A Comparative Study of the Novel Cholesterol Absorption Inhibitor Ezetimibe with Atorvastatin and Atorvastatin Alone in Type II Diabetes Mellitus Patients with Primary Hypercholesterolemia


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Conflict of Interest Statement:
There are no financial or material gains that may involve the subject matter of the manuscript.

Keywords:
Type II Diabetes Mellitus, Primary Hypercholesterolemia, Ezetimibe, Ezetimibe with Atorvastatin

Acknowledgements
We thank the administration and the staff of Sri Ramachandra Medical College and Research, Chennai for their support with respect to the study. No grants, equipment, or drugs were sponsored by any pharmaceutical company.
ABSTRACT

Background: CHD is the leading cause of death in patients with Type 2 DM. Despite the efficacy of statins in lowering LDL-C levels, many patients require additional LDL – C level reduction. A new cholesterol absorption inhibitor, Ezetimibe is licensed for the treatment of primary hypercholesterolemia either for co-administration with a statin or as monotherapy.

Aims and objectives: To compare the safety and efficacy of Atorvastatin and Atorvastatin + Ezetimibe after treatment for 8 weeks by calculating the percentage changes from baseline in LDL-Cholesterol in type 2 diabetes mellitus patients with primary hypercholesterolemia.

Materials and methods: This is randomized, parallel group, open–label, comparator–controlled 8-week trial, of Atorvastatin 10 mg daily and Atorvastatin 10 mg daily + Ezetimibe 10 mg daily, was conducted at the outpatient clinics of Sri Ramachandra Medical College and Research, Chennai, between 2004-05. The eligible 60 participants were randomized into Atorvastatin (Atv) and Atorvastatin + Ezetimibe (AtvEz) treatment groups, with 30 patients in each group. At the end of 8 weeks, all 60 patients were analyzed. Statistical analysis was done using Graph Pad InStat, Graph Pad Software Inc, CA, USA.

Results: Significant reductions of LDL-C, TC and TG levels were noted in the AtvEz group. The HDL-C levels were significantly raised in the AtvEz group. Safety and tolerability was similar in both groups.

Conclusion: The addition of ezetimibe to statin therapy should be considered for Type 2 Diabetes Mellitus patients not achieving their NCEP ATP III LDL-C goals while receiving statin therapy alone.
INTRODUCTION

Cardiovascular disease, or coronary heart disease, is the number one cause of death in both men and women in the developed countries. Atherosclerosis remains a major cause of cardiovascular diseases. High concentrations of total cholesterol (T.C), low density lipoprotein cholesterol (LDL – C), and triglyceride (TG), and low levels of high density lipoprotein cholesterol (HDL – C), are associated with an increased risk of cardiovascular events, making the identification and management of hyperlipidaemia in patients at risk of future vascular events a priority.

Type 2 diabetes mellitus (DM) is associated with a two to three-fold risk of death from coronary heart disease (CHD) and a doubling of CHD events post-myocardial infarction. CHD is the leading cause of death in patients with Type 2 DM, wherein factors such as increased total cholesterol, increased LDL-cholesterol, haemoglobinA1c, hypertension, retinopathy, smoking and albuminuria have all been shown to increase cardiovascular event rates in diabetic patients.

Recently, diabetic patients with cardiovascular disease were categorized as being at very high risk, which prompted even more aggressive targets for one major modifiable risk factor-the plasma concentration of LDL-C. The current mainstay of medical treatment of hyperlipidemia is the administration of hydroxy-methyl-glutaryl coenzyme A (HMG CoA) reductase inhibitors. The HMG CoA reductase inhibitors block cholesterol synthesis in the liver, resulting in the increased uptake of serum LDL cholesterol. This results in predictable and dose-related decrements in serum LDL cholesterol. Side effects include gastrointestinal discomfort, liver toxicity, and myopathy. Currently the HMG CoA reductase inhibitors that are in use are Atorvastatin, Simvastatin, Lovastatin, and Rosuvastatin.

Despite the efficacy of statins in lowering Low-density lipoprotein (LDL-C) levels, many patients for heart disease with hypercholesterolemia require additional LDL – C level reduction. A new cholesterol absorption inhibitor, Ezetimibe, is the first agent of a new class of lipid-lowering compounds that selectively inhibits the intestinal absorption of cholesterol and related phytosterols, which received US Food and Drug Administration approval in October 2002 and was launched in U.K. It is licensed for the treatment of primary hypercholesterolemia either for co-administration with a statin or as monotherapy. In clinical trials, Ezetimibe produced significant reductions in LDL – cholesterol both alone and when added to statin therapy.
AIM AND OBJECTIVES

This study was conducted with the following aims.

Primary

To compare efficacy of Atorvastatin and Atorvastatin + Ezetimibe after treatment for 8 weeks by calculating the percentage changes from baseline in LDL-Cholesterol in patients with primary hypercholesterolemia with diabetes mellitus.

Secondary

- To compare the safety and tolerability of Atorvastatin and Atorvastatin + Ezetimibe in diabetes mellitus patients with primary hypercholesterolemia
- To determine the effects of eight weeks of treatment with Atorvastatin and Atorvastatin + Ezetimibe on Total Cholesterol (TC), HDL Cholesterol, Triglycerides, TC/HDL ratio and LDL/HDL ratio

MATERIAL AND METHODS

Study Design:

Consent, demographic profile and medical history were recorded during the 0-2 weeks of the trial. Physical, general and systemic examination was also done along with recording of basal lipid profile, biochemical, hematological, and urine analysis data. The participants were advised to discontinue any lipid-lowering drug and any supplements and instructed to comply with NCEP Step I diet, and advised to return after 2 weeks. Patients were randomized into the two treatment groups at day 0 and were given respective drugs (see box below). They were given a telephone number to which they have to dial if they experience any adverse event. Patients were advised to return back after 2 weeks.

Trial Design:

This is randomized, parallel group, open-label, comparator-controlled, 8-week trial, of Atorvastatin 10 mg daily and Atorvastatin 10 mg daily + Ezetimibe 10 mg daily, was conducted at the outpatient clinics of Department of Medicine Sri Ramachandra Medical College and Research, (D.U), Porur, Chennai, between May 2004 and April 2005. The protocol was submitted to the Institutional Ethics Committee and approval was obtained for the same. The work was conducted in compliance with Institutional Review Board/Human Subjects Research Committee requirements.

After discontinuation of any lipid lowering drug or supplements, patients entered the two week dietary lead-in period during which they were instructed to follow the NCEP step I diet. Patients who were compliant with the diet and met lipid criteria were randomized into two treatment groups. The Atv group that would receive Atorvastatin 10mg tablets and the AtvEz group that would receive Atorvastatin 10mg+Ezetimibe 10 mg tablets.
Dosage of study medication: Atv Group: Tablet Atorvastatin – 10 mg daily, AtvEz Group: Tablet Atorvastatin – 10 mg + Ezetimibe 10 mg daily.

Mode of administration:

Orally with standardized ½ glass of water after dinner.

Drug compliance assessed and appropriate amount of tablets were issued for the next visits. The physical, general and systemic examination was repeated at the Day-0, 0+2 weeks, 0+5 weeks, 0+8 weeks, and 0+10 weeks. The lipid profile, biochemical, hematological, and urine analysis was performed at Day-0 and 0+8 weeks. Adverse events were enquired and monitored during all the subsequent visits including 0+10 weeks. The administration of the drugs was stopped at the end of 0+8 weeks. Figure 1 and table 1 summarizes the study design and data collected during the study.

Patients:

All the participants gave informed consent before any trial procedure was initiated. All the eligible participants that entered the study were informed about their freedom to withdraw from the study without giving any reason at any given time and while doing so they will not be denied the option of continuing quality medical care in the same Institute. Case record forms was prepared for each of the patient and kept with the Investigator.

Blood sugar levels were maintained under normal levels by treating the patient with oral hypoglycemic agents as advised by the endocrinologist.

Inclusion criteria:

- Men and women with age ranging from 40 – 80 years,
- Patients with type II diabetes mellitus (as defined using World Health Organization criteria)
- Patients with hypertension, ischemic heart disease and other metabolic disease,
- Patients with primary hypercholesterolemia based on criteria laid down by NCEP ATP III guidelines. These patients will be enrolled if following lipid profile criteria are satisfied at the time of enrollment, a) LDL cholesterol > 160 mg/dl and / or Total cholesterol > 240 mg/dl, b) Triglycerides < 400 mg/dl.

Exclusion criteria:

- Patients unwilling or unable to give informed consent
- Patients with known hypersensitivity to statins
- Women who are breast-feeding or pregnant
- Patients with secondary hypercholesterolemia
- Patients with drug induced dyslipidemia (via. Beta blockers, thiazides, oral contraceptives and retinoic acid)
• Uncontrolled hypertension
• Uncontrolled diabetes mellitus with fasting serum glucose > 180 mg/dl or glycated Hb >9%
• History of malignancy
• Patients with clinically significant gastrointestinal, respiratory, hepatic, renal, cardiac (including unstable angina or severe heart failure), endocrine or hematological disorder or any other severe concurrent illness or major surgery
• Patient with active liver disease or hepatic dysfunction defined by alanine aminotransferase (ALT) or aspartate aminotransferase (AST) greater than three times the upper limit of normal (> 3 X ULN)
• Patients with serum creatinine > 2.5 mg/dl
• Patients requiring treatment with beta–blockers, thiazide diuretics, oral contraceptives, corticosteroids, prazosin or isoretinoin (retinoic acid)
• Patients on concurrent therapy with medication known to affect lipoprotein metabolism including oral contraceptives, fish oils, anion exchange resins, nicotinic acid or analogues and probucol (either concomitantly or within preceding six months)
• Patients on concurrent therapy with drugs known to be associated with rhabdomyolysis in combination with HMG–CoA reductase inhibitors e.g. cyclosporine, erythromycin, azole antifungals
• Patients with alcohol or drug abuse
• Participation in another study concurrently or within 30 days before study entry

Of the 64 participants who were eligible to participate in the study, 4 patients (2 from each group) withdrew their consent to participate in the study before commencement. The remaining 60 participants were randomized into Atorvastatin (At) and Atorvastatin + Ezetimibe (AtvEz) treatment groups, with 30 patients in each group. At the end of 8 weeks, all 60 patients were analyzed.

MEASUREMENT AND STATISTICAL ANALYSIS

Serum lipid and lipoprotein measurements:

Blood samples were collected with the patient fasting for at least 12 h. Biochemical and hematological measurements were made by a central laboratory. The following parameters were measured: total serum cholesterol, LDL-cholesterol, HDL-cholesterol, TG. Serum cholesterol and TG concentrations were measured by an automated enzymatic method. Blood samples were collected once before randomization, at randomization, and 8 weeks after start of treatment. All lipid and lipoprotein analysis were done at a single laboratory, throughout the study.

Adverse events:

All patients are questioned about adverse events at each follow-up visit. Both serious and non-serious adverse events were recorded and the data reviewed. It was agreed that if a serious adverse event occurs, the investigator may interrupt or discontinue study drug at his/her discretion. Safety assessment included recording of treatment–emergent adverse events
(adverse events that started or worsened during randomized treatment), hematological and clinical chemistry measurements that were performed at the same laboratory. Also physical, general and systemic examination was performed during the study. All the patients who received the drugs were included in the safety analysis, and safety data summarized descriptively without statistical analysis.

Statistical Analysis:

Primary end point is percentage change in LDL – Cholesterol from the base line to 8 weeks. The base line was the mean of two values (value obtained before randomization and the value at randomization). A 6% difference between treatment groups in the LDL – Cholesterol reduction was predefined as clinically meaningful.

Statistical analysis was done using Graph Pad InStat, Graph Pad Software Inc, Oberlin drive, San Diego, CA, United States of America.

RESULTS

The results of the efficacy were analyzed and compared after 8 weeks of drug treatment in Atorvastatin and Atorvastatin + Ezetimibe groups.

Patient Characteristics

Base line characteristics (Table 2) were very similar and identical between both Atorvastatin and Atorvastatin + Ezetimibe groups. Both the groups were similar in having approximately equal number of patients with family history of CHD, smokers and history of hypertension. Drug compliance was assessed at the end of 2, 5 and 8 weeks by tablet count and was found to be similar between both treatment groups.

Efficacy

At the end of 8 weeks of study period the reduction of LDL – Cholesterol was extremely significant in both the groups. The reduction in LDL – cholesterol in the Atorvostatin group was 41.5% (p <0.0001) while that in the AtvEz group was also very significant at 54.01% (p <0.0001).

In the final analysis, the proportion of people who met with National Cholesterol Education Programme (NCEP) LDL–Cholesterol goals was almost double when Atorvostatin was used along with Ezetimibe. Table 3 and figure 2 summarize the efficacy data noted in both the groups.

At the end of 8 weeks of study period, the reduction of total cholesterol was extremely significant in both the groups. In the Atv group, the reduction in total cholesterol was 31% (p <0.0001) while that in the AtvEz group was 44.05% (p<0.0001) when compared to the baseline levels.

A highly significant reduction of triglycerides in both the Atv group (22.5 %;
p< 0.0001) and the AtvEz group (33.6%; p< 0.0001%) was noted.

The elevation of HDL–cholesterol was highly significant in the AtvEz group where in it increased by 9.8% (p<0.0001) when compared to the Atv group, where the increase was only 5.7% (p<0.001) and was significant.

Safety

Over all the trial treatment were well tolerated in both groups at the end of 8 weeks treatment. The overall percentage of people who withdrew after commencement of treatment in both the groups was around 7.5%.

In the Atorvastatin group, one patient had to stop further drug therapy due to development of gastritis after a period of 6 weeks, which subsided after 2 weeks of stopping the drug. Another patient withdrew from the study without any reasons.

In the Atorvastatin plus Ezetimibe group, 2 participants stopped the drug treatment mid way. One participant developed pain in the thighs and arms after one week of drug consumption and this disappeared after 3 weeks of stopping the drug. Another patient developed gastritis after 2 weeks of drug intake, which completely subsided after 3 weeks of stopping the drugs. There were no other adverse events reported in the study.

Also there was no change in biochemical, hematological and hepatological parameters that were evaluated at the end of 8 weeks study period in both the groups.

DISCUSSION

CVD events are four times more common in individuals with diabetes, occur at a younger age, and have a much greater case fatality rate. The risk of CVD conferred by diabetes is so great that the National Cholesterol Education Program (NCEP) Adult Treatment Panel III identifies diabetes as a CVD risk equivalent—a condition that requires aggressive care to prevent future vascular events in people with known vascular disease. The Centers for Disease Control and Prevention recently reported that 70–97% of individuals with diabetes have dyslipidemia. While therapeutic lifestyle changes (TLC) remain an essential modality in clinical management, the inclusion of patients with diabetes in the high-risk category and the benefits of LDL-lowering therapy in these patients has been well established.

The present study compared the lipid-lowering efficacy of Atorvastatin alone and when added with the novel drug Ezetimibe in Type II Diabetes Mellitus patients with primary hypercholesterolemia. Both the drugs were given after a dietary run in period of 2 weeks, during which the participant did not take any drugs or cholesterol supplements that could have an effect on the lipid parameters.

It is well established that statins exhibit most of their LDL–Cholesterol reducing effects within 2 weeks and produce full
effects by 4 to 6 weeks. Despite their established efficacy, however, studies have noted that the number of patients who are able to attain and maintain LDL cholesterol (LDL-C) levels recommended by the US National Cholesterol Education Program Adult Treatment Panel III (ATP III) is suboptimal, which indicates a gap between lipid goals and clinical practice. Statin doses often are not titrated to achieve goals. The ACCESS study reported that about 72% of the patients with CHD achieved the ATP II goal at a maximum titration (up to 80 mg). However, maximum dosages of atorvastatin has been associated with increased incidence of elevated liver enzymes, hepatotoxicity and myalgias. These findings necessitate the need of an adjuvant drug that can effectively add up to the actions of the statins while reducing the dosage required and bringing about the best possible attainment of the NCEP goals.

Our study indicated a 30.1% higher reduction in the LDL-C levels when both Atorvostatin and Ezetimibe were administered. This greater reduction of LDL–C resulted in a higher percentage of participants who achieved their National Cholesterol Education Program (NCEP) goals. The efficacy was 71.2% higher in relation to HDL-C levels with the combination treatment. Further, a 40.1% higher reduction in the total cholesterol levels were noted the AtvEz group showing greater efficacy of the combination in reducing total cholesterol levels. Similarly, a 49.3% higher reduction in the triglyceride levels was noted in the combination group. There are several double-blind, placebo-controlled trials that have investigated the efficacy of ezetimibe co-administered with a statin when compared with statin therapy alone in patients with primary hypercholesterolaemia.

An 8 week trial which consisted of 769 patients taking stable doses of atorvastatin (10 to 80 mg daily), simvastatin (10 to 80 mg daily), lovastatin (10 to 40 mg daily) fluvastatin (20 to 80 mg daily), pravastatin (10 to 40 mg daily) or cerivastatin (0.2 to 0.8 mg daily) noted that co-administering ezetimibe 10 mg daily in these patients significantly reduced LDL-C levels when compared with statins and a placebo (25.1% vs 3.7%, p<0.001).

Three other 12 week trials randomized patients to different doses of a statin either alone or in combination with ezetimibe 10 mg daily. One of the trials which comprised of 668 patients reported a significant reduction in LDL-C than simvastatin alone (49.9% vs 36.1%, p<0.01) when compared to ezetimibe plus simvastatin 10 to 80 mg daily.

Ezetimibe plus atorvastatin 10 to 80 mg daily was evaluated in another trial with 628 participants. Here it was noted that the combination therapy reduced LDL-C by 54.5% when compared with 42.4% for atorvastatin alone (p<0.01). Further, the combination provided additional triglyceride reductions of 30% to 40%, and HDL-C increases of 5% to 9%, were also noted depending on atorvastatin dose when used alone.
From the same trial, 246 patients were enrolled in a 12-month extension to study the safety and efficacy of ezetimibe in combination with atorvastatin and comparing it with atorvastatin alone. After 6 weeks, the combination therapy produced greater reductions in LDL-C (-53 vs. -37%), TC (-38.8 vs. -26.0%) and TG (-28 vs. -12%) compared to monotherapy. Further, these changes were maintained and significant at 1 year (p < 0.01 for LDL-C, TC and TG). 21

The third 12 week trial (n=538) compared the efficacy of ezetimibe plus pravastatin 10 to 40 mg daily and reported a significantly higher reduction in LDL-C than with pravastatin alone (37.7% vs 24.3%, p<0.01). 22

The combination therapy was well tolerated in our study wherein a total of 3 patients withdrew due to adverse effects. The adverse effects included gastritis (in both groups) and pain in the thighs (in the AtvEz group) which subsided following withdrawal of the treatment. Several studies have reported that the safety, tolerability and incidence of liver and muscle adverse experiences of the combination therapy are similar to atorvastatin alone. 20, 23-25 A long term (12 months) study by Ballantyne et al also reported that the incidence and treatment of adverse events were similar in both groups (ATV and ATV+EZE) and neither clinically significant elevations in hepatic transaminases or creatine kinase nor any cases of myopathy or rhabdomyolysis were noted during the study period. 21

LIMITATIONS

There were a few limitations noted in the study. The study involved a small population from South India whose results may not be generalized to all. This was an open label study and hence there may be psychological effect on the outcome which cannot be confirmed. The outcomes were dependent upon the patient compliance which was recorded based on the number of tablets left in the strips at each visit. Thereby absolute compliance could not be predicted.

CONCLUSION

The 8 week combination drug therapy (Atorvostatin 10mg with Ezetimibe 10mg, daily) was noted to be more effective than monotherapy in type 2 diabetes mellitus patients with primary hypercholesterolemia. The combination therapy was more effective than statin alone in improving the lipid profile of patients with hypercholesterolemia. Ezetimibe plus statin was well tolerated and had a similar safety profile in both the groups. The addition of ezetimibe to statin therapy should be considered for Type 2 Diabetes Mellitus patients not achieving their NCEP ATP III LDL-C goals while receiving statin therapy alone.

ACKNOWLEDGEMENTS

We thank the administration and the staff of Sri Ramachandra Medical College and Research, Chennai for their support with respect to the study. No grants, equipment, or drugs were sponsored by any pharmaceutical company.
REFERENCES


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Vijaybabu K, Punnagai K et al; Comparative study of Cholesterol absorption Inhibitor

FOOTNOTES

a National Cholesterol Education Programme (NCEP) “Step I” diet advocates the following goals:

i) Restriction of caloric intake to prevent obesity and maintain a desirable weight, or

reduce weight in those who are overweight

ii) Consumption of less than 30% of total daily caloric intake from fat.

iii) Consumption of approximately 8-10% of total calories from saturated fat

iv) Consumption up to 10% of total calories from polyunsaturated fatty acids

v) Consumption to 15% of total calories of monounsaturated fatty acids.

vi) Consumption of 55% to 60% of calories as complex carbohydrates.

vii) Consumption of less than 300mg per day of cholesterol.

TABLES

Table 1. Data recorded during the study

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<td>Drug supply</td>
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<td>Atorvastatin + Ezetimibe</td>
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<td>Male/female (%)</td>
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<td>Physically active %</td>
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<tr>
<td>LDL-C (mean ± SEM) mg/dl</td>
<td>177.2 ± 1.9</td>
<td>179.4±1.1</td>
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<td></td>
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<tr>
<td>Total cholesterol (mean±SEM) mg/dl</td>
<td>264.6 ± 3.1</td>
<td>264 ± 1.5</td>
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<tr>
<td>Triglycerides (mean ± SEM) mg/dl</td>
<td>171.4 ± 2</td>
<td>172.2 ± 1.4</td>
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<tr>
<td>HDL-C (mean ± SEM) mg/dl</td>
<td>44.5 ± 0.83</td>
<td>46.1 ± 0.8</td>
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Table 3. Mean Percentage Changes From Baseline LDL – Cholesterol, HDL – Cholesterol, Total Cholesterol and Triglycerides in Both Atorvastatin And Atorvastatin + Ezetimibe Group

<table>
<thead>
<tr>
<th>PARAMETERS</th>
<th>ATORVASTATIN</th>
<th>ATORVASTATIN + EZETIMIBE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosage/day(n)</td>
<td>10 mg(30)</td>
<td>10 mg + 10 mg(30)</td>
</tr>
<tr>
<td><strong>LDL – CHOLESTEROL</strong> BL (mean ± SEM) mg/dl</td>
<td>177.2 ± 1.9</td>
<td>179.4±1.1</td>
</tr>
<tr>
<td>% Change from BL</td>
<td>- 41.50</td>
<td>- 54.01</td>
</tr>
<tr>
<td>p value *</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>HDL – CHOLESTEROL</strong> BL (mean ± SEM) mg/dl</td>
<td>44.5 ± 0.83</td>
<td>46.1 ± 0.8</td>
</tr>
<tr>
<td>% Change from BL</td>
<td>+ 5.70</td>
<td>+ 9.80</td>
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<tr>
<td>p value *</td>
<td>&lt;0.001</td>
<td>&lt;0.0001</td>
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<td><strong>TOTAL – CHOLESTEROL</strong> BL (mean ± SEM) mg/dl</td>
<td>264.6 ± 3.1</td>
<td>264 ± 1.5</td>
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<tr>
<td>% Change from BL</td>
<td>- 31.10</td>
<td>- 44.05</td>
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<tr>
<td>p value *</td>
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<td>&lt;0.0001</td>
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<td><strong>TRIGLYCERIDES</strong> BL (mean ± SEM) mg/dl</td>
<td>171.4 ± 2</td>
<td>172.2 ± 1.4</td>
</tr>
<tr>
<td>% Change from BL</td>
<td>- 22.50</td>
<td>- 33.60</td>
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<tr>
<td>p value *</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

* p value <0.0001 is considered as extremely significant; p value <0.001 is considered as significant.
FIGURE LEGENDS

Figure 1. Study Design

Figure 2. Percentage changes in the cholesterol levels in comparison to baseline levels. TC=Total serum cholesterol; LDL-C=LDL-cholesterol; HDL-C=HDL-cholesterol; Tg=Triglycerides; Atv= Atorvostatin group; AtvEz= Atorvostatin plus Ezetimibe group
How to cite this article


Vijaybabu K Punnagai K et al; A Comparative Study of the Novel Cholesterol Absorption Inhibitor Ezetimibe with Atorvastatin and Atorvastatin Alone in Type II Diabetes Mellitus Patients with Primary Hypercholesterolemia

Available at:
ijbms.com
April 2010 issue1 volume 1