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EFFICACY OF ATORVASTATIN ON C-REACTIVE PROTEIN AND LIPID PROFILE IN PATIENTS WITH CARDIOVASCULAR DISEASE

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Abstract

Cardiovascular disease (CVD) is the major cause of death in the developed countries. C-reactive protein (CRP), markers of inflammation that have been associated with an increased risk of atherosclerotic disease. Atorvastatins have proved highly effective in reducing the risk of cardiovascular events in both primary and secondary prevention studies. However, the magnitude of risk reduction associated with atorvastatins is greater than that predicted on the basis of low-density lipoprotein (LDL) cholesterol lowering alone. A likely explanation for this effect is the anti-inflammatory action of atorvastatin. The present study was therefore designed to determine the effects of atorvastatin on CRP in patients with or at risk of CVD. Thirty patients with or without risk of CVD were recruited for the study of which fifteen belongs to control (untreated) and fifteen were test groups (patients who received atorvastatin 10 mg/day). The patients were followed for over a period of 4 weeks. For entire study population, CRP along with lipid profile were measured 1st day and at the end of 4th week of the treatment. There was significant reduction in the levels of both atherogenic lipoproteins and CRP as compared with control and untreated test group. The results of this study demonstrated that treatment with atorvastatin for CVD might significantly improve clinical outcomes in the group of patients. The findings from these studies should guide clinicians to more effective use of these agents in a greater variety of patients. The findings should be confirmed in a larger, prospectively studied cohort.

Keywords: CVD, Atherosclerosis, CRP, Atorvastatin and Lipid profile.

1. Introduction

Cardiovascular disease (CVD) is the primary cause of death in world wide. It is a class of diseases that involve the heart, blood vessels (arteries, capillaries, and veins) or both (Karino *et al*., 2014). In 2008, 30% of all global death is attributed to CVD and also higher in low- and middle-income countries. It has been leading cause of morbidity and mortality in India. It is also estimated that by 2030, over 23 million people will die from cardiovascular diseases each year (Pillai and Ganapathi, 2013). Evidence suggests that a number of risk factors for heart diseases it includes age, gender, high blood pressure, hyperlipidemia, diabetes mellitus, tobacco smoking, processed meat consumption,

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excessive alcohol consumption, sugar consumption, family history, obesity, lack of physical activity, psychosocial factors, and air pollution (Finks *et al*., 2012).

Although, long standing research has identified variables such as hypertension and hypercholesterolemia as traditional CVD risk factors, many have reported their absence in a substantial portion of individuals experiencing clinical vascular events. In the last decade, compelling evidence has evolved at both the basic science and clinical level for the importance of inflammation in the pathogenesis of atherosclerosis and its complications. The pathology of the atherosclerotic plaque, rather than the degree of stenosis is now recognized as a pivotal feature in determining plaque stability and hence the risk of acute ischaemic events (Libby, 1995). A number of studies have tested the hypothesis that lipid-lowering therapies would reduce the degree of high-grade coronary stenoses (Blankenhorn *et al.,* 1993; Waters *et al.,* 1994).

Current evidence supports a central role for inflammation in all phases of the atherosclerotic process from lesion initiation through to progression and ultimately, the thrombotic complications of atherosclerosis (Ross, 1999; Blake and Ridker, 2003). The growing appreciation of the role of inflammation in atherogenesis has focused attention on whether circulating levels of inflammatory biomarkers may help identify those at risk of future cardiovascular events. In addition, there is debate among the medical community regarding the extent to which the decrease in cardiovascular risk observed with therapies, such as statins, derives from changes in inflammatory parameters (Plutzky, 2001).

An increasing number of distinct markers have been studied from a clinical point of view, risk assessment by inflammatory biomarkers has to be standardized, easy to determine and cost effective. In this respect, CRP emerged as the biomarker for risk assessment with the highest clinical value. CRP is involved both in innate immunity and in the removal of necrotic and apoptotic cells (Bharadwaj *et al.,* 1999). CRP has pro- and anti-inflammatory properties. In cell culture CRP stimulates IL-18 production, a recently discovered cytokine that appears to be a very strong independent predictor of CAD risk in middle-aged men (Blankenberg *et al.,* 2003; Szalai, 2002).

Clinical data have clearly established the efficacy of lipid-lowering modes of therapy in reducing cardiovascular risk. First-line lipid-lowering therapy for most individuals is the initiation of therapeutic lifestyle changes (TLC). Components of TLC that have been shown to be effective in lowering LDL cholesterol levels include dietary changes, commencement of regular physical activity, smoking cessation, and weight loss. Although a number of pharmacologic agents are available to modify lipid levels, data from multiple prospective outcomes trials have demonstrated that 3- hydroxy-3-methylglutaryl coenzyme a reductase inhibitors (statins) are the most effective agents to reduce risk of CVD (Downs *et al.,* 1998; Shepherd *et al.,* 1995). Although the primary mechanism by which statins reduce CVD risk is via LDL cholesterol reduction, the anti-inflammatory activity associated with statins may explain some of their efficacy, particularly in patients who do not have elevated cholesterol levels. The anti-inflammatory effect of statins has been demonstrated in a number of recent trials (Nissen *et al.,* 2004; Sager *et al.,* 2003).

Circulating levels of several inflammatory markers rise in individuals at risk for atherosclerotic events. While improving the understanding of atherosclerotic disease, current insights hold promise for meaningful clinical applications in risk assessment and guidance to targeted therapy. Atorvastatin has been significantly reduces cardiovascular events, and it is remain unknown whether CRP levels can be reduces in patients with CVD. On the basis of available evidence, this study is aimed to investigate the benefits of atorvastatin on CRP and lipid profile in patients with cardiovascular diseases.

2. Materials and Methods

2.1. Study Protocol

Thirty patients with or without at a risk of CVD were recruited for the study. Fifteen were control (untreated), who entered to one-day health check program. Fifteen belongs to test group, (those patients who received atorvastatin 10 mg/day). The patients were categorized under control, which included 11 males and 4 females with a mean age of 58.3±5.4 and in test group included 9 males and 6 females with a mean age of 61.2±6.2. Most of the patients in test group were found to have more than one kind of complications and in control most of them normal and some of them were undergoing treatment for diabetic and hypertension (Table - 1).

2.2. Biochemical parameters and Assay

A venous blood sample was obtained after a 12 hours overnight fast for the estimation of lipids and serum levels of CRP. CRP was measured by using Immunoturbidometry method. Estimation of total cholesterol (TC), serum triglycerides (TG) and high-density lipoprotein (HDL) cholesterol were performed using commercial kits.

The value of LDL cholesterol, and very low-density lipoprotein cholesterol (VLDL), were calculated using Friedwald's equation. Blood samples were drawn in the morning during fasting conditions (first day and after the end of 6^{th} week of treatment). Further analysis was done as per the procedure given in the kit using the supplied reagents. All randomized patients completed the study and all patients gave written informed consent before the study. Table - 2 shows the diagnostic kit, (with its company) for quantitative *in vitro* determination of CRP, TC, TG and HDL cholesterol by auto analyzer.

2.3. Statistical Analysis

Statistical analysis was performed with SPSS 12 statistical software package. Data were recorded on a pre-designed performed and managed on an Excel spreadsheet. All the entries were checked for any error. Descriptive statistics for quantitative variables were computed by mean and standard deviation. Means in the two groups were compared by Student's test. In this study, $p<0.05$ has been considered as statistically significant.

Table - 1: Patients characteristics of study participants (age, sex and types of complication)

Subject	Age	Male/Female n = 30	Types of Complication
Control (Untreated)	58.3±5.4	11/4 = 15	Normal, Hypertension and Diabetic
Test group (Treated)	61.2±6.2	9/6 = 15	Diabetic, Hypertension, Angina, CVD, Acute myocardial infarction, Inferior wall infarction and Severe left ventricular dysfunction

Table - 2: Diagnostic Kits

Parameters	Manufactured By	Reference
C – reactive protein	The Quality System of Diagnostic Products, USA.	Tietz, 1995
Total cholesterol	Raichem. Division of Hemagen Diagnostics, Inc. San Diego, CA 92111-1203.	Allain *et al.*, 1974
Triglycerides	Reagents Applications, Ind. San Diego, CA 92111-1203.	Trinder, 1969
HDL – cholesterol	Nicholas Piramal India Ltd., Navi Mumbai, 400 705	Friedewald *et al.*, 1972
LDL – cholesterol	Nicholas Piramal India Ltd., Navi Mumbai, 400705	Friedewald *et al.*, 1972
VLDL – cholesterol	Nicholas Piramal India Ltd., Navi Mumbai, 400705	Friedewald *et al.*, 1972

3. Results

Baseline characteristic of the patients were shown in the Table - 3 (Age, sex, alcohol consumption, smoking history, diabetes, hypertension and medical conditions). The present study demonstrates that considerable variability is observed between control and test group. The baseline mean C-reactive protein (CRP) concentration increased significantly in patients with complication than the control. The mean level of CRP in control (untreated - UT) 0.4±0.2 and 0.4±0.2, and in treated (T) test group 1.9±0.6 and 1.0±0.2 in the 1st day and in the end of 4th week respectively (Fig. 1).

The mean total cholesterol (TC) in control (untreated - UT) 163.6±32.9 and 165.4±27.1, and in treated (T) test group 217.1±43.9 and 175.8±12.3 in the 1st day and in the end of 4th week respectively (Fig. 2). The mean triglyceride (TG) in control (untreated - UT) 148.8±54.7 and 146.5±82.6 and in treated (T) test group 189.0±67.0 and 167.9±36.6 in the 1st day and in the end of 4th week respectively (Fig. 3). From the result, there is a significant increased in TC and TG levels in both test group than the control.

The mean high-density lipoprotein (HDL) in control (untreated - UT) 40.1±4.3 and 44.1±8.4, and in treated (T) test group 36.8±4.0 and 41.2±8.7 in the 1st day and in the end of 4th week respectively (Fig. 4). The mean very low-density lipoprotein (VLDL) in control (untreated - UT) 30.6±12.9 and 28.4±15.9, and in treated (T) test group 37.2±12.5 and 34.8±7.0 in the 1st day and in the end of 4th week respectively (Fig. 5). The mean level of LDL cholesterol or "bad cholesterol" found in this study in control (untreated - UT) 91.2±33.4 and 90.2±19.1, and in treated (T) test group 140.8±38.3 and 103.0±17.7 in the 1st day and in the end of 4th week respectively (Fig. 6). There is a significant increase were noted in the mean levels of TC and LDL cholesterol in both test group. This indicates the elevated level of CRP, lipid profile is a strong indicator of cardiovascular risk. Fig. 1 to 6 shows the baseline mean levels of the CRP, TC, TG,

HDL cholesterol, LDL cholesterol and VLDL cholesterol.

4. Discussion

Hyperlipidemia is common and can be divided into primary anomalies, which cannot be linked to an identifiable underlying disease, or secondary manifestations of some other condition. The later usually disappear when the underlying conditions is treated. Elevated plasma cholesterol and triglyceride concentrations are both linked to an increased risk of CHD and increased this further when HDL cholesterol is also low. Convincing evidence from large-scale randomized clinical trials has demonstrated the importance of lowering plasma cholesterol following myocardial infarction.

The results of the present study indicate that an elevated CRP level is a strong indicator of CVD events. Patients with high CRP levels thereafter or believed to suffer from multiple complication. Based on part of these data, high-sensitivity assays for CRP have become available in standard clinical laboratories. However, clinical application of CRP testing will depend not only on demonstration of independent predictive value, but also on demonstration that addition of CRP testing to traditional screening methods improves cardiovascular risk prediction. Furthermore, application of CRP as a tool to assist clinical characteristics of CRP evaluation and magnitude of risk of future coronary events that can be expected at each level of CRP. Infection and tissue injury if diagnosed in the early phase, can be treated accordingly by antibiotics or anti-inflammatory drugs.

In sustain to the present investigation, a number of large-scale epidemiological studies have shown that plasma CRP levels are an independent predictor of risk of future cardiovascular events, such as myocardial infarction, stroke and peripheral arterial disease (Koenig *et al.,* 1999; Danesh *et al.,* 2000 and Ridker *et al.,* 1998). In addition, among patients with acute coronary ischemia (Toss *et al.,* 1997), stable angina pectoris (Lindahl *et al.,* 2000), and a history of myocardial infarction (Haverkate *et al.,* 1997), levels of CRP have been associated with increased vascular event rates. Emerging evidence also suggest that CRP may not only be a useful marker of inflammation but may also play an active role in the pathogenesis of atherosclerosis.

The most important finding of the present study, however, is that the simultaneous assessment of inflammatory marker and blood lipids may improve the prediction of future cardiovascular events compared to the measurement of only one of these markers. Patients with a combination of elevated levels of CRP and total cholesterol or LDL cholesterol showed the highest risk. This approach was first reported by Ridker and colleagues in apparently healthy adults in primary prevention (Ridker *et al.,* 1998). Recent data from a large, prospective Swedish study of 6063 initially healthy men support this concept. They showed that TC alone, without simultaneously elevated inflammatory markers (fibrinogen, α1-antitrypsin, haptoglobin, ceruloplasmin, and orosomucoid), was only a poor predictor of myocardial infarction and stroke compared to the combined elevation of TC and more than two of these inflammatory markers (Engstrom *et al.,* 2002).

The present findings suggest that this simple, multimarker approach might also be useful for risk assessment in clinically stable patients with CVD. The promising principle of a "multimarker" approach has recently been demonstrated in patients with an acute coronary syndrome, i.e., a simultaneous assessment of CRP (as a marker of inflammation) were associated with improved prognostic information in unstable patients (Sabatine *et al.,* 2002). Both inflammation and lipid deposition are characteristic features of the atherosclerotic process. Modifying the risk factors or maintaining a healthy lifestyle, such as losing excess weight, not smoking, and taking regular exercise, can be a recommended way to reduce CRP and lipid profile levels and the risk of CVD.

Based upon the data presented in Fig. 1 to 6, atorvastatin seems unique in its ability to

preferentially lower those components most elevated within each dyslipidemic category: TC and LDL cholesterol. This suggests that atorvastatin primarily reduces the lipid fraction most available, rather than targeting only one lipid fraction. The figure shows only those patients who received atorvastatin 10 mg/day, significant reduction in CRP and lipid profile. Despite the LDL cholesterol-lowering ability of statins that is probably responsible for most of their CVD and stroke prevention benefit, the full benefit or these drugs may be partly the result of other mechanisms.

Statins have biological effects beyond LDL cholesterol level reduction, including antiproliferative effects on smooth muscle cells, restoration of endothelial activity, antithrombotic effects, antioxidant effects, and anti-inflammatory effects, which have been identified in a number of experimental settings (Fenton and Shen, 1998; Rosenson and Tangney, 1998; Berkenboom, 1998; Weissberg, 1999).

The present study shows changes in CRP levels with atorvastatin use. This reduction of CRP by atorvastatin has increased awareness of anti-inflammatory effects of statins and the possible contribution of such an effect to the rapid clinical efficacy of the treatment in cardiovascular patients. The prognostic value of the CRP and its modification with statins has been evaluated in several studies, both in primary and in secondary prevention.

Indeed, the PRINCE study has demonstrated that pravastatin reduces CRP levels at both 12 and 24 weeks in a LDL cholesterol-independent manner (Albert *et al.,* 2001). Moreover, it seems that atorvastatin exerts a more potent effect on the reduction of CRP than pravastatin, as demonstrated by the ARBITER study (Taylor *et al.,* 2002). This result has been confirmed by the REVERSAL study, which confirms that atorvastatin induces a greater reduction in CRP levels that pravastatin (Nissen *et al.,* 2001), and seems also to be more potent that simvastatin (Wiklund *et al.,* 2002).

Reversal demonstrated that lowering CRP levels in patients with coronary disease by intensive statin therapy resulted in reduced atherosclerotic lesion progression; in some patients there was even atheromatous regression, as measured by intravascular ultrasonography. These findings suggest that to maximize the benefit of statin therapy, physicians may need to monitor CRP levels in addition to LDL cholesterol levels for secondary prevention of CVD. The Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) trial again clearly demonstrated that CRP is a marker of cardiovascular risk in primary and secondary prevention (Ridker *et al.,* 2005).

The observation on CRP levels are extensively reduced through treatment with atorvastatin at 4 weeks may be of particular interest in view of new data on early intervention with statins in acute coronary syndromes. These data show a significant benefit for early statin treatment as compared to controls with conventional, non-invasive therapy. Whether this clinical benefit is due to an improvement of endothelial function or plaque stabilization, either via lowering of lipids or via reduction of inflammatory processes remains, to be elucidated. Since recent data indicate (Tsunekawa *et al.,* 2001) that endothelial dysfunction can be improved through statin therapy within days, it is conceivable that chronic inflammation can consecutively be improved within a short period.

The 3-hydroxy-3-methylglutaryl coenzyme A (HMGCoA) reductase inhibitors (statins) can achieve relatively large reductions in plasma cholesterol levels and represent an established class of drugs for the treatment of hypercholesterolemia. Several clinical trials have demonstrated that statins can ameliorate vascular atherosclerosis, and reduce cardiovascular-related morbidity and mortality, in patients with and without coronary artery disease (CAD) symptoms. The data obtained from the present study and statistical analysis support the following conclusion.

The results shows that elevated levels of TC, LDL cholesterol promote atherosclerosis, similarly, decreased levels of HDL cholesterol is associated with the development of atherosclerosis. Atorvastatin reduces TC and LDL cholesterol, in patients with CVD and also reduces LDL cholesterol and TG and produces variable increases in HDL cholesterol.

The results show that the elevated level of serum concentration of CRP, serves as an alarm or indicator of either inflammation or CVD. The results show that CRP adds predictive value to that afforded by standard lipid screening. This prognostic value of CRP has led to their widespread use when stratifying cardiovascular risk. The administration of 10 mg/day of atorvastatin from the time of diagnosis of CVD significantly decreases CRP plasma concentrations after 4 weeks of treatment. This effect is independent of changes in lipid values. The results demonstrate better clinical evolution in the treated patients than the control and untreated patients, although this should be corroborated by new and larger patient population studies.

Table 3: Baseline characteristics of study participants

Characteristic	**Control n=15**	**Test group n=15**
Age	58.3±5.4	61.2±6.2
Male/Female	11/4 = 15	9/6 = 15
Alcohol consumption (%)	1(7)	3(20)
Smoking history (%)	4(27)	8(53)
Snuff (%)	1(7)	2(13)
History of Hypertension (%)	5(33)	10(67)
Diabetes (%)	5(33)	7(47)
Low physical activity(%)	10(67)	11(73)
Obesity (%)	1(7)	2(13)
Drug Therapy		
Oral hypoglycemic (%)	4(27)	6(40)
Insulin (%)	1(7)	1(7)
Antihypertensive (%)	5(33)	10(67)
Atorvastatin (%)	Nil (0)	15(100)

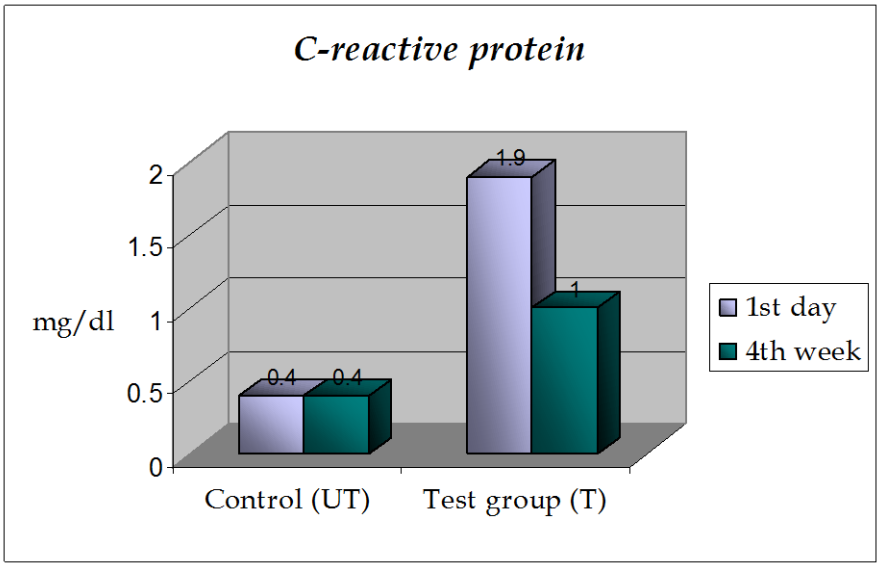

Figure – 1: Baseline mean levels of C-reactive protein

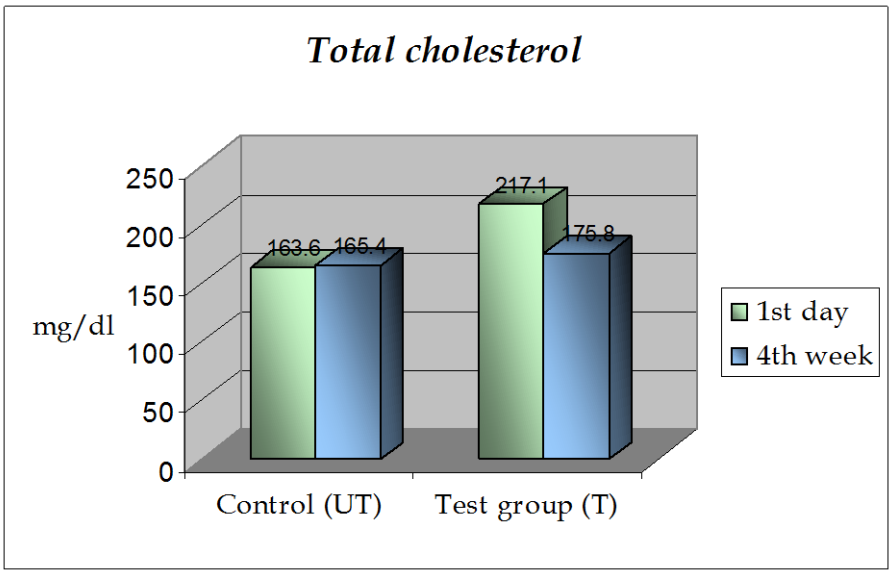

Figure - 2: Baseline mean levels of Total cholesterol

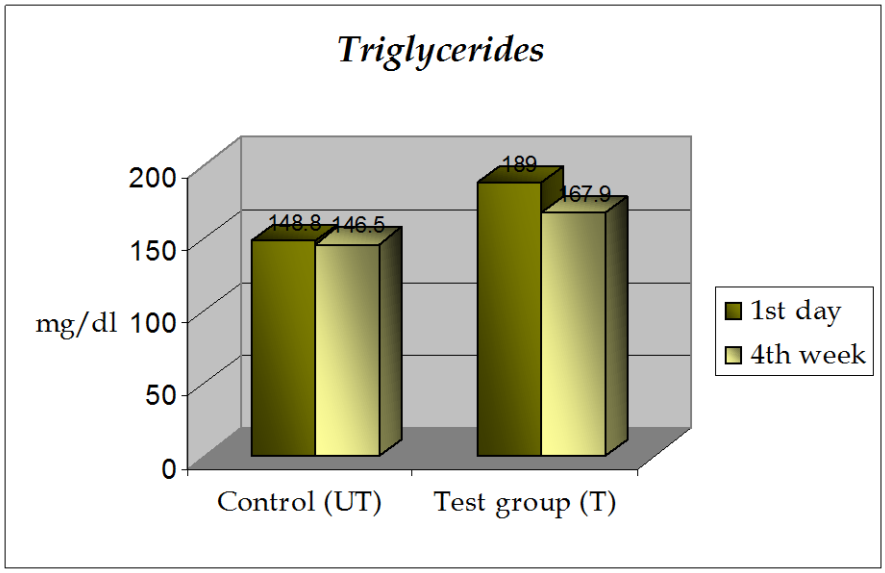

Figure – 3: Baseline mean levels of Triglycerides

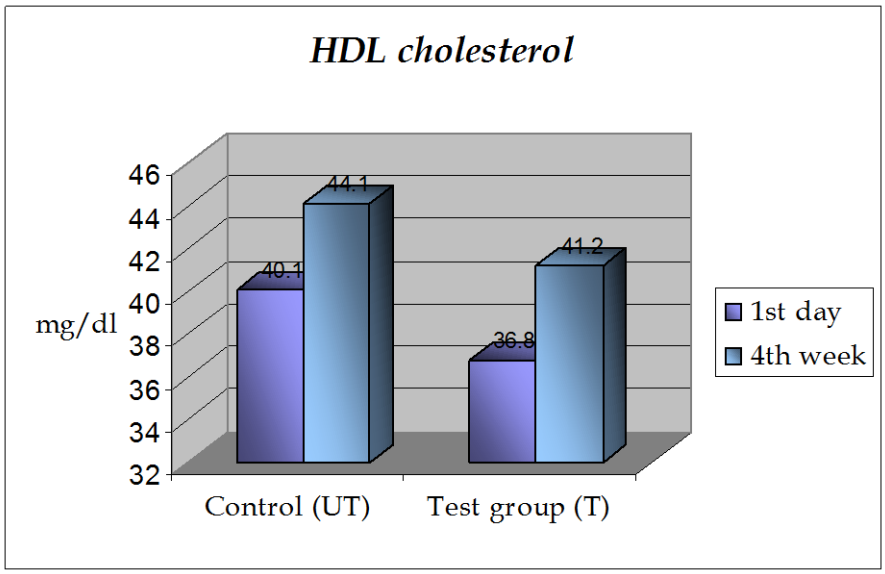

Figure - 4: Baseline mean levels of HDL cholesterol

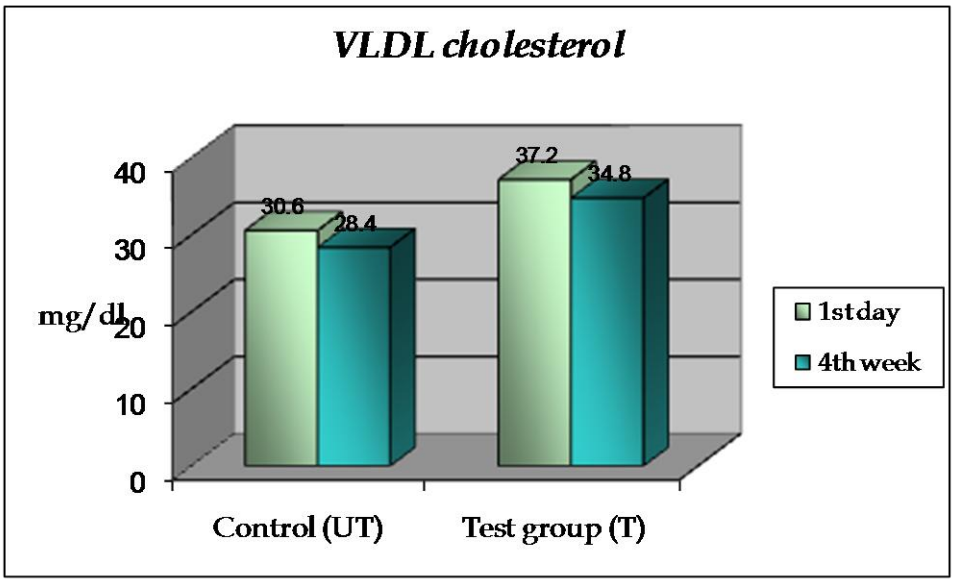

Figure – 5: Baseline mean levels of VLDL cholesterol

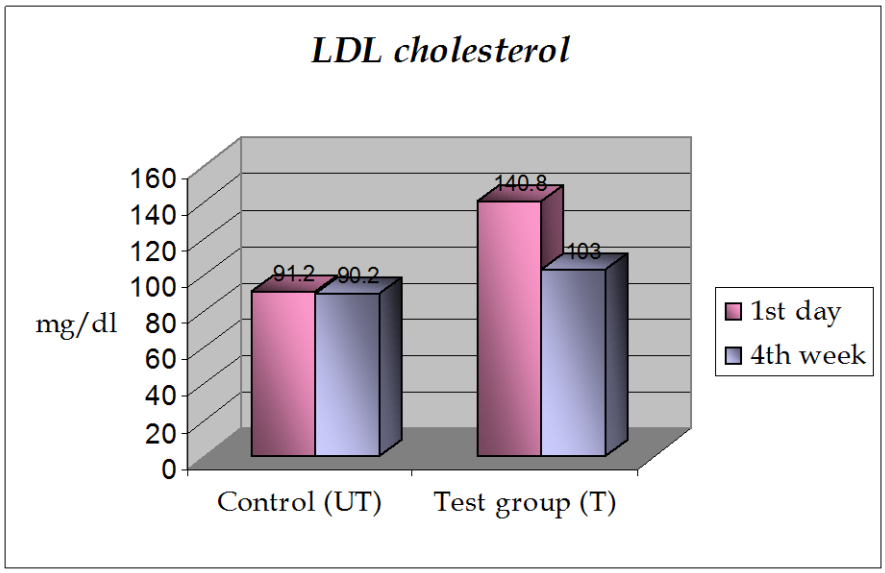

Figure – 6: Baseline mean levels of LDL cholesterol

6. References

1) Albert MA, Danielson E, Rifai N, Ridker PM, The PRINCE Investigators: (2001) Effect of statin therapy on C-reactive protein levels: the Pravastatin Inflammation/CRP Evaluation (PRINCE): a randomized trial and cohort study. JAMA. 286:64-70.
2) Allain, C.C., Poon, L.S., Clan, C.S.G, Richmond, W. and Fu, P.D., (1974) *Clin.chem.* 20:470.
3) Berkenboom G. (1998) Unstable atheroslerotic plaque: pathophysiology and therapeutic guidelines. Acta Cardiol. 53:235-241.
4) Bharadwaj D, Stein MP, Volzer M, Mold C, Du Clos TW. (1999) The major receptor for C-reactive protein on leukocytes is fcgamma receptor II. *J Exp Med.* 190:585– 90.
5) Blake GJ, Ridker PM. (2003) C-reactive protein: a surrogate risk marker or mediator of atherothrombosis? *Am J Physiol Regul Integr Comp Physiol.* 285:R1250–2.
6) Blankenberg S, Barbaux S, Tiret L. Adhesion molecules and atherosclerosis. Atherosclerosis. 2003 Oct;170(2):191-203.
7) Blankenhorn DH, Azen SP, Kramsch DM, et al., (1993) and the MARS Research Group. Coronary angiographic changes with lovastatin therapy. The Monitored Atherosclerosis Regression Study (MARS). *Ann Intern Med.* 119:969–76.
8) Danesh J, Whincup P, Walker M, Lennon L, Thomson A, Appleby P, Gallimore JR, Pepys MB: (2000) Low grade inflammation and coronary heart disease: prospective study and updated meta-analyses. BMJ. 321:199-204.
9) Downs JR, Clearfield M, Weis S, Whitney E, Sharpio DR, Beere PA et al. (1998) Primary prevention of acute codronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/T ex CAPS. Air Force/Texas Coronary Atherosclerosis prevention Study. *JAMA.* 279:1615-1622.
10) Engstrom G, Lind P, Hedblad B, Stavenow L, Janzon L, Lindgarde F. (2002) Effects of cholesterol and inflammation-sensitive plasma proteins on incidence of myocardial infarction and stroke in men. Circulation. 105: 2632–2637.
11) Fenton JW II, Shen GX. (1998) Statins as cellular antithrombotics. Haemostasis. 29:166-169.
12) Finks SW, Airee A, Chow SL, Macaulay TE, Moranville MP, Rogers KC, Trujillo TC. Key articles of dietary interventions that influence cardiovascular mortality. Pharmacotherapy. 2012; 32: 54-87.
13) Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem. 1972 Jun;18(6):499-502.
14) Haverkate F, Thompson SG, Pyke SD, Gallimore JR, Pepys MB: (1997) Production of C-reactive protein and risk of coronary events in stable and unstable angina. European Concerted Action on Thrombosis and Disabilities Angina Pectoris Study Group. Lancet. 349:462-466.
15) Karino S, Willcox BJ, Fong K, Lo S, Abbott R, Masaki KH. Total and differential white blood cell counts predict eight-year incident coronary heart disease in elderly Japanese-American men: The Honolulu Heart Program. Atherosclerosis. 2014; 238: 153-158.
16) Koenig W, Sund M, Frohlich M, Fischer HG, Lowel H, Doring A, Hutchinson WL, Pepys MB: (1999) C-Reactive protein, a sensitive marker of inflammation, predicts future risk of coronary heart disease in initially healthy middle-aged men: results from the MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) Augsburg Cohort Study, 1984 to 1992. Circulation. 99:237-242.

17) Libby P. (1995) Molecular bases of acute coronary syndromes. *Circulation.* 91:2844– 50.
18) Lindahl B, Toss H, Siegbahn A, Venge P, Wallentin L, for the FRISC study group. (2000) Markers of myocardial damage and inflammation in relation to long-term mortality in unstable coronary artery disease. N Engl J Med. 343:1139– 47.
19) Nissen S. (2001) Coronary angiography and intravascular ultrasound. Am J Cardiol. 87:15A–20A [Suppl.].
20) Pillai HS, Ganapathi S. Heart failure in South Asia. Curr Cardiol Rev. 2013; 9: 102-111.
21) Plutzky J. Inflammatory pathways in atherosclerosis and acute coronary syndromes. Am J Cardiol. 2001 Oct 18;88(8A):10K-15K
22) Ridker PM, Cannon CP, Morrow D, Rifai N, Rose LM, McCabe CH, Pfeffer MA, Braunwald E. (2005) Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) Investigators 2005. C-reactive protein levels and outcomes after statin therapy. New Engl J Med. 352:20-8.
23) Ridker PM, Rifai N, Pfeffer MA, et al. (1998) for the Cholesterol and Recurrent Events (CARE) Investigators. Inflammation, pravastatin, and the risk of coronary events after myocardial infarction in patients with average cholesterol levels. Circulation. 98:839– 44.
24) Rosenson RS, Tangney CC. (1998) Antiatherothrombotic properties of statins: implications for cardiovascular event reduction [Review]. JAMA. 27;279(20):1643-50.
25) Ross R. (1999) Atherosclerosis: an inflammatory disease. *N Engl J Med.* 340:115-226.
26) Sabatine MS, Morrow DA, de Lemos JA, Gibson CM, Murphy SA, Rifai N, McCabe C, Antman EM, Cannon CP, Braunwald E. Multimarker approach to risk stratification in non-ST elevation acute coronary syndromes: simultaneous assessment of troponin I, C-reactive protein, and B-type natriuretic peptide. Circulation. 2002 Apr 16;105(15):1760-3.
27) Sager PT,Melani L, Lipka L, Strony J, Yang B, Suresh R, et al, (2003) Ezetimibe Study Group. Effect of coadministration of ezetimibe and simvastatin on high-sensitivity C-ractive Protein. *Am J Cardiol.* 92:1414-8141.
28) Shepherd J, Cobbe SM, Ford l, isles CG, Lorimer AR, Macfarlane PW, et al. (1995). Prevention of coronary heart disease with pravastatin in men with hyper cholesterolemia. West of Scotland Coronary prevention Study Group. *N Engl J Med.* 333:1301-1307.
29) Szalai AJ. (2002). The biological functions of C-reactive protein. *Vascul Pharmacol.* 39:105–7.
30) Taylor AJ, Kent SM, Flaherty PJ, Coyle LC, Markwood TT, Vernalis MN. (2002) ARBITER: Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol: a randomized trial comparing the effects of atorvastatin and pravastin on carotid intima medical thickness. Circulation. 106:2055-60.
31) Tietz NW (1995) Editor. Clinical guide to laboratory tests. 3rd ed. Philadephaia:WB Saunders:358.
32) Toss H, Lindahl B, Siegbahn A, Wallentin L. (1997) Prognostic influence of increased fibrinogen and C-reactive protein levels in unstable coronary artery disease. Frisc Study Group. Fragmin during instability in coronary artery disease. Circulation. 96:4204– 10.
33) Trinder, P. (1969) Determination of glucose in blood using glucose oxidase with an alternative oxygen receptor, Ann. Clin. Biochem. 6, 24-27.
34) Tsunekawa T, Hayashi T, Kano H et al. (2001) Cerivastatin, a hydroxy methyl coenzyme A inhibitor, improves endothelial function in elderly diabetic

patients within 3 days. Circulation. 104: 376–9.

35) Waters D, Higginson L, Gladstone P, et al. (1994) Effects of monotherapy with an HMG-CoA reductase inhibitor on the progression of coronary atherosclerosis as assessed by serial quantitative arteriography. The Canadian Coronary Atherosclerosis Intervention Trial. *Circulation.* 89:959–68.
36) Weissberg PL. (1999) Atherosclerosis involves more than just lipids: plaque dynamics. Eur Heart J. 1 (suppl): T13-T18.
37) Wiklund O, Mattsson-Hulten L, Hurt-Camejo E, Oscarsson J. (2002) Effects of simvastatin and atorvastin on inflammation markers in plasma. J Intern Med 251:338-47.