

Table I

Effects of niacin or fenofibrate in combination with atorvastatin on serum lipid level

Lipid profile (mg/dL)	Niacin plus atorvastatin		%Change	Fenofibrate plus atorvastatin		%Change
	Before treatment	12 weeks after treatment		Before treatment	12 weeks after treatment	
Triglyceride	207.8 ± 60.2	178.6 ± 52.8 <sup>a</sup>	-14.0	289.7 ± 86.6	188.2 ± 49.3 <sup>a</sup>	-35.0
Total cholesterol	213.5 ± 28.5	158.6 ± 19.5 <sup>a</sup>	-25.7	224.6 ± 26.1	156.7 ± 24.8 <sup>a</sup>	-30.2
LDL-C	136.8 ± 23.6	84.2 ± 15.4 <sup>a</sup>	-38.4	134.5 ± 28.6	82.6 ± 20.1 <sup>a</sup>	-38.6
HDL-C	35.3 ± 3.6	38.8 ± 3.8 <sup>a</sup>	+10.0	35.0 ± 4.0	37.6 ± 3.5 <sup>a</sup>	+7.2

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A comparative study on the effects of niacin plus atorvastatin with that of fenofibrate plus atorvastatin in dyslipidemia patients

## A comparative study on the effects of niacin plus atorvastatin with that of fenofibrate plus atorvastatin in dyslipidemia patients

Salim Ahmed<sup>1</sup>, A. K. M. Mosharrof Hossain<sup>1</sup>, Sudhangshu Ranjan Dey<sup>2</sup>,  
A. K. M. Akhtaruzzaman<sup>2</sup>, and Musammath Moriom Siddika<sup>3</sup>

Department of <sup>1</sup>Pharmacology, <sup>2</sup>Cardiology and <sup>3</sup>Pediatrics, Sylhet M. A. G. Osmani Medical College, Sylhet 3100, Bangladesh.

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### Abstract

The study was designed to evaluate and compare the effects of co-administration of atorvastatin (10 mg) either with niacin (1 g) or fenofibrate (200 mg) daily for 12 weeks in 67 coronary heart disease patients with dyslipidemia. There were no significant differences among the two groups (35 patients in Group I and 32 patients in Group II) in serum lipid profile except in level of triglyceride reduction where fenofibrate-atorvastatin combination yielded significant ( $p < 0.001$ ) results. SGPT level significantly raised and fasting blood glucose level decreased in fenofibrate-atorvastatin treated group than niacin-atorvastatin combination. Serum creatinine level decreased in niacin-atorvastatin treated group compared to fenofibrate-atorvastatin, but the changes was within normal limit. This study shows that both combinations are equally effective in dyslipidemia. Although, fenofibrate-atorvastatin combination decreased more triglyceride and niacin-atorvastatin combination appeared safer considering some adverse effects.

### Introduction

Globally, cardiovascular disease contributes to one in three deaths (Eckardstien, 2005). Though cardiovascular disease death rates are declining in the developed countries (Chockalingam and Campbell, 2005) it becomes a leading cause of morbidity and mortality in the developing countries (Bovet et al., 2006). Every year, more than 15 million deaths occur in worldwide due to cardiovascular disease. Of them 9 million deaths are accounted for the developing countries (Chockalingam and Campbell, 2005).

The Americans and the South Asians exhibit the highest prevalence of coronary artery disease and coronary risk factors are more as compared with Caucasians (Deedwania and Singh, 2005). The coronary artery disease

rates among Indians were 6 times higher than the Chinese and 4 times higher than the other Asian Americans (McKeigue et al., 1989).

In Bangladesh, cardiovascular diseases are becoming a significant burden on health care services (Sultana et al., 2002). Dyslipidemia plays an important role for provocation of cardiovascular disease (Miller, 2003). The major detrimental components of dyslipidemia are low high density lipoprotein cholesterol (HDL-C), high triglyceride and elevated low density lipoprotein cholesterol (LDL-C). Recent publications and guidelines have raised awareness of the need to prompt treatment of dyslipidemia to reduce cardiovascular risks in patients with diabetes or metabolic syndrome (Davidson, 2003).



Low HDL-C is an independent risk factor for coronary artery disease and its prevalence is high and increasing (Gordon et al., 1977). The prevalence of low HDL-C appears to be high in Latin American subjects, as shown by surveys carried out in Mexico (92.1% in men, 96.6% in women) and Brazil (50% both men and women). In Mexico, the prevalence of low HDL-C increased by 2-3% within a period of only 7 years (Bruckert, 2006). The prevalence in UK showed that approximately one man in four and about one woman in twelve had low HDL-C (Patel et al., 2004). The overall prevalence of low HDL-C was 33% in men and 40% in women. An elevated triglyceride often accompanies low HDL-C, found in 47-57% of men and 44-48% of women. Combined lipid abnormalities occurred together in 21-26% of men and 25-27% of women (Bruckert, 2006).

According to Framingham study, in older men and women from age 49 to 82 years, the most potent risk factor for coronary artery disease was low HDL-C. Low HDL-C had an inverse association with coronary artery disease in men and women. The association between LDL-C was weaker than HDL-C (Gorden et al., 1977). Low HDL-C together with elevated triglyceride is common dyslipidemia feature found in patients with coronary heart disease. In Veterans Affairs HDL intervention Trial (VA-HIT) on 8,500 coronary heart disease patients, 87% had elevated LDL-C levels, 64% also had low HDL-C levels and 33% had elevated triglyceride level (Rubins et al., 1995).

Optimal dyslipidemia management, including therapeutic life style changes (TLC), is recommended for all patients at risk of coronary artery disease. However, TLC has limited effects on low HDL-C and therefore drugs are needed to help dyslipidemic patients to achieve lipid profile goals (Fodor et al., 2000).

At present available drug classes that modify lipid and lipoprotein metabolism are: Statin, bile acid sequestrants, fibrate derivatives, nicotinic acid and ezetimibe. The mechanism of action of statins, fibrates and nicotinic acid are distinct. The statin blocks the rate limiting step in cholesterol biosynthesis (Weirzbicki et al., 2003) and has the most powerful LDL-C lowering effects out of all lipid modifying agents (Deedwania and Singh, 2005). Niacin inhibits the release of free fatty acids from adipose tissue, increases lipoprotein lipase activity and decreases the hepatic production of VLDL-C and LDL-C production. Fibrates belong to the drug classes that exert their effect by activating PPAR- $\alpha$  (Barter and Rye, 2006). Individually nicotinic acid and fibrates are the most effective pharmacological agents

for dyslipidemia by raising HDL-C and reducing triglyceride (Grundny et al., 2004). Results of clinical trials with fibrates or nicotinic acid showed improve total lipid profile; strongly suggested a benefit (Barter and Rye, 2006).

The rationale for combination therapy is that drugs with complementary mechanism of action can provide complementary effects on the lipid profile (Venkataraman et al., 2004). The HDL Atherosclerosis Treatment Study (HATS) showed that combined effect of niacin or a fibrate with a statin improved HDL-C and LDL-C which inhibited the progression of atherosclerosis and reduced cardiovascular events in a high risk population with established coronary heart disease (Taylor, 2006).

Combination of statin-niacin therapy is associated with flushing and is usually transient but hepatic effects and myopathy are uncommon. The common adverse effects of statin-fibrate therapy are myopathy, elevated hepatic enzyme and gastrointestinal upset (Koh et al., 2005).

Previous studies established that statin in combination with fenofibrate significantly improved lipid profile than monotherapy in people with type 2 diabetes, dyslipidemia, and history of coronary artery disease (Derosa et al., 2004). Another combination therapy of statin-niacin, reduced LDL-C significantly more than niacin alone and HDL-C level significantly raised more than statin administration alone. It was also more effective in reducing triglyceride levels than either monotherapy (Misra et al., 2004). There is no significant interaction between statin administered in combination either with niacin or fibrate.

Therefore, the present study was designed to evaluate and compare the effects and safety of combination therapy of statin-niacin and statin-fenofibrate on dyslipidemic patients of high-risk group. The result of study would suggest for rational use of lipid lowering agents and thereby reduce morbidity and mortality of cardiovascular disease.

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## Materials and Methods

This prospective interventional study was carried out during the period of July 2006 to June 2007. The patients admitted in coronary care unit with diagnosis of a coronary heart disease and dyslipidemia were taken as study population. Adult male and female patients of 30-65 years of age having coronary heart disease with dyslipidemia (LDL-C level was detected more than 100 mg/dL, triglyceride more than 200 mg/dL, total

cholesterol more than 200 mg/dL and HDL-C level less than 40 mg/dL in male, 50 mg/dL in female), defined as high-risk category by updated NCEP ATP-III Guidelines 2004 were included in this study (Grundy et al., 2004). Exclusion criteria were chronic hepatic disorder, renal impairment, pregnant and lactating mothers, on going treatment with other drugs that affect lipids ( $\beta$ -blocker, steroid therapy, etc.), extreme level of triglyceride ( $>400$  mg/dL), hypersensitivity to any component of this medication, those who did not give informed consent and on going treatment with lipid lowering agents.

After selection of the participants, written consent was obtained after explanation of the objectives, nature, purpose and potential risk of all procedures used for the study to the patient and accompanying persons. Detail history (particulars of the patient, personal history, family history of coronary heart disease and associated disease like hypertension, diabetes) and clinical examination (pulse, blood pressure, jaundice, height and weight, etc.) were taken in a prescribed data collection form. Blood samples were collected from the study subjects after 12 hours overnight fasting for estimation of serum level of glucose, triglyceride, total cholesterol, HDL-C, LDL-C, SGPT and serum creatinine.

Initially there were 132 study populations, among them 24 were excluded. 108 patients satisfied the inclusion, exclusion criteria and they were allocated to Group I (64 patients) and Group II (44 patients). Group I was treated with niacin 1 g (500 mg twice daily) plus atorvastatin 10 mg daily for 12 weeks and Group II was treated with fenofibrate 200 mg plus atorvastatin 10 mg daily for 12 weeks. Among Group I, 26 patients did not turn to follow-up (dropped out), 3 died while 35 patients completed the study. Of them 28 were males and 7 were females. In Group II, 11 patients did not turn to follow-up, 1 died and 32 patients completed the study. Of them 30 were males and 2 were females. A total number of 67 patients completed the study.

Average duration of hospital stay of the patients was 5 to 7 days. All patients of both groups were instructed to maintain TLC such as low fat diet during the trial period. During discharge from hospital all the study participants were instructed about possible adverse effects and to report to the principal investigator if they experience any sort of drug related adverse events such as warming of the face, neck and shoulder; intense muscle pain, headache, yellow coloration of skin and

eye, etc. within this period either over telephone or physically.

All the participants were advised to report to the cardiology outpatient department following overnight fasting, 12 weeks after initiation of lipid lowering drug. On that day along with clinical examination blood samples were collected and relevant test was done and test results were also recorded.

From each study subject 5 mL fasting venous blood sample was collected by disposable plastic syringe with all aseptic precautions. The needle was detached from the nozzle and blood was transferred immediately into a dry, clean and plain plastic test tube without any anticoagulant with a gentle push to avoid hemolysis. Serum was separated by centrifugation at the rate of 3,000 rpm for 15 min. Estimations were carried out as early as possible. Whenever there was delay, sample was stored at  $-20^{\circ}\text{C}$ .

Data were collected through preformed data collection sheet by pre-tested questionnaire, clinical examination, ECG and biochemical examinations. After an overnight fasting, total cholesterol and HDL-C were measured by CHOD-PAP method using reagents of Biocon® Germany by spectrophotometer. Triglycerides were also measured by GPO-PAP method using reagents of Biocon® Germany by spectrophotometer (Gowland, 1998). LDL cholesterol was calculated by Friedewald formula (in mg/dL) [ $\text{LDL-C} = \text{TC} - (\text{TG}/5 + \text{HDL-C})$ ]. Estimation of serum glucose was done by GOD-PAP method (McLauchlan, 1998). Estimation of SGPT was performed by colorimetric method (Handerson and Donald, 2001). For estimation of serum creatinine kinetic method was used (David and Chistopher, 2001).

All statistical analyses were done by SPSS software package, 12.0 for windows. Values were presented as mean  $\pm$  SD. 95% significance level ( $p < 0.05$ ) was considered statistically significant. Paired t-test was done to compare between means within groups and 'Z' proportion test was done to see any significant difference between the study parameters.

The study was approved by Ethics Review Committee of Sylhet M.A.G. Osmani Medical College. Informed written consent was taken from all participants prior to study.

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## Results

Mean ages for Group I and II were  $50.7 \pm 10.0$  years and

Table I

## Effects of niacin or fenofibrate in combination with atorvastatin on serum lipid level

Lipid profile (mg/dL)	Niacin plus atorvastatin		%Change	Fenofibrate plus atorvastatin		%Change
	Before treatment	12 weeks after treatment		Before treatment	12 weeks after treatment	
Triglyceride	207.8 ± 60.2	178.6 ± 52.8 <sup>a</sup>	-14.0	289.7 ± 86.6	188.2 ± 49.3 <sup>a</sup>	-35.0
Total cholesterol	213.5 ± 28.5	158.6 ± 19.5 <sup>a</sup>	-25.7	224.6 ± 26.1	156.7 ± 24.8 <sup>a</sup>	-30.2
LDL-C	136.8 ± 23.6	84.2 ± 15.4 <sup>a</sup>	-38.4	134.5 ± 28.6	82.6 ± 20.1 <sup>a</sup>	-38.6
HDL-C	35.3 ± 3.6	38.8 ± 3.8 <sup>a</sup>	+10.0	35.0 ± 4.0	37.6 ± 3.5 <sup>a</sup>	+7.2

<sup>a</sup>Significance of difference at  $p < 0.001$ ; '-' sign indicates reduction of lipid level in percentage; '+' sign indicates increase of lipid level in percentage; Data are mean ± SD

47.6 ± 8.3 years respectively. There was no significant difference between Group I and II in their age distribution. Of the study subjects 25 (71.4%) of Group I and 27 (84.4%) of Group II were smokers. Family history of coronary heart disease were found in 23 (65.7%) and 20 (62.5%) patients of Group I and II respectively. Obesity (BMI > 25 kg/m<sup>2</sup>) was detected 12 (34.3%) in Group I and Group 11 (34.4%) in II. History of sedentary life style was 10 (28.6%) in Group I and 8 (25.6%) in Group II. Around 34% of the study subjects were diabetic in both groups, while 42.9% of Group I and 62.5% of Group II were hypertensive. All patients of both groups were match in respect to age, risk factors (history of smoking, family history of coronary heart disease, obesity, sedentary life style) and associated diseases (diabetes, hypertension).

Before administration of niacin-atorvastatin combination, fasting serum lipid profile was measured (Table I). Serum levels of triglyceride, total cholesterol, LDL-C, HDL-C levels were 207.8 ± 60.2 mg/dL, 213.5 ± 28.5 mg/dL, 136.8 ± 23.6 mg/dL and 35.3 ± 3.6 mg/dL respectively. After 12 weeks of treatment, triglyceride level was reduced from 207.8 ± 60.2 mg/dL to 178.6 ± 52.8 mg/dL. This change was statistically significant ( $t = 4.677$ ,  $p < 0.001$ , 95% CI 16.47 to 41.80). Triglyceride decreased by 14.03%.

Total cholesterol level was reduced from 213.5 ± 28.5 mg/dL to 158.6 ± 19.5 mg/dL and this change was statistically significant ( $t = 14.706$ ,  $p < 0.001$ , 95% CI 47.350 to 62.535). Reduction of total cholesterol was 25.7% from the baseline level.

LDL-C level was observed to decrease from 136.8 ± 23.6 mg/dL to 84.2 ± 15.4 mg/dL and this reduction was statistically significant ( $t = 15.448$ ,  $p < 0.001$ , 95% CI 45.631 to 59.455). Percentage change of LDL-C was 38.4% decrease from baseline.

HDL-C level increased from 35.3 ± 3.6 mg/dL to 38.8 ± 3.8 mg/dL which was statistically significant ( $t = 7.218$ ,  $p < 0.001$ , 95% CI 4.540 to 2.545). Niacin-atorvastatin treated group demonstrated increase in HDL-C level by 10.0% from pre-treatment level.

Before initiation of treatment of fenofibrate-atorvastatin combination fasting serum level of triglyceride, total cholesterol, LDL-C and HDL-C were 289.7 ± 86.6 mg/dL, 224.6 ± 26.1 mg/dL, 134.5 ± 28.6 mg/dL and 35.0 ± 4.0 mg/dL respectively. After completion of 12 weeks of treatment, triglyceride level was decreased from 289.7 ± 86.6 mg/dL to 188.2 ± 49.3 mg/dL. This change was statistically highly significant ( $t = 6.854$ ,  $p < 0.001$ , 95% CI 71.276 to 131.661). Triglyceride decreased by 35.0%.

Total cholesterol level was reduced from 224.6 ± 26.1 mg/dL to 156.7 ± 24.8 mg/dL and this changes was statistically significant ( $t = 14.366$ ,  $p < 0.001$ ; 95% CI 58.239 to 77.511). Percentage decrease of total cholesterol was 30.2%.

LDL-C level reduced from 134.5 ± 28.6 mg/dL to 82.6 ± 20.1 mg/dL and the reduction was statistically highly significant ( $t = 12.501$ ,  $p < 0.001$ ; 95% CI 43.438 to 60.375). Percentage change of LDL-C by 38.6% from baseline was observed.

HDL-C level was observed to be increased from 35.0 ± 4.0 mg/dL to 37.6 ± 3.5 mg/dL. These changes of increment was statistically significant ( $t = 4.079$ ,  $p < 0.001$ , 95% CI 3.797 to 1.266). Fenofibrate-atorvastatin combination caused increase of HDL-C by 7.2%.

Z-proportion test was done to see the difference in percentage change of lipid profile between two treatment groups after 12 weeks of administration. In fenofibrate-atorvastatin treatment group more effective reduction of triglyceride level noted, compared to

Table II				
Effects of niacin or fenofibrate in combination with atorvastatin on blood glucose, SGPT, and serum creatinine level				
Biochemical parameters	Niacin plus atorvastatin		Fenofibrate plus atorvastatin	
	Before administration (n = 35)	After 12 weeks (n = 35)	Before administration (n = 35)	After 12 weeks (n = 35)
Fasting blood glucose (mmol/L)	7.2 ± 2.7	6.6 ± 1.3 <sup>NS</sup>	8.5 ± 4.4	6.5 ± 2.0 <sup>a</sup>
SGPT (U/L)	36.8 ± 16.4	35.3 ± 10.1 <sup>NS</sup>	30.2 ± 7.8	45.6 ± 24.8 <sup>a</sup>
Serum creatinine (mg/dL)	1.2 ± 0.3	1.0 ± 0.2 <sup>a</sup>	1.1 ± 0.3	1.0 ± 0.1 <sup>NS</sup>

<sup>a</sup>Significant difference before and after 12 weeks administration of drug at  $p < 0.001$ ; NS= No significant difference at  $p > 0.05$ , Data are mean ± SD

Table III		
Adverse drug reactions in course of treatment		
Symptoms	Niacin plus atorva- statin (n = 35)	Fenofibrate plus atorvastatin (n = 32)
Flushing	5	--
Headache	2	1
Fatigue	4	4
Abdominal pain	2	2
Dyspepsia	--	2
Myalgia	--	2
Total	13	11

niacin-atorvastatin combination therapy ( $Z=2.05$ ,  $p < 0.05$ ). But there was no differences in total cholesterol, LDL-C and HDL-C modifying effects between these two combination treatment groups.

Before initiation of niacin-atorvastatin combination, fasting blood glucose level was  $7.2 \pm 2.7$  mmol/L (Table II). After 12 weeks of treatment, fasting blood glucose was detected as  $6.6 \pm 1.3$  mmol/L. There was no significant change in fasting blood glucose ( $t=1.71$ ,  $p > 0.05$ ; 95% CI 0.111 to 1.30) level.

Before administration of niacin plus atorvastatin, mean SGPT was  $36.8 \pm 16.4$  U/L. After 12 weeks of treatment SGPT was detected as  $35.3 \pm 10.1$  U/L. There was no significant difference of SGPT level ( $t=0.561$ ,  $p > 0.05$ ; 95% CI -4.048 to 7.134).

Before initiation of Group I treatment serum creatinine level was  $1.2 \pm 0.3$  mg/dL and after completion of 12 weeks of treatment, serum creatinine level was  $1.0 \pm 0.2$  mg/dL. Serum creatinine level significantly decreased from pre-treatment level ( $t=3.56$ ,  $p < 0.001$ ; 95% CI 0.073

to 0.269). But the change was not associated with renal impairment.

In Group II before initiation of treatment, fasting blood glucose was  $8.5 \pm 4.4$  mmol/L. After completion of 12 weeks of treatment fasting blood glucose was  $6.5 \pm 2.0$  mmol/L. The fasting blood glucose decreased significantly ( $t=3.82$ ,  $p < 0.001$ ; 95% CI 0.946 to 3.116) but the change was within normal limit.

Before administration of fenofibrate-atorvastatin combination, SGPT was  $30.2 \pm 7.8$  U/L. After 12 weeks of treatment, SGPT was detected as  $45.6 \pm 24.8$  U/L ( $t=-3.67$ ,  $p < 0.001$ ; 95% CI -23.96 to -6.85). SGPT in this group increased significantly.

Before initiation of treatment, serum creatinine was  $1.1 \pm 0.3$  mg/dL. After 12 weeks of treatment, serum creatinine level was detected as  $1.0 \pm 0.1$  mg/dL. The changes in serum creatinine level was not significant ( $t=1.69$ ,  $p > 0.05$ ; 95% CI -0.019 to 0.201).

Treatment related adverse effect was reported in 37.1% of patients receiving niacin plus atorvastatin therapy and in 35% of patients receiving another combination of fenofibrate plus atorvastatin (Table III). 14.3% of Group I treated patients experienced transient flushing which was a feeling of warmth, itching and redness of the skin especially face as well as neck while none of them complaints in Group II. 5.7% of niacin plus atorvastatin-treated patients and 3.6% of fenofibrate plus atorvastatin-treated patients experienced headache. 11.4% of Group I treated patients and 12.5% of Group II treated patient's had complained of fatigue. Abdominal pain experienced by 5.7% in Group I and 6.3% in Group II. 6.3% of fenofibrate plus atorvastatin treated patient's complaints of dyspepsia and myalgia while none of the niacin plus atorvastatin treated patients, experienced dyspepsia or myalgia.

## Discussion

This study shows that combined therapy of either niacin-atorvastatin or fenofibrate-atorvastatin for 12 weeks significantly decreased total cholesterol, triglyceride and LDL-C from baseline in dyslipidemic patients. The individual combination also significantly increased HDL-C in same groups of patients. This study also revealed that combined fenofibrate-atorvastatin appeared more effective than niacin-atorvastatin in reduction of triglyceride. Previously, similar combinations of lipid lowering agents produced qualitatively similar effects in dyslipidemic patients (Stein et al., 1996; Guyton et al., 1998; Athyros et al., 2002; Klosiewicz-Latoszek et al., 2004). However, a study conducted by Deb (2006) where atorvastatin administered in combination with ezetimibe produced significant reduction of LDL-C and total cholesterol, but did not show any significant effect on HDL-C and triglyceride level compared to baseline.

In the present study, niacin administered in combination with atorvastatin significantly decreased triglyceride by 14.0%, total cholesterol by 25.7% and LDL-C by 38.4% and increased HDL-C by 10.0% from baseline. This result was similar to that reported by Stein et al., (1996) who observed that niacin at a dose of 1.5 g administered in combination with simvastatin at a dose of 10 mg per day was highly effective in lowering the serum lipids of triglyceride by 31%, LDL-C by 29% while HDL-C level increased by 31% after 17 weeks of treatment. The greater lipid modifying effects might be due to high doses of niacin and long duration of treatment.

Guyton et al., showed that 1.5 g niacin in combination with 10 mg simvastatin lowered level of total cholesterol by 23%, LDL-C by 32%, triglyceride by 30% and increased levels of HDL-C by 26% after 48 weeks of therapy. The difference of percentage of lipid profile was probably due to longer duration and higher dose of niacin.

Niacin mainly acts by inhibition of lipolysis of triacylglycerol in adipose tissue via inhibition of hormone sensitive triglyceride lipase leading to reduction in circulating levels of non-esterified fatty acid. As a result, there is a reduction in plasma level of VLDL-triglyceride, LDL and decreases the rate of removal of apoA-1 (the major apolipoprotein of HDL) by the liver (Chapman et al., 2004). There is also evidence that nicotinic acid stimulates cholesterol efflux via an ATP-binding cassette transporter A1 (ABCA-1) mediated

mechanism (Rubic et al., 2004) and decrease HDL uptake by the liver (Sakai et al., 2001) which contribute to the HDL raising effect. Atorvastatin inhibits HMG-CoA reductase, the most effective agent for lowering LDL-C (Miller, 2003).

On the other hand, the present study shows that fenofibrate plus atorvastatin therapy decreased LDL by 38.6%, total cholesterol by 30.2%, triglyceride by 35.0% and increased HDL-C by 7.2% from the baseline. The changes might be caused by fenofibrate that activates peroxisome proliferator-activator receptors (Staels and Auwerx, 1998) which induce an increase in lipoprotein lipase activity causing hydrolysis of triglycerides in chylomicron and VLDL particles and an increase in apo A-1 as well as a reduction in cholesterol ester transfer protein activity; thereby reduction of triglyceride, total cholesterol and increase HDL-C. Atorvastatin decreases LDL-C by inhibition of HMG-CoA reductase (Watts and Dimmit, 1999).

The study of Athyros et al. (2002) showed that combination therapy of atorvastatin (20 mg)-fenofibrate (200 mg) causes reduction of total cholesterol, LDL-C, triglyceride and a significant increase in HDL-C which was highly beneficial in patients with type 2 diabetes and dyslipidemia. The differences of lipid profile probably due to higher doses of atorvastatin and longer duration of treatment which was twice that of the present study.

Another study conducted by Klosiewicz-Latoszek et al. (2004) on fenofibrate (200 mg) administered with simvastatin (20 mg) therapy observed reduction of total cholesterol, triglyceride and LDL-C and increased HDL-C from baseline level. This study apparently consistent with the present study where simvastatin (20 mg) used in place of atorvastatin (10 mg) and duration of treatment was 12 months.

According to NCEP ATP-III and most recent guidelines of European Society of Cardiology recommended that reduction of LDL-C by statin and simultaneously elevation of HDL-C by niacin or fibrate contributes to prevention of cardiovascular disease and atheromatous lesions, consequently decrease morbidity and mortality (Grundy et al., 2004; Sirtori, 2006). Regarding these two parameters niacin-atorvastatin has similar effect in relation to fenofibrate-atorvastatin combination.

A study conducted by Barter and Rye (2006) showed that an 8% increase in HDL-C predicted a coronary heart disease risk reduction of 23% whereas a 7% reduction in LDL-C predicted a 15% reduction in

coronary heart disease events. Another study reported by Gordon et al. (1977) suggests that a one percent increment in HDL-C equated with a 1% lowering of cardiovascular risk.

In our study niacin-atorvastatin treated subjects exhibit some adverse effects such as, transient flushing, headache, fatigue and abdominal pain. In addition, this group did not experience either myalgia or dyspepsia. In the study conducted by Millers, (2003), the incidence of flushing was 10%, which was almost similar to the present observation and mediated by PGD<sub>2</sub>. Millers, (2003) also reported that there was no complaints of myopathy and 0.5% of patients had increased aminotransferase level three times more than the upper limit of normal. The present study differs from Miller, (2003) where there was neither significant increment of aminotransferase nor any sorts of clinical events.

Fenofibrate in combination with atorvastatin treated group complaints of headache, fatigue, abdominal pain, dyspepsia and myalgia. However, flushing was not observed in this study group. Davidson, (2003) observed that long duration of treatment by fenofibrate with high dose of statin combination causes myopathy and rhabdomyolysis.

There was a significant difference of serum creatinine level after 12 weeks of treatment with niacin-atorvastatin while no significant difference was observed in fenofibrate-atorvastatin. However, this change was within normal limit.

After 12 weeks of treatment neither of the treated group shows any significant increment of plasma glucose level. This study also analyzed serum alanine aminotransferase to assess liver function test in both Groups. Persistent elevation of ALT, three times higher than the upper limit of normal is considered clinically important (Illingworth et al., 2001). The present study showed that after completion of niacin-atorvastatin treatment, there was no significant difference in SGPT level. But SGPT level was significantly increased in fenofibrate-atorvastatin treated group. Adverse effect did not require withdrawal of drugs in any group. But significantly raised SGPT level in fenofibrate-atorvastatin combination implies that monitoring of liver function should be done to assess hepatic impairment with this regimen.

This study suggests that both combinations are equally effective in dyslipidemia. Although, fenofibrate-atorvastatin combination decreased more triglyceride

level and niacin-atorvastatin combination appeared safer considering some adverse effects.

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## Conclusion

This study was conducted on a small number of patients, in a single center and follow-up was limited for 12 weeks only. As the trial duration was short, analysis of long-term effects and safety was not possible. Other limitations were lack of randomization and matching of sex in female as a risk factor. Assessment of creatinine phosphokinase level for evaluation of muscle related adverse events was not done in this study. This study needs further extensive investigation with randomized double blind, multicentre trials with different dose schedule and different combination for better assessment of long-term effects and safety profile.

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## Conflict of Interest

Authors declare no conflict of interest

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**Author Info**

A. K. M. Mosharrof Hossain (Principal contact)  
e-mail: ahmosharrof@hotmail.com