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Management of Hyperlipidemia in Very High Risk and High Risk Cardiovascular Patients: a Prospective, Interventional Phase IV Multicenter Study Focusing on The Safety and Efficacy of Ezetimibe in Combination of Atorvastatin

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Abstract

Objective: The purpose of this study was to observe the efficacy, safety and tolerability of Ezetimibe in combination of Atorvastatin in very high risk and high risk cardiovascular patients.

Methods: This was a prospective, interventional phase IV multicenter study with the use of purposive sampling technique, conducted from February 2016 till December 2016. After taking the ethical approval and informed consent, 240 patients between age > 18 and < 70 years with LDL-C above optimal levels (optimal levels < 100 mg/dl) and prior history of at least one cardiac event (myocardial infarction) who were stabilized clinically after acute phase were included in the study. Out of the total of 240 patients, 211 patients completed the study. Among them, 60(28 %) cases were assessed for the total lipid profile outcome, however all patients were evaluated for LDL-C level. The total lipid profile including LDL, VLDL, HDL and triglycerides were done from the Agha Khan University Hospital Laboratory, Karachi. The basic demographic variables were recorded at the base line like age, gender and weight. The history of smoking and previous cardiac events was recorded. Those who failed to follow up, had any contraindication, hypersensitivity or intolerance for Ezetimibe and Atorvastatin and pregnant women were excluded from the study.

Each patient was followed up for a period of three months. Three study visits were performed at baseline, at 4th week and at 12th week. Incidence of adverse events (AEs) and serious AEs (SAEs) were recorded. Data analysis was done through SPSS version 20.0.

Result: Out of the total 211 patients, 85 (40%) were in high risk group and 126 (60%) were in very high risk group. In high risk and very high risk patients the mean of LDL cholesterol at base line was 162.07 mg/dl and 146.92 mg/dl with standard deviation of 58.54 mg/dl and 49.49 mg/dl respectively. At 12th week of treatment it was 109.39 mg/dl and 104.93 mg/dl with a significant p value of < 0.001. The overall reduction and achievement of the goal regardless of the category projected that in 135 (67.5%) patients there was a reduction in the LDL-C level from 30 to 50%. The overall adverse events of the therapy were almost negligible with muscle cramps and myalgia in only 2% and 2% cases respectively. Around 95% of the cases did not report any adverse events. Moreover, there was no serious adverse event reported.

Conclusion: The combined use of Ezetimibe with Statin was observed to be effective in reducing the LDL-C levels and decreased the cardiovascular risk factor.

Keywords: *Hyperlipidemia; High risk and very high risk cardiovascular patients; Ezetimibe; Atorvastatin*

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Introduction

The primary reason of death in Pakistan is Coronary heart disease (CHD), and accounted for 111.4 thousand deaths in 2012 alone [WHO statistical profile.2015]. Likewise, CHD is the important cause of death in adults in USA, which has been related with raised levels of low-density lipoprotein cholesterol (LDL-C) and decreased levels of high-density lipoprotein cholesterol (HDL-C). The major manifestation of hyperlipidemia is premature coronary atherosclerosis which is the major cause of CHD, subsequently the monitoring of plasma lipid level is important. Therefore, hyperlipidemia also results in increase in pulmonary artery disease, CHD, high blood pressure, myocardial infarction and stroke. The person with advancing age, history of smoking and positive family history of premature ischemic heart disease increases the risk for life to many folds. Scientific explorations confirmed the reduction of cardiovascular events in patients with myocardial infarction after management of LDL-C [Pedersen., *et al.* 2005; The Lancet. 1994]. Dyslipidemia is one of the significant risk factors for cardiovascular disease [Luo., *et al*. 2016]. A reduction of LDL-C decreases the risk and ameliorates the symptoms of CHD by causing a decrease in atherosclerotic lesions [Brown., *et al.* 1990].

There is a direct association between serum LDL cholesterol and the occurrence of CHD and other macro vascular complications [Chatterjee., *et al.* 2011; Murray., *et al.* 1997]. Likewise, a contrary association exists between HDL cholesterol and CHD. The reduction in the LDL-C and consequently CHD is observed by the management with range of drugs including statins, fibrates, bile acid resins, and niacin. The National Cholesterol Education Program (NCEP) proposes the screening for CHD with measurement of total cholesterol (TC), LDL cholesterol, HDL cholesterol, and triglyceride (TG) concentrations for all adults over the age of 20 years, while management choices primarily established on LDL cholesterol concentrations [JAMA. 2001]. In spite of its clinical importance, LDL-C elements are infrequently assessed routinely even in high risk patients [Misra., *et al*. 2004; Joshi. 2003]. In high risk persons, the recommendation of LDL cholesterol therapeutic goal is < 100 mg/dL, with possible objective of < 70 mg/dL or a 30-40% decrease in LDL-C levels [Grundy., *et al.* 2004].

The methods of risk assessment for screening and management of patients having hyperlipidemia and cardiovascular diseases can be classified into five broad risk categories: 1. Very High – Recent acute coronary syndrome, CHD or non-coronary atherosclerotic vascular disease and one of the following: - Diabetes mellitus - Metabolic Syndrome, Current smoking, chronic kidney disease 2. High – CHD or CHD risk equivalent. Patients with widespread subclinical atherosclerosis, chronic kidney disease and receivers of solid organ transplant

are also at high risk. 3. Moderately High – No CHD with > 2 risk factors and 10 years CHD risk 10-20%. 4. Moderate –No CHD with > 2 risk factors and 10 years CHD risk < 10%. 5. Lower – No CHD with < 1 risk factor [Patrick., *et al*. 2017].

However, it is difficult to achieve these target levels with the administration of a statin alone [Weng., *et al*. 2010]. Lipids are closely involved in coronary artery disease due to their contribution in atherogenic process. Therefore, the beneficial mediations are intended for satisfactory modifications of lipoprotein metabolism, predominantly reducing low-density lipoprotein cholesterol (LDL-C), which is the keystone of management for primary and secondary cardiovascular disease. The statins are a group of 3-Hydroxy-3-methylglurtaryl coenzyme A inhibitors that are important medications for patients with CAD to decrease the threat of adverse cardiovascular events through their LDL-C-lowering consequence. Substantial proof exists for a strong relationship between LDL-C level and cardiovascular event rate, supporting the "lower the better" hypothesis [Flather., *et al*. 2010; Armitage., *et al*. 2010; Cannon., *et al.* 2004].

Recently, the National Cholesterol Education Program Adult Treatment Panel recommended an optical LDL goal of < 70 mg/dl for individuals with higher risk, including cardiovascular disease patients with additional high-risk factors: diabetes mellitus, multiple cardiovascular risk factors, multiple risk factors of metabolic syndrome, or severe or poorly controlled risk factors, especially smoking [Grundy., *et al*. 2004].

Ezetimibe is the medication that inhibits cholesterol absorption at brush borders of the intestine and has no effect on the absorption of triglycerides and fat soluble vitamins. Thus it impairs dietary and biliary absorption of cholesterol [Matsue., *et al*. 2013]. The objective of this study was to observe the efficacy, safety and tolerability of Ezitimibe in combination with Atorvastatin in very high risk and high risk patients in Pakistan.

Methods

Study Population

After taking the informed consent, 240 patients were selected for the study. Patients of either gender who gave consent to participate with the age > 18 and < 70 years with LDL-C levels above optimal levels (optimal levels < 100 mg/dl) with prior history of at least one cardiac event (myocardial infarction) but stabilized clinically after acute phase were included in the study. Those who did not give the consent, failed to follow up, having any contraindication to Ezetimibe and Atorvastatin like active liver pathology or unexplained raise of alanine aminotransferase or aspartate aminotransferase levels, with history of substantial myopathy or rhabdomyolysis with any statin or Ezetimibe, sensitivity to Ezetimibe or Atorvastatin, and pregnant women were disqualified from the study.

Study Design

This was a prospective, interventional phase IV multicenter study conducted in 30 medical centers across Pakistan. The ethical approval was taken from the Institutional Review Board of Isra University, Hyderabad and the duration of the study was from Feb 2016 till December 2016.

In the total of 240 patients included using purposive sampling technique, 211 patients completed the study. Among 211, 60 cases (28%) were assessed for the total lipid profile outcome, however all patients were evaluated for LDL-C level. The total lipid profile including LDL, VLDL, HDL and triglycerides were done from the Agha Khan University Hospital Laboratory, Karachi. The basic demographic variables were recorded at the base line like age, gender and weight along with the history of smoking and previous cardiac event. The patients were classified into very high risk and high risk category on the basis of history of previous cardiac event, diabetes mellitus, dyslipidemia, smoking, advancing age. The patients who had history of any of the cardiac event like heart attack, angina, or any of the previous cardiac surgery were classified into very high risk category and the patients who were having advance age, history of smoking, and hyperlipidemia were classified as high risk patients.

All patients were treated with Ezetimibe and Atrovastatin 10 + 40 mg/day orally for 12 weeks. Patients were instructed to take each dose at the same time every day, regardless of mealtime. Every patient was monitored for a period of 03 months. 03 study visits were performed; baseline, 04 weeks and at 12 weeks. The total Lipid profile was assessed at 12th week.

Safety and Efficacy Evaluation

Serum LDL-C levels were noted at baseline and at 12th week for assessing the effectiveness of the combination. The safety valuations comprised of observing and documenting all adverse events (AEs) and serious adverse events (SAEs).

Statistical Analysis

Data was analyzed by SPSS version 20.0. For continuous variables, summary statistics included mean, standard deviation, median, minimum and maximum values, as well as frequencies and percentages for categorical variables are presented. The paired t-test was used to see the significance at different levels of treatment at 4th week and at 12th week. P-values of < 0.05 were considered to be significant.

Results

Out of the total number of 211 patients 85 were in high risk group and 126 were in very high risk group. The mean age of the patients in high risk group was 51.5 (± 11.2) years. The mean age of the patients in very high risk group was 52.3 (± 11.0) years. Male to female ratio was 1:2 in both the high risk and very high risk categories. (Table 1) Among 85 patients of high risk group 22 (26%) were having the history of smoking and were present smokers as well. Whereas in very high risk group 38 (30%) of the patients were having the history of smoking and were present smokers as well

	High Risk		Very High Risk	
	Age	Weight	Age	Weight
N	85	85	126	126
Mean	51.5	70.5	52.33	74.18
Std. Deviation	11.2	13.6	11.085	13.183
Minimum	22	45	24	40
Maximum	69	125	85	140
Gender	High Risk		Very High Risk	
Male	33%		32%	
Female	67%		68%	

N, Number of patients; Std. Deviation, standard deviation.

Table 1: *Patient demographics.*

In high risk patients the mean of heart rate at base line was 85 beats/min whereas, the mean of heart rate at 4th week of treatment was 81 beats/min with a significant p value of 0.001. In very high risk patients the mean of heart rate at base line was 81 beats/min whereas, the mean of heart rate at 4th week of treatment was 78 beats/min with a significant p value of 0.001. In high risk patients the mean of systolic blood pressure at base line was 139.7 mmHg whereas, at 4th week of treatment it was 138.7 mmHg with insignificant p value of 0.635. In very high risk patients the mean of systolic blood pressure at base line was 144.2 mmHg whereas, at 4th week of treatment it was 138 mm/Hg with a significant p value of < 0.001. In high risk patients the mean of diastolic blood pressure at base line

was 86.4 mm/Hg whereas, at 4th week of treatment it was 88.5 mm/Hg with insignificant p-value of 0.11. In very high risk patients the mean of diastolic blood pressure at base line was 87.8 mm/Hg whereas, at 4th week of treatment it was 85.8 mm/Hg with a significant p value of 0.029. (Table 2).

The comparison of low density lipoprotein-cholesterol levels was done in 211 patients. Out of these 126 were in very high risk category having the history of any of the cardiac event like, heart attack, angina, or any of the previous cardiac surgery and 85 were in high risk category having advance age, history of smoking, and hyperlipidemia. In high risk patients the mean of LDL cholesterol at base line was 162.07 mg/dl with standard deviation of 58.54 mg/dl. Whereas, the mean of LDL cholesterol at 12th week of treatment was 109.39 mg/dl with standard deviation of 58.36 mg/dl with a significant p value of < 0.001. In very high risk patients the mean of LDL cholesterol at base line was 146.92 mg/dl with standard deviation of 49.49 mg/dl. Whereas, the mean of LDL cholesterol at 12th week of treatment was 104.93 mg/dl with standard deviation of 40.21 mg/dl, with a significant p value of < 0.001. (Table 2)

Categories	Variables		Mean	Std. Dev	P-value
High Risk (85)	Heart Rate (/min)	At baseline	85.1	11.1	0.001
		At 4th week	81.3	8.9	
	Systolic Blood Pressure (mm Hg)	At baseline	139.7	19	0.635
		At 4th week	138.7	16.8	
	Diastolic Blood Pressure (mm Hg)	At Baseline	86.4	10.6	0.11
		At 4th week	88.5	7.8	
	Serum LDL Cholesterol (mg/dl)	At baseline	162.07	58.54	< 0.001
		At 12th week	109.39	58.36	
Very High Risk (126)	Heart Rate (/min)	At baseline	81.6	8.6	< 0.001
		At 4th week	78.5	7.6	
	Systolic Blood Pressure (mm Hg)	At baseline	144.2	17.9	< 0.001
		At 4th week	138.7	14.4	
	Diastolic Blood Pressure (mm Hg)	At Baseline	87.8	9.5	0.029
		At 4th week	85.8	7.1	
	Serum LDL Cholesterol (mg/dl)	At baseline	146.29	49.49	< 0.001
		At 12th week	104.93	40.21	
Paired t-test is used to assess the significance					

Table 2: *Systolic and Diastolic Blood Pressure of High Risk and Very High Risk at Baseline and 4th Week.*

The overall reduction and achievement of the goal regardless of the category predicted that, in 135 (67.5%) patients there was a decrease in the LDL-C level from 30% to 50%. (Figure 1)

In high risk group out of 85 patients 66 (79%) achieved the goal whereas in very high risk 38 (30%) of the patients achieved the goal despite of the higher level of the baseline LDL-C in both the categories. (Table 3)

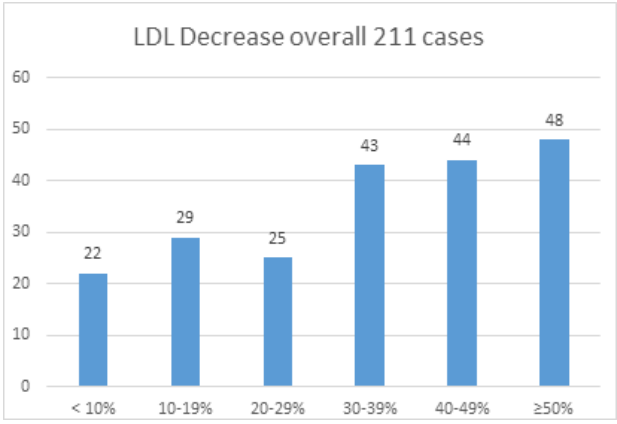

Figure 1: *Over All decrease in LDL Cholesterol.*

High Risk n = 85 LDL Goal 100 mg/dl		Very High Risk n = 126 LDL Goal 70 mg/dl	
Frequency	Percentage	Frequency	Percentage
66	79	38	30

Table 3: *LDL Cholesterol Goals according to the guideline in High Risk and Very High Risk.*

In 60 patients, who were evaluated for the whole lipid profile serum cholesterol was 210.72 mg/dl with standard deviation of 47.97 mg/dl at base line and it was 151.25 with standard deviation of 38.72 at 12th week after the treatment with the significant p-value of < 0.001. The triglycerides was 205.58 mg/dl with standard deviation of 86.35 mg/dl at base line and it was 161.40 with standard deviation of 85.05 at 12th week after the treatment with the significant p-value of 0.006.Serum HDL was 41.03 mg/dl with standard deviation of 10.99 mg/dl at base line and it was 38.13 with standard deviation of 8.41 at 12th week after the treatment with the significant p-value of 0.0032. Serum LDL was 143.67 mg/dl with standard deviation of 42.26 mg/dl at base line and it was 114.57 with standard deviation of 33.38 at 12th week after the treatment with the significant p-value of < 0.001. Serum VLDL was 39.0 mg/dl with standard deviation of 20.40 mg/dl at base line and it was 32.38 with standard deviation of 15.93 at 12th week after the treatment with the significant p-value of < 0.009. (Table 4)

Variables (n = 60)	Follow-up	Mean	Std. Dev	P-value
Serum Cholesterol mg/dl	Baseline	210.72	47.97	< 0.001
	12th week	151.28	38.72	
Serum Triglycerides mg/dl	Baseline	205.58	86.35	0.006
	12th week	161.40	85.05	
Serum HDL Cholesterol mg/dl	Baseline	41.03	10.99	0.0032
	12th week	38.13	8.41	
Serum LDL Cholesterol mg/dl	Baseline	143.67	42.26	< 0.001
	12th week	114.57	43.38	
VLDL Cholesterol mg/dl.	Baseline	39.00	20.40	0.009
	12th week	32.38	15.93	
Paired t-test is used to assess the significance				

Table 4: *Lipid Profile in High Risk and Very High Risk at Baseline and 12th Week.*

The overall adverse events of the therapy were almost negligible with muscle cramps and myalgia in only 2% and 2% cases respectively. Around 95% of the cases did not report any of the adverse events. Moreover, none of the patients reported any serious adverse event (Figure 2).

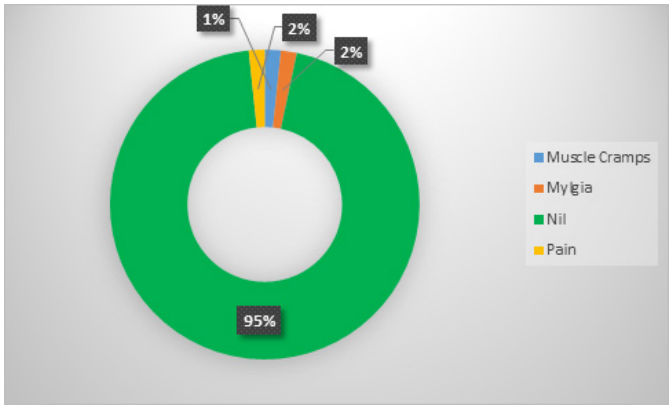

Figure 2: *Adverse Events reported by Patients.*

Discussion

The aim of any cholesterol lowering intervention is to decrease around 40% to 50% of LDL-C in order to decrease the threat of any cardiovascular event in both very high and high risk patients. In patients with high or very high risk of coronary heart disease (CHD) and similar critical conditions, (LDL-C) should be reduced by at least 30-50% in order to obtain a clinical benefit [Whayne., *et al.* 2013]. According to the guidelines formulated by American College of Cardiology (ACC) and American Heart Association (AHA), the reduction of LDL-C to 100 mg/dl in both the high risk and very high risk cardiovascular patients is greatly recommended. [ATP4. 2014]

High-risk patients need intensive lipid-modifying remedy to attain LDL-cholesterol objectives [Baigent., *et al.* 2010; Flather., *et al.* 2010]. Therefore, the first choice for reducing the LDL-cholesterol are statins, but their combination with Ezetimibe produce considerable decrease [Davis., *et al.* 2007; Catapano., *et al*. 2006]. The decrease in intestinal absorption of cholesterol with Ezetimibe at a dose of 10 mg/kg is more than 90% and for chylomicron and VLDL the reduction is 87% [Repa., *et al.* 2005]. Ezetimibe is metabolized mainly in the small intestine and liver through glucuronide conjugation to ezetimibe-glucuronide in humans, and is excreted through bile and kidney.

In another study in patients with metabolic disease, a comparable effect was acknowledged with combination therapy attaining a better decrease in LDL-C and non-HDL-C and greater increase in HDL-C as related to atorvastatin mono therapy [Hamilton-Craig., *et al.* 2010].

In one of the study there was around 21% greater reduction with combination therapy as compared to the mono therapy with Statins alone [Robinson., *et al*. 2009]. The study by Davis., *et al*. stated that the combination therapy of Ezetimibes 40 mg/d with statin resulted in 52% reduction of LDL-C level in acute coronary syndrome subjects [Davis., *et al.* 2001].

Ezetimibe is stated to decrease the cholesterol content in chylomicrons with apoB48, commencing a course that apparently diminishes the cholesterol content of large VLDL and subsequently decreases VLDL fragments and LDL-C [Deharo., *et al*. 2014].

Whereas in our study the LDL-C was reduced to 35% to 40% to the baseline both in the very high risk and very high risk categories which is in agreement to the guidelines by National Cholesterol Education Program (NCEP) through the Adult Treatment Panel ATP IV. However, the HDL-C levels did not alter substantially in our study which is inconsistent with the study by Hamilton., *et al*. which documented greater increase in its level [Hamilton-Craig., *et al*. 2010].

There is a clear evidence for safety of ezetimibe as monotherapy or in combination with other lipid-modifying drugs including statins [Pandor., et al. 2009; Robinson., *et al*. 2009]. Although adverse events have been labeled with all lipid-altering treatments such as statins, niacin, and fibrates, lethal toxicities are occasional and the complete safety profile of these therapies is reasonably satisfactory [Baigent., *et al.* 2005; Guyton., *et al.* 2007; Davidson., *et al.* 2007].

A meta-analysis of seven randomized precise trials revealed that myositis is not associated with monotherapy and combination therapy [Kashani., *et al*. 2008] however ezetimibe is efficient in inhibiting the rise in intestinal sterols absorption, but increases the endogenous cholesterol production [Assmann., *et al*. 2008].

The above findings are contrary to our study in which we had found no adverse events in 95% of the patients. The muscle cramps, myalgia and pain were reported in 2%, 2% and 1% cases respectively. However no serious adverse event was reported.

The advantages of this study are that our appropriate assortment approach has assured that we have sampled the accounts of extensive range of physician observations and patient's perspectives and their abilities of handling the patients of dyslipidemia in very high risk and high risk category. Furthermore, it conveys extensive extractions of the practitioner's perceptions. However, witness and recall bias were few limitations of the study. Reflecting the opinions of patients and experience and to what range they are reliable with other treatment options would be enlightening and valuable to overcome the risk of CHD and management of dyslipidemia.

Conclusion

The combined use of Ezetimibe with Statin is useful in reducing the LDL-C levels and decreases the cardiovascular risk factor. It is more useful because of its efficacy and few adverse events. The medicating of simple once regular dosage increases the compliance over many existing agents as well.

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Conflict of interest

The designer and benefactor of the study was Hilton Pharma Pvt Ltd. Furthermore it was involved in data organization, data evaluation, drafting and appraisal of the text. NM and AS are full-time employees of Hilton Pharma Pvt ltd. The authors report no other

encounters of attention. The honesty of the study was not traded for any monetary benefit. The remuneration was given to the observers for examining and entry of the data during the study duration.

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