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A comparative study of efficacy and safety of Ezetimibe and Fenofibrate versus Atorvastatin alone in the treatment of dyslipidemia

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Abstract
Background: *The incidence of dyslipidemia is on the rise in our country due to lifestyle changes and exposure to fast food. This study was done to determine the efficacy and safety of the combination of ezetimibe plus fenofibrate as an alternative to statin monotherapy in patients with dyslipidemia attending our hospital.*
Methods: *This prospective cross-sectional study was done in the Departments of General Medicine and Pharmacology, Kakatiya Institute of Medical Sciences and MGM Hospital, Warangal from May 2018 to January 2019 (9 Months). A total of n=110 patients were identified with dyslipidemia. However, 10 were excluded because they were not fitting in inclusion and exclusion criteria. The remaining n=100 patients were randomly assigned into two groups of n=50 each. Two patients in group I left the study on their own hence in group total number of patients was n=48. They were given Ezetimibe (10 mg/day) and Fenofibrate (160 mg/day) combination. In Group II out n=50 patients one patient left the study and two were lost in follow up hence the total number of patients was n=47. They were prescribed Atorvastatin 20mg/day.*
Results: *The comparison of baseline parameters with that of post-treatment (8 weeks) was done there was a significant decrease in all the lipid parameters in the group I indicated by all the p values that were found to be significant. Similarly in group II the comparison of parameters post 8 weeks therapy showed a significant decrease in all the lipid parameters except for Apo A values. When intergroup comparison of change of parameters was done the p values were not found to be significant in any of the parameters indicating no significant differences between the decreases of lipid parameters in both the groups.*
Conclusion: *the present study concluded that ezetimibe 10mg/day plus fenofibrate 160mg/day appeared to affect the lipid metabolism similarly to monotherapy with Atorvastatin 20mg/day. The combination, as well as monotherapy with a statin, was tolerated well and incidences of minor adverse effects were similar in both the groups of patients.*
Keywords: *Ezetimibe and Fenofibrate, Atorvastatin, dyslipidemia.*

Introduction

Lipids are important constituents of food and they are also synthesized in the liver[1]. Hyperlipidemia is a major cause of atherosclerosis and associated conditions like coronary artery diseases, peripheral vascular diseases, and ischemic

cerebrovascular diseases. There is a strong association between raised LDL cholesterol with the initiation and progression of coronary atherosclerosis. Global burden of metabolic risk factor studies have reported that the total cholesterol levels in different countries of the world have shown that the total cholesterol levels increased in India and other low income and lower-income countries [2, 3] Recognition that dyslipidemia is a risk factor has led to the development of drugs that reduce cholesterol levels. Their drugs provide benefits in patients across the entire spectrum of cholesterol levels, primarily by reducing levels of low-density lipoprotein cholesterol (LDL-C). In well-controlled clinical trials, fatal and non-fatal CHD events and strokes were reduced by as much as 30% and 40%[4-8]. The 3-hydroxy-3-methylgluteryl-coenzyme A [HMGCoA] reductase inhibitors (statins) are the most potent and commonly used group of drugs for dyslipidemia. Statin therapy has shown a decrease in the rates of major vascular complications in patients with established vascular diseases [9]. Although statins were used as the first line of drugs in dyslipidemia and they are well tolerated by the majority of patients. However, certain side effects are known to occur that include elevation of transaminases, myalgias, myositis and rarely rhabdomyolysis[10]. Until recently, there were no safe, effective and well-tolerated alternatives to statin therapy for the management of dyslipidemia in patients with vascular diseases. Ezetimibe is a cholesterol absorption inhibitor that prevents cholesterol absorption by inhibiting the transport of cholesterol across the intestinal wall. Studies have shown that the treatment of ezetimibe as monotherapy results in the reduction of LDL-C by approximately 18%[11]. Its tolerability and safety profile is very good as compared to a placebo in several studies[12,13]. But a comparison of ezetimibe to statins on the lowering of LDL-C appears to show only modest benefits [14]. Fenofibrate is a fibric acid derivative of peroxisome proliferator-activated receptor alpha and alters lipoprotein synthesis[15]. Treatment of fenofibrate monotherapy has also shown to provide modest benefits for LDL-C reductions [16]. While both drugs have shown to be of modest benefits when administered as monotherapy they have shown to significantly reduce LDL-C when used in combination and they are being used in patients who are intolerant to statins[14]. The safety and efficacy of the combination have shown that they are well tolerated and efficacious when used in combination[17, 18]. Hence we in this study tried to evaluate the outcomes of the combination of fenofibrate and Ezetimibe compared with Atorvastatin in dyslipidemic patients visiting our tertiary care hospital.

Material and Methods

This prospective cross-sectional study was done in the Departments of General Medicine and Pharmacology, Kakatiya Institute of Medical Sciences and MGM Hospital, Warangal from May 2018 to January 2019 (9 Months). Institutional Ethical Committee approval was obtained for the present study. Written consent was obtained from all the participants of the study. A total of n=110 patients were identified with dyslipidemia. However, 10 were excluded because they were not fitting in inclusion and exclusion criteria. The remaining n=100 patients were randomly assigned into two groups of n=50 each. Two patients in group I left the study on their own hence in group total number of patients was n=48. They were given Ezetimibe (10 mg/day) and Fenofibrate (160 mg/day) combination. In Group II out n=50 patients one patient left the study and two were lost in follow up hence the total number of patients was n=47. They were prescribed Atorvastatin 20mg/day.

Inclusion Criteria

1. Patients aged ≥18 years with hypercholesterolemia and a history of CHD.
2. Clinical evidence of atherosclerosis or a CHD-risk equivalent (other clinical forms of atherosclerotic disease [peripheral arterial

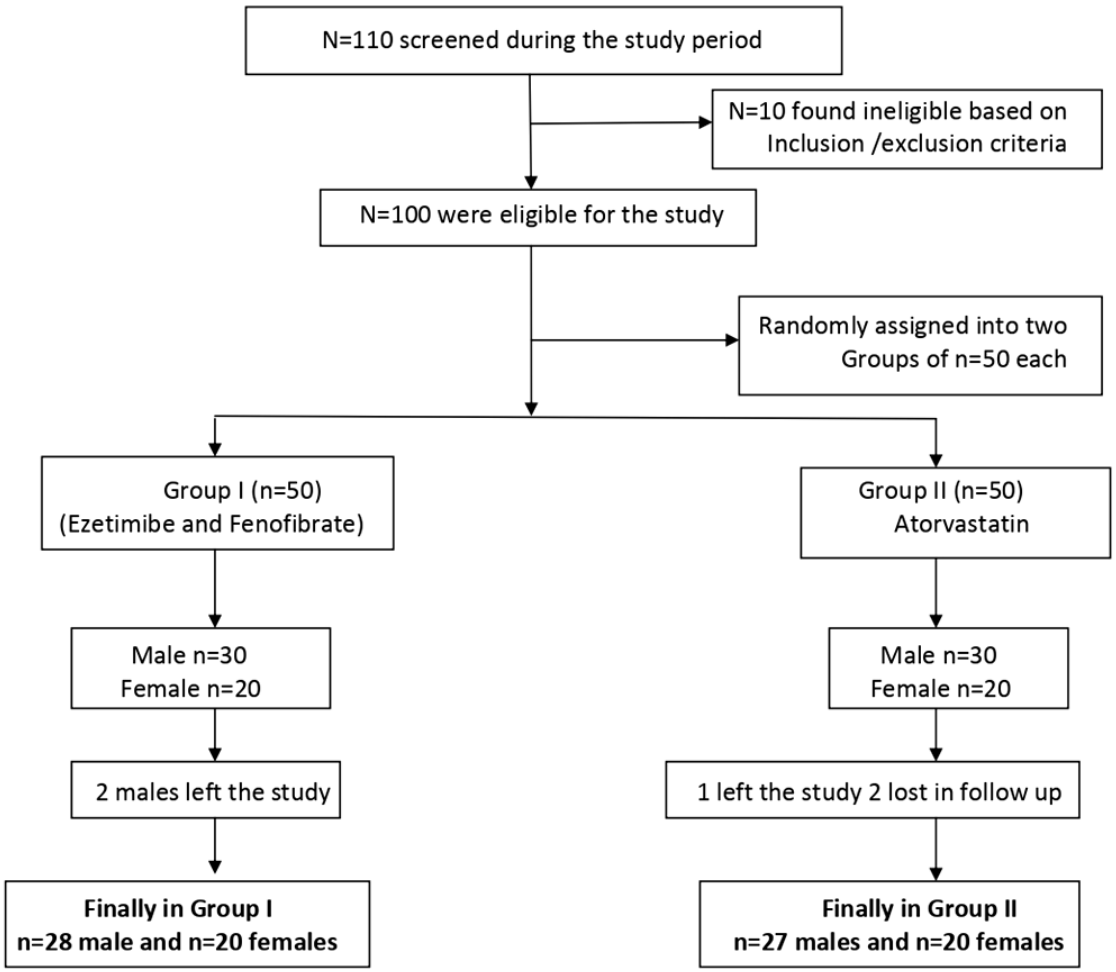
disease, abdominal aortic aneurysm or symptomatic carotid artery disease (transient ischemic attacks, stroke of carotid origin, or > 50% obstruction of a carotid artery)

3. Baseline lipid levels were suggestive of dyslipidemia.

Exclusion Criteria

1. A history of hypersensitivity to statins
2. Pregnancy/lactation
3. Active liver diseases/hepatic dysfunction
4. The patient has a history of severe myalgia or myositis.
5. A serious or unstable medical or psychological condition that could compromise
   the patient's safety or successful trial participation.
6. Those not willing to participate in the study.

All the patients underwent a detailed evaluation with a complete medical history and clinical examination. The patients were evaluated with ECG, Echo, and laboratory investigation for lipid profile, Liver function Tests, Kidney function tests were done before the beginning of treatment and the values were kept as baseline values. The patients were prescribed medicines based on their groups and they were advised to follow up at the end of 8 weeks for evaluation of lipid profile. The pre and post values were compared for the percentage change in lipid values to determine the efficacy and safety of the lipid-lowering agents. All the obtained data were recorded in the MS Excel spreadsheet on windows format and evaluated using statistical software SPSS version 17 on the Windows platform.



Flow chart: showing a detailed description of the steps involved in the conduction of the study

Results

Of the total n=48 patients in group I n=28 (58.33%) were male and n=20(41.67%) were females. Most of the patients were belonging to the age group 56 - 60 years and > 60 years having n=15(31.25%) of patients. In group II out of n=47 males were n=27 (57.44%) and females were n=20 (42.55%). The common age group of the patients involved in the study also was 56 -60 years and >60 years having a combined value of n=33(70.21%) of the patients included. The other demographic parameters age-wise and gender-wise are shown in table 1.

Table 1: showing the demographic profile of patients involved in the study

Age Group	Group I (Ezetimibe and Fenofibrate)		Total (%)	Group II (Atorvastatin)		Total (%)
	Male	Female		Male	Female	
40 – 45	1	2	3 (6.25)	2	0	2 (4.2)
46 – 50	6	3	9 (18.75)	5	2	7 (14.89)
51 - 55	4	2	6 (12.5)	3	2	5 (10.64)
56 - 60	9	6	15 (31.25)	10	7	17 (36.17)
> 60	8	7	15 (31.25)	7	9	16 (34.04)
Total	28	20	48 (100)	27	20	47 (100)

The baseline lipid parameters were measured before the start of the therapy which included total cholesterol (TC), Low-density lipoprotein [LDL], High-Density lipoprotein [HDL] Triglycerides and Total cholesterol and HDL ratio. The mean values of hsCRP were also determined in both the group of patients. The mean values of each with standard deviations have been given in table 2.

Table 2: showing the mean baseline lipid parameters of patients in both groups

Lipid parameters	Group I (Ezetimibe and Fenofibrate)		Group II (Atorvastatin)	
	Mean	± SD	Mean	± SD
Total cholesterol (mmol/L)	5.52	0.84	5.91	0.95
Low Density Lipoprotein (mmol/L)	3.40	0.56	3.88	0.62
High Density Lipoprotein (mmol/L)	1.30	0.27	1.44	0.36
Triglycerides (mmol/L)	1.82	0.43	1.75	0.39
TC/HDL Ratio	4.50	0.82	4.41	0.66
Mean hsCRP (mg/L)	3.21	0.92	2.99	0.62

The baseline blood pressure readings were obtained and recorded in all the patients. The mean SBP values in Group I were 135.5 ± 12.5 mmHg, the mean diastolic blood pressure was 84.2 ± 7.54 mmHg, and the mean arterial pressure readings were 98.5 ± 10.5 mmHg. In group II the mean systolic pressure was found to be 132.0 ± 11.5 mmHg, mean diastolic pressure reading was 83.5 ± 7.45 mmHg. Mean arterial pressure reading was 97.5 ± 8.85 mmHg.

Table 3: Showing the mean blood pressure recordings in both groups

Blood Pressure readings	Group I (Ezetimibe and Fenofibrate)		Group II (Atorvastatin)	
	Mean	± SD	Mean	± SD
Systolic Blood Pressure mmHg	135.5	12.5	132.0	11.5
Diastolic Blood Pressure mmHg	84.2	7.54	83.5	7.45
Mean arterial pressure mmHg	98.5	10.5	97.5	8.85

The comparison of baseline parameters with that of post-treatment (8 weeks) was done there was a significant decrease in all the lipid parameters in the group I indicated by all the p values that were found to be significant. Similarly in group II the comparison of parameters post 8 weeks therapy showed a significant decrease in all the lipid parameters except for Apo A values. When intergroup comparison of change of parameters was done the p values were not found to be significant in any of the parameters indicating no significant differences between the decreases of lipid parameters in both the groups. Details of which are shown in table 4.

Table 4: Baseline characteristics before treatment and after treatment of 8 weeks on lipid parameters in both groups and comparison of the two groups

Lipid parameters	Group I (Ezetimibe and Fenofibrate)				Group II (Atorvastatin)				Comparison between two groups	
	Baseline	8 weeks	% change	P-value	Baseline	8 weeks	% change	P-value	% difference	P-value
Total cholesterol (mmol/L)	5.52	4.1	- 25.72	<0.01	5.91	4.6	-24.7	<0.01	-0.7	0.732
Low-Density Lipoprotein (mmol/L)	3.40	2.5	-32.47	<0.01	3.88	2.25	-30.5	<0.01	1.93	0.56
High-Density Lipoprotein (mmol/L)	1.30	1.5	11.33	<0.05	1.44	1.62	9.5	<0.05	1.75	0.61
Triglycerides (mmol/L)	1.82	1.2	-24.06	<0.01	1.75	1.56	-12.5	<0.02	-11.0	0.078
TC/HDL Ratio	4.50	3.1	-29.11	<0.002	4.41	3.22	-27.5	<0.01	-0.23	0.12
Apo A	1.29	1.41	4.8	<0.03	1.26	1.32	1.38	0.233	3.5	0.312

No serious adverse effects were noted in the present study. All the adverse effects reported were minor and were managed adequately. The details of adverse effects have been provided in table 5.

Table 5: showing the frequency of adverse reactions to the treatment

Adverse effects	Group I (Ezetimibe and Fenofibrate) N=48	Group II (Atorvastatin) N=47
Nausea	2 (4.1%)	1 (2.12%)
Chest pain	1 (2.08%)	0 (0.0%)
URTI	2 (4.1%)	0 (0.0%)
Pharyngitis	1 (2.08%)	2 (4.25%)
Headache	2 (4.1%)	2 (4.25%)
Increase in ALT AST	1 (2.08%)	0 (0.0%)
others	0 (0.0%)	0 (0.0%)

Discussion

In India, there are rapid changes with increasing population, economic prosperity, and aging with increased risk factor transition. Changes in lifestyles and greater use of tobacco and intake of unhealthy diets with sedentary lifestyles have all contributed to increased cardiovascular risks[19 – 21]. The INTERHEART studies have reported that apolipoproteins like ApoA1 and Apo B as well as high LDL-C are important risk factors globally as well in South Asian Countries [22]. The LDL-C reduction in the present study was comparable in both the groups of patients and a slightly better reduction of Apo A in the atorvastatin group. Studies have shown that even a modest reduction of LDL-C by 1.4mmol/L would result in a reduction in major coronary even by 32% [23]. In the present study, we found the combination of ezetimibe plus Fenofibrate produced nearly identical alterations in serum lipid profile levels when compared to monotherapy with 20mg of atorvastatin. However, combination therapy with ezetimibe and fenofibrate produced small and statistically significant increases in apolipoprotein A levels compared to atorvastatin alone. The combination also seemed to do better concerning levels of triglycerides then atorvastatin. Both the treatment did not report any significant adverse effects and they were generally tolerated well and no patient discontinued the treatment because of adverse effects. In our study, we used a dose of 20mg of atorvastatin and the effects of atorvastatin are a dose-dependent and greater reduction in LDL-C, TC, TC: HDL ratio is expected with the higher dose of atorvastatin which is generally given for patients with dyslipidemia and established cardiovascular diseases[24]. The dose of ezetimibe and fenofibrate used in this study was optimal and no further titration was possible. In contrast to statin therapy, that is supported by several studies for its efficacy and prevention of cardiovascular events. Ezetimibe nor fenofibrate alone or in combination have been shown to produce similar reductions in cardiovascular morbidity and mortality [25, 26]. Statins are still widely considered first-line therapy for the management of dyslipidemia in patients with cardiovascular disease and combination therapy may be reserved as a second-line treatment in patients with adverse effects on statins. The combination therapy is generally more expensive and compliance of patients to two drugs is lesser compared to a single drug. Robinson JG et al;[27] assessed the lipid-lowering efficacy of Ezetimibe/simvastatin 10/20mg versus atorvastatin 10 or 20 mg, and Ezetimibe/ simvastatin 10/40 mg versus atorvastatin 40 mg in 1128 patients with hypercholesterolemia and the metabolic syndrome. Ezetimibe/simvastatin was more likely to results in lipid treatment endpoints than atorvastatin and was generally well tolerated at the doses. This study shows that the overall reduction in lipid parameters with both group of patients were comparable and more studies are needed for longer period of time to get the actual long term effects on patients.

Conclusion

The present study concluded that ezetimibe 10mg/day plus fenofibrate 160mg/day appeared to affect the lipid metabolism similarly to monotherapy with atorvastatin 20mg/day. The combination, as well as monotherapy with a statin, was tolerated well and incidences of minor adverse effects were similar in both the groups of patients. However, due to cost considerations lack of data regarding the effects of combination therapy and the question of compliance for combination therapy, statins will be still considered as the first line of drugs and combination therapy may be used in patients who are intolerant to statins.

Conflict of Interest: None
Source of support: Nil
Ethical Permission: Obtained

References

1. Scandinavian Simvastatin Survival Study. A randomized trial of cholesterol

lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4s). Lancet, 1994, 344:1383-89.

2. Farzadfar F, Finucane MM, Danaei G, et al; National, regional and global trends in serum total cholesterol since 1980: systematic analysis of health examination surveys and epidemiological studies with 321 country-years and 3.0 million participants. Lancet 2011; 377:578–86.
3. Anand SS, Yusuf S. A global tsunami of cardiovascular risk. Lancet 2011; 377:502–505.
4. Shepherd J, Cobbe S.M, Ford I., et al; Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. N Engl J Med. 1995; 333:1301-07.
5. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. N Engl J Med 1998,339:1349-57.
6. Heart Protection Study Collaborative Group. MRC/BHF Heart ProtectionStudy of cholesterol-lowering with simvastatin in 20,536 high-risk individuals: a randomized placebo-controlled trial. Lancet 2002; 306:7-22.
7. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: A randomized placebo-controlled trial. Lancet, 2003, 361:2005-2016.
8. Law M.R. Wald N.J. Rudnnicka, A.R. Quantifying effect of statins on Low-Density Lipoprotein Cholesterol, Ischaemic Heart Disease, and stroke: Systematic review and meta-analysis. BMJ 2003, 326:1423.
9. Collins R, Armitage J, Parish S, et al; MRC/BHF Heart protection study of cholesterol-lowering with simvastatin in 20,536 high-risk individuals: a randomized placebo-controlled trial. Lancet 2002; 360:7-22.
10. Pasternak RC, Smith SC, Bairey-Merz CN, Grundy SM, et al American college of cardiology, American Heart Association. National Heart, Lung, Blood Institute: ACC/AHA/NHLBI. Clinical advisory on the use and safety of statins. Circulation 2002; 106:1024-28.
11. Knopp RH, Gitter H, Truitt T, Bays H, et al; Ezetimibe, a new cholesterol absorption inhibitor, effect on plasma lipids in patients with primary hypercholeste-rolemia. Eur Heart J 2003;24:729-41.
12. Kosoglou T, Statkevich P, Jhonson Levonas AO, Paolini JF, et al; Ezetimibe: A review of its metabolism, pharmaco-kinetics, and drug interactions. Clinical pharmacokinetics 2005;44:467-94.
13. Bays HE, Moore PB, Drehobl MA, Rosenblatt S, Toth PD et al; Effectiveness and tolerability of ezetimibe in patients with primary hypercholesterolemia: a pooled analysis of two-phase II studies. Clin Ther 2001:1209-30.
14. Ballantyne CM, Houri J, Notrabartolo A et al; effect of ezetimibe coadministered with atorvastatin in 628 patients with primary hypercholesterolemia. Circulation 2003; 1072409-2415.
15. Kosaglou T, Statkevich P, Fruchart JC, et al; Pharmacodynamic and pharmacokinetic interaction between fenofibrate and ezetimibe. Curr Med Res Opin 2004; 20:1197-207.
16. Ramjatt BR, Collaghan DJG, Theiss U: Efficacy and tolerability of supra-bioavailable formulation of fenofibrate in patients with dyslipidemia: A pooled analysis of two open-label trials. Clin Ther 2002; 24:1105-16.

17. Franir M, Freeman MW, Macdonnell G, Perevozskaya I, et al; Efficacy and safety of the coadministration of ezetimibe with fenofibrate in patients with mixed hyperlipidemia. Eur Heart J 2005:26:897-05.
18. McKenny JM, Franier M, Lo KW, Bays HE, Perevozkaya I, safety and efficacy of long term coadministration of fenofibrate and ezetimibe in patients with mixed hyperlipidemia. J Am Coll Cardio 2006; 47:1584-87.
19. Gupta R, Gupta KD. Coronary heart disease in low socioeconomic status subjects in India: an evolving epidemic. Indian Heart J. 2009;61:358–367.
20. Defo K. Beyond the transition frameworks: the cross-continuum of health, disease and mortality framework. Global Health Action. 2014;15:24804.
21. Patel V, Chatterji S, Chisholm D, et al. Chronic diseases and injuries in India. Lancet. 2011;377:413–428.
22. Karthikeyan G, Teo KK, Islam S, et al. Lipid profile, plasma apolipoproteins, and risk of a first myocardial infarction among Asians: an analysis from the INTERHEART Study. J Am Coll Cardiol. 2009;53:244–253.
23. Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, et al; Efficacy and safety of cholesterol-lowering treatment prospective meta-analysis of data from 90056 participants in 14 randomized trials of statins. Lancet 2005; 366:1267-78.
24. Genest J, McPherson R, Frolich J, Anderson T, Campbell N, Carpentier A, et al; 2009 Canadian cardiovascular society/ Canadian guidelines for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease in adult 2009 recommendations. Can J Cardiol 2009; 25(10):567-579.
25. Kastelein JJ, Akdim F, Stroes Es, Zwinderman AH, et al; Simvastatin with or without ezetimibe in familial hypercholesterolemia. N Engl J Med 2008; 358:1431-43.
26. Keech A, Simes RJ, Barter P, Best J, Scott R, et al; Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (The field study): a randomized controlled trial. Lancet 2005;366:1849-61.
27. Jennifer G. Robinson, Christie M. Ballantyne, Scott M. Grundy, Lipid-Altering Efficacy and Safety of Ezetimibe/ Simvastatin Versus Atorvastatin in Patients with Hypercholesterolemia and the Metabolic Syndrome (from the VYMET Study). Am J Cardiol 2009;103: 1694- 02.