ALTERNATE REGIME IN DYSLIPIDEMIA

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CERTIFICATE

This to certify that this dissertation entitled **"Alternate Regime in Dyslipidemia"** by the candidate Dr.R.Lenin for M.D (Pharmacology) is a bonafide record of the research work done by him, under the guidance of Dr.G.Hemavathy,M.D.Professor, Department of Pharmacology, Govt.Stanley Medical College, during the period of study (2012 - 2015), in the Department of Pharmacology, Govt. Stanley Medical College, Chennai - 600001.

I also certify that this dissertation is the result of the independent work on the part of the candidate.

Dr.G.Hemavathy M.D,
Professor,
Department of Pharmacology,
Govt.Stanley Medical College.

Dr.K.Vasanthira D.G.O., M.D,
Professor & Head,
Department of Pharmacology,
Govt.Stanley Medical College.

Dr.AL.MeenakshiSundaram M.D., D.A,
DEAN,
Govt.Stanley Medical College.
Chennai-1

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CONTENTS

Abbreviations

ACAT – Acyl Coenzyme A Cholesterol Acyl Transferase

ALT – Alanine amino Transferase

AST- Aspartate amino Transferase

ATP – Adenosine Triphosphate

CAD – Coronary Artery Disease

CABG – Coronary Artery Bypass Graft

CE – Cholesteryl Ester

CETP – Cholesteryl Ester Transfer Protein

CHD – Coronary Heart Disease

CM – Chylomicron

CPK – Creatine Phospho Kinase

CRP – C Reactive Protein

DALY- Disease Adjusted Life Years

FA – Fatty Acid

FFA – Free Fatty Acid

HDL-C- High Density Lipoprotein Cholesterol

HL – Hepatic Lipase

HMG Co A – Hydroxy Methyl Glutaryl Coenzyme A

HTGL- Hepatic Triglyceride Lipase

IDL – Intermediate Density Lipoprotein

LCAT- Lecithin Cholesterol Acyl Transferase

LDL-C - Low Density Lipoprotein Cholesterol

LP (a) – Lipoprotein a

LPL – Lipoprotein Lipase

LRP – LDL Receptor related Protein

MTP – Microsomal Triglyceride Transfer Protein

NCEP – National Cholesterol Education Programme

NPC1L1- Niemann Pick C1- like 1 protein

PPAR - Peroxisome Proliferator Activated Receptors

SR – Scavenger Receptor

SREBP- Sterol Regulatory Elemental Binding Protein

TC – Total Cholesterol

TG – Triglyceride

VLDL – Very Low Density Lipoprotein

Alternate Regime in Dyslipidemia

Dr.R.Lenin M.D (Pharm) Postgraduate*, Prof.Dr.G.Hemavathy M.D (Pharm)

Dept. of Pharmacology, Govt.Stanley Medical College, Chennai-01.

ABSTRACT

Introduction: Dyslipidemia, which includes hypercholesterolemia and reduced level of HDL-C are the major reason for increased risk of atherogenesis. The sedentary life style &genetic disorders with diets rich in saturated fat & cholesterol contributes this non communicable disease. The drugs most commonly used for dyslipidemia are statins and fibrates. Though the therapy may be started with either statin or fibrates, ultimately most of these patients require both the drugs or some other combination therapy.

Methods: Eligible patients with dyslipidemia were randomly allotted into 2 equal groups- daily regime group (group 1) and alternate regime group (group 2). Patients in group 1 received atorvastatin 10 mg and fenofibrate 160 mg daily and group 2 received on alternate days, respectively for 6 weeks & follow up by 12th week. Mean percentage change from baseline in total cholesterol (TC), triglycerides (TGs), low-density lipoprotein cholesterol (LDL-C), VLDL-C, HDL-C and TC-HDL ratio, incidence of adverse effects, and cost-effectiveness were compared in both the groups.

Results: Among 93 patients screened, 60 were randomized into 2 groups as group1 & 2 with 30 patients in each. The TC, LDL-C,TGs,VLDL-C decreased by 46.03%, 47.23%, 58.67%, and 45.39% in alternate regime group and by 46.67%, 48.01%, 59.88%, and 46.31% in daily regime group. The HDL-C levels increased by 29.32% in alternate day therapy group compared to 32.11% in daily therapy group. No statistically significant difference was seen between both the groups in mean

percentage change in lipid parameters from baseline to end of 12 weeks. TC-HDL ratio was 3.50 in group1 and 3.54 in group 2.Incidence of adverse events were reasonably less in alternate day therapy group.

Conclusion: Alternate regime of atorvastatin 10 mg on one day & fenofibrate 160 mg on other day is equally efficacious to daily regime of both atorvastatin10 mg and fenofibrate 160 mg with better cost effectiveness & better patient compliance in patients with secondary dyslipidemia.

KEYWORDS:

Alternate regime, atorvastatin, fenofibrate, cost-effectiveness, dyslipidemia

INTRODUCTION

Dyslipidemia is one of the most important risk factor predisposing for the ischemic cardiovascular diseases, cerebro vascular diseases and peripheral vascular diseases[1]. This is an important cause for morbidity and mortality among middle aged & older adults worldwide.

Dyslipidemia, which includes hypercholesterolemia and decreased level of HDL-C are the major reason for increased risk of atherogenesis. The sedentary life style &genetic disorders with diets rich in saturated fat & cholesterol contributes this non communicable disease [1]. Nowadays, increased mortality is attributable to non communicable diseases & more than half of these are due to cardiovascular diseases. The main reason being hyperlipidemia; more than one third occurs in middle aged adults.

The current NCEP Adult Treatment Panel (ATP) III guidelines (updated in 2004) for managing dyslipidemia is primordial prevention that targets cessation of smoking, weight management,exercise,healthy eating habits, low cholesterol and glucose levels & maintaining normal BP [2]. The drugs most commonly used for dyslipidemia are statins and fibrates. Though the therapy may be started with

either statin or fibric acid derivatives, ultimately most of these patients require both the drugs or some other combination therapy.

Statins & fibric acid derivatives are prescribed as fixed dose formulation or the patients take both these drugs separately at the same time. Statins are known to cause myopathy & hepatotoxicity [3]. Fibric acid derivatives also cause myopathy syndrome [4]. When both the drugs are combined together, the incidences of adverse effects are higher & the patients may avoid taking drugs.

Hence it was decided to conduct the study, where a statin namely atorvastatin 10 mg given on one day & fibric acid derivative namely fenofibrate 160 mg given on next day, that is atorvastatin 10 mg & fenofibrate 160 mg given on alternate days & the results are compared with both drugs given together daily.

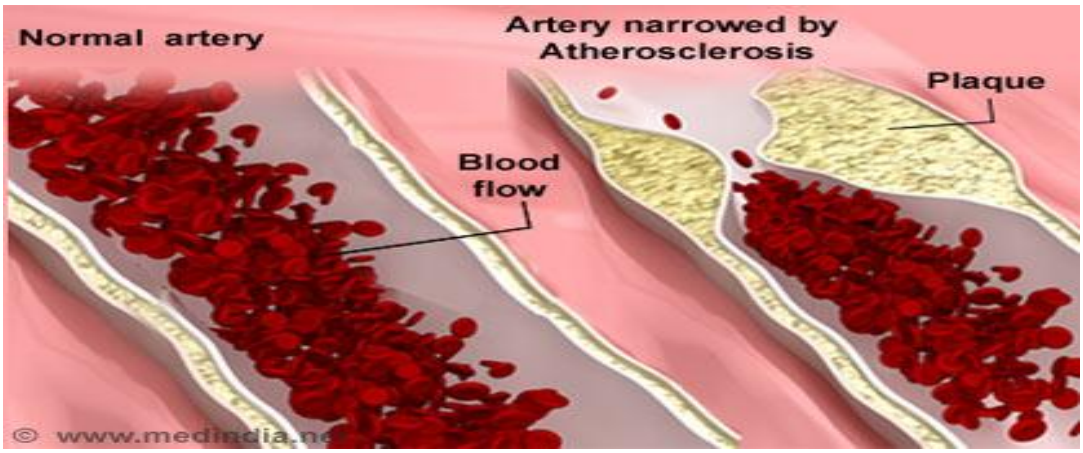
Certain drugs are given as fixed dose combination. The purpose is to reduce the dose of individual drug, enhance the therapeutic benefit and to minimize the adverse effect. But in our study it is designed to find out the same benefits are achieved by giving the drugs (atorvastatin & fenofibrate) separately & on alternate days. In alternate day therapy, the total dosage of atorvastatin 10 mg & fenofibrate 160 mg is only half of both the drugs given together daily. So this study is conducted to assess the benefit & risk of alternate day therapy with daily therapy.

REVIEW OF LITERATURE

DYSLIPIDEMIA

Dyslipidemia is a major cause for the development of ischemic diseases. Dyslipidemia is the disorder of the metabolism of lipoproteins. They manifest as one or more of the following [5]-

- Increased TC levels.
- Increased TG levels.
- Increased LDL-C levels.
- Decreased HDL-C levels.



Courtesy – Medindia.net

HYPERLIPIDEMIA & ATHEROSCLEROSIS

Atherosclerosis is the pathologic process by which cholesterol & calcium plaque accumulates within the arterial wall. Atherosclerosis was first described on autopsy [6],as the term "athero" means porridge & "sclerosis" means scarring .

The first person to demonstrate the role of cholesterol in the development of atherosclerosis was **Nikolai N. Anichkov** (1885–1964). His classic experiments in rabbits in 1913 opened the path for our current understanding about the importance of cholesterol in CVS diseases [7].

Dr.**Nikolai.N.Anichkov** (courtesy – Anichkov Family)

The discovery by Brown and Goldstein of LDL receptors and the mechanisms of cholesterol metabolism permitted testing of "cholesterol hypothesis" (mechanical injury would increase the infiltration of plasma components into the artery) with efficient pharmacologic & genetic tools in our day to day life [7].

Myocardial infarction & angina pectoris are mainly due to atherosclerosis of the coronary arteries. Similarly, atherosclerosis of the arteries supplying the CNS often provokes stroke & transient ischemic attack[8]. In the peripheral circulation, atherosclerosis leads to gangrene & intermittent claudication which can jeopardize limb viability. Mesenteric ischemia may occur due to splanchnic circulation involvement. It can also affect the kidneys either directly (e.g., renal artery stenosis) or as an important site of atheroembolic manifestation [8].

Epidemiology

In the western world, atherosclerosis leads as the major cause of death & serious morbidity. The WHO has predicted, that in near future it will also become the leading cause of mortality in the entire world [6]. The total number of peoples dying from cardiovascular disorders is about 30% of all deaths worldwide [9]. Also, when the burden of disease is measured as DALYs lost the increasing global impact is about 25% of the DALYs lost[10]. A rapid increase in the burden of coronary artery disease is now emerging, partly because of longer life expectancy with many more people in CHD prone ages but also because age-specific CHD mortality rates are accelerating[11].

In India, it is estimated that there were approximately 46.9 million patients during the year 2010[10]. Premature deaths seem to be more common in India as 52% of the CAD deaths occurred below 65 as compared to 22% in developed countries [12]. On Comparing with other countries, India has the greatest loss in potentially productive years of the life due to the atherosclerosis associated diseases, with a high mortality in middle aged adults mainly in urban areas. During the past 30 years, Coronary artery

disease rates increased twice in India, whereas reduced to half in most of the developed countries like US[13].

Incidence of CAD has been increased in urban areas than rural areas reflecting the acquisition of risk factors like alcoholism, tobacco consuming, unhealthy diet, obesity, etc… In one study, the prevalence of ischemic heart diseases among adults (based on clinical & ECG criteria) was estimated at 96.7 per 1000 population in the urban & 27.1 per 1000 in rural areas [10]. There is significantly higher body mass index in urban peoples than rural peoples (24 Vs 20 in male; 25 Vs 20 in female) in India. An increased rate of abdominal obesity is seen among the urban population. Urban males are having waist hip ratio of 0.99 Vs 0.95 in rural males [13].

RISK FACTORS FOR ATHEROSCLEROTIC DISEASE [14]

Non Modifiable Factors

- Age (> 45 years in males ; > 55 years in females)
- H/O of premature CHD in the family.
- Family H/O Hereditary Dyslipoproteinemias
- Ethnic Group (migrants moving from one community to another)
- Established Vascular disease (intermittent claudication is a risk factor for both stroke & aortic aneurysm)

Major Modifiable Risk Factors

- Current smoking (smoking within past one month).
- HT (BP ≥ 140/90 or usage of drugs to treat hypertension, irrespective of BP)
- Reduced HDL (< 40 mg/dl in males & < 50 mg/dl in females)
- Sedentary life style.

Other Factors

- Type 2 Diabetes Mellitus.
- Obesity.
- Homocysteinemia.
- Psychosocial Environment.
- Exogenous Estrogens.
- Type A personality.
- Alcohol.
- Infection (Chlamydia Pneumoniae) [6]

HISTOPATHOLOGY

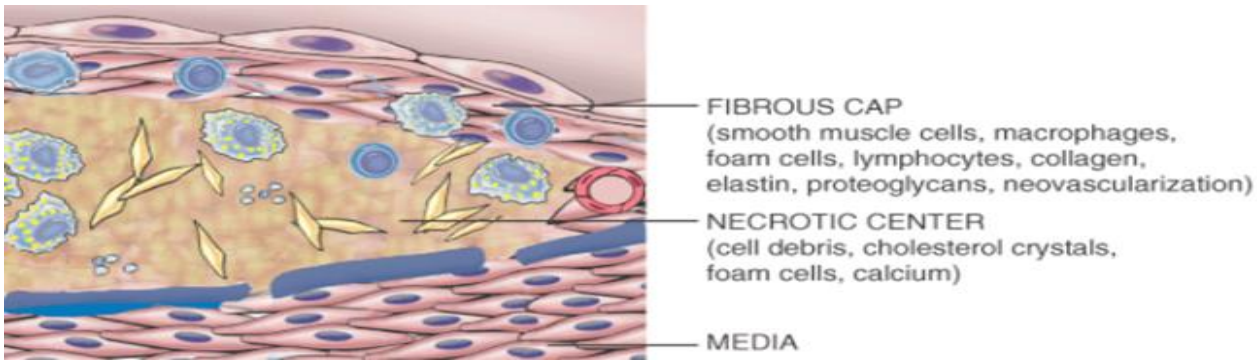
Normal Artery

The healthy artery consists of 3 histologically distinct layers. Tunica intima is the innermost layer which surrounds the lumen, with a single layer of endothelial cells[15]. The Tunica media surrounding the intima consists of a single layer of vascular smooth muscles. The tunica adventitia is a connective tissue layer which encloses tunica media of all arteries .It also contains nerves and blood vessels.

Atherosclerotic vessel

Atherosclerosis is a disease mainly affecting the intimal layer of elastic arteries. Most often involved in the order of frequency are coronary, carotid, cerebral, aorta & renal arteries. The lower limb arteries are also vulnerable [6]. But, the internal mammary artery is almost always spared, making it invaluable for CABG surgery. Atherosclerotic lesions develop for many years & pass through several overlapping stages. The earliest lesion histologically, is lipid laden macrophage foam cells &T lymphocytes which are accumulated in sub endothelial position, called fatty *streak*. On gross examination they are visible as yellow streaks which follow the direction of blood flow[16].

Atheromatous Plaque



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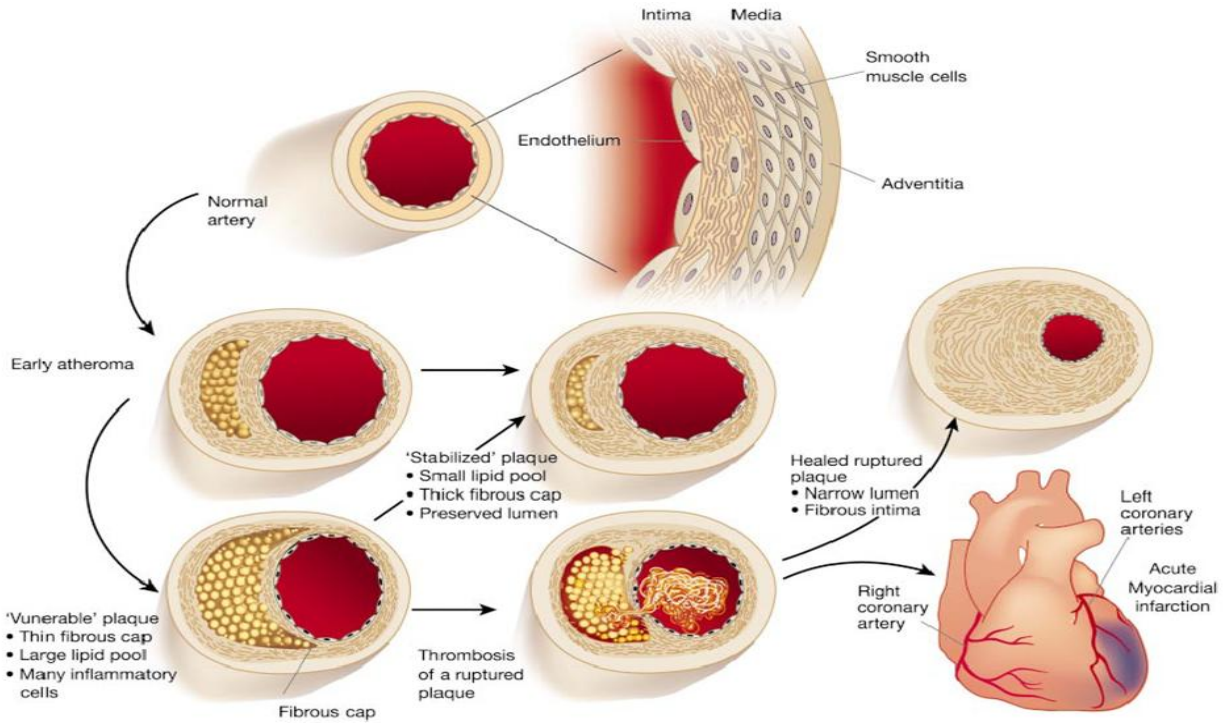
Pathophysiology of atherosclerosis



(Illustration from Libby P: Inflammation in Atherosclerosis. Nature 202)

PATHOGENESIS [17]

The important steps involved in atherosclerotic process are -

- Endothelial injury
- Lipoprotein deposition
- Inflammatory reaction
- Fibrous cap formation

Injury of endothelial cell: This is the initial factor which starts the process of atheromatous plaque formation. As the endothelium is regularly exposed to blood circulation, the toxin like tobacco& diabetes, dyslipidemia can result in damage. The continuous physical force acting upon the endothelium plays a main role in the atheromatous plaque that occurs mostly at bifurcations of the left anterior descending artery & left main coronary artery.

Lipoprotein deposition: When there is injury in endothelium, the lipoprotein molecules enters where they are modified by oxidation (via oxidizing enzymes) or glycation (diabetes). This lipoprotein which is modified becomes inflammatory & is ingested by macrophages forming foam cells in the arterial wall.

Inflammatory reaction: The LDL modified becomes antigenic & starts attracting the inflammatory cells into vessel wall. The inflammatory mediators are released after the injury of endothelium, which further increases the leukocyte recruitment.

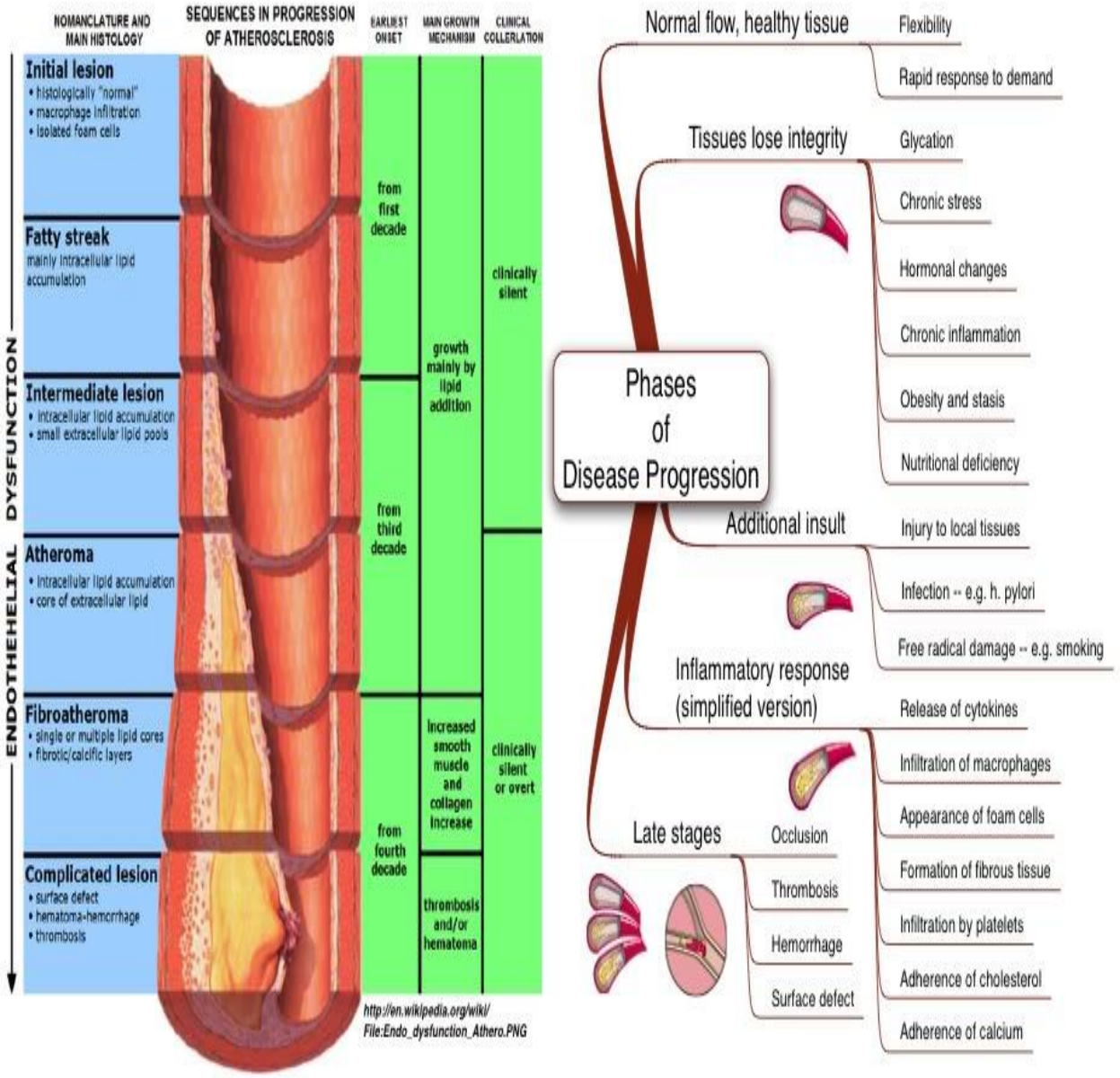
Smooth muscle cell cap: These cells slowly migrate to the plaques' surface forming fibrous cap. Thick capped atherosclerotic plaque is stable, but thin capped are more prone to rupture or erosion leading to thrombosis.

Inspite of obstructing the blood flow, the atherosclerotic plaque can also rupture leading to vessel thrombosis & arterial aneurysm.

SECONDARY CAUSES OF DYSLIPIDEMIA[18]

S.No	***DISORDER***	***MAJOR LIPID EFFECT***
1.	Diabetes Mellitus	Triglyceride > Cholesterol; low HDL
2.	Alcohol use	Triglyceride > Cholesterol
3.	Contraceptive usage	Triglyceride > Cholesterol
4.	Nephrotic syndrome	Triglyceride > Cholesterol
5.	Estrogen use	Triglyceride > Cholesterol
6.	Glucocorticoid excess	Triglyceride > Cholesterol
7.	Obstructive liver disease	Cholesterol > Triglyceride
8.	Hypothyroidism	Cholesterol > Triglyceride

PHASES IN PROGRESSION OF ATHEROSCLEROSIS



(Courtesy- **Nicole K. Brogden, PharmD**, *University of Kentucky HealthCare, Lexington)*

ATP III Guidelines for Lipid Profile[19]

Table 2. ATP III Classification of Cholesterol Levels

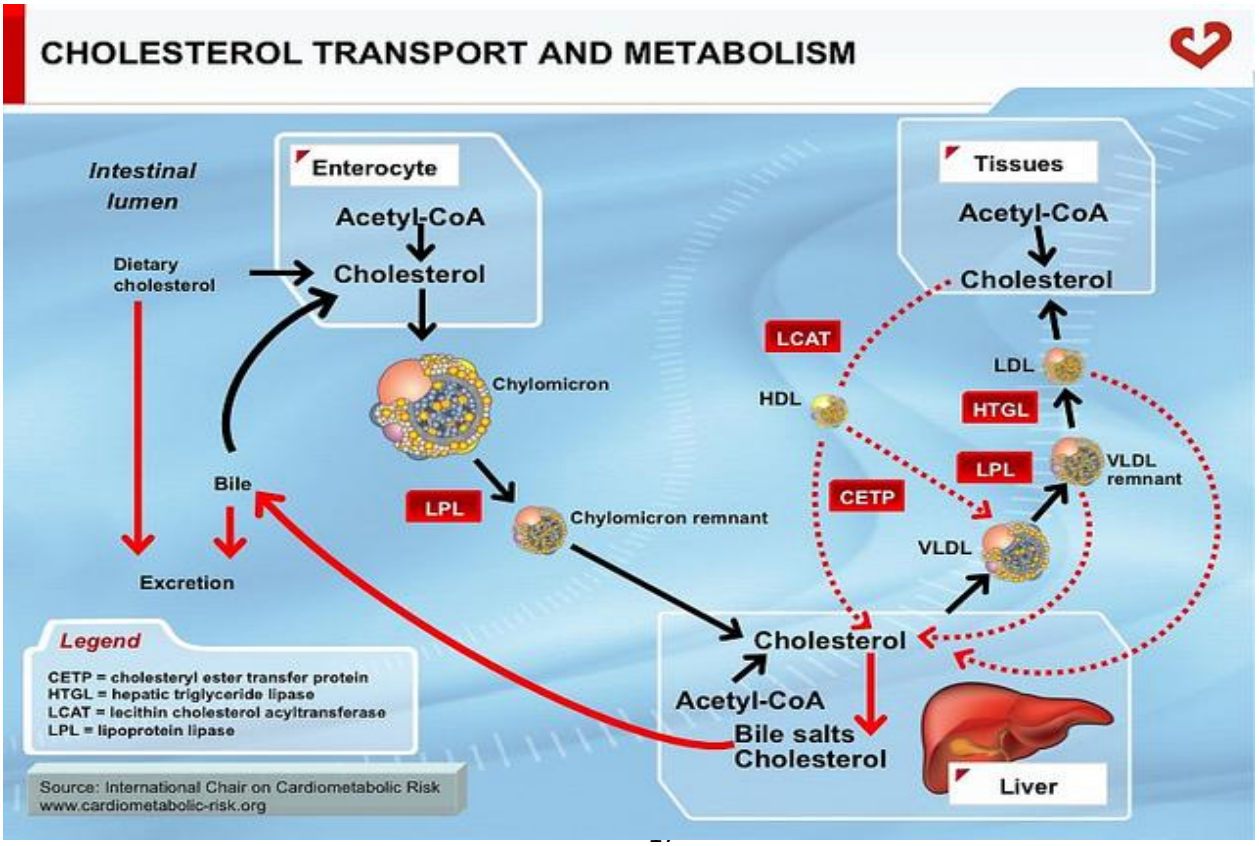
Total Cholesterol	
<200	Desirable
200-239	Borderline high
≥240	High
LDL Cholesterol	
<100	Optimal
100-129	Near optimal/above optimal
130-159	Borderline high
160-189	High
≥190	Very high
HDL Cholesterol	
<40	Low
≥60	High
Triglycerides	
<150	Normal
150–199	Borderline high
200–499	High
>500	Very high

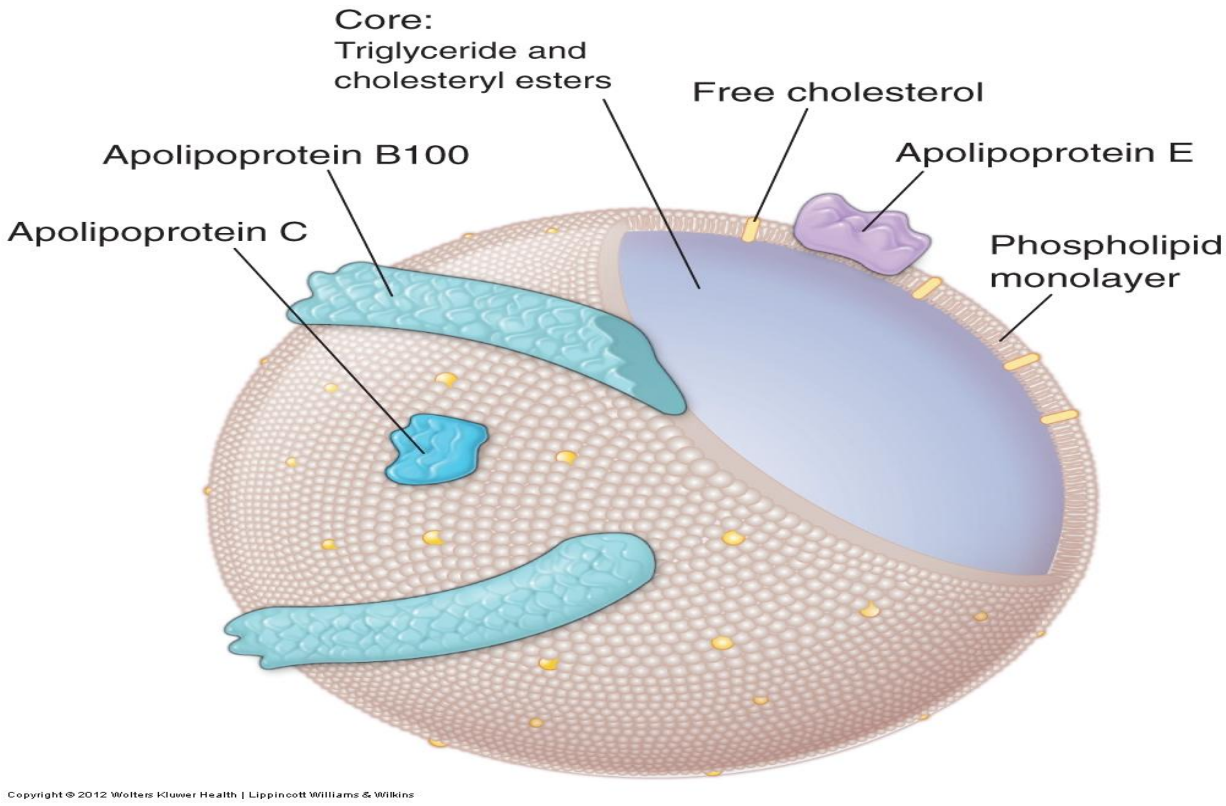
ATP III: The National Cholesterol Education Program Adult Treatment Panel III.
Source: Reference 2.

PLASMA LIPOPROTEIN METABOLISM

Lipoproteins are macromolecular assemblies which contains lipids & proteins. TGs, esterified and free cholesterol, phospholipids are the lipid constituents[20].

Lipids are sparingly soluble or insoluble molecules which are needed for biogenesis of membrane & maintenance of its integrity[21]. The protein components (apolipoproteins) give structural integrity to the lipoproteins, which may function as ligands in lipoprotein receptor interactions or as cofactor in enzymatic processes that regulate lipoprotein metabolism [20].





Structure of Lipoprotein Particles

Lipoproteins are microscopic spherical particles about 7-100 nm in diameter[22]. In all the spherical lipoproteins, the water insoluble TGs, cholesteryl esters constitutes the core components & the water soluble, more polar apoproteins, unesterified cholesterol &phospholipids forms the surface components.

CHYLOMICRONS

Chylomicrons are the largest plasma lipoproteins which are synthesized from the fatty acids of dietary TGs & cholesterol which is absorbed from the intestine by epithelial cells. Intestinal cholesterol and plant sterol absorption is mediated by the NPC1L1protein that appears to be the target of cholesterol absorption inhibitor[20]. Triglyceride synthesis is regulated by the diacylglycerol transferase in many tissues. After their synthesis in ER, triglycerides are transferred by the TG transfer protein to the place where newly synthesised apoB-48 is present to form chylomicrons.

The apolipoproteins of chylomicrons includes that are produced by intestinal epithelial cells (apoB-48, apoA-I, IV), and that acquired from HDL (apoE, apoC-I, II, III) after chylomicrons have been secreted into the lymph & enter the plasma. Apo B48 which is synthesized only by the intestinal epithelial cells is unique to Chylomicrons.

ApoB48 lacks the portion of sequence of apoB100 which allows apoB-100 binding to the LDL receptor, so that apoB-48 primarily function as a structural component of chylomicrons. Dietary cholesterol is esterified by the ACAT-2 [23].

ACAT-2 is present in the intestine & liver, where the free cholesterol is esterified before the chylomicrons & VLDL are assembled. It also regulates the absorption of dietary cholesterol in the intestine & thus forms a potential pharmacological target for decreasing blood cholesterol levels.

After entering into the circulation through thoracic duct, CMs are initially metabolized at the capillary luminal surface of tissues which synthesize LPL, TG hydrolase. These tissues include adipose tissue, lactating breast, skeletal and cardiac muscle.

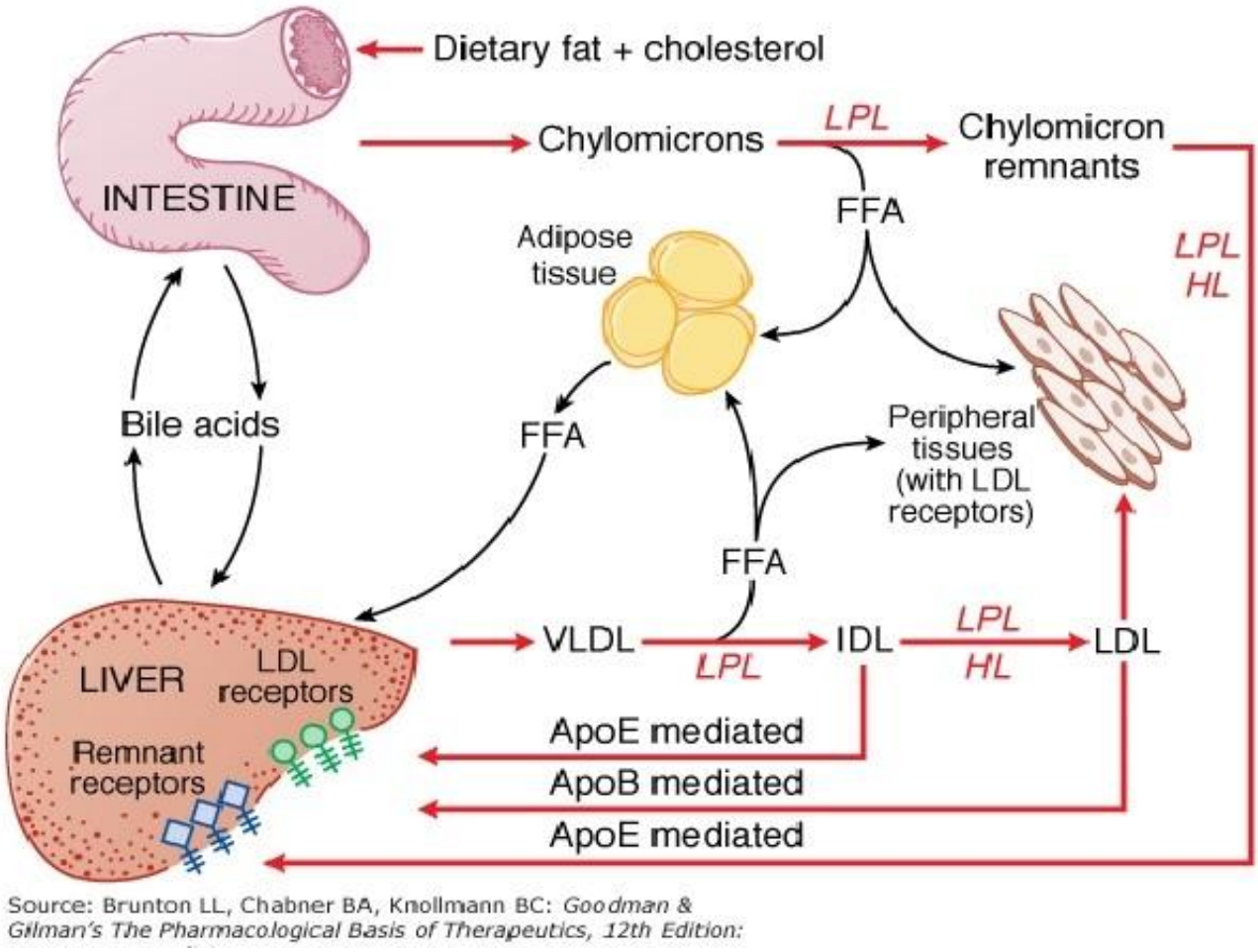
As the triglycerides are hydrolyzed by LPL, the resulting free fatty acids are utilized by the adjacent tissues. The interaction of chylomicrons & LPL requires apoC-II as a cofactor[24].

The absence of functional LPL or apoC-II prevents the hydrolysis of triglycerides in CMs & leads to severe hypertriglyceridemia & pancreatitis during childhood & infancy (chylomicronemia syndrome) [24]. The plasma concentration of CMs can be primarily controlled by dietary fat consumption reduction.

Chylomicron Remnants

After lipoprotein lipase mediated removal of most of the dietary TGs, the CM remnants containing all of the dietary cholesterol, are detached from the capillary vessel surface & the liver removes them from circulation. Firstly, apo E sequesters the CM remnants with the heparan sulfate proteoglycans interactions & are processed by the hepatic lipase enzyme. Next, the remnant uptake is mediated by apo E by interaction with LRP[25].

LRP is important in the lipid metabolism, because it is the backup receptor which is responsible for the uptake of apoE-enriched remnants of CMs & VLDL. During the initial hydrolysis of chylomicron triglycerides by Lipoprotein Lipase, apoA-I & phospholipids are shed from the chylomicrons surface & remain in the plasma. This is one mechanism by which nascent HDL is generated. Chylomicron remnants are not precursors of LDL, but the dietary cholesterol delivered by CM remnants to the liver enhances the plasma LDL levels.



Major Pathways involved in the metabolism of Chylomicrons

VERY LOW DENSITY LIPOPROTEINS (VLDL)

VLDL is synthesized in the liver when TG production is stimulated by the raised flux of FFA or the de novo production of fatty acids by the liver. VLDL particles size about 40 to100 nm in diameter and are larger to form plasma turbidity.

Liver synthesizes apoB-100, apoC-I, II, III, apoE and incorporates into VLDL[26]. The newly produced apoB-100 is degraded by the liver cells, when the TGs are not available to form VLDL.Triglycerides are synthesized in the ER & are transferred to the site in the ER by MTP, where newly formed apoB-100 is available to synthesize precursor VLDL.

Very low density lipoprotein is then catabolized by Lipoprotein Lipase in capillary beds. As the TG hydrolysis is completed, the VLDL remnants are released from capillary endothelium and it reenters the circulation. ApoB-100 contains small VLDL and IDL (half life of <30 mins), have 2 potential fates.

About 40-60% is cleared by the liver from the plasma via interaction with LDL receptors & LRP. LPL & hepatic lipase convert the remaining IDL to LDL by removing the additional TGs. The apoA-V, C apoproteins and apoE redistribute to HDL. ApoE plays a major role in the metabolism of TG-rich lipoproteins (CM, chylomicron remnants, VLDL & IDL).

About 50% of the apoE in the plasma of fasting subjects is associated with triglyceride-rich lipoproteins, and the other 50% is a constituent of HDL. About 75% of the apoE in plasma is synthesized by the liver. Brain and

macrophages synthesize the rest. In transgenic mice, over expression of apoE by macrophages prevents hypercholesterolemia-induced atherogenesis

LOW DENSITY LIPOPROTEIN

In the circulation, virtually all of the LDL particles are derived from VLDL. The LDL particles have t½ of 1.5-2 days, which is the reason for the raised plasma level of LDL. In persons without hyperlipaemia, 2/3rd of plasma cholesterol is present in the LDL.

LDL receptors primarily mediate the plasma clearance of low density lipoprotein particles. The most common cause of Autosomal dominant hypercholesterolemia involves mutations of the LDL receptor gene. Greater than 900 mutations of the LDL receptor gene have been found to be associated with defective or absent LDL receptors which may lead to Familial hypercholesterolemia[27].

The primary apolipoprotein of LDL is ApoB-100, which acts as the ligand binding LDL to its receptor. 3000-3700 residues in the carboxyl-terminal sequence are essential for binding. A mutation in this region affects binding and causes Autosomal dominant hypercholesterolemia (familial defective apoB-100).

Liver expresses a greater complement of LDL receptors and helps in removing 75% of all LDL from plasma. By manipulating the liver LDL receptor gene expression, plasma LDL levels can be effectively modulated. Thyroxine & estrogen raises LDL receptor gene expression thereby lowers LDL[27].

Regulation of LDL receptor expression is by which cells regulate their free cholesterol content. This regulatory process is mediated by transcription factors such as SREBPs and Scap [28].

Scap is both a sensor of CH content in the endoplasmic reticulum & an escort of SREBPs from the ER to Golgi apparatus. LDL becomes atherogenic by oxidation[29], a required step for LDL uptake by the scavenger receptors of macrophages which leads to foam-cell formation in arterial lesions.2 scavenger receptors (SRs) involved are SR-AI/II & CD36. By knocking out either receptor in transgenic mice retards the uptake of oxidized LDL by macrophages. Expression of the 2 receptors is different.SR-AI/II expressed more in early atherogenesis, and CD36 expressed greater as foam cells during disease progression.

HIGH DENSITY LIPOPROTEIN (HDL)

ApoA-I is the major HDL apoprotein.The plasma concentration of apo A-I forms the more powerful inverse predictor of CHD risk[30]. For normal production of HDL, ApoA- I synthesis is essential. Mutations in the apoA-I gene cause HDL deficiency leading to accelerated atherogenesis. The over expression of apoA-I in transgenic mice protects experimentally induced atherogenesis.

HDL is protective lipoprotein which decreases the CAD risk. This protecting effect is because of HDL participating in the reverse cholesterol transport (excess cholesterol obtained from cells is excreted, by transferring to the liver).HDL also protects atherogenesis by mechanisms which are not directly related to reverse cholesterol transport such as putative anti-inflammatory, anti-oxidative, platelet anti-aggregatory, anticoagulant & profibrinolytic activities[31].

Lp (a)

Lipoprotein (a) mainly contains an LDL particle that has a 2nd apoprotein along with apoB-100 [32]. It is attached by means of one disulfide bond, to apoB-100.It never functions as a lipid-binding apoprotein. A structural relation of apo (a) is seen with plasminogen .It is atherogenic as it interferes with fibrinolysis of thrombi on surface of plaque.

CHARACTERISTICS Of PLASMA LIPOPROTEINS[33]

Lipoprotein Class	**Major lipid constituent**	**TG:Cholesterol ratio**	**Significant apoproteins**	**Mechanism of catabolism**
ChyloMicron & Remnants	Dietary TG &Cholesterol	10:1	B48,E,AI,AIV, CI,CII,CIII	TG hydrolysis by LPL,remnant uptake by liver mediated by apoE
VLDL	Endogenous or liver TG	5:1	B100,CI, CII,CIII,E	TG hydrolysis by LPL
IDL	Cholesteryl esters & Endogenous TGs	1:1	B100,E,CII, CIII	50% converted to LDL, 50% apo E mediated uptake by liver
LDL	Cholesteryl esters	Not significant	B100	Apo B100 mediated uptake by LDL receptor
HDL	Phospholipids, Cholesteryl	Not significant	AI,AII,E,CI,CII, CIII	Transfer of Cholesteryl ester

	esters			to VLDL & LDL
Lp(a)	Cholesteryl esters	Not significant	B100,apo (a)	Unknown

LABORATORY INVESTIGATIONS[34]

- Routine blood & urine examination
- Fasting lipid profile
- Random blood sugar
- Blood urea & Serum creatinine
- Liver function test, CPK

MANAGEMENT OF DYSLIPIDEMIA[35]

Non Pharmacological

- Restrict dietary saturated fat and cholesterol.
- By taking 3 times /day, the plant sterols & esters reduces LDL -C by 10%.
- Exercise.
- Weight reduction.

PHARMACOLOGICAL

- ***Competitive HMG -CoA reductase inhibitors*** (Statins):

  Simvastatin, pravastatin, lovastatin, atorvastatin, rosuvastatin, pitavastatin.

- ***Bile Acid Sequestrants*** (Resins):

  Cholestyramine, colesevelam, colestipol.

- ***Lipoprotein lipase activators (PPARα activators -Fibrates):***

  Clofibrate, Fenofibrate, Gemfibrozil, Bezafibrate.

- ***Lipolysis & TG synthesis inhibitor:***

  Nicotinic Acid

- ***Sterol absorption inhibitor:***

  Ezetimibe.

- ***Omega 3 fatty acids (Fish oils)***

STATINS

The statins are the most effective & best tolerated drugs routinely used to treat dyslipidemia. These drugs are the competitive HMG Co A reductase inhibitors, that catalyses the rate limiting step in cholesterol synthesis.

HISTORY

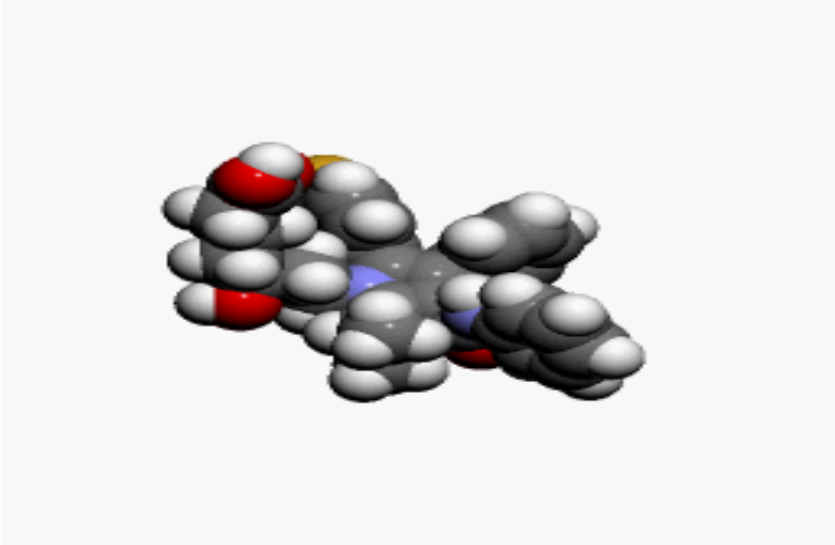
Statins were isolated from the fungus, *Penicillium citrinum*. Endo & colleagues[36]identified stains as cholesterol biosynthesis inhibitors in 1976. Subsequent studies by Brown and Goldstein established that statins act by inhibiting HMG CoA reductase. The first statin studied in humans was compactin renamed as mevastatin. Lovastatin was the first statin approved for use in humans (formerly known as mevinolin), that was isolated from *Aspergillus terrus*.

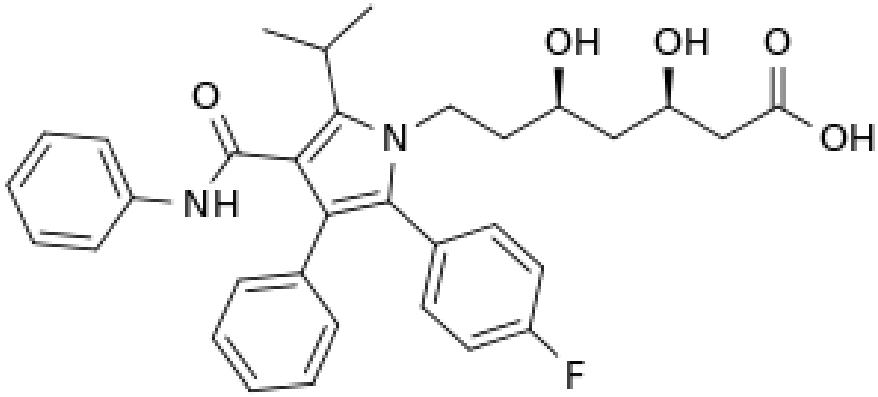
Pravastatin & simvastatin were chemically modified derivatives of lovastatin.

Atorvastatin, fluvastatin, rosuvastatin, pitavastatin were synthetic compounds.

ATORVASTATIN

CHEMICAL STRUCTURE[37]





CHEMICAL NAME [37]

[R-(R*, R*)]- 2-(4- Fluor phenyl)-γ, δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenyl amino) carbonyl]-1H-pyrrole-1-heptanoicacid calcium salt

Mol. Formula- $C_{33}H_{35}Ca_2FN_2O_5$

Mol. Mass - 558.64 g/mol

Physical Properties[37]

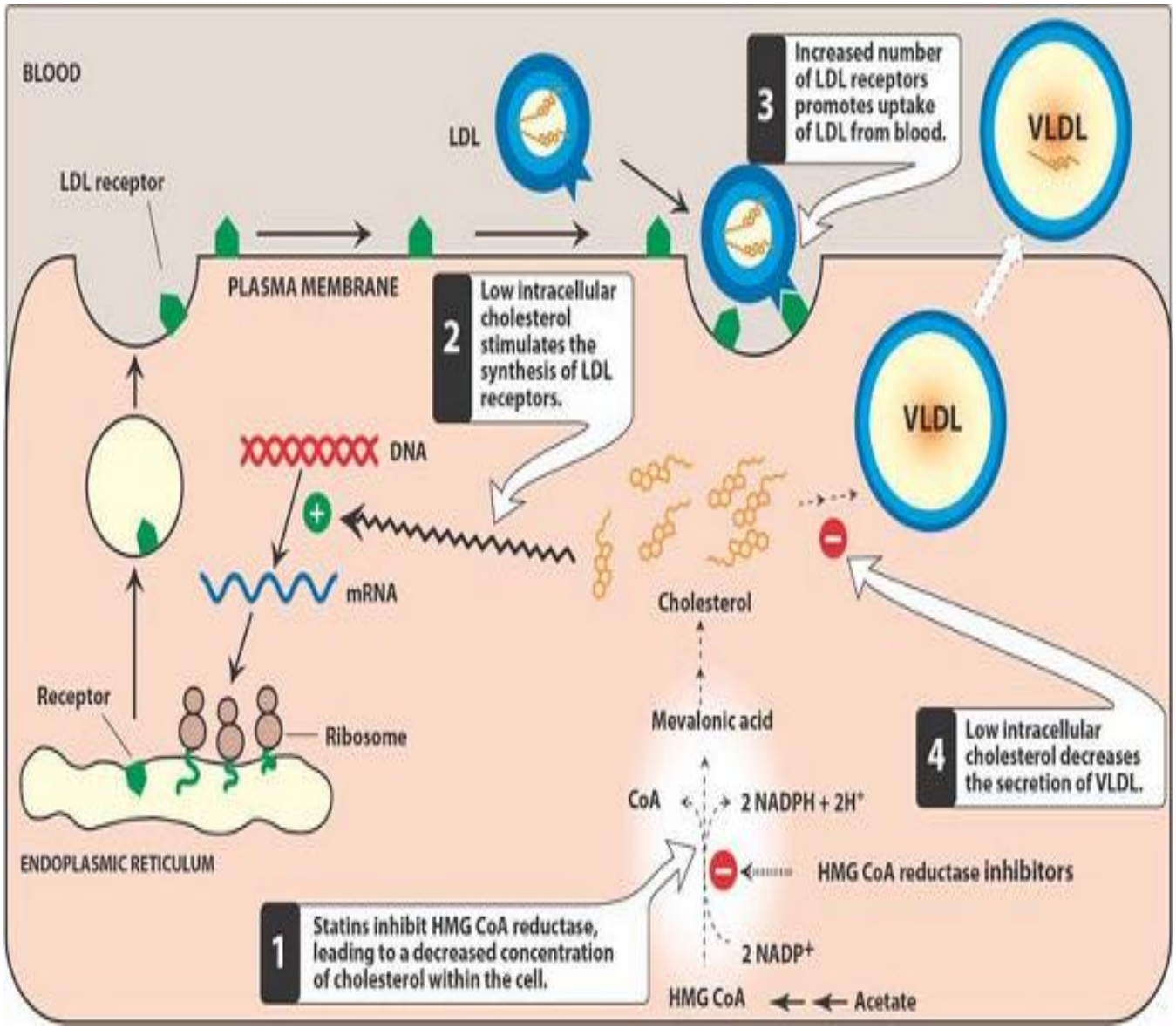
It is an off-white crystalline powder, which is synthesised chemically. This compound is stable with no marked effect of heat, common solvents or pH. It is insoluble in water pH < 4, very slightly soluble in phosphate buffer and acetonitrite & easily soluble in methanol, tetrahydrofuran. Upon exposure to sunlight the atorvastatin readily decomposes into 3 major byproducts – lactam isomers, phenantherenes and diketoepoxide.

Mechanism of Action

The statins reduces LDL-C levels by competitively inhibiting HMG CoA reductase enzyme. By decreasing the conversion of HMG CoA to mevalonate, they block the rate limiting step.

Statins reduces the cholesterol level by blocking the hepatic cholesterol synthesis .This leads to raised expression of LDL receptor gene. Due to the decreased free cholesterol content within the liver cells, the membrane bound SREBPs are sequestered by the protease enzyme & are translocated to the nucleus. The transcription factors then bind with the SRE of the LDL receptor gene, enhancing the LDL receptors synthesis[38]. There is also reduction in LDL receptors degradation.

The major metabolites of atorvastatin are the *para*- & *ortho*-hydroxy metabolites & a glucuronide conjugate of the O-hydroxy metabolite [37].The *para*- and *ortho*-hydroxy metabolites are active showing the blocking effects towards HMG CoA reductase *in vitro* human liver micro enzymes. About 70% of the HMG CoA reductase inhibition of atorvastatin has been attributed to its active metabolites.



Mechanism of Action of Atorvastatin

Statins on TG levels

TG > 250 mg/dl are substantially decreased by statins and the percentage reduction obtained is same as that of LDL cholesterol. The hypertriglyceridemia patients who take higher doses of Atorvastatin experience a 35-45% decrease in fasting TG levels[39].

Statins on HDL-C levels

In patients with increased LDL levels & gender appropriate HDL-C levels, an increase in HDL of 5-10% was found irrespective of the dose. However, in patients with decreased HDL-C (<35 mg/dl) statins may differ in their effects by increasing the HDL-C & apoA-I levels[40].

Statins on LDL-C levels

Depending on the type and dose of statins used, they lower LDL-C by 20-55%. Greater reduction of LDL-C noted at higher dose of Atorvastatin. These

drugs are effective in almost all patients with elevated LDL-C levels except those with homozygous familial hypercholesterolemia because both alleles of the LDL receptor gene code for dysfunctional LDL receptors. LDL-C is reduced by about6% with each dose doubling [41]. Maximal effect on plasma lipid levels are reached within 7-10 days. Statin therapy does not cause reduction of LP (a) levels.

POTENTIAL CARDIO PROTECTIVE EFFECTS

The **Non Lipid Roles of Statins** are –

- ***Endothelial function*** → Treatment with statin induces endothelial synthesis of the NO, which leads to enhanced endothelial function that is independent of changes in plasma cholesterol levels.

- ***Statins & Plaque stability*** → Statins act by inhibiting monocyte infiltration into the vessel wall & macrophage production of matrix metalloproteinase *in vitro.* They also inhibit smooth muscle cells proliferation & enhance apoptosis.

- ***Statins & Inflammation*** → They have an anti inflammatory role. They reduce the risk of CHD & CRP levels. Metabolic syndrome & body weight are associated with raised levels of highly sensitive CRP [42].

- ***Statins & Coagulation*** → The important evidence of non lipid lowering effect of a statin is reduction in venous thromboembolism .They decrease platelet aggregation & deposition of thrombi. They also have variable effects on the fibrinogen levels.

ABSORPTION, METABOLISM, EXCRETION

The intestinal absorption of the statins is 30-85%, after oral administration. Maximum plasma concentration occurs within 1-2 hours. Atorvastatin is administered in the β-hydroxy acid form which inhibits HMG CoA reductase. Atorvastatin has extensive first pass metabolism, mainly mediated by OATP1B1 [43].

Its absolute bioavailability is 14% & the systemic availability of inhibitor activity is about 30%. The decreased systemic availability is due to high presystemic clearance in GI mucosa & liver. In the plasma, >95% of statin & their metabolites are protein bound.

The t½ of atorvastatin is ~ 20 hours. This longer t½ of atorvastatin contributes to their greater cholesterol lowering efficacy[43]. Primary excretion is in the hepatic circulation & atorvastatin is metabolised by cytochrome P 450 3A4 in the liver, subsequently eliminated in faeces [37].

ADVERSE EFFECTS & DRUG INTERACTIONS

Hepatotoxicity:

The post marketing surveillance studies of statin showed a raise in liver transaminase levels > 3 times the upper normal limit (incidence > 1%). This incidence appeared to be dose related. In placebo controlled outcome clinical trials, the incidence of 3 fold rise in transaminases was 1-3% compared to placebo when 10-40 mg dose of atorvastatin, pravastatin, simvastatin were used[44]. It is therefore essential to measure ALT before & after study when clinically indicated.

Observational studies & a prospective trial suggests that the transaminase elevations in patients with nonalcoholic fatty liver disease & hepatitis C are not at risk of statin induced hepatotoxicity [45]. This is important, as many insulin resistant patients are affected by nonalcoholic fatty liver disease & have rise in transaminases.

Insulin resistant patients are associated with increased CVD risk seems to be benefiting from statins (Cholesterol Treatment Trialists'

Collaborators, 2008). It is reassuring that these patients with elevated transaminases can safely take statins.

Myopathy:

The main adverse effect of statins is myopathy [46]. The risk of myopathy & rhabdomyolysis rises in proportion to statin dose & plasma concentration. The factors inhibiting statin catabolism are associated with increased myopathy risk such as elderly age (> 80 yrs), renal/hepatic dysfunction, perioperative periods, diabetes mellitus, and hypothyroidism [47]. The most common interactions are seen with gemfibrozil (38%), warfarin (4%), cyclosporine (4%), digoxin (5%), macrolide (3%), azole antifungals (1%) and others such as protease inhibitors, amiadarone, nefazadone, and niacin (rare) [47].

Gemfibrozil, the drug most commonly associated with statin induced myopathy, inhibits the uptake of the active hydroxy forms of statins into hepatocytes by OATP1B1. Other fibrates, especially fenofibrate do not interfere with glucuronidation of statins and pose less risk of myopathy when combined with statin therapy. When niacin is administered with statin,

myopathy is caused by an enhanced inhibition of skeletal muscle cholesterol synthesis.

Drugs that interfere with statin oxidation are those metabolised primarily by CYP3A4 which includes erythromycin, itraconazole, cyclosporine, nefazadone (anti depressant), protease inhibitors and amiadarone[48]. These interactions are due to the increased plasma concentrations of statins and their active metabolites. Atorvastatin is primarily metabolised by CYP3A4 & 3A5.

Despite the rarity of ten-fold elevations of CK, many patients complain of myalgia while taking statins. It is unclear if such myalgias are caused by taking statins. Replacing Vit D in patients with a Vit D deficiency reportedly reduces statin related myalgias & improves statin tolerance. It is potentially significant, because Vit D deficiency is associated with myopathy, insulin resistance & increased incidence of CVD.

Pregnancy & Lactation: The safety of statins during pregnancy has not been established. During child bearing years, while taking statins are advised to take better contraception. Nursing mothers better to avoid taking statins.

THERAPEUTIC USES

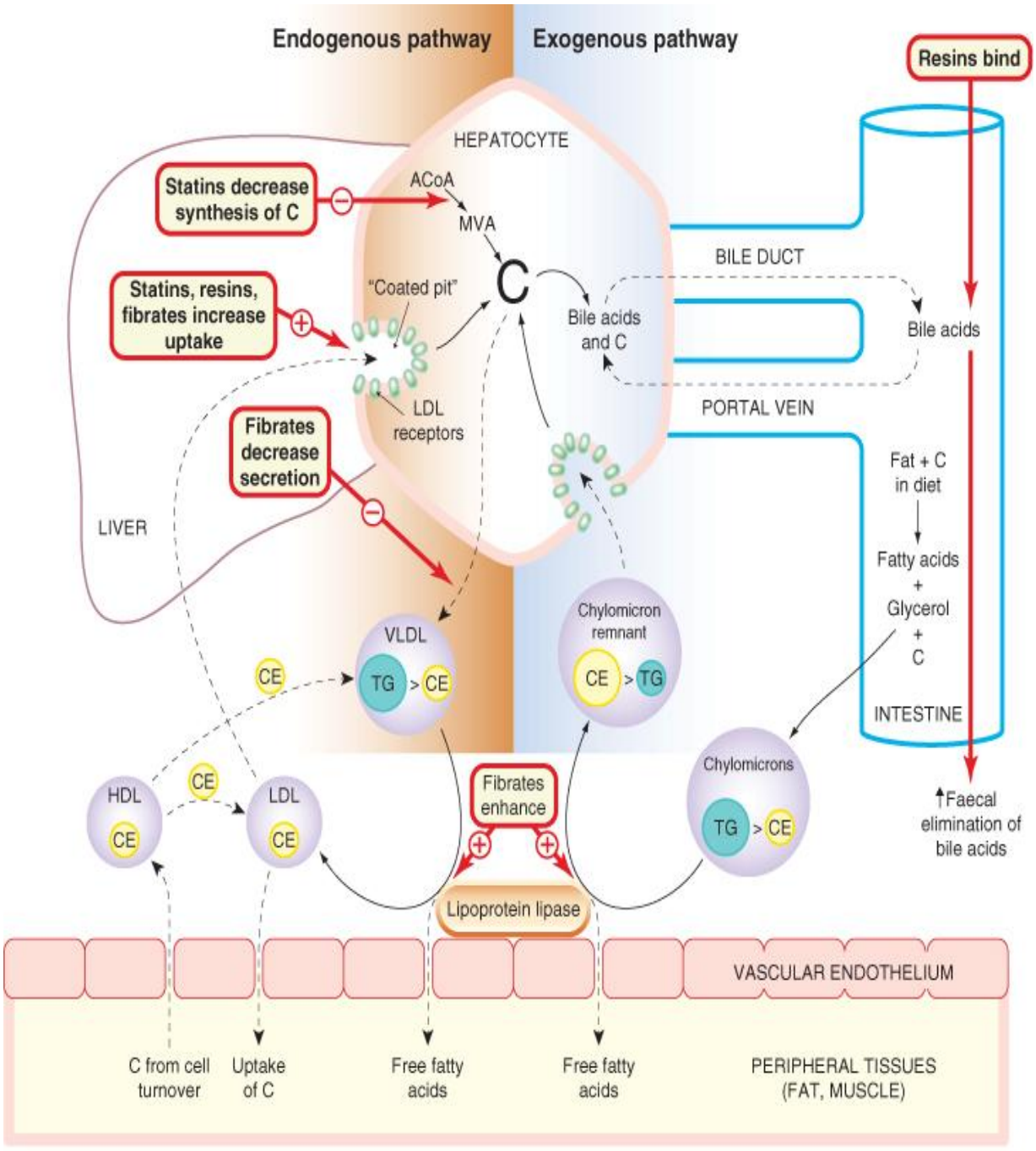
Lipid lowering effect

Cholesterol synthesis is maximal in between midnight & 2 am. As atorvastatin has a long t½, it can be administered at any time of the day with minimal dose of 10 mg and maximal dose of 80 mg per day[49]. It is marketed combined with CCB (amlodipine) for patients with HT, angina and hypercholesterolemia. The drug to be initiated with 5-10 mg daily, increasing stepwise, if needed, until myopathy incidence is better defined. If combined with gemfibrozil, the dose must not exceed 10 mg.

The choice of statins is based on efficacy (reduction in LDL-C) and cost. The documented safety records of the statins should be considered, mainly in younger patients while starting therapy. A baseline determination of ALT and test is repeated at 3-6 months interval. If ALT is normal, then it can be done once every 6-12 months. CK is not routinely measured, unless the patient is on treatment with drugs that enhances the risk of myopathy[49].

Statins in combination with other lipid lowering drugs

Statins combined with cholestyramine & colestipol, produces 20-30% greater reductions in LDL-C than statins alone. Niacin also enhances the statin effect, but myopathy occurrence rises when doses > 25% of maximum are used with niacin. Fenofibrate (least to interfere with statin metabolism) appears to be the safest fibrate to use with statins[50]. Combination therapy with resins, niacin and statins can reduce LDL upto 70%.



Cholesterol Transport in the Tissues, With Sites of Action

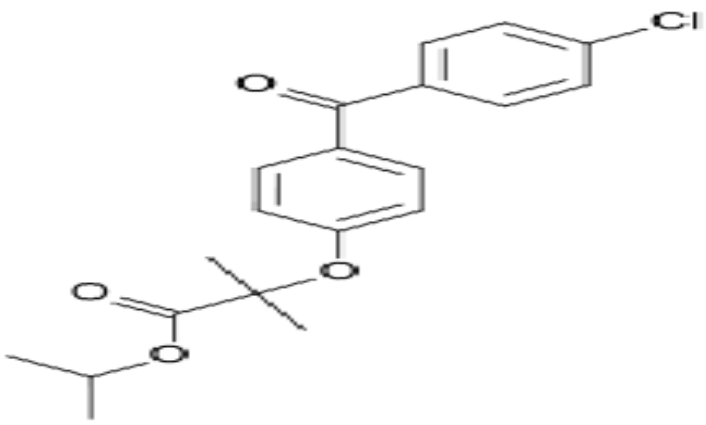
FIBRATES (PPAR activator)

HISTORY

In 1962, Thorp and Waring reported that ethyl chlorophenoxyisobutyrate lowered lipid levels in rats. In 1967, the ester form (clofibrate) was approved for use in the U.S. and became the most widely prescribed hypolipidemic drug. Its use declined dramatically, however, after the WHO reported that, despite a 9% reduction in cholesterol levels, clofibrate treatment did not reduce fatal cardiovascular events, although nonfatal infarcts were reduced.

FENOFIBRATE

CHEMICAL STRUCTURE[51]



Chemical Name

***2*-[4-(4-chlorobenzoyl) phenoxy]-2-methylpropanoic acid1-methylethylester.**

Mol.Formula $C_{20}H_{21}ClO_4$

Mol.mass **360.831 g/mol**

Physical Properties [51]

Fenofibrate is a whitish, crystalline powder that is tasteless & odourless. It is a fibric acid derivative, an analogue of clofibrate, which is synthesized chemically. It differs from clofibrate by the substitution of a chlorobenzoyl ketone group for a chlorine atom.

MECHANISM OF ACTION

The effects of fibrates on plasma lipid levels are due to their interaction with peroxisome proliferator-activated receptors (PPARs) [52]. There are 3 PPAR isotypes (α, β, γ). They bind to PPAR, which is expressed mainly in the hepatocytes & brown adipose tissue and to a smaller extent in kidney, heart & skeletal muscle. They reduce TGs through PPAR-mediated stimulation of fatty acid oxidation, raised LPL synthesis & decreased apo C III expression. Fibrates increases HDL-C mainly by PPAR stimulation of apoA-I & apoA-II. Among all fibrates fenofibrate is more effective in increasing HDL levels.

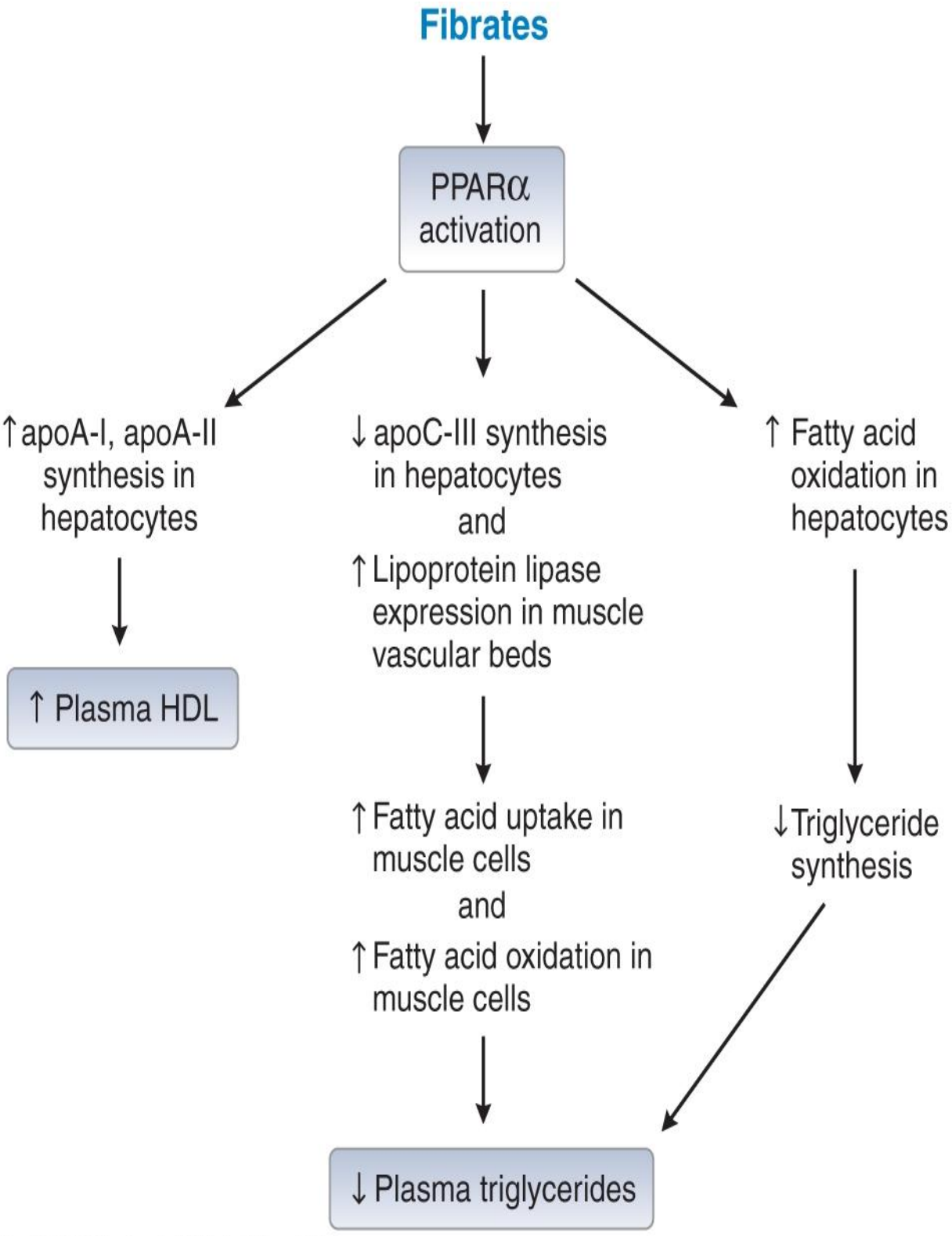
LDL levels are unchanged or fall in, especially for those whom TG levels are not increased or who are taking a 2nd-generation agents like fenofibrate, bezafibrate, or ciprofibrate. The decrease in LDL levels may be due to changes in the cholesterol and triglyceride contents of LDL that are mediated by CETP.

Most of the fibrates have potential antithrombotic effects, like blocking coagulation & enhancing fibrinolysis[52]. These effects could alter the cardiovascular diseases unrelated to any of the hypolipidemic activity.

Effects on Lipoprotein Levels

In patients with mild hypertriglyceridemia (TG < 400 mg/dL), treatment with fibrate reduces TG levels up to 50% & rises the HDL-C levels by 15%. Fenofibrate lowers VLDL level, but also reduce LDL levels by 15-20%. In marked hypertriglyceridemia (400-1000 mg/dL), a similar fall in TGs occurs, but LDL-C increases by 10-30%.

Usually fibrates are the treatment of choice for severe hypertriglyceridemia & chylomicronemia syndrome. The primary therapy is to avoid alcohol & fat rich diet. Fibrates act by increasing triglyceride clearance and reducing hepatic TG synthesis. In chylomicronemia syndrome patients, maintenance therapy with fibrate and a low-fat diet keep TG levels < 1000 mg/dL and hence prevent the episodes of pancreatitis[52].



ABSORPTION, FATE & EXCRETION

These drugs are absorbed rapidly & effectively (>90%) when taken along with food. The ester bond is hydrolyzed rapidly & the peak plasma levels are reached within 1-4 hours.

Fenofibrate is completely metabolised to fenofibric acid. More than 95% are bound exclusively to albumin. The plasma half life of fenofibrate is 20 hours .This drug is widely distributed in the body & the concentration in kidney, liver & intestine exceeds the plasma level.

The fibrates are excreted mainly by glucuronide conjugation; about 60-90% of oral dose administered is excreted in the urine, with lesser amount in the feces. Excretion is affected in renal failure[52]. The fibrates usage is contraindicated in renal failure patients.

THERAPEUTIC USES

Fenofibrate is available in 2 different formulations. The first preparation developed is the dimethyl ethyl ester of fenofibrate, which is poorly water soluble & poorly absorbed. After uptake by the liver, this is hydrolyzed to form fenofibric acid (active moiety). Recently, a choline salt of fenofibric acid which is highly soluble in water & readily absorbed was developed. The effects of both formulations are similar with respect to changes in plasma lipid concentrations[53]. Choline fenofibrate is indicated for combination with statins.

Fibric acid derivatives are the drug of choice for treating patients with type III hyperlipoproteinemia and severe hypertriglyceridemia (TG >1000 mg/dL) who are at risk for pancreatitis. Fibrates have an important role in patients with raised TG & decreased HDL levels associated with metabolic syndrome or type 2 DM. When fibrates are used in these patients, the LDL levels to be monitored; if LDL levels increases, then a low dose of a statin may need to be added. Many physicians now give treatment to such patients initially with statin (Heart Protection Study Collaborative Group, 2003) and then add a fibrate, based on the reported benefit of fibrate therapy. Careful monitoring for myopathy is needed when this combination is used.

ADVERSE EFFECTS & DRUG INTERACTIONS

GI upsets occur in about 5%. Rash, urticaria, hair loss, myalgias, , headache, impotence, fatigue and anemia are reported infrequently. Minimal elevations in liver transaminases and alkaline phosphatase also have been reported.

Fibrates have been found to enhance the activity of oral anticoagulants, by displacing them from their albumin binding sites. So, it is essential to carefully monitor the PT and reduce the dose of anticoagulant before starting treatment with fibrate.

Myopathy syndrome may occur in patients on fenofibrate. To diminish this risk, it is better to reduce doses of statin when combined with fibrate. Several drug interactions may be the reason for this adverse response. Patients receiving combination therapy should be advised to be aware of these symptoms & to be followed up at every 3-month intervals. Fenofibrate undergoes glucuronidation by enzymes which are not associated with statin glucuronidation.

Hence, fenofibrate + statin have less possibility to cause myopathy. All of the fibrates increase the lithogenicity of bile. They should be avoided in renal patients. Fibrates are contraindicated in children & pregnant women.

AIM & OBJECTIVES

AIM:

To study the efficacy of alternate day therapy of atorvastatin 10 mg & fenofibrate 160 mg on plasma lipid profile and to compare it with daily therapy of atorvastatin 10 mg & fenofibrate 160 mg .

OBJECTIVES:

(1) To see if the alternate day therapy is equally efficacious or not when compared to daily therapy.

(2) To see if the alternate day therapy has better side effect profile when compared to daily therapy.

MATERIALS & METHODS

SCREENING & ENROLLMENT

After obtaining approval from the Institutional Ethics committee the study was conducted. Details of the study were explained to the patients who attended the outpatient section of Department of Medicine & Diabetology in Government Stanley Hospital, Chennai. Written informed consent was obtained in their native language, from those who were willing to participate in this study.

The patients were screened for dyslipidemia & the patients who suit our inclusion and exclusion criteria were selected for the study. The participants of this study were randomized into 2 groups with 30 patients allotted in each group.

After clinical examination, participants were investigated for hematological & biochemical tests. The baseline demographic characters were recorded including patients name, age, sex, outpatient number, occupation & address.

STUDY DESIGN: Prospective, Randomized, Open label, comparative, case control study.

STUDY CENTRE: Out Patient section, Dept of Medicine & Diabetology, Government Stanley Hospital, Chennai-01

STUDY PERIOD: 1.12.2012 to 30.11.2013

DURATION OF STUDY: 6 weeks for each patient.

SAMPLE SIZE: 60 patients (30 patients in each group)

DRUGS USED IN THE STUDY:

Fenofibrate 160mg → Fenobate 160(East west Pharmaceuticals)

Atorvastatin 10 mg → (Hospital supply)

SELECTION CRITERIA: (For both groups)

INCLUSION CRITERIA:

1) Both male & female patients.
2) Age between 45 – 55 years.
3) Newly diagnosed cases of dyslipidemia.
4) Patients with elevated levels of LDL, VLDL, Triglycerides & total cholesterol as follows[19] -
   a) Patients with elevation of Total cholesterol → >200 mg/dl.
   b) Patients with elevation of Triglycerides → > 200 mg/dl.
   c) Patients with HDL < 40 mg/dl.
   d) Patients with elevation of LDL >100 mg/dl.
   e) Patients with elevation of VLDL >30 mg/dl
5) Patients with Diabetes Mellitus (Type 2) and dyslipidemia.
6) Patients with Hypertension and dyslipidemia.

EXCLUSION CRITERIA:

(1) Patients with H/O primary hyperlipidemia.

(2) Patients < 45 & > 55 years of age.

(3) Patients with H/O MI, Cerebro vascular disease, Peripheral vascular disease, Hypertension with complications & other neuromuscular disorders.

(4) Patients with H/o hepatic damage, smoking & alcoholism.

(5) Patients with Thyroid dysfunction.

(6) Patient with high level of Triglyceride alone & LDL alone.

(7) Patients who are on antiplatelet drugs.

METHODOLOGY

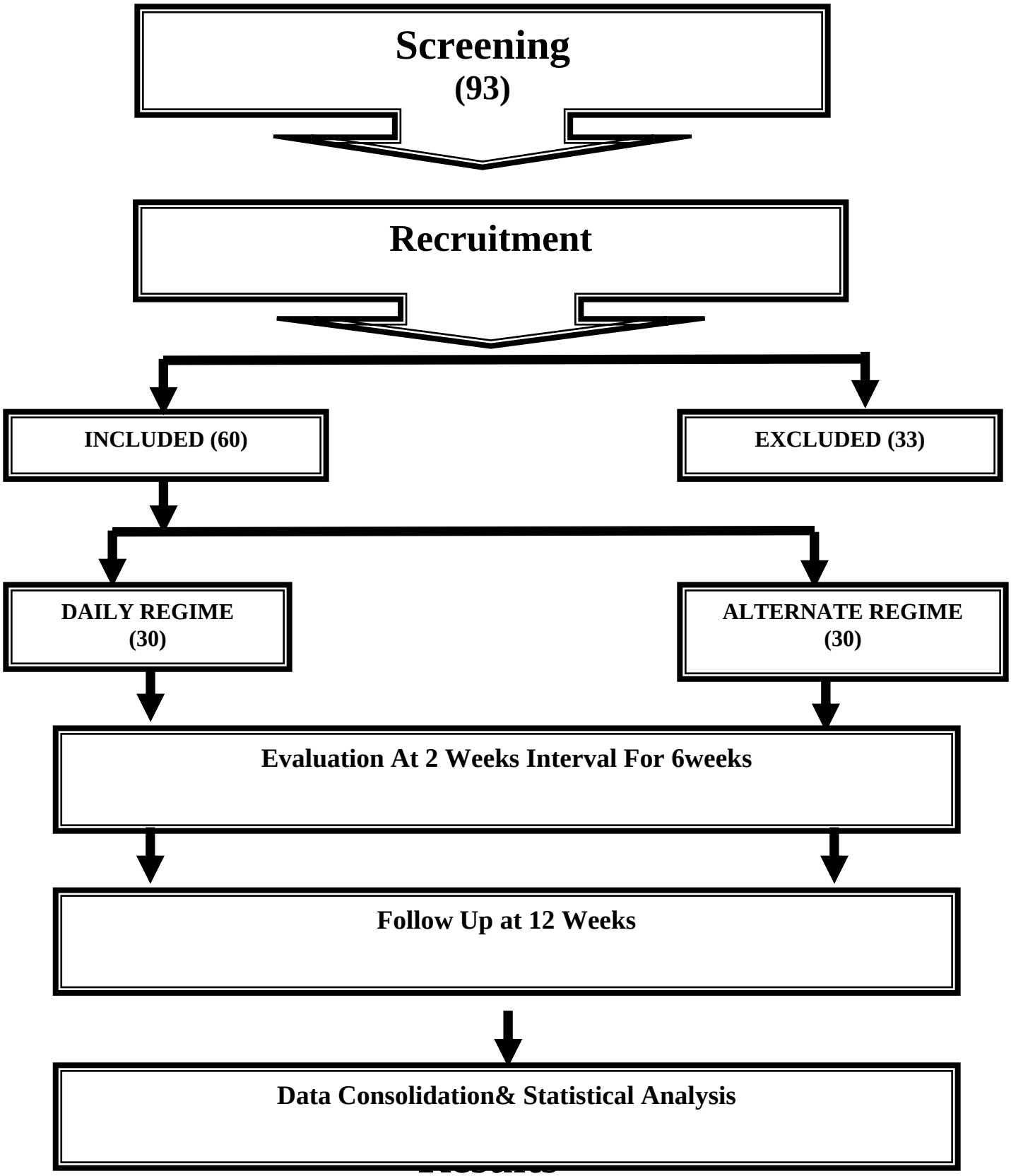
The selected patients were randomized into two groups namely 1 & 2, with the 30 patients in each group.

Group 1 (Control)	Atorvastatin 10 mg & Fenofibrate 160 mg are given together at bed time daily for 6 weeks
Group 2 (study group)	Atorvastatin 10 mg at bed time on one day & Fenofibrate 160 mg at bed time on next day

Lipid profile including Total cholesterol, LDL, HDL, TG, VLDL were done for both the groups at the baseline and then at the end of 2^{nd} week, 4^{th} week, 6th week &12^{th} week (follow up).

Routine investigation like Hb, blood sugar, blood urea, serum creatinine, SGOT,SGPT,CPK were all evaluated before & after the study.

Patients were allowed to take medications for other associated conditions like Hypertension, Diabetes Mellitus.


Screening
(93)
Recruitment
INCLUDED (60)
EXCLUDED (33)
DAILY REGIME
(30)
ALTERNATE REGIME
(30)
Evaluation At 2 Weeks Interval For 6weeks
Follow Up at 12 Weeks
Data Consolidation& Statistical Analysis

This study was conducted, to evaluate the effect of alternate day therapy of Atorvastatin 10 mg & Fenofibrate 160 mg on plasma lipid profile and to compare it with daily therapy of atorvastatin 10 mg & fenofibrate 160 mg.

Out of 93 patients screened, 60 patients were included in this study. 33 patients were excluded based on Selection criteria. 60 patients were randomly allocated into 2 groups as Group 1 & Group 2 and treated according to the methodology.

The clinical & Laboratory investigational results obtained for both control and study group at the baseline & at the end of 2^{nd}, 4^{th}, 6^{th} and 12^{th} week (follow up) were analyzed statistically. The Parameters analyzed were TC, LDL, TG, VLDL and HDL.Biochemical parameters like Hb, RBS, Blood urea, S.creatinine, AST,ALT, and CPK of both the groups were performed before & after study and analyzed for significant changes.

Table No: 1a Age Distribution (Mean Age)

Group	N	Mean	Std. Deviation	Student independent 't' test
Control	30	50.29	2.989	t=0.09
Study	30	50.33	3.011	P= 0.991

Figure No: 1a Age Distribution (Mean Age)

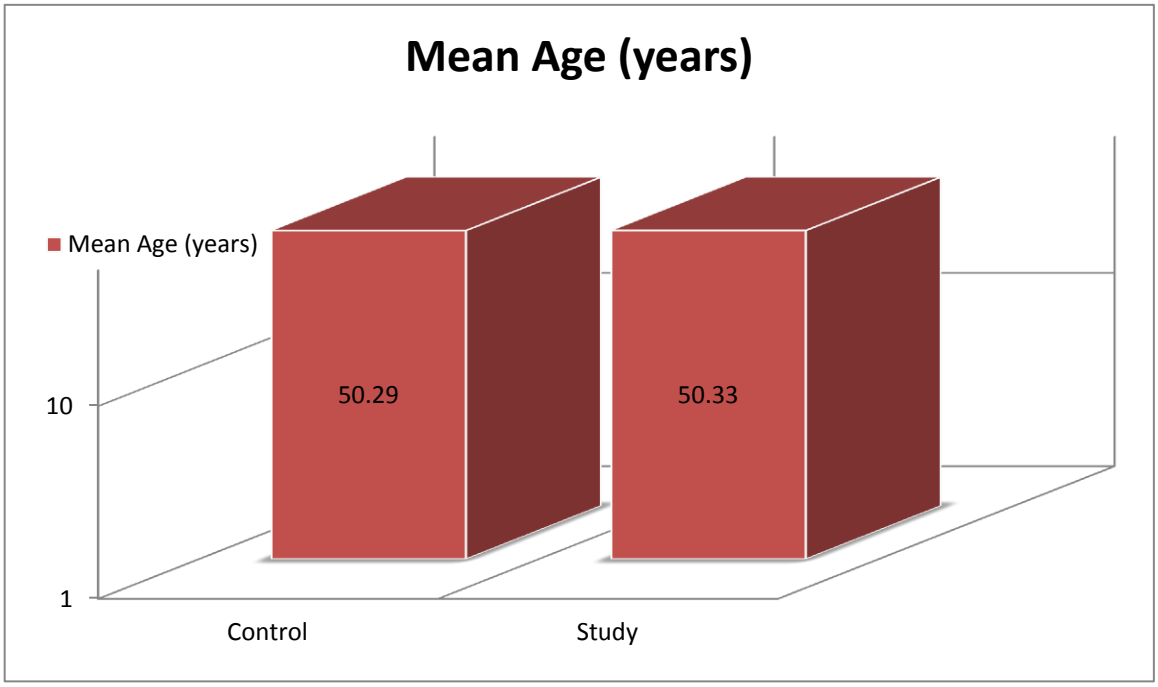


Table No: 1a shows

- Mean age distribution of both control & study groups with mean age of 50.29 in control group and 50.33 in study group.
- Analysis done by using Student independent‘t’ test.
- ‘p’ value – Not significant.

Figure No: 1a shows

- Bar diagrammatic representation of mean age distribution (Table No :1a)

Table No: 1b Age Distribution (N (%))

Age in years	Control		Study		Pearson Chi-square test
	N	%	N	%	
45-50	12	40%	13	43.33%	$\chi 2 = 0.705$,p=0.951
51-55	18	60%	17	56.67%	

Figure No: 1b Age Distribution (%)

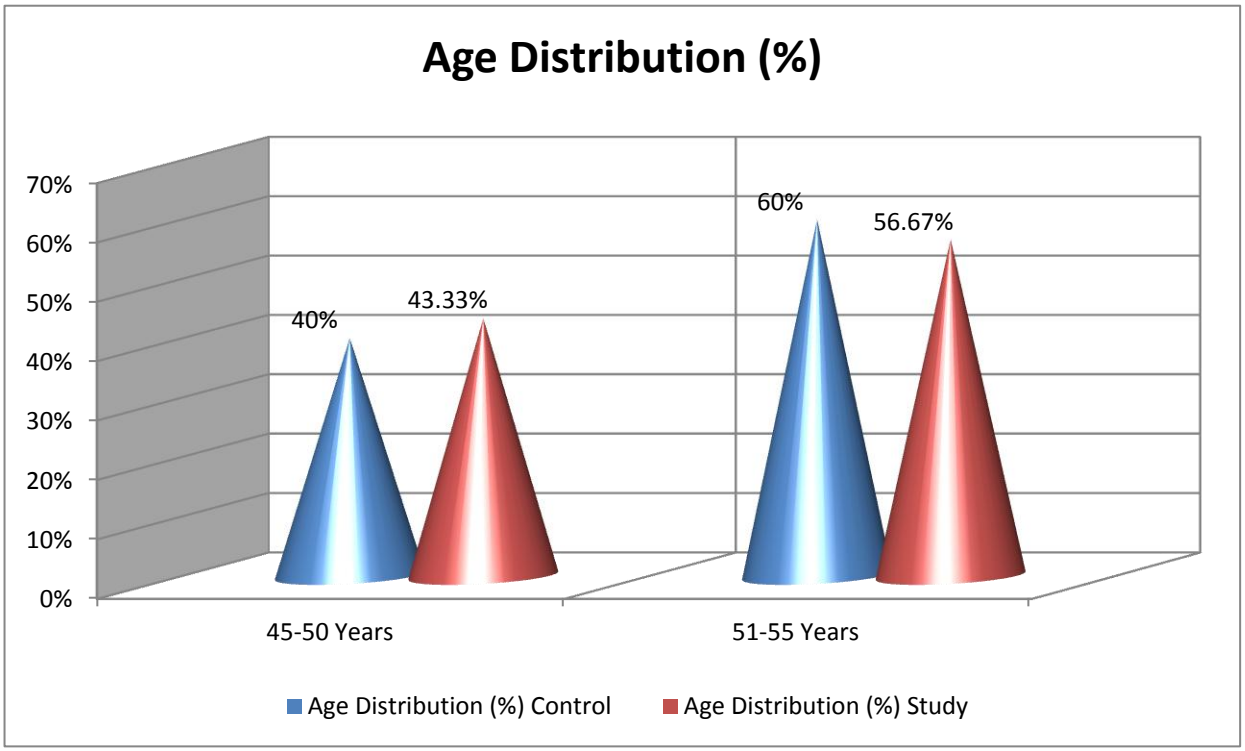


Table No: 1b shows

- Age distribution (N (%)) in both control and study groups.
- 40% of patients in control group & 43.33% of patients in study group were in the age group of 45-50 years and 60% of patients in control group & 56.67% in study group were in the age group of 51-55 years.
- Statistical analysis done by Pearson Chi Square Test.
- 'p' value was not significant.

Figure No: 1b represents

- Bar Diagrammatic representation of Age Distribution (%) (Table No: 1b)

Table No .2: SEX DISTRIBUTION

Sex	*Group*				Pearson Chi square Test
	Control		Study		
	N	%	N	%	
MALE	17	56.7%	17	56.7%	$\chi 2 = 0.00$
FEMALE	13	43.3%	13	43.3%	P= 1.00
Total	30	100.0%	30	100.0%	

P ≤ 0.05 → significant; P≤ 0.01→highly significant; P≤0.001 very high significant.

Figure No -2a: SEX DISTRIBUTION (Control group)

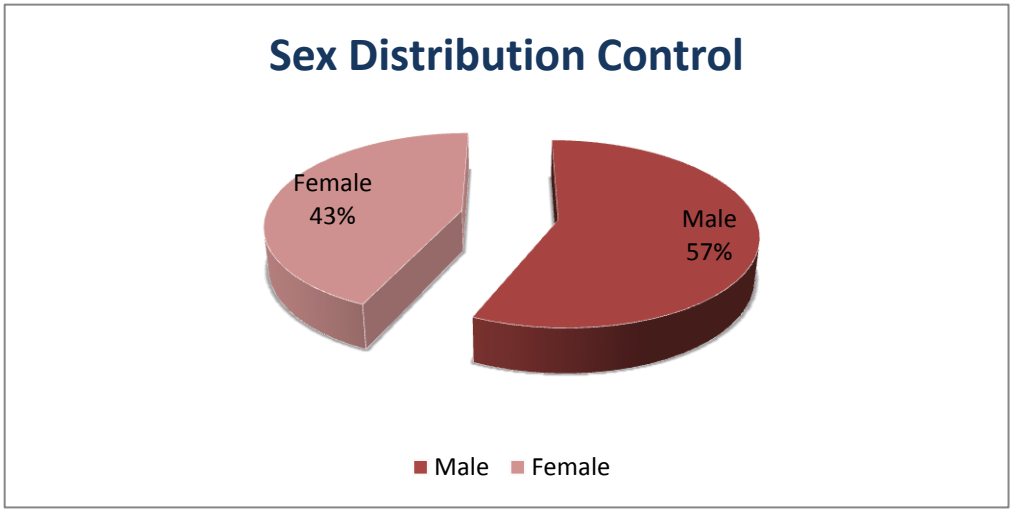


Figure No-2 b: SEX DISTRIBUTION (Study group)

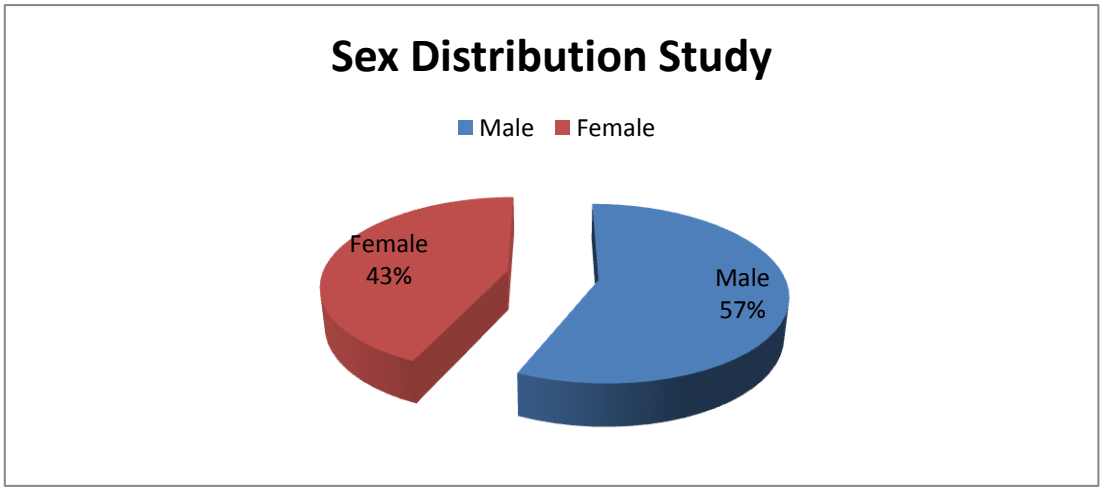


Table No: 2 shows

- Sex distribution in both groups.
- Statistical analysis done by Chi square test.
- 'p' value was not significant.

Figure No: 2a shows

- Pie Chart diagrammatic representation of sex distribution in control group in Table No:2

Figure No: 2b shows

- Pie Chart diagrammatic representation of sex distribution in study group in Table No:2

Table No 3: TOTAL CHOLESTEROL

	GROUP	N	Mean(mg/dl)	Std. Deviation	'p' value	% Reduction from Baseline
TC Baseline	1	30	285.77	18.873	0.640	0
	2	30	288.13	20.046		0
TC 2nd week	1	30	226.57	26.666	0.151	20.71
	2	30	237.23	30.038		21.45
T C 4th week	1	30	182.97	18.314	0.158	35.97
	2	30	189.43	16.650		34.25
TC 6th week	1	30	159.57	14.486	0.513	44.16
	2	30	161.87	12.533		43.82
TC 12th week	1	30	152.40	15.138	0.382	46.67
	2	30	155.50	11.930		46.03

Repeated Measures of ANOVA

Within Groups : F= 1801.3 , P < 0.001

Between Groups : F= 1.28 , P = 0.268

$P \leq 0.05$ → significant; $P \leq 0.01$ → highly significant; $P \leq 0.001$ very high significant.

Figure No 3: TOTAL CHOLESTEROL

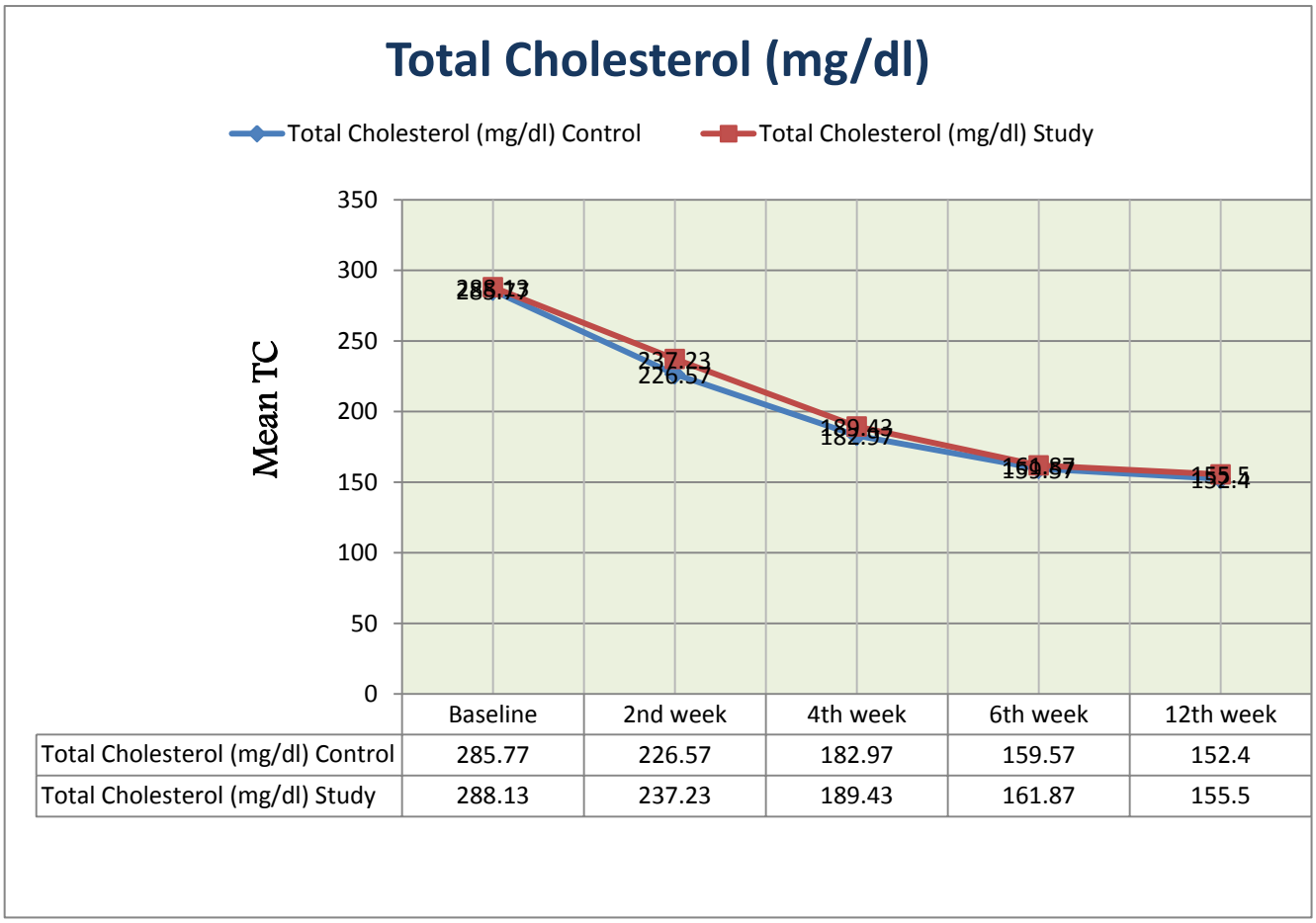


Table No: 3 shows

The mean, SD and % reduction of Total cholesterol in both the groups.

Statistical analysis was done by using Student independent‘t’ test.

The mean value of TC in the control group (Group 1) was 285.77 mg/dl & in the study group (Group 2) was 288.13 mg/dl in the baseline (‘p’ value =0.640; not significant).

At the end of 2nd week, mean value of TC in group 1 was 226.57 mg/dl & group 2 was 237.23(‘p’ value = 0.151; Not significant).At the end of 4th week, mean value of TC in group 1 was 182.97 & group 2 was 189.43 (‘p’value= 0.158; not significant).

At the end of 6th week, mean value of TC in group 1 was 159.57 & group 2 was 161.87 (‘p’value= 0.513; not significant).At the end of 12th week (Follow up), mean value of TC in group 1 was 152.40 & group 2 was 155.50 (‘p’value= 0.382; not significant).

The % reduction from the baseline of TC at the end of 2nd week was 20.71% in group 1 & in group 2 it was 21.45%, at the end of 4th week the reduction

was 35.97% in group 1 & 34.25% in group 2, by the end of 6th week it was 44.16% & 43.82% and at the follow up it was 46.67% & 46.03% .

Repeated measures of ANOVA –Within groups ('p' value <0.001) was significant; between groups ('p' value = 0.268) was not significant.

There were no statistically significant differences in mean TC levels of both control & study groups.

Figure No: 3 shows

- Line diagrammatic representation of mean TC level in Table No: 3

Table No 4: LOW DENSITY LIPOPROTEIN

	GROUP	N	Mean (mg/dl)	Std. Deviation	'p' Value	% reduction from baseline
LDL Baseline	1	30	180.73	18.605	0.061	0
	2	30	173.53	16.706		0
LDL 2nd week	1	30	142.47	17.591	0.645	21.17
	2	30	144.67	19.139		18.66
LDL 4th week	1	30	112.27	11.907	0.553	37.87
	2	30	110.50	11.026		35.89
LDL 6th week	1	30	95.00	6.314	0.601	47.43
	2	30	95.77	4.890		45.61
LDL 12thweek	1	30	90.33	6.070	0.921	48.01
	2	30	90.50	6.897		47.23

Repeated Measures of ANOVA

Within Group : F= 903.89 , P < 0.001

Between Groups: F= 0.36 , P= 0.551

P ≤ 0.05→significant; P≤ 0.01 → highly significant; P≤0.001 very high significant.

Figure No 4: LOW DENSITY LIPOPROTEIN

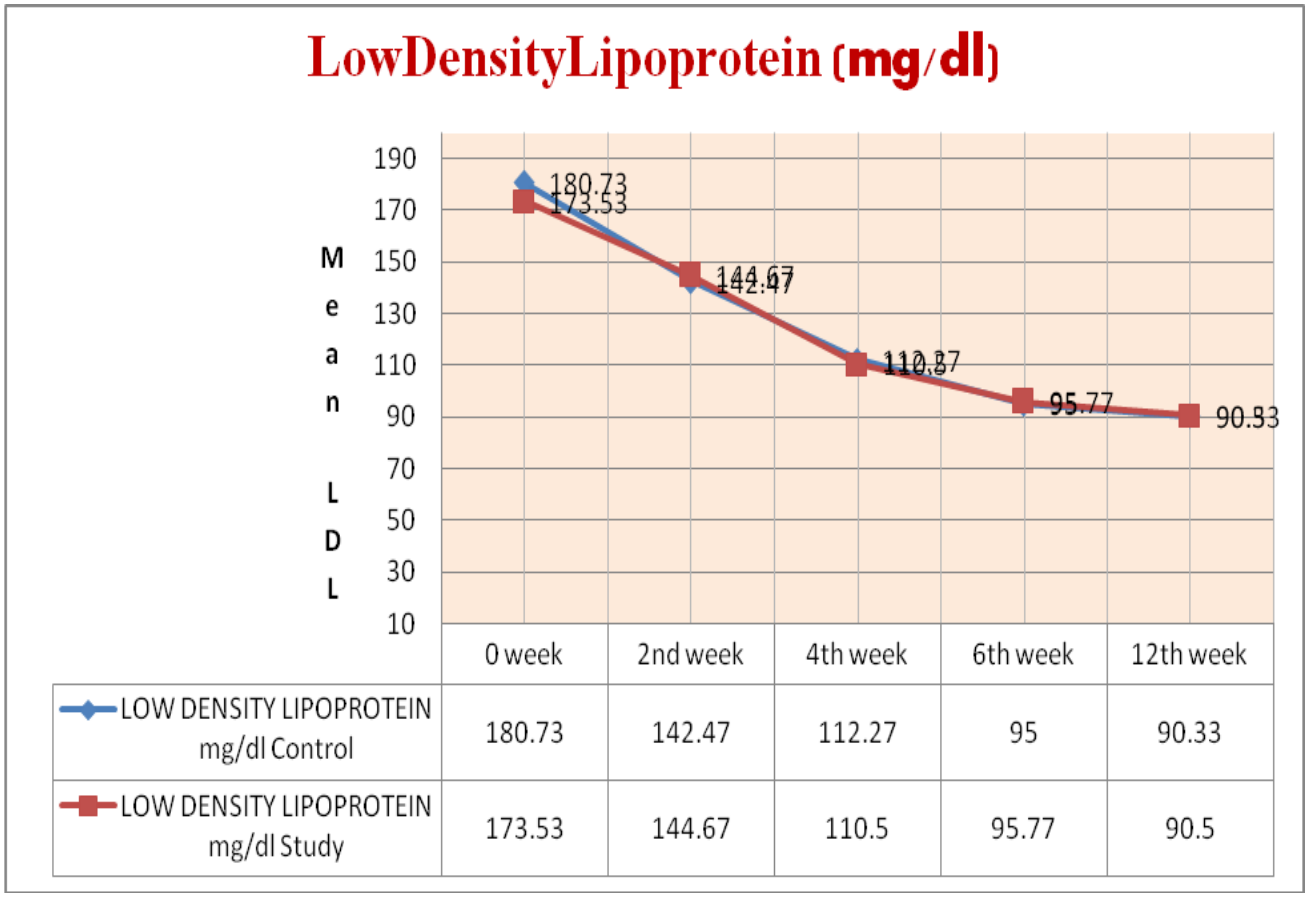


Table No: 4 shows

The mean, SD and % reduction of LDL in both the groups.

Statistical Analysis was done by using Student independent‘t’ test.

At the baseline, the mean LDL in group 1 was 180.73 mg/dl & group 2 was 178.53mg/dl (‘p’ value =0.061; not significant).By the end of 2nd week, the mean LDL in group 1 was 142.47 mg/dl and in group 2 was 144.67mg/dl (‘p’ value = 0.645; not significant). By the end of 4th week, the mean LDL in group 1 was 112.27 mg/dl and in group 2 was 110.50 mg/dl (‘p’value= 0.553; not significant).

At the end of 6th week, the mean LDL in group 1 was 95.00 mg/dl & in group 2 was 95.77mg/dl (‘p’value= 0.601; not significant).At the end of 12th week, the mean LDL in group 1 was 90.33mg/dl & in group 2 was 90.50 mg/dl (‘p’value= 0.921; not significant).

The % reduction of LDL from baseline to the end of 2nd week was 21.17% in group 1 and 18.66% in group 2, by the end of 4th week was 37.87 % & 35.89%, by the end of 6th week it was 47.43% & 45.61% and by the end of 12th week was 48.01 % & 47.23%.

Repeated measures of ANOVA – Within groups (‘p’ value <0.001) was significant; between groups (‘p’ value = 0.551) was not significant.

There were no statistically significant differences in LDL levels of both Control & Study groups.

Figure No: 4 shows

Line diagrammatic representation of mean LDL level in Table No: 4

Table No 5 : TRIGLYCERIDE

	GROUP	N	Mean (mg/dl)	Std. Deviation	'p' value	% reduction from Baseline
TG Baseline	1	30	254.07	19.314	0.449	0
	2	30	258.17	22.242		0
TG 2nd week	1	30	182.23	12.945	0.290	28.27
	2	30	187.13	21.531		27.51
TG 4thweek	1	30	131.37	11.845	0.128	48.29
	2	30	136.80	12.152		47.02
TG 6thweek	1	30	100.10	6.733	0.439	58.67
	2	30	101.47	6.837		57.32
TG 12thweek	1	30	94.23	6.235	0.290	59.88
	2	30	95.77	4.797	.	58.67

Repeated Measures of ANOVA

Within Group: F= 2277.98 , P <0.001

Between Groups : F= 4.38, P= 0.052

$P \leq 0.05$ → significant; $P \leq 0.01$ → highly significant; $P \leq 0.001$ very high significant.

Figure No 5 : TRIGLYCERIDE

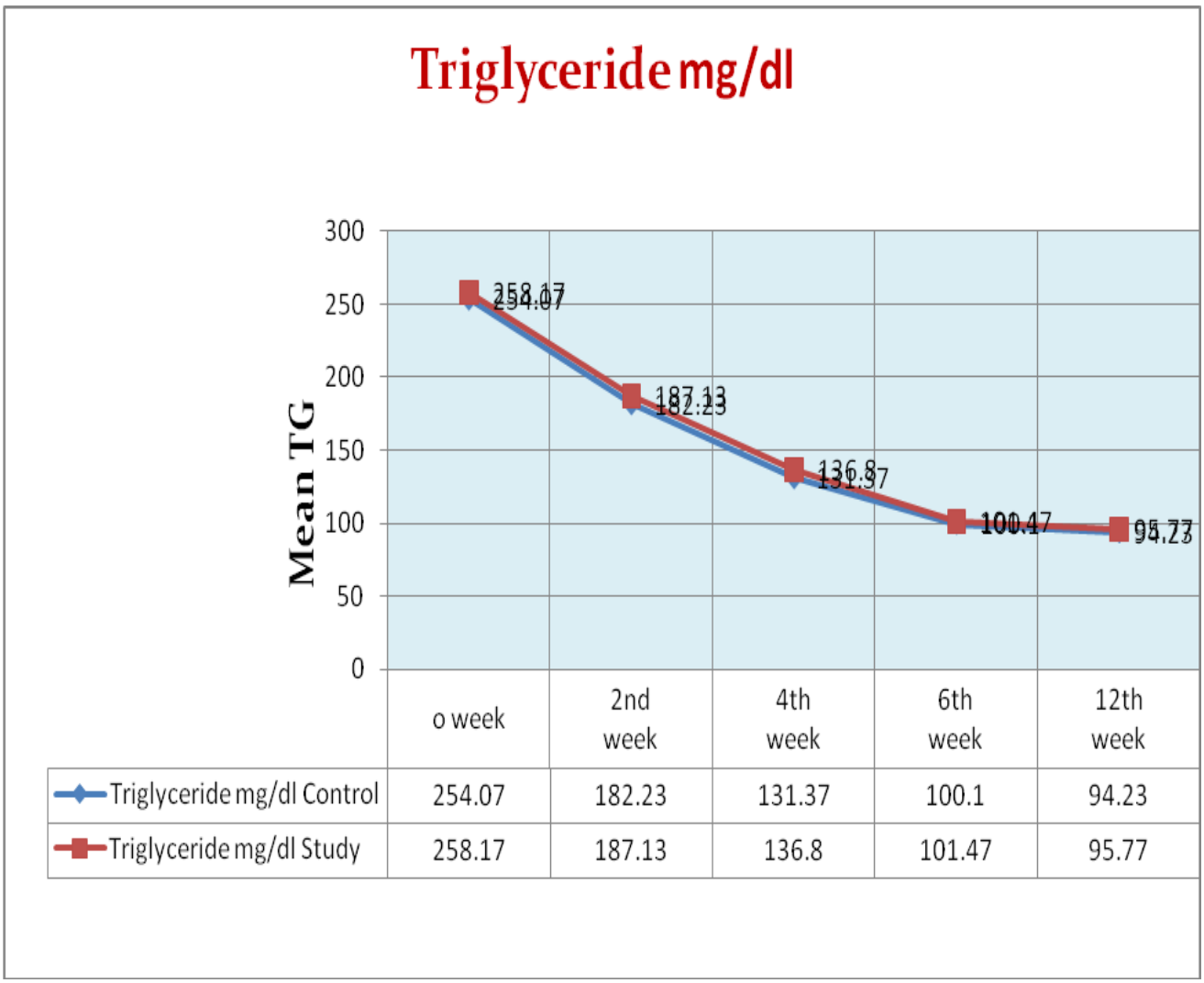


Table No: 5 shows

The mean, SD and % reduction of Triglyceride in both the groups.

Statistical Analysis was done by using Student independent‘t’ test.

The mean TG level in Group 1 was 254.07 mg/dl & in Group 2 was 258.17 mg/dl in the baseline (‘p’ value =0.449; not significant).At the end of 2nd week, mean TG in Group 1& Group2 was 182.23mg/dl &187.13mg/dl (‘p’ value = 0.290; not significant).

At the end of 4th week, the mean TG in Groups 1& 2 was 131.37mg/dl &136.80 mg/dl (‘p’value= 0.128; not significant).At the end of 6th week, the mean TG in Group 1 was 100.10 & in Group 2 was 101.47 (‘p’value= 0.439; not significant).At the follow up, the mean value of TG in Group 1 was 94.23 mg/dl & in Group 2 was 95.77 mg/dl (‘p’value= 0.290; not significant).

The % reduction from baseline of TG by the end of 2nd week was 28.27% in group 1& 27.51% in group 2, by the end of 4th week was 48.29 %& 47.02%, by the end of 6th week was 58.67% & 57.32 % and at the follow up was 59.88% & 58.67%.

Repeated measures of ANOVA – Within groups (‘p’ value <0.001) was significant; between groups (‘p’ value = 0.052) was not significant.

There were no statistically significant differences in TGL levels of both Control & Study groups.

Figure No: 5 shows

Line diagrammatic representation of mean TG levels in Table No: 5

Table No 6: VERY LOW DENSITY LIPOPROTEIN

	GROUP	N	Mean(mg/dl)	Std. Deviation	'p' value	% reduction from baseline
VLDL Baseline	1	30	52.40	4.507	0.091	0
	2	30	53.23	3.730		0
VLDL 2nd week	1	30	45.07	4.291	0.816	14.26
	2	30	47.98	4.559		13.67
VLDL 4thweek	1	30	38.93	4.472	0.054	25.70
	2	30	40.12	4.324		24.17
VLDL 6thweek	1	30	33.13	4.214	0.058	43.91
	2	30	32.89	4.366		42.23
VLDL 12thweek	1	30	30.11	2.998	0.173	46.31
	2	30	29.97	2.399		45.39

Repeated Measures of ANOVA

Within Group: F= 1205.70 , P<0.001

Between Groups: F= 0.81 , P =0.373

P≤ 0.05 →significant; P≤ 0.01→highly significant; P≤0.001→very high significant.

Figure No 6: VERY LOW DENSITY LIPOPROTEIN

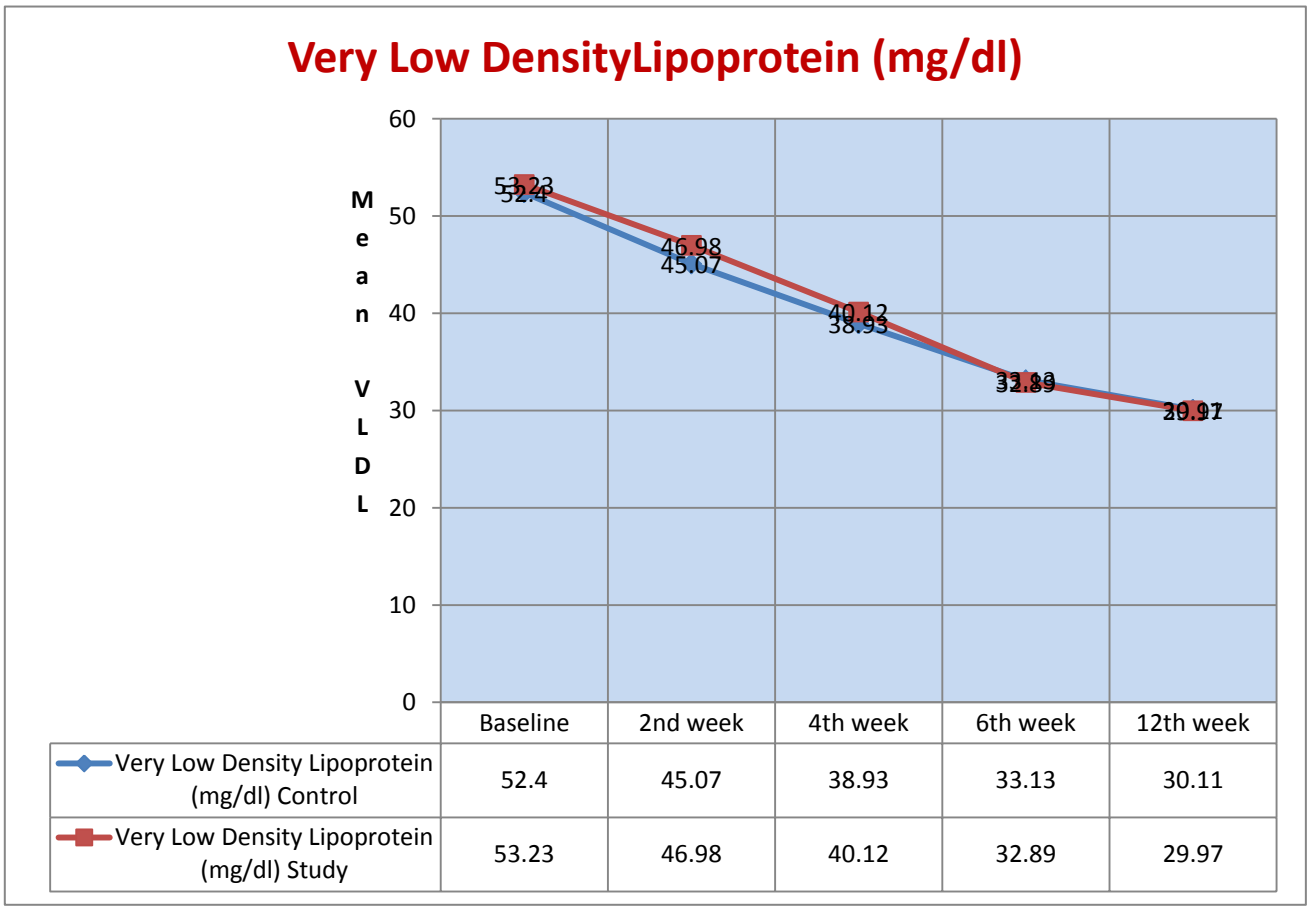


Table No: 6 shows

The mean, SD and % reduction of VLDL in both the groups.

Statistical Analysis was done by using Student independent‘t’ test.

The mean VLDL in Group 1 was 52.40mg/dl & in Group 2 was 53.23mg/dl in the baseline (‘p’ value =0.091; not significant). At the end of 2nd week, the mean VLDL in Group 1 & 2was 45.07mg/dl and 47.98mg/dl (‘p’ value = 0.816; not significant).

At the end of 4th week, the mean VLDL in Group 1 was 38.93mg/dl and in Group 2 was 40.12mg/dl (‘p’value= 0.054; not significant).At the end of 6th week, the mean VLDL in Group 1 was 33.13 mg/dl and Group 2 was 32.89 mg/dl (‘p’value= 0.058; not significant).At the follow up, mean VLDL in Groups 1 & 2 were 30.11 mg/dl & 29.97mg/dl (‘p’value= 0.173;not significant).

The % reduction of VLDL from baseline to the end of 2nd week was 14.26% in group 1 and 13.67% in group 2, by the end of 4th week was 25.70 %& 24.17%, by the end of 6th week was 43.91% &42.23 %and at the follow up it was 46.31% & 45.39%.

Repeated measures of ANOVA – Within groups (‘p’ value <0.001) was significant; between groups (‘p’ value = 0.373) was not significant.

There were no statistically significant differences in VLDL levels of both Control & Study groups.

Figure No: 6 shows

Line diagrammatic representation of mean VLDL level in Table No:6

Table No 7 : HIGH DENSITY LIPOPROTEIN

	GROUP	N	Mean (mg/dl)	Std. Deviation	'p' value	% increase from baseline
HDL Baseline	1	30	33.60	3.058	0.256	0
	2	30	34.53	3.235		0
HDL 2nd week	1	30	38.01	3.129	0.672	16.66
	2	30	37.67	2.940		12.09
HDL 4th week	1	30	41.97	3.499	0.120	23.91
	2	30	40.63	3.023		18.66
HDL 6th week	1	30	43.53	3.461	0.103	31.50
	2	30	42.17	2.902	.	27.96
HDL 12thweek	1	30	43.79	3.605	0.061	32.11
	2	30	42.97	3.824		29.32

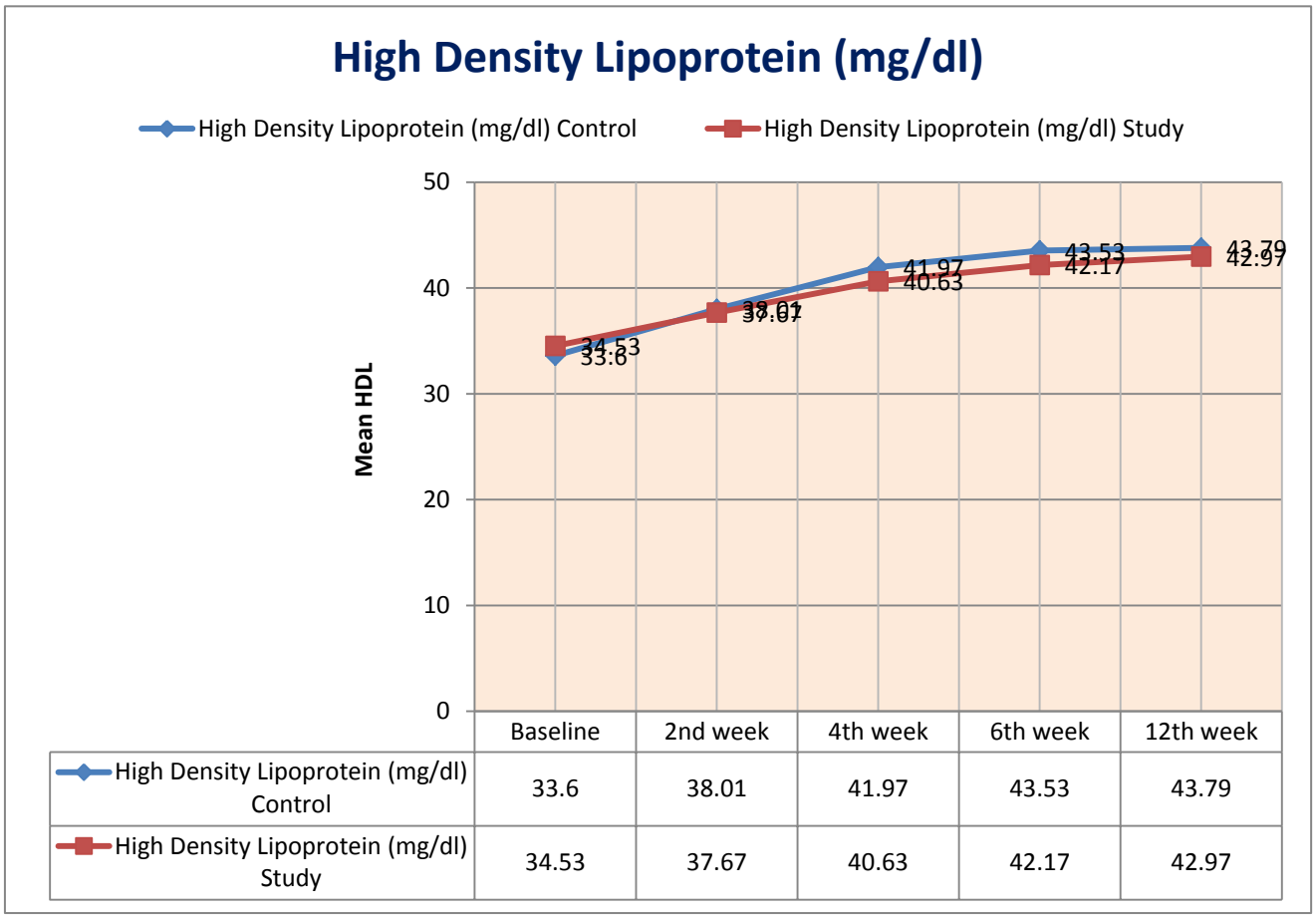
Repeated Measures of ANOVA

Within Group : F= 427.18, P<0.001

Between Groups: F=1.34 , P=0.251

P ≤ 0.05→significant; P≤ 0.01→ highly significant; P≤0.001 →very high significant.

Figure No 7 : HIGH DENSITY LIPOPROTEIN



	Baseline	2nd week	4th week	6th week	12th week
High Density Lipoprotein (mg/dl) Control	33.6	38.01	41.97	43.53	43.79
High Density Lipoprotein (mg/dl) Study	34.53	37.67	40.63	42.17	42.97

Table No: 7 shows

The mean, SD and % increase of HDL in both the groups.

Statistical Analysis was done by using Student independent‘t’ test.

The mean HDL in Group 1 & 2 were 33.60 mg/dl and 34.53mg/dl in the baseline (‘p’ value =0.256; not significant).At the end of 2nd week, the mean HDL was 38.01mg/dl in Group 1 and 37.67 mg/dl in Group 2 (‘p’ value = 0.672; not significant).

By the end of 4th week, mean HDL in Group 1 was 41.97mg/dl & in Group 2 was 40.63mg/dl (‘p’value= 0.120; not significant). By the end of 6th week, the mean HDL in Group 1 & 2 were 43.53mg/dl & 42.17mg/dl (‘p’value= 0.103; not significant).At the follow up, the mean HDL in Group 1 was 43.79 mg/dl & in Group 2 was 42.97 mg/dl (‘p’value= 0.061;not significant).

The % increase in HDL from baseline to the end of 2nd week was 16.66% in group 1 & 12.09% in group 2, by the end of 4th week it was 23.91 % & 18.66%, by the end of 6th week the reduction was 31.50% & 27.96 % and at the follow up the reduction was 32.11% & 29.32%.

Repeated measures of ANOVA – Within groups (‘p’ value <0.001) was significant; between groups (‘p’ value = 0.251) was not significant.

There were no statistically significant differences in HDL levels of both Control & Study groups.

Figure No: 7 shows

Line diagrammatic representation of mean HDL level in Table No: 7

Table No: 8 TC/HDL Ratio

S.No	Weeks of treatment	TC/HDL Ratio	
		Control Group	Study Group
1.	Baseline	8.5	8.34
2.	2^{nd} week	5.96	6.29
3.	4^{th} week	4.36	4.66
4.	6^{th} week	3.66	3.73
5.	12^{th} week	3.50	3.54

Table No: 8 shows

- The Total cholesterol : HDL ratio of control and study groups at baseline, at the end of 2^{nd},4^{th} ,6^{th} ,12^{th} weeks(follow up).

Table No 9: HEMATOLOGICAL PARAMETERS IN CONTROL GROUP

(Paired t test)

		Mean	Std. Deviation	'p' Value
Hb%	Before	12.40	1.329	
	After	12.60	1.192	0.089
RBS (mg/dl)	Before	145.20	21.228	
	After	142.97	18.072	0.052
B.Urea (mg/dl)	Before	27.97	3.634	
	After	27.67	3.078	0.231
S.Creatinine (mg/dl)	Before	.753	.0937	
	After	.777	.1040	0.090
AST (U/L)	Before	29.67	4.011	
	After	29.43	3.308	0.428
ALT (U/L)	Before	35.37	5.702	
	After	35.57	5.212	0.467
CPK (U/L)	Before	73.77	9.457	
	After	73.37	9.419	0.396

$P \leq 0.05$ → significant; $P \leq 0.01$ → highly significant; $P \leq 0.001$ → very high significant.

Table No: 9 shows

- ❖ Hematological parameters in control group before and after the study.
- ❖ Statistical analysis was done by using Student paired‘t’ test.
- ❖ There were no statistically significant changes in hematological parameters between baseline and end of the study.

Table No 10: HEMATOLOGICAL PARAMETERS IN STUDY GROUP (Paired‘t’ test)

		Mean	Std. Deviation	‘p’ value
Hb%	Before	12.40	1.329	
	After	12.60	1.192	0.831
RBS (mg/dl)	Before	146.67	22.472	
	After	145.30	18.943	0.236
B.Urea (mg/dl)	Before	27.97	3.634	
	After	27.67	3.078	0.231
S.Creatinine (mg/dl)	Before	0.753	.0937	
	After	0.777	.1040	0.092
AST (U/L)	Before	29.60	3.936	
	After	29.43	3.308	0.562
ALT (U/L)	Before	35.40	5.512	
	After	35.53	5.108	0.587
CPK (U/L)	Before	73.77	9.457	
	After	73.37	9.419	0.396

$P \leq 0.05$ → significant; $P \leq 0.01$ → highly significant; $P \leq 0.001$ very high significant.

Table No: 10 shows

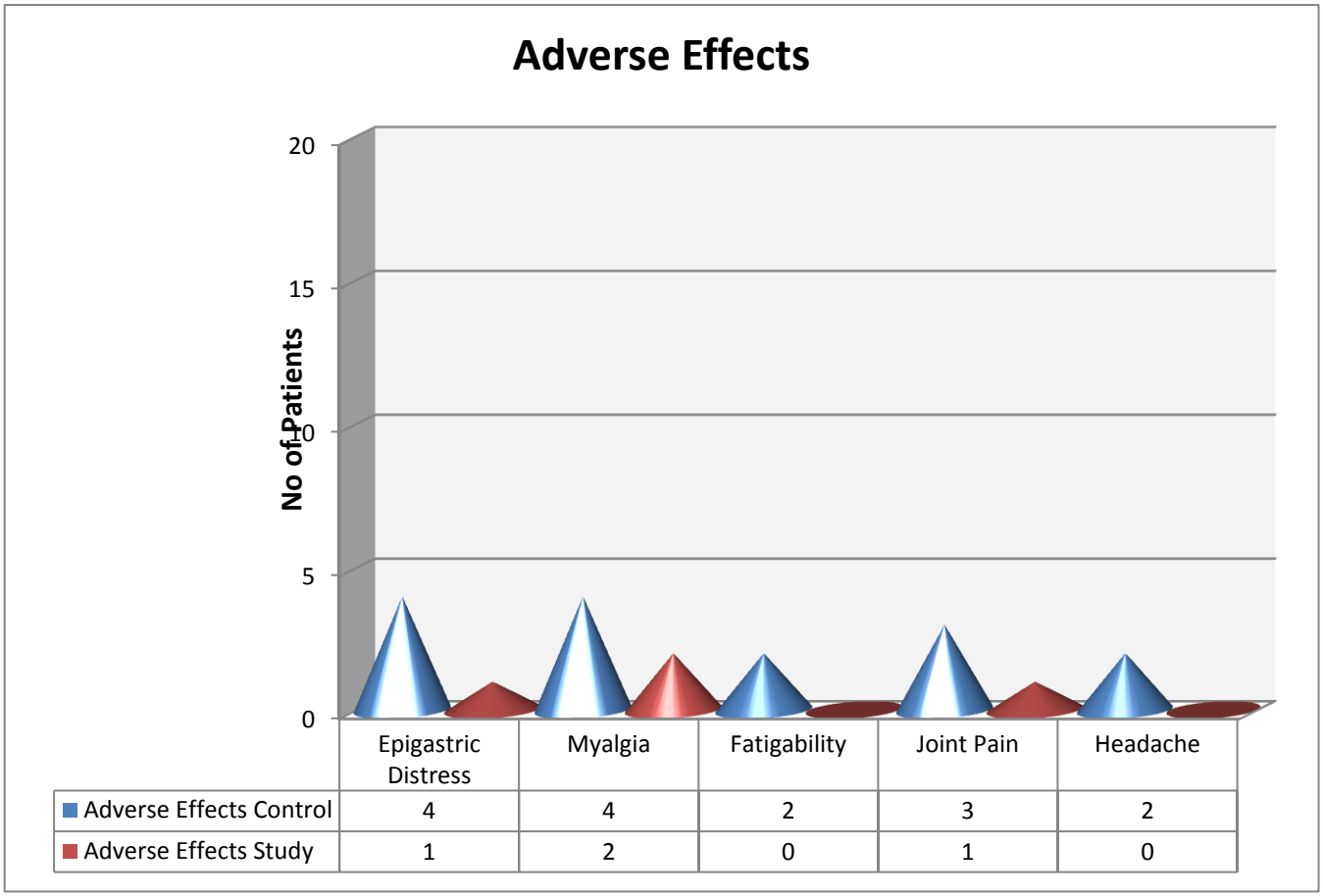
- Hematological parameters in study group before and after the study.
- Statistical analysis was done by using Student paired‘t’ test.
- There were no statistically significant differences in hematological parameters between baseline and end of the study.

Table No: 11 ADVERSE EFFECTS

S.No	Adverse Effects	Group 1 (Control) (30)		Group 2 (Study) (30)	
		N	%	N	%
1.	Epigastric distress	4	13.3%	1	3.3%
2.	Myalgia	4	13.3%	2	6.6%
3.	Fatigability	2	6.6%	0	0
4.	Joint pain	3	10%	1	3.3%
5.	Headache	2	6.6%	0	0

N= Number of patients

Figure No: 8 Adverse Effects (No. of Patients)



	Epigastric Distress	Myalgia	Fatigability	Joint Pain	Headache
Adverse Effects Control	4	4	2	3	2
Adverse Effects Study	1	2	0	1	0

Table No: 11 shows

The adverse effects reported in both control & study groups.

In control group, 4 (13.3%) patients had epigastric distress, 4 (13.3%) had myalgia, 2 (6.6%) complained of fatigability, 3(10%) with joint pain, 2(6.6%) had headache. In study group, 1(3.3%) patient had epigastric distress, 2(6.6%) had myalgia, 1(3.3%) had joint pain.

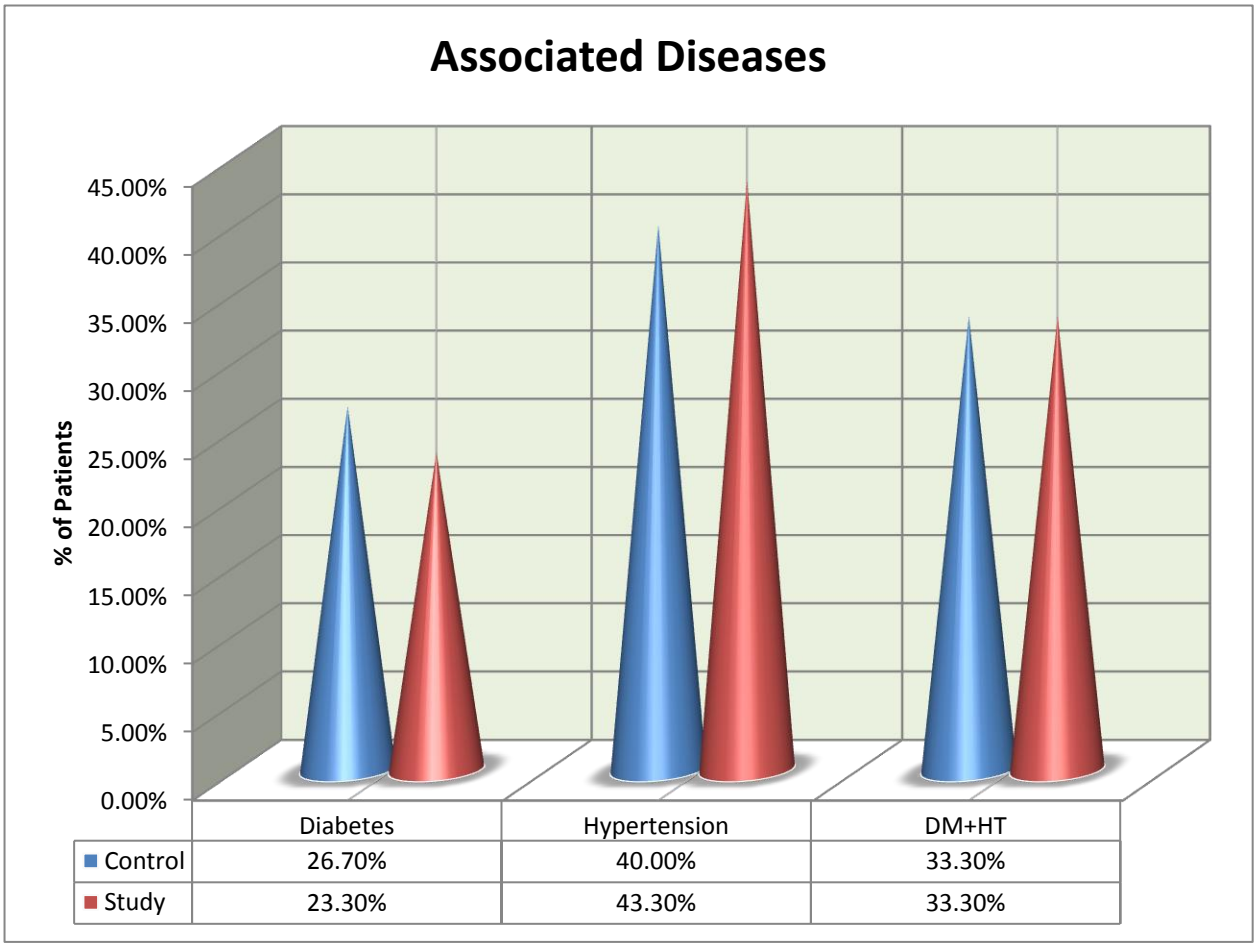
Figure No: 8 shows the bar diagrammatic representation of adverse effects (No. of patients) of both the groups.

Table No: 12 Associated Diseases

S.No	Associated Diseases	Group				Total N/60 (%)
		Control (30)		Study (30)		
		N/30	%	N/30	%	
1.	Diabetes	8	26.7	7	23.3	15 (25%)
2.	Hypertension	12	40.0	13	43.3	25 (41.7%)
3.	DM + HT	10	33.3	10	33.3	20 (33.3%)

N = Number of patients

Figure No : 9 Associated Diseases



	Diabetes	Hypertension	DM+HT
Control	26.70%	40.00%	33.30%
Study	23.30%	43.30%	33.30%

Table No:11 shows

- The number and % of patients having diabetes mellitus, hypertension, both diabetes mellitus & hypertension associated with dyslipidemia.
- Group 1 (26.7%) & Group 2 (23.3%) patients have diabetes mellitus.
- Group 1 (40.00%) & Group 2 (43.3%) patients have hypertension.
- Group 1 (33.3%) & Group 2 (33.3%) patients have DM + HT.

Figure No: 9 shows

- Bar diagrammatic representation of Table No: 11

DISCUSSION

Cardiovascular and cerebrovascular ischemic diseases are leading causes of morbidity and mortality worldwide, especially in middle aged adults.A major cause for the development of ischemic diseases is related to dyslipidemia , which is the disorder of the metabolism of lipoproteins.

Our study was conducted, to compare the efficacy of alternate day therapy of atorvastatin 10 mg & fenofibrate 160 mg with daily regime of both the drugs on plasma lipid profile.

Duration of study for each patient was 6 weeks and lipid profile was evaluated for both the groups at baseline, at the end of 2^{nd} week, 4^{th} week, 6^{th} week and then they were asked to come for the follow up at the end of 12^{th} week.

The results of our study showed that, the mean age of patients in control & study groups were 50.29 and 50.33 years. No statistically significant differences were seen between the groups (vide Table 1a & Figure 1a). It was found that, most of the patients were in the age group of 51 to 55 years (vide Table 1b & Figure 1b). Hence, the study & control groups were comparable in terms of mean age & age distribution (%).

The sex distribution of the patients were found to be similar in group 1 & group 2 and most of them were males (M: F = 56.7%: 43.3%) (Vide Table 2 & Figure 2).

From the results, it is clear that, at the end of 2^{nd} week the percent reduction of mean TC from baseline in control group was 20.71%. Further reduction seen at the end of 4^{th} week & at the end of 6^{th} week were 35.97% & 44.16%.In study group, at the end of 2^{nd} week the % reduction of mean TC from baseline was 21.45% and by the end of 4^{th} & 6^{th} week the values were 34.25% and 43.82% which were found to be almost similar to control group (Vide Table 3&Fig 3). On comparing the control and study groups, the % reduction of mean TC from baseline was statistically not significant.

The % reduction of mean LDL from baseline in control group was 21.71% by the end of 2^{nd} week. It was 37.87% and 47.43% at the end of 4^{th} &6^{th} week. In study group, at the end of 2^{nd} week the % reduction of mean LDL from baseline was 18.66%. By the end of 4^{th} and 6^{th} week, the values were 35.89% and 45.61% which were almost similar to control group (Vide Table 4& Fig 4). On comparing both the groups there were no statistically significant differences in % reduction in mean LDL levels.

In control group, the percent reductions of mean TG from baseline at the end of 2nd & 4th week were 28.27% and 48.29%. The percent reduction was greater at the end of 6th week and it was 58.67%. In study group, the values at the end of 2nd & 4th week were 27.51% & 47.02%. By the end of 6th week, the % reduction of mean TG value was 57.32% almost similar to control group (Vide Table 5& Fig 5). On comparing both groups, the % reductions of mean TG were similar & statistically not significant.

On comparing both control & study groups, the % reduction of mean VLDL levels at the end of 2nd week were 14.26% Vs 13.67%. By the 4th and 6th week, the values were 25.70% and 43.91% in control group and 24.17% and 42.23% in study group which were almost similar and statistically not significant (Vide Table 6 & Fig 6).

The mean HDL value at the baseline in control and study group was 33.60 mg/dl Vs 34.53 mg/dl. By the end of 2nd week, the mean value was 38.01mg/dl Vs 37.67 mg/dl.At the end of 4th & 6th week, there was further increase in mean HDL value as 41.97 mg/dl and 43.53 mg/dl in control group Vs 40.63 mg/dl and 42.17 mg/dl in study group (Vide Table 7& Fig 7). On comparing both the groups, there were no statistically significant differences in mean HDL levels.

By the follow up, all the lipid profile parameters were maintained as that of 6^{th} week values. The TC: HDL ratio has been recognized as a more important determinant of CAD risk. While in ratio of ≤ 3.5 is considered desirable, a ratio of > 4.5 is associated with high risk[54]. At the baseline, both the groups showed TC: HDL ratio of 8.5 & 8.34. By the end of 6^{th} week, the ratio has reached the desirable level (Vide Table 8).

The % reduction values of TC, LDL, TG and VLDL for alternate day regime were similar to that of daily regime because of the long t ½ (~ 20 hours) of atorvastatin, which leads to prolonged pharmacological action. It also increases surface LDL receptors (upregulation) which takes up the cholesterol. Even when the Atorvastatin is not given daily, the upregulated LDL cholesterol remains active and reduces the LDL cholesterol[37].

Atorvastatin is also having effect on VLDL & TGs. It can reduce TG level even when the plasma level is > 250 mg/dl. In study group, though atorvastatin and fenofibrate were given on alternate day, there was significant reduction in TG levels (Vide Table 5& Fig 5). This can be attributed to the indirect action of atorvastatin on TGs, which is by reduction of cholesterol synthesis. Atorvastatin also impairs VLDL particles assembly & secretion, thereby reduces VLDL & TG levels[37]. Similarly, increased LDL receptor expression also brings

down TG level by increased binding of VLDL & LDL remnant particles. This may be the cause of persistent effect on VLDL & TG reduction in study group. Atorvastatin 10 mg can reduce LDL by 30-35% with a concurrent fall of plasma TG level by 10-30% and a modest rise in HDL by 5-15%[55].

Fenofibrate has mean plasma t ½ of 22.1 hours. It is completely metabolised to fenofibric acid, an active metabolite by plasma & tissue esterases. This active metabolite may be responsible for the effective reduction in TGs, even when the drug is given on alternate days. Though fenofibrate mainly act on plasma TG levels, it is also having effect on LDL levels[56]. The fall in LDL level is due to change in the cholesterol & TG contents of LDL and also due to increased LDL receptors. This may contribute to persistent effect on LDL & cholesterol levels even though both the drugs were not given every day in study group. Fenofibrate has greater HDL raising effect than other fibrates[57] .The rise in HDL is atleast in part due to transfer of surface lipid components from catabolized VLDL to HDL, and partly due to increased synthesis of HDL apoproteins (apo A-I, apo A-II)by the liver. In these patients, fenofibrate reduces the TG level by20- 50% and HDL is increased by10- 15%[57].VLDL level is reduced upto 20% and it clears LDL level by 20%.

It is well known that atorvastatin & fenofibrate has their own adverse effects. In our study, in control group 4 patients had epigastric distress, 4 had myalgia, 2 complained of fatigability, 3 had joint pain and 2 had headache. But in study group, 1 patient had epigastric distress, 2 had myalgia and1 had joint pain. Moreover, the hepatic enzymes like AST, ALT were within normal limits and also CPK was normal in both the groups. There were no serious adverse events reported in both the groups.

The effect of drugs on plasma lipoproteins in daily and alternate day regime found to be same, though in study group the patients received atorvastatin 10 mg on one day & fenofibrate 160 mg on other day. So in study group, the total dosages of the drugs given are less than that given in control group. The number of tablets taken by the patients in alternate day therapy was less than that of daily therapy. During the treatment period of 6 weeks, each patient in control group received 42 tablets of atorvastatin 10 mg & 42 tablets fenofibrate 160 mg. But in study group, each received 21 tablets of atorvastatin 10 mg & 21 tablets of fenofibrate160 mg. This in turn increases the patients' compliance to the therapy in study group.

The other added advantage is cost effectiveness of alternate regime than daily regime. The cost of atorvastatin 10 mg (Tab.Atorva 10) 10 tablets is

Rs.104.49 .The cost of fenofibrate 160 mg (Tab. Fenobate 160) 10 tablets is Rs.86.00.In daily regime, patients received Tab.Atorva 10mg 1 OD for 6 weeks ,cost about Rs.440.58 & Tab. Fenobate 160mg 1 OD for 6 weeks, cost about Rs.361.20. So, total cost is Rs.801.78. In alternate regime, patients received Tab.Atorva 10mg 1 OD on alternate days for 6 weeks, cost about Rs.220.29 & Tab. Fenobate 160mg 1 OD on alternate days for 6 weeks, cost about Rs.180.60. So, total cost is Rs.400.89.

Hence, the patients in alternate regime have to spend only half the drug cost of that of daily regime patients. Therefore, this alternate regime is cost effective with the same therapeutic benefits.

In control group, there were 8 patients with DM, 12 with HT & 10 with DM and HT. In study group, there were 7 patients with DM, 13 with HT and 10 with DM and HT.On comparing both groups, they were found to be similar. They are likely to be on multiple drug therapy for HT & DM. So, the alternate regime is better in dyslipidemic patients with associated diseases because of less cost & less total dose of atorvastatin and fenofibrate, with better patient compliance & lesser drug interactions than the daily regime.

Conclusion

Alternate regime of atorvastatin 10 mg and fenofibrate 160 mg is equally efficacious to daily regime of both atorvastatin 10 mg and fenofibrate 160 mg with better cost effectiveness and better patient compliance in patients with secondary dyslipidemia.

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PROFORMA

Name

Age

Sex

Hospital Number

Complaints

Present History

Past History

Personal History

Treatment History

General Examinations:

- Pulse
- BP
- Anemia
- Pedal Edema
- Jaundice

Systemic Examination:

- CVS
- RS
- Abdomen
- CNS

BASELINE CHARACTERISTICS

1. Name of patient
2. Age
3. Sex
4. IP/OP no
5. Address

6. Drug given: Tab. Atorvastatin 10 mg (Hospital Supply)

7. Drug given: Tab. Fenobate 160 mg

   Batch no:

   Date of purchase:

BIOCHEMICAL PARAMETERS

S.no	Lipid Profile	Initial	2nd week	4th week	6th week	% reduction
1.	Total Cholesterol (mg/dl)					
2.	LDL (mg/dl)					
3.	Triglyceride(mg/dl)					
4.	VLDL(mg/dl)					
5.	HDL(mg/dl)					

Other biochemical parameters measured before & after study:

S.No	Parameters	Before study	After study
1.	AST(SGOT) (U/L)		
2.	ALT(SGPT) (U/L)		
3.	CPK (U/L)		
4.	Hb%		
5.	RBS (mg/dl)		
6.	Blood urea (mg/dl)		
7.	S.creatinine (mg/dl)		