Review of Literature
Atherosclerosis and its clinical sequelae coronary artery disease (CAD) is the leading cause of death in most industrialized countries, and its importance as a major public health problem is increasing in developing countries. The initial connection between cholesterol and atherosclerotic plaques began in 1912 when Anitschkow reported finding atherosclerotic plaques similar to those occuring in humans, in rabbits fed with diets high in cholesterol.

Atherosclerosis in coronary arteries is nearly always seen in epicardial (extramural) portion of vessels, while the intramural coronary arteries are spared. The highest incidence is at a short distance from the ostia. Main stem of four major coronary arteries are involved. Right, Left main, Left Anterior descending and Left circumflex. The atherosclerotic plaque is composed of fibrous tissue (80%), extracellular lipid (5%), calcium (5%), macrophages and other cells 10%). The fibrous tissue increases as the plaque size increases.

**Risk Factors For Atherosclerosis:**

1. Male gender
2. Family history of premature IHD.
3. Hyperlipidemia.
4. Cigarette smoking
5. Hypertension.
6. Low HDL cholesterol
7. Diabetes mellitus
8. Hyperinsulinemia.
9. Abdominal obesity

10. High lipoprotein a levels.

11. Personal history of cerebrovascular disease (CVD) or peripheral vascular disease (PVD).

Risk factor concept implies that a person with either one or more risk factors is more likely to develop a clinical atherosclerotic event than a person with no risk factors. The most potent risk factors out of the above listed are hyperlipidemia, hypertension and cigarette smoking.

**Endothelial Function And Lipid Metabolism In Arterial Wall**

Normal arterial wall consists of 3 layers; intimia, media and adventitia. Intact endothelium regulates vascular tone by elaborating endothelium derived relaxing factor (EDRF) EDRF is actually nitric oxide (NO) or NO containing donor that mediates its vasodilator effects by activating guanylate cyclase (through c-AMP) EDRF inhibits monocyte adhesion, inhibits vascular smooth muscle contraction (VSMC) by EDRF and also inhibits abnormal growth of VSMC. It also inhibits platelet aggregation and adhesion (by prostacyclin PGI₂ and EDRF). Endothelial dysfunction could thus result in initiation of atherosclerosis.

Arterial wall cells can synthesize fatty acids, triglycerides, phospholipids and cholesterol from endogenous substrates for its repair and regeneration of membrane, but VSMC preferentially utilize lipids from plasma lipoproteins that are transported through endothelial cells in pinocytic vesicles.

VSMC possess specific receptors on the surface for some apoproteins present on the surface of these lipoproteins. Thus pinocytic vesicles (containing lipoproteins) gain entry inside SMC and fuse with lysosomes, where lysosomal enzymes cause breakdown of protein part
from lipoprotein and cholesterol ester get liberated which later gets converted into free cholesterol inside VSMC.

**Hyperlipidemia And Atherosclerosis:**

Several factors have been considered to predispose to atherosclerosis, but of these only elevated LDL cholesterol concentration and low levels of HDL cholesterol are the direct risk factors. All the other risk factors cited above worsen the atherosclerotic process but in the absence of direct risk factors they do not cause atherosclerosis.

**A. Serum Total Cholesterol (STC)**

Cann et al, (1977) reported higher levels of STC in proven CAD cases than those without CAD. Kannel et al, (1977) found that the incidence of CAD at STC levels of 220 mg/dl was nearly two fold than at levels of 180mg/dl. Kannel and co-workers also established the role of hypercholesterolemia in causing CAD in the Framingham heart study (1971). Studies at Oslo (West Lund, 1964; Nicolasayen, 1966) have elaborated the role of lipids in atherosclerosis. Martin and colleagues reported on unequivocal relationship between baseline total serum cholesterol (STC) and mortality from cardiovascular disease in Multiple Risk Factor Intervention Trial (MRFIT). They reported 3 fold increase in risk of CAD at STC levels above 240 mg/dl than at levels less than 200 mg/dl.

Garret et al, (1964) attempted to relate the extent of vascular damage to STC. High cholesterol levels were reported in cases of sudden death due to myocardial infarction by Chajman and Marney, (1964).

Henry Scott et al, (1982) did quantitative analysis of epicardial coronary artery and showed relation of STC and STG levels to the amount and extent of coronary artery narrowing by atherosclerotic plaque in coronary heart disease. He showed that the subjects with normal STC and
STG levels (group I) had significantly fewer major coronary arteries severely narrowed by atherosclerotic plaque than did the subjects with hypercholesterolemia (group II) or hypertriglyceridemia (group III) or both (group IV).

Increase in both degree and duration of lipemia in patients with evidence of CAD has been reported by many workers. (Waldow et al, 1954, Barritt, 1956; Bronte Stewart and Blackburn, 1958; Bouchier and Bronte Stewart, 1961).

At young age (35-50 years) myocardial infaction is associated with higher triglyceride levels while in higher age group (> 50 years) plasma total cholesterol levels are more than plasma triglyceride levels. (Carlson, 1960).

**B. Serum Total Triglycerides (STG)**

Several studies have shown that an elevation of STG is common in patients with CAD (Albrink et al, 1959; Hulley et al, 1980) Carlson and Bottiger, (1972) reported that incidence of CAD rose linearly with increasing plasma triglycerides. However, there is a great debate as to whether VLDL is the directly operating factor in producing CAD or is it the association of increased LDL and decreased HDL levels which is causative (Bilheimer, 1972).

**C. Low Density Lipoprotein (LDL) Cholesterol**

Concentration of LDL cholesterol is directly related to and is predictive of the risk for CAD. (Gordon et al, 1981; Hulley and Rhodes, 1982; Kannel et al, 1984). Mortality rate due to CAD in different communities are directly and linearly related to STC and LDL cholesterol levels (Lewis et al, 1978).
Increase in STC levels is associated with an increase in LDL levels. LDL exists in three forms - small LDL, dense LDL and LDL pattern B. It is now known that dense LDL fraction is more atherogenic.

Levgyama et al demonstrated that native LDL had no inhibitory effect on endothelium whereas oxidized LDL totally abolished endothelial dependant vasorelaxation. Peroxidation of polyunsaturated fatty acids in LDL occurs in VSMC and endothelial cells (EC) of the vessel wall. This LDL is chemoattractant to monocytes and facilitates the recruitment of circulating monocytes. It also increases production of growth factors and cytokines by macrophages and endothelial cells. The degradation of endothelial nitric oxide (NO) by oxidized LDL leads to decreased vasodilation and increased vasoconstriction in coronary arteries. LDL is also cytotoxic in its own right.

Plaque morphology rather than its size determines the development of acute coronary episode. Plaques rich in lipid, having high macrophage density and thin fibrous cap are more prone to rupture, resulting in formation of occlusive thrombus. Such plaques are known as unstable plaques. Coree and colleagues reported that increase in the lipid pool of plaque increases its chances of rupture. The oxidized LDL probably acts by its cytotoxic effect on endothelial smooth muscle or other cells and also stimulates macrophages to secrete a metalloproteinase that digests the connective tissue matrix of the plaques' fibrous cap, thus weakening it to hemodynamic stress.

**D. High Density Lipoprotein (HDL) Cholesterol**

HDL Cholesterol concentrations are even more strongly predictive of the risk for CAD in most studies. (Miller and Miller, 1975; Goldbouurt and Medalis, 1979; Gordon et al, 1981). The ability of HDL cholesterol to
predict development of coronary atherosclerosis is eight times more than that of STC (Gordon et al, 1977).

HDL carries 20% of STC. Subclasses of HDL can be fractioned by zonal ultracentrifugation, most abundant of which are HDL and HDL₂. Out of these HDL₂ appears to have stronger inverse relationship with occurrence of CAD and accounts for different levels of HDL cholesterol between men and women (Gofman et al, 1954). It is reasonable to view low HDL as an additive atherosclerotic risk factor if LDL is elevated but not when LDL level is low. Framingham Study showed that low HDL level was a more potent risk factor for CAD than either STC or LDL.

**Possible mechanisms of antiatherogenic effect of HDL:**

(i) Reversal of cholesterol transport from the peripheral cells to liver for removal from the body. (Miller and Miller, 1975).

(ii) Inhibition of LDL uptake by cells at the LDL receptor site.

(iii) Cholesterol efflux: HDL stimulates endothelial repair and PGI-2 synthesis by endothelial cells. PGI-2 in turn hydrolyze cholesterol esters in SMC thus forming free cholesterol. This can be easily removed from cells in arterial wall.

(iv) Inhibition of vascular smooth muscle cells.

(v) Facilitates metabolism of very low density lipoproteins (VLDL) and intermediate density lipoproteins (IDL).

**Factors modulating plasma lipids and lipoproteins in humans:**

**A. Age and Sex:**

Significant relationship between sex and age of a person and his plasma lipid levels has been seen. Some workers have reported that the mean level among females never exceed 85 mg% while in men the mean
level reaches its maximum in age group 40-59 years and is about 107 mg% (Schaefer and Mechemias, 1965). In another study females were found to have a markedly lower level (mean value 130 mg/dl) than males (mean value 185 mg/dl).

In most populations, women have been shown to have a higher level of HDL than men at all ages following puberty. A drop in HDL levels seen in males at around the time of puberty has been related to the degree of sexual maturation (Frenichs et al, 1978; Morrison et al, 1979) Transient rise in HDL₂ is also reported at or near the time of ovulation (Bareley et al, 1965).

HDL levels also change with age. In males, levels are stable till puberty, show a decline during adolescence, relatively stable levels in adulthood then plateau in old age. Females show a small linear increase in HDL from childhood to about 60 years after which no effect of age is apparent. (Heise et al, 1980).

An age dependant increase of triglyceride levels during 3rd and 4th decades of life have been reported in a study of 500 swiss males (Hyden, 1967; Dyerberg and Hijerne, 1972).

**B. Weight:**

Albrink et al, (1962) assumed that the rise in triglycerides and cholesterol levels with age might be due to age related weight gain. Increasing hypertriglyceridemia in weight gainers has been reproted (Hyden, 1969).

**C. Diurnal and Seasonal Variation ;**

Cholesterol and phospholipids show a minimal diurnal variation. A seasonal variation is often seen in triglyceride levels with the value being higher in winters than in summers (Carlson and Lindstadt, 1968).
D. Obesity:

HDL levels are lower in obese individuals as compared to non-obese (Wilson et al, 1972; Carlson et al, 1975). In some studies, increase in HDL levels along with a fall in VLDL and TG concentrations have been reported during the course of weight loss (Wilson et al, 1972).

E. Physical Activity:

Accelerated rate of chylomicron removal after exercise and its accentuation after habituation to exercise has been observed (Kmt et al, 1963). Definite fall in TG levels after exercise has been reported by many workers. (Kenttinan, 1963; Hellesey et al, 1964). High levels of HDL are reported with high level of endurance type exercise like long distance running, tennis and soccer. (Weed et al, 1977; Lehtonen et al, 1978; Vedak et al, 1980), whereas a drop in HDL was observed with calorie restriction in the absence of exercise (Weltman et al, 1980).

According to the National Cholesterol Education Programme (NCEP) expert panel on detection, evaluation and treatment of high Blood Cholesterol in adults (Adults treatment Panel III), major risk factors (exclusive of LDL cholesterol) for CHD are as follows:

- Cigarette smoking
- Hypertension (blood pressure ≥ 140/90mm of Hg or on antihypertensive medication).
- Family history of premature CHD (CHD in male first degree relative <55yrs; CHD in female first degree relative <65 years).
- Age (men ≥ 45 years; women ≥ 55 years).
Diabetes is regarded as a coronary heart disease risk equivalent i.e. a condition that carries an absolute risk for developing new CHD equal to the risk for having recurrent CHD events in persons with established CHD.

Hence forth, hypercholesterolemia and hypertriglyceridemia are considered as directly and indirectly predisposing factors for ischemic heart disease and it is presumed that lipid lowering drugs may be beneficial in the primary and secondary prevention.

**Statins**

The statins are the most effective and best-tolerated agents for treating dyslipidemia. These drugs are competitive inhibitors of 3-hydroxy-3methylglutaryl coenzyme A (HMG-CoA) reductase, which catalyzes an early, rate-limiting step in cholesterol biosynthesis. Higher doses of the more potent statins (e.g., atorvastatin and simvastatin) also can reduce triglyceride levels caused by elevated VLDL levels. Some statins also are indicated for raising HDL-C levels, although the clinical significance of these effects on HDL-C remains to be proven.

Five large, well-controlled clinical trials have documented the efficacy and safety of simvastatin, pravastatin, and lovastatin in reducing fatal and nonfatal CHD events, strokes, and total mortality.

**Mechanism of Actions:**

Statins exert their major effect – reduction of LDL levels – through a mevalonic acid like moiety that competitively inhibits HMG-CoA reductase by product inhibition (Alberts et al., 1980).

Statins affect blood cholesterol levels by inhibiting cholesterol-genesis in the liver, which results in increased expression of the LDL receptor gene, which increases the synthesis of LDL receptors (Brown and Goldstein,
Degradation of LDL receptors also is reduced (Brown et al., 1978). The greater number of LDL receptors on the surface of hepatocytes results in increased removal of LDL from the blood (Bilheimer et al., 1983), there by lowering LDL-C levels.

Some studies suggest that statins also can reduce LDL levels by enhancing the removal of LDL precursors (VLDL and IDL) and by decreasing hepatic VLDL production.

Triglyceride levels greater than 250mg/dl are reduced substantially by statins and the percent reduction achieved is similar to the percent reduction in LDL-C. If baseline triglyceride levels are below 250mg/dl reduction in triglycerides do not exceed 25 percent irrespective of the dose of statin used.

Pontrelli L Parris W. Adelik, Cheung RC et al investigated the potential hypolipidemic effects of atorvastatin, a 3- hydroxy, 3- methyl glutaryl coenzyme A reductase inhibitor with good triglyceride lowering properties, in patients with combined dyslipidemia and evidence of impaired fasting glucose or type II diabetes 20 patients were recruited for the study and two subgroups were made, one group receiving atorvastatin (80mg/day) with other placebo for 60 days. At the end of study treatment with atorvastatin resulted in a statistically significant reduction in total cholesterol (41%) LDL cholesterol (55%). triglycerides (32%)and apoB (40%). Mean LDL particle diameter significantly increased 25.29± 0.24nm to 26.51.

Results suggested that atorvastatin beneficially alters the atherogenic lipid profile in these patients.

treatment on the fibrinolytic system and systemic inflammatory status and on apoptosis in hyperlipidemic patients with coronary artery disease. Study population consisted of 36 hyperlipidemic patient with stable CAD, untreated with lipid lowering medications, they received 10 mg/day atorvastatin for 12 weeks. After treatment LDL decreases by 39%, total cholesterol decreases by 32% and triglycerides decreased by 22% and HDL-C increased by 13%. These effects were associated with a decrease in plasma fibrinogen from 331-298 mg/dl and SL selection levels from 666 ± 201-584 ± 62 ng/ml. and S Fas level & GFC increased from 3754-4873 pg/ml and from 3.5-5.6 us/ml respectively. There results suggest that lipid lowering with atorvastatin therapy significantly increases GFC, decrease fibrinogen levels and cause leukocyte deactivation.

Parhofer KG laubach E, Bamett PH studied the effect of atorvastatin on postprandial lipoprotein metabolism in hypertriglyceridemic patients and found that atorvastatin improves postprandial lipoprotein metabolism in addition to decreasing fasting lipid levels in hypertriglyceridemia.

Spostto AC, Santos RD, Amaricso RF, Ramires JA, John chapman M, Maramhoo RC, studied the effect of atorvastatin (10mg) at low dose and high dose (40mg) upon the intravascular metabolism and plasma kinetics of chylomicron like emulsions in 45 hyperlipidemis subjects for 6 wks, and found that atorvastatin treatment accelerates the plasma clearance of chylomicron like emulsions and reduce recirculation of fatty acids in subject with atherogenic hyperlipidemia.

Hepatic lipase activity is significantly higher in population compared with an age matched control group without diabetes. Hepatic lipase is involved in the metabolism of several lipoprotein and may contribute to the atherogenic lipid profile in type 2 diabetes. Berk-Planken H, Hoogerbrugge N, Stolk RP, Bootsma AH, Jarsen H et al studied the
atorvastatin 10mg and atorvastatin 80mg an Hepatic lipase activity in 198 patients with type 2 diabetes for 30 wks. [Diabetes Atorvastatin Lipid Intervention study] and found that Atorvastatin treatment in diabetic dyslipidemia results in a significant dose dependent decrease in Hepatic lipase activity.

The GREEK Atorvastatin and Coronary heart disease Evaluation (GREACE) study compared two standards of lipid lowering treatment in 1000 patients with coronary heart disease. Structured care aimed at achieving the low density lipoprotein cholesterol (100mg/lld), goal described in the NCEP ATP II & III guidelines for patients with CHD. Structured care was associated with a significant reduction in overall mortality and coronary events compared to usual care

Schaefer EJ. Mc Namara JR. Tayler T. Daly JA. Gleason JA. Seman LJ. Ferrari A. Rubenstein JJ studied the effects of atorvastatin on fasting and postprandial lipoprotein subclasses in coronary heart disease patients versus control subjects in 2002 Oct. The effects of atorvastatin at 20, 40, and 80 mg/day on plasma lipoprotein subclasses were examined in a randomized, placebo-controlled fashion over 24 weeks in 103 patients in the fasting state who had coronary heart disease (CHD) with low-density lipoprotein (LDL) cholesterol levels \(\rightarrow 130 \text{ mg/dl}\). The effects of placebo and atorvastatin 40 mg/day were examined in 88 subjects with CHD in the fasting state and 4 hours after a meal rich in saturated fat and cholesterol. These findings were compared with results in 88 age- and gender-matched control subjects. Treatment at the 20, 40, and 80 mg/day dose levels resulted in LDL cholesterol reductions of 38%, 46%, and 52% [all \(p \leftarrow 0.0001\)], triglyceride reductions of 22%, 26%, and 30% (all \(p \leftarrow 0.0001\)), and high-density lipoprotein [HDL cholesterol increases of 6%, 5%, and 3%, respectively (all \(p \leftarrow 0.05\) at the 20- and 40-mg doses). The lowest total cholesterol/HDL cholesterol ratio was observed with the 80 mg/day
dose of atorvastatin (p \leq 0.0001 vs placebo). Remnant-like particle (RLP) cholesterol decreased 33%, 34%, and 32%, respectively (all p \leq 0.0001). Lipoprotein(a) [Lp(a)] cholesterol decreased 9%, 16%, and 21% (all p \leq 0.0001), although Lp(a) mass increased 9%, 8%, and 10%, respectively (all p \leq 0.01). In the fed state, atorvastatin 40 mg/day normalized direct LDL cholesterol (29% below controls), triglycerides (8% above controls), and RLP cholesterol (10% below controls), with similar reductions in the fasting state. At this same dose level, atorvastatin treatment resulted in 39%, 35%, and 59% decreases in fasting triglyceride in large, medium, and small very LDLs, as well as 45%, 33%, and 47% reductions in cholesterol in large, medium, and small LDL, respectively, as assessed by nuclear magnetic resonance [all significant, p \leq 0.05], normalizing these particles versus controls (77 cases vs 77 controls).

Stern RH. Yang BB. Hounslow NJ. MacMahon M. AbelRB. Olson SC studied the pharmacodynamics and pharmacokinetic-pharmacodynamic relationships of atorvastatin, an HMG – CoA reductase inhibitor and found that following initiation of dosing, statistically significant decreases in total cholesterol. LDL-cholesterol and LDL-apolipoprotein B were observed within 24 hours and in LDL-C within 72 hours. Following discontinuation of drug dosing, statistically significant increases were observed in total cholesterol and LDL-cholesterol within 48 hours and in LDL-cholesterol and LDL apolipoprotein B within 72 hours. In conclusion, atorvastatin produces marked LDL – cholesterol reductions the mean dose-response relationship is log linear, almost all individual dose-response curves parallel the mean dose response curve onset and cessation of action are rapid, the estimated and measured LDL – cholesterol are the same, LDL-cholesterol and LDL-Apo B reductions are similar, and plasma concentrations are not correlated with LDL-cholesterol reduction at a given dose.
Statins and Endothelial Function:

Statins improve coronary vasodilation in response to acetylcholine. Statins stabilize endothelial cell nitric oxide synthase mRNA, thereby enhancing synthesis of endothelial cell nitric oxide (Laufs et al., 1998). Statin therapy reverses endothelial dysfunction as monitored by vasoactivity within a short period of one month.

Statins and Plaque Stability:

As discussed earlier, the vulnerability of plaques to rupture and thrombosis is of greater clinical relevance than the degree of stenosis they cause (Gutstein and Fuster, 1999). Statins may affect plaque stability in a variety of ways. There are reports that statins inhibit monocyte infiltration into the artery wall in a rabbit model (Bustos et al., 1998) and inhibit macrophage secretion of matrix metalloproteinases in vitro (Bellosta et al., 1998). The metalloproteinases degrade all extracellular matrix components and thus weaken the fibrous cap of atherosclerotic plaques.

Statins and Inflammation:

Appreciation of the importance of inflammatory processes in atherogenesis is growing (Ross, 1999), and statins have been suggested to have an antiinflammatory role. So they are helpful in prevention of atherosclerosis.

Statins and Coagulation:

Statins reduce platelet aggregation (Hussein et al., 1997a), and in vitro model systems indicate that statins reduce the deposition of platelet thrombi on porcine aorta.

Nicotinic Acid (Niacin):

Nicotinic acid (niacin, pyridine-3-carboxylic acid) is one of the oldest drugs used to treat dyslipidemia and is the most versatile in that it
favorably affects virtually all lipid parameters. Niacin is a water-soluble B-complex vitamin that functions as a vitamin only after its conversion to nicotinamide adenine dinucleotide.

The hypolipidemic effects of niacin require larger doses than are required for its vitamin effects. Niacin is the best agent available for increasing HDL-C (increments of 30% to 40%); it also lowers triglycerides by 35% to 45% (as effectively as fibrates and the more potent statins) and reduces LDL-C levels by 20% to 30%. Niacin also is the only lipid-lowering drug that reduces Lp (a) levels significantly, by about 40%.

**Mechanism of Action:**

In adipose tissue, niacin inhibits the lipolysis of triglycerides by hormone-sensitive lipase, which reduces transport of free fatty acids to the liver and decreases hepatic triglyceride synthesis. In the river niacin reduces triglyceride synthesis by inhibiting both the synthesis and esterification of fatty acids.

Niacin raises HDL-C levels by decreasing the fractional clearance of apoA-I in HDL rather than by enhancing HDL synthesis.

Elam MB humringhake DB Davis KB, Garg R, Johnson C, Egan D, Kostis JB. Shefis DS, Brinton EA, et al studied the effect of niacin on lipid and lipoprotein levels and glycemic control in patients with diabetes and peripheral arterial disease. Study was conducted on 468 patients out of which 125 are of diabetes with peripheral arterial disease, patients received 3000 mg/day or maximum tolerated dosage of niacin for 60 wks. [12 with active run-in and 48 wk double blind]. After treatment niacin significantly increased HDL-C by 29% and 29% and decreased triglycerides by 23% and 28% and low density lipoprotein cholesterol by 8% and 9% respectively in patients with and without Diabetes. Levels of HbAIC were unchanged from baseline to follow up in participants with diabetes treated with niacin.
Study suggests that lipid modifying dosage of niacin can be safely used in patients with diabetes and that niacin therapy may be considered as an alternative to statin drugs or fibrates for patients with diabetes in whom these agents are not tolerated or fail to sufficiently correct hypertriglyceridemia or low HDL-C levels.

Grundy SM, vegaGL, Me gavern MC, Tulloch BP Kendall DM, Fitz Patrick D, Ganda OP et al studied the efficacy, safety and tolerability of once-daily niacin for the treatment of dyslipidemia associated with type 2 diabetes. Diabetic dyslipidemia is characterized by high triglyceride level, low high density lipoprotein cholesterol, small dense low density lipoprotein particle, with high free fatty acids. Study was done on 148 patients 49 were taking placebo. 45 were taking 1000 mg ER Niacin for 16 weeks. After 16 weeks. Treatment, dose dependent increase in HDL cholesterol level [ ± 19% & ± 24] and reduction in triglyceride levels (-13% & -28%) were observed. Baseline & 16 wk glycosylated Hb levels were 7.13% & 7.11% respectively in the placebo group, 7.28% & 7.3% respectively in 1000 mg ER Niacin group and 7.2% and 7.5% respectively in the 1500mg ER niacin group. The study shows that low doses of ER Niacin ( 1000 or 1500 mg/dl) are a treatment option for dyslipidemias in patients with type 2 diabetes.

High dose of niacin has been shown to impair glucose control in patients with non insulin dependent Diabetes mellitus. Rindos JR. Achacosa S, et al undertook a study to determine, if low dose niacin has a similar effect in patients receiving niacin 500mg three times daily for 2 month with fasting bid. Sugar was measured after every 2 weeks and hemoglobin A (Ic) and lipid profile determined after 8 week, statistical analysis was performed using a t-test for related groups. Mean fasting blood sugar was statically higher during niacin therapy versus baseline (131 mg/dl ± 27 vs 161mg/dl ± 40), no change was noted in HbA1C, there
was a trend in a decrease in total cholesterol, LDL - and triglyceride. HDL was statistically higher after niacin therapy.

Pair J, Lin M, Kesala RL, Von J, charles MA et al tested the hypotheses that niacin is effective for the separate treatment of abnormalities of LDL particle size, HDL2 percentage and LP(a) without potential negative effect on glycosylated Hb, and found that after niacin therapy LDL particle size increases, small dense LDL particle mass decreases, total HDL-C mass increased and LP(a) decreases. Mean HbAIC levels was improved during treatment using increased oral agents and insulin treatment doses in more that 90% of the patients.

**Fibric Acid Derivatives - Fenofibrate**

**Mechanism of Action**

Despite extensive studies in human beings, the mechanisms by which fibrates lower lipoprotein or raise HDL levels, remain unclear. recent studies suggest that many of the effects of these compounds on blood lipids are mediated by their interaction with peroxisome proliferator-activated receptors (PPARs). Fibrates reduce triglycerides through PPARα-mediated stimulation of fatty acid oxidation, increased LPL synthesis, and reduced expression of apoC-III. Fibrate-mediated increases in HDL are due to PPARα stimulation of apoA-I and apoA-II expression (Staels and Auwerx, 1998), which increases HDL levels. Most of the fibric acid agents have potential antiatherothrombotic effects, including inhabitation of coagulation and enhancement of fibrinolysis. These salutary effects also could after cardiovascular outcomes by mechanisms unrelated to any hypolipidemic activity.

Sasaki J. Yamamoto K. Ageta M studied effects of tenofibrate on high density lipoprotein particle size in patients with hyperlipidemia, in it fifty hyperlipidemic patients [31 men, 19 women; mean (SD)) age, 54.6
(12.7) years] were enrolled. Serum total cholesterol and triglyceride levels were significantly reduced with fenofibrate treatment compared with placebo [9.4% (P = 0.007) and 34.4% (P 0.001)], respectively, whereas HDL-C levels were significantly elevated [by 25.8% (P = 0.001)]. Lipoprotein lipase [LPL] activity, LPL protein level, and hepatic triglyceride lipase activity increased by 10.5%, 13.4%, and 11.4%, respectively. The amount of HDL3 increased significantly with fenofibrate compared with placebo [P = 0.001]. Fenofibrate was well tolerated during the study. These findings indicate that fenofibrate therapy increased the HDL subfraction with the smallest diameter [HDL3], which is largely responsible for withdrawing cholesterol from peripheral cells.

Fenofibrate has consistently been shown to increase HDL, with relative change, ranging from 15% to 30%. When baseline HDL is < 35 mg/dl the increase is much more pronounced and may even reach 40% to 50%. In two trials conducted in clinical practice settings in Belgium (6 months n=1545) and Germany (3 months n=9884) treatment with fenofibrate resulted in significant increase in HDL of 19% and 23% respectively. The increase in HDL were baseline dependent and were most marked when baseline HDL was < 35 mg/dl where mean increase reached 41% and 44% respectively In both trials, a high percentage of patients reached post treatment levels that were > 45 mg/dl.

In the German trial. The over all increase in mean HDL were observed across a variety of subgroups. In the Belgium trial 735 patients took part in a 6 month extension phase. During this extension phase, the increases in HDL observed on fenofibrate treatment in the first 6 month period were maintained over the 12 month period.

A high density lipoprotein cholesterol level < 1mmol/L is associated with increased cardiovascular morbidity and mortality. Ic Raux CW,
Marphy E, Seed M, studied the fenofibrate 267 mg/d and found that fenofibrate 267 mg/d is well tolerated and can achieve significant increase in HDL-C levels in clinical practice.

Micronised fenofibrate is indicated for the treatment of dyslipidemia. Recently a new tablet formulation of micronised fenofibrate has become available with greater bioavailability than the older capsule formulation. The micronised fenofibrate 160mg tablet is bioequivalent to 200mg capsule. Microised fenofibrate 200mg capsule once daily produced greater improvement in TG, and generally in HDL levels than HMG-CoA inhibitor simvastatin (10 or 20mg/day) parvastatin 20mg/day or atorvastatin 10-40mg/ld. Micronised fenofibrate 200mg once daily was associated with significantly greater improvements from baseline in TC.LDL-C, HDL-C, and TG levels than placebo in patients with type 2 diabetes mellitus enrolled in the double blind randomised Diabetes atherosclerosis intervention study [DAIS] Moreover angiography showed micronised fenofibrate was associated with significantly less progression of coronary atherosclerosis than placebo.