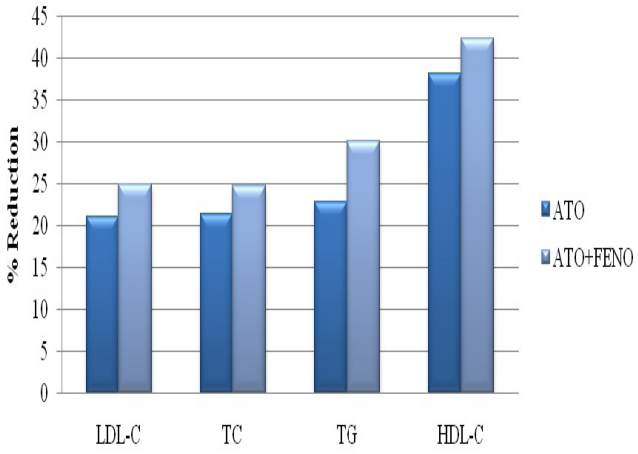


**Figure 2: % Reduction in Lipid Profile at Baseline and at 12 weeks**

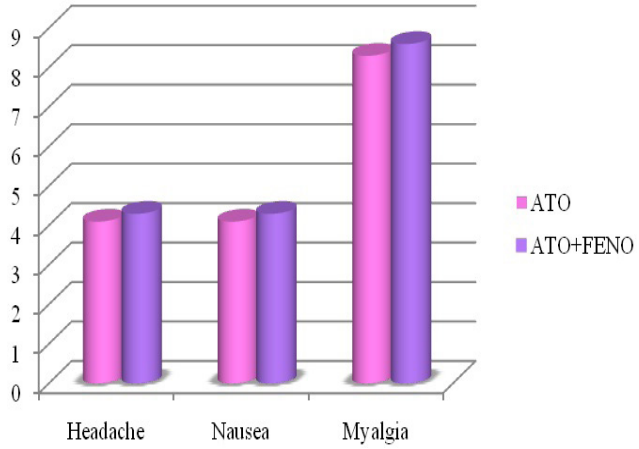


**Figure 3: Adverse Events related to different treatment**

The result of this study shows % reduction in LDL-C, TG and TC 21.1%, 22.84% and 21.31% respectively and increasing HDL-C 38.2% in ATO group, while 24.86%, 30.13% and 24.81% respectively and increasing HDL-C 42.37% in ATO + FENO group. In present study ATO + FENO was associated with a TG reduction of 30.13%/mg (atorvastatin 10 mg + fenofibrate 160 mg for 12 weeks), whereas previously reported studies found a decrease in TG of – 0.31%/mg (atorvastatin 40 mg + fenofibrate 135 mg for 12 weeks),[12] –0.25%/mg (atorvastatin 20 mg + fenofibrate 200 mg for 24 weeks),[10] and –0.29%/mg (atorvastatin 10 mg + fenofibrate 200 mg for 8 weeks).[13]

The findings of this 12-week prospective study suggest that the Combination therapy provided effective management of lipids then monotherapy in Hyperlipidemic patients. Decreases in TC, LDL-C, TG and increases in HDL-C with Combination therapy were significantly greater than atorvastatin monotherapy. Our findings are also supported by previously reported research by Michael *et al*; (2009) they found combination had either comparable or significantly greater improvements in lipid variables.[14]

In present study, the lowering of TG by the Combination therapy relative to the sum of the lowering by the individual monotherapy (atorvastatin alone) supports the concept of pharmacokinetic/pharmacodynamics interactions between the drugs and a resulting influence on lipid pathways.[14] The monotherapy (ATO) lowers 22.84% TG, whereas the Combination (ATO + FENO) was associated with a change of 30.13% in TG. This conceptual pharmacokinetic/pharmacodynamics interaction was evident in other statin/fenofibrate studies that compared monotherapy with the respective co-administration regimens.[10,12,14] An interaction between statin and fibrate for the TG and LDL-C pathways was clearly evident in previous trials.[10-14] The present study found an improved efficiency of lipid lowering similarly to the previously studies[10-14] reported with hyperlipidaemia patients.

The two Hypolipidemic drugs used in the present study have complementary modes of action. Atorvastatin is a potent inhibitor of hydroxymethylglutaryl-CoA reductase, which decreases LDL cholesterol in plasma by up regulating LDL receptor activity.[14] It has been shown

that atorvastatin significantly reduced circulating levels of all major LDL subspecies: light, intermediate, and dense.[19] the latter is believed to be responsible for the TG-lowering effect of atorvastatin and has profound effects at higher doses.[20, 21]

Fenofibrate activates peroxisome proliferators–activated receptors,[22] which induce an increase in LP lipase activity and a reduction in cholesterol ester transfer protein activity.[16] These result in TG level reduction, redistribution of LDL particle size, and an HDL cholesterol increase. The significant reduction of TG, and increase in HDL cholesterol, seen in this study with atorvastatin and fenofibrate combination is indicative of a beneficial increase in LDL particle size.[18]

Importantly, no patients were withdrawn from our study as the result of serious adverse effects. The primary risk of using statins in combination with fibrates is believed to be hepatotoxicity and myopathy. In most studies combination therapy was no more hepatotoxic than the statin itself.[17] The use of statin/fibrate combination therapy in clinical practice has raised concerns about the increased risk of muscle-associated AEs, such as myositis, myalgia, and Rhabdomyolysis.[14] Use of lower-dose statins and fibrates is recommended to avoid muscle related as well as liver and renal toxicities.[15,19] In the present study, the Combination therapy was not associated with any cases of myositis or Rhabdomyolysis, whereas 4.1% of patients reported headache, 4.1% of patients reported nausea and 8.3% of patients reported myalgia.[12] In general, the Combination treatment was associated with a lower number of total AEs, compared with fenofibrate or atorvastatin alone.

## LIMITATION OF THIS STUDY

Limitations to consider when evaluating the clinical applicability of this study should include the constraints of the inclusion and exclusion criteria, which limit the extrapolation of these results to the general population. Other possible limitations are the dyslipidaemia criteria for patient eligibility, the population size of each treatment arm and the short duration of the study. Hence, further studies in a large number of patients and for longer duration are necessary to assess the long–term safety of this combination.

In summary, present study suggests that combined atorvastatin/fenofibrate therapy is comparatively safe and has beneficial additive effects on all lipid parameters and it is a very effective therapeutic approach of patients with Hyperlipidemia supporting the updated National Cholesterol Education Program Adult Treatment Panel IIIguidelines.[15] These properties reduce CAD risk, expand the spectrum of therapeutic choices, and enhance the individualization of hypolipidemic treatment in patients with Hyperlipidemia.[10]

## CONCLUSION

In this 12-week prospective study, patients with hyperlipidaemia treated with the atorvastatin/fenofibrate 10/160-mg had a significantly greater reduction in TG, also decreases in non–HDL-C, LDL-C, TC and increases in HDL-C than those treated with atorvastatin 10 mg alone. The combination therapy also shows less adverse effects than atorvastatin monotherapy.

Monotherapy with statins is considered the gold standard for treatment of mixed Hyperlipidemia, but greater benefits were observed with combination therapy. Hence, monotherapy may not effectively control all lipid abnormalities whereas, long term Fenofibrate plus Atorvastatin combination therapy is efficacious, safe and well tolerated.

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